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Concentrations of endogenous sex steroid hormones and SHBG in healthy postmenopausal women

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Abstract

Studies reporting age-specific reference ranges of endogenous sex steroid hormones in postmenopausal women are relatively scarce. If levels differ by age, dosing and treatment regimens should vary among postmenopausal women accordingly. Our objective was to establish reference ranges for sex steroid hormones and sex hormone binding globulin (SHBG) by age group and overall, and to investigate their association with demographic characteristics.

Serum samples were obtained from 1207 healthy postmenopausal women aged 41 to 92, not using hormone therapy, at the baseline visit of 3 clinical trials. Estrone (E_1), estradiol (E_2), and total testosterone (T) were measured by radioimmunoassay with preceding purification steps; SHBG was measured by direct chemiluminescent immunoassay. Free T (FT) was calculated.

Women were categorized by 5-year age groups. There was little change in the mean estrogen levels among the different age groups (E_2: 10–12 pg/mL; E_1: 33–35 pg/mL. Mean total T levels increased gradually with age from 22.2 to 26.2 ng/dL, but FT mean levels were relatively constant (4.4–4.6 pg/mL). Mean SHBG levels increased with age from 45 to 54 nmol/L. A generalized linear model tested the association of each demographic characteristic with the hormones and SHBG. A significant association was derived.

Our study provides valuable insight into the profiles of serum sex steroid hormones and SHBG in different healthy postmenopausal women aged 41 to 92 years.

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Keywords

estradiol; estrone; testosterone; sex hormone binding globulin; postmenopausal; reference ranges

1. Introduction

It is well recognized that reference ranges for circulating hormone levels can help limit false diagnosis and unnecessary treatment. Reference ranges of sex steroid hormone concentration are well defined for women of reproductive age, but such ranges are not well established for postmenopausal women [1]. Cessation of ovarian estrogen production at menopause results in very low serum levels of the principal biologically active estrogen, estradiol (E_2) and the less active estrogen, estrone (E_1), and is accompanied by postmenopausal symptoms such as hot flashes and urogenital atrophy. Similarly, low production of the principal biologically active androgen, testosterone (T) is often accompanied by lack of energy and low libido. Treatment of these postmenopausal symptoms requires knowledge about normal circulating levels of the estrogens and T since postmenopausal women may respond differently to treatment. If levels of these hormones differ in younger versus elderly postmenopausal women, then dosing and treatment regimens of each group may vary to account for these differences.

Peripheral adipose tissue serves as an important source for sex steroid hormones. A number of studies have reported the impact of obesity on endogenous sex steroid hormone levels in postmenopausal women [2,3]. Although studies have reported on the association of sex steroid concentrations with age and body mass index (BMI) [4], their endogenous concentrations have not been identified in a reasonably large sample of postmenopausal women by age groups, controlled for BMI and type of menopause (natural vs. surgical).

In addition, studies have also reported on associations of alcohol use and smoking with endogenous estrogens in postmenopausal women. The data show that women with a moderate intake of alcohol have higher concentrations of estrogens and T in serum compared to non-drinkers [5]. In contrast, circulating levels of estrogens and androgens are diminished in postmenopausal women who smoke cigarettes [6].

Here we report mean serum concentrations of E_2, E_1, total T and FT, and SHBG by age group and overall reference ranges in healthy postmenopausal women, using well-validated radioimmunoassays (RIAs) to measure the hormones. We also report the effect of various factors including age, BMI, race and ethnicity, type of menopause, years since menopause, cigarette smoking, and alcohol use on the circulating levels of those hormones and SHBG.

2. Materials and Methods

2.1 Subjects and samples

Sex steroid hormones and SHBG were measured in serum samples obtained from the baseline visit of 3 randomized controlled trials of postmenopausal women conducted at the Atherosclerosis Research Unit of the University of Southern California, Keck School of Medicine. The clinical trials are: Estrogens in the Prevention of Atherosclerosis Trial

(EPAT) [7], Early versus Late Intervention Trial of Estradiol (ELITE) [8], and Women's Isoflavone Soy Health (WISH) trial [9]. EPAT was designed to evaluate the effect of daily E_2 therapy on progression of subclinical atherosclerosis over 2 years. ELITE was designed to assess the effect of estrogen therapy (ET) on the progression of subclinical atherosclerosis in postmenopausal women randomized to either ET or placebo in 2 strata: within 6 years since menopause, and 10 years or more since menopause. WISH evaluated the effect of isoflavone soy protein supplementation on subclinical atherosclerosis over 2 years. All 3 trials had similar inclusion criteria, including postmenopausal women with E_2 levels <25 pg/mL who were amenorrheic for at least 6–12 months; the women were not taking hormone therapy currently and were free from clinically evident cardiovascular disease, diabetes, thyroid or renal disease, cancer, or life-threatening conditions.

2.2 Assays

The sex hormones and SHBG were measured in the pre-randomization baseline serum samples, which were stored at −80 °C. All the samples were analyzed together. E_1, total E_2, and total T were measured by RIA after extraction with ethyl acetate:hexane (3:2) and subsequent separation by Celite column partition chromatography using ethylene glycol as the stationary phase, as described previously [10]. The extraction step removes the glucuronidated and sulfated steroids, which comprise a substantial number of metabolites. T was eluted off the column using 40% toluene in isooctane. The lower limit of quantitation (LLOQ) was 1.0 ng/dL, and the intraassay and interassay coefficients of variation (CVs) were 9.0% at 32.8 ng/dL and 10.4% at 6.1 ng/dL, respectively. Elution of E_1 from the column was carried out with 15% ethyl acetate in isooctane. The LLOQ was 5 pg/mL, and the intraassay and interassay CVs were 7.9% and 12%, respectively, at 26 pg/mL. E_2 was eluted with 40% ethyl acetate in isooctane. The LLOQ was 2.5 pg/mL, and the intraassay and interassay CVs were 8.9% and 13.0%, respectively, at 14 pg/mL. High specificity was achieved in the T and estrogen assays due to the extraction step, which removes the glucuronidated and sulfated steroid metabolites, and the subsequent chromatographic step, which removes most of the unconjugated metabolites. Also contributing to the high specificity is the low cross-reaction (<1%) with relevant metabolites (androstenedione, DHEA, and dihydrotestosterone) in the T RIA, and E_1 and 2-methoxyestradiol in the E_2 RIA, as well as E_2 in the E_1 RIA. In addition, we have shown, using mass spectrometry, that there is negligible interference by E_2 metabolites in the E_2 RIA [11].

SHBG was quantified by a solid-phase, 2-site chemiluminescent immunoassay on the Immulite analyzer (Siemens Healthcare Diagnostics, Deerfield, IL). The LLOQ was 1 nmol/L and the intraassay and interassay CVs were 5.2% at 63 nmol/L and 6.6% at 80 nmol/L, respectively.

FT was calculated using an algorithm based on equations derived from Vermeulen and coworkers [12]. The algorithm utilizes measured concentrations of total T and SHBG, as well as an average concentration of albumin.

2.3 Statistical methods

Sex steroid hormone and SHBG levels were normalized by log transformation. Individual outliers were identified as levels greater than the mean+3SD on a log-scale and were excluded from the analysis. Demographic characteristics are presented as mean (SD) for continuous variables and as frequency (percent) for categorical variables. Sex steroid hormones and SHBG are reported among the total participants and by 5-year age group as mean (SD), minimum, maximum, and reference range. The reference range was calculated as the mean ±2SD on a log-scale and back-transformed. A generalized linear model was used to test the association of each demographic characteristic: age, BMI, type of menopause (natural vs surgical menopause), years since menopause, smoking (never, past and current smoker) and alcohol (never, 0–1, 1–2 and >2 drinks per day) with the sex steroid hormones and SHBG. Estimated mean hormone/SHBG levels and 95% confidence interval from the model were reported by levels of each characteristic. Trend tests were conducted for age, BMI and amount of alcohol consumption in association with the sex steroid hormones and SHBG. All analyses were performed with SAS 9.4.

3. Results

Baseline sex hormone and SHBG levels of 1207 participants from the 3 randomized clinical trials were examined. Eighteen participants with outlying values, including E_1 ≥127 pg/mL (6 women), E_2 ≥62 pg/mL (11 women), total T ≥96.9 ng/dL (5 women), or FT ≥20.8 pg/mL (4 women), were excluded from the analysis. Among a total of 1187 participants that were included in the analysis, 212 (17.8%) were from EPAT, 632 (53.2%) were from ELITE, and 345 (29.0%) were from WISH. The mean (SD) age of the participants was 60.9 (7.0) years with an age range of 41–92 years. The mean time since menopause was 11.4 (8.2) years with a range of 0.1–50 years. Most participants (87.5%) had a natural menopause. In the youngest group (age <50 years), the mean (SD) age of the women was 48 (± 2.1) years, 28% had a surgical menopause, and in 77% of them the mean time since menopause was <6 years. More than half of participants were non-Hispanic white (65.1%). Mean BMI was 27.4 (5.4) kg/m^2 with roughly one-third of the participants in each of the normal, overweight, and obese categories. Approximately half of the participants reported that they never smoked (57.8%) or never drank alcohol (48.8%). (Table 1)

Mean (SD) levels, reference ranges, and minimum and maximum levels of sex steroid hormones and SHBG are shown by age groups and among the total participants in Table 2. Mean SHBG levels were incrementally higher across the age groups, from 45 nmol/L at age 50–54 years to 49 nmol/L at age 60–64 years. Thereafter, the levels were substantially higher with greater incremental values across the older age groups (54 and 68 nmol/L at ages 70–74 and ≥75 years, respectively). In contrast, mean E_2 and E_1 levels were relatively stable across all age groups. The E_2 and E_1 levels changed by 3 pg/mL from the lowest to highest values (9 to 12 pg/mL and 33 to 35 pg/mL, respectively. As for total T, mean levels were higher with increasingly older age groups, with levels of 19.9 and 22.2 ng/dL at ages <50 and 50–54 years, respectively, whereas the mean level in the 70–74 age group was 26.2 ng/dL. In contrast to total T, mean FT levels were generally stable across the age groups.

Based on our data, the overall reference ranges of sex steroid hormones among all postmenopausal women (N=1187) are as follows: E_1 = 14 – 69 pg/mL; E_2 = 3 – 27 pg/mL; total T = 8.2 – 54.6 ng/dL; SHBG = 16 – 115 nmol/L; and FT = 1.5 – 10.5 pg/mL.

When each demographic characteristic was considered separately, sex steroid hormone and SHBG levels were significantly associated with age, race/ethnicity, BMI, type of menopause, years since menopause, smoking and alcohol intake. The associations of the estimated mean sex steroid hormone and SHBG levels from the model with demographic characteristics are shown in Table 3.

Trend tests indicated a significant trend of the sex steroid hormone and SHBG levels with age, BMI, and greater alcohol consumption (all p-values <0.001). Higher BMI was associated with increased E_1, total T and FT, and E_2, but lower SHBG. When compared with never drinkers, drinking higher amounts of alcohol was associated with lower E_1 levels, but higher E_2, total T, FT, and SHBG levels.

4. Discussion

In the present study, we measured sex steroid hormones and SHBG in postmenopausal women by 5-year age groups to gain a better understanding of the reference range of these compounds during the span of postmenopausal life. Previously available data obtained by either immunoassay or mass spectrometry have been limited by either small sample size, limited or no classification of age groups, and/or inadequate assay methodology.

We measured SHBG because it regulates the access of androgens and estrogens to target tissues. Also, SHBG can be used to determine FT using a validated algorithm, which we employed in the present study. The mean SHBG levels increased by 17% from age 50–54 to 70–74 years. There was a particularly large increase from age 70–74 to ≥75 years (14 nmol/L increase). Although the sample size of the ≥75-year group was relatively small, our findings agree with those observed in a larger study by Davison and coworkers [13] who showed a sharp increase in SHBG levels in women aged 65–75 years.

In contrast to SHBG, both mean E_2 and E_1 levels did not change much across the different age groups. Ke and coworkers [14] also showed that mean baseline serum E_1 and E_2 levels were generally similar in postmenopausal women aged 50–79 years; they used LC-MS/MS assays for the measurements. The age-specific intervals in their study were 10 years and the number of women in each group ranged from 42 to 50. These findings suggest that the activity of the enzymes involved in the peripheral conversion of androgens to estrogens does not change much during the postmenopausal years. The enzymes include aromatase, which transforms androstenedione and T to E_1 and E_2 respectively; 17β-hydroxysteroid dehydrogenase (17β-HSD) type 1, which converts E_1 to E_2; 17β-HSD type 5, which converts androstenedione to T; and 17β-HSD type 2, which converts E_2 to E_1 and T to androstenedione.

In a recent study, Davis and coworkers [15] measured circulating sex steroid hormone levels in older postmenopausal women participating in the Aspirin in Reducing Events in the Elderly (ASPREE) study to establish age-specific reference ranges at 5-year intervals

for women 70 – ≥85 years of age using LC-MS/MS. The reference group consisted of 5326 women with a mean age of 75.1 (± 4.2) years and a range of 70 to 94.7 years. The conclusion of the study was that median E_1 increased from the age of 70 years by 11.7%. E_2 levels were below the sensitivity of the assay method in 66.1% of the samples and were not reported.

The reported mean E_1 value in the 70–74 age group in the study by Davis and coworkers [15] was 57 pg/mL. The E_1 levels obtained in that study are substantially higher (63%) than those found in our study in women aged ≥70 years (57 vs. 35 pg/mL). In the study by Ke and coworkers [14] mentioned earlier, mean E_1 levels were 17.2 pg/mL in the 70–74 year age group. In a study by Wang and coworkers [16], serum E_1 levels measured in postmenopausal women by LC-MS/MS were compared using values from 7 different studies. Mean or median E_1 concentrations ranged from 11.8 to 37.4 pg/mL, with an overall mean of 22.8 pg/mL. Inter-laboratory variations in measurements of E_1 and E_2 can be attributed to differences in selection and characterization of populations and assay methodology, as well as lack of assay standardization.

It is surprising that the E_1 levels in the study by Davis and coworkers [15] are so much higher than in the other studies. One possible explanation for the large difference in the mean E_1 levels may be the very high E_1 levels (outliers) found in some of the participants, which were included in calculating the mean E_1 levels. The reported range of E_1 levels was 3.7 to 5768.9 pmol/L. The upper range plasma level of 5768.9 pmol/L (1559 pg/mL) in a postmenopausal woman is not physiologically plausible. No explanation is given for the outliers. Such outliers may be due to sample mix-up, assay error, a disorder such as an adrenal feminizing tumor, or some other reason. The only way to explain questionable E_1 outliers is to eliminate the possibility of each potential factor that may be responsible for the abnormally elevated levels.

In contrast to the estrogens, mean total T levels in our study increased progressively from the <50-year group to the 70–74 year group (19.9 to 26.2 ng/dL), which is about a 30% increase. After that there was an approximate 8% drop in the levels. In contrast, mean FT levels were fairly constant, but they did drop by 24% in the ≥75-year age group.

Studies reporting age-specific reference ranges for circulating T are limited. Ke and coworkers [14] showed that there was an approximate 15% increase in total T levels from ages 50–59 to 60–79 years. Davison and coworkers [13] measured both total and FT by decade in a reference group of 595 women aged 18–75 years using a commercial RIA kit with no preceding purification step. The results show that mean total T and FT decline with age from the early reproductive years until 55–64 years and increase at age 65–75 years by 8–10%. In another study, Haring and coworkers [17] reported age-specific ranges for total T and FT by decade in 985 women aged 20–80 years using LC-MS/MS. Their results show that total T was essentially unchanged from age 40–49 to 70–80 years, and FT was also unchanged, except that the levels dropped in the seventh decade. The findings by Haring and coworkers [17] of unchanged total T and FT during the postmenopausal years differ slightly from those obtained in our study and the study by Davison and coworkers [13]. This difference may be due to the fact that total T was measured by LC-MS/MS in the study by

Haring and coworkers [17] in contrast to a direct RIA used in the study by Davison and coworkers [13] and the RIA with preceding purification steps used in the present study.

In order to establish the overall reference range for the sex steroid hormones and SHBG, we excluded outlier values from the data set. The outliers were identified by values above the mean +3 SDs on a log scale. The reference ranges for the estrogens (E_1 = 14–69 pg/mL; E_2 = 3–27 pg/mL; total T = 8.2–54.6 ng/dL; SHBG = 16–115 nmol/L; FT = 1.5–10.5 pg/mL) appear to be physiologically plausible. These ranges can be affected by a variety of factors. Our data show significant associations of sex steroids and SHBG with age, BMI, race and ethnicity, type of menopause, and years since menopause, as well as smoking and alcohol intake.

One strength of the present study is that serum samples were obtained from well-characterized healthy postmenopausal women who participated in 3 of our clinical trials. Also, we were able to include a sufficiently large number of samples in most of the 5-year age groups. A minimum number of 120 values is recommended for each subclass by the Clinical and Laboratory Standards Institute [18]. Another strength of our study is that we used validated specific and sensitive RIAs to measure the estrogens and total T. The RIAs included preceding organic solvent extraction to remove water-soluble conjugated steroid metabolites followed by separation of potential interfering unconjugated metabolites using Celite column partition chromatography. Additional specificity was achieved using highly specific antisera in the RIAs. These assays were developed in the 1970s and a substantial knowledge of the role of steroid hormones in reproductive endocrinology is based on studies using these assays. One limitation in our study is that the extreme age groups had relatively smaller sample sizes. Another limitation is that we limited our study participants to an E_2 level of <25 pg/mL during the screening process. Also, the generalizability of this pooled analysis may be limited since the 3 clinical trials were conducted at a single center that recruited primarily from Los Angeles County, California, USA and non-Hispanic white women were over-represented in the study. Thus, our study may have some limitations in generalizability to a general population of postmenopausal women and may be applicable to postmenopausal women without a prior history of cardiovascular disease.

In conclusion, our findings provide valuable insight into the profiles of serum sex steroid hormone and SHBG concentrations in different healthy postmenopausal women aged 41 to 92 years, and how the levels are affected by various demographic characteristics. Similar studies using LC-MS/MS to measure the sex steroids are warranted.

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Highlights:

- Age-specific sex steroid hormone ranges are not well defined in postmenopausal women
- They were measured in serum samples from 1207 postmenopausal women aged 41 to 92
- Estradiol and estrone levels were relatively constant
- Total and free testosterone increased gradually, but SHBG increased sizably with age
- The steroid levels show a significant association with demographic characteristics

Table 1.

Demographic characteristics of participants in the analysis (n=1187).

		Mean (SD) or frequency (%)
Age (years)		60.9 (7.0)
Age (years)	<50	39 (3.3%)
	50–54	210 (17.7%)
	55–59	324 (27.3%)
	60–64	285 (24.0%)
	65–69	204 (17.1%)
	70–74	95 (8.0%)
	≥75	31 (2.6%)
Race/ethnicity	White Non-Hispanic	773 (65.1%)
	Black Non-Hispanic	101 (8.5%)
	Hispanic	187 (15.7%)
	Asian or Pacific Islander	113 (9.5%)
	Other	14 (1.2%)
BMI (kg/m^2)		27.4 (5.4)
BMI (kg/m^2)	Normal (<24.9)	429 (36.1%)
	Overweight (25–29.9)	426 (35.9%)
	Obese (≥30)	333 (28.0%)
Type of menopause	Natural menopause	1036 (87.4%)
	Surgical menopause	149 (12.6%)
Time since menopause (years)		11.4 (8.2)
Time since menopause (years)	<6	452 (37.5%)
	6-<10	80 (6.6%)
	≥10	673 (55.8%)
Smoking	Never smoker	687 (57.8%)
	Past smoker	472 (39.7%)
	Current smoker	30 (2.5%)
Alcohol (drinks per day)	Never	580 (48.8%)
	0 to 1	477 (40.1%)
	1 to 2	99 (8.3%)
	>2	33 (2.8%)

Table 2.

Sex steroid hormones and SHBG by age group.

		<50 yrs	50–54 yrs	55–59 yrs	60–64 yrs	65–69 yrs	70–74 yrs	≥75 yrs	Total
Estrone (pg/mL)	N	39	210	324	283	204	95	31	1187
	Mean (SD)	34 (11)	34 (15)	33 (14)	33 (13)	33 (13)	34 (15)	35 (14)	33 (14)
	Reference range	17 – 62	14 – 71	14 – 69	14 – 66	14 – 67	13 – 77	14 – 75	14 – 69
	Min-Max	17 – 64	10 – 109	8 – 107	12 – 73	11 – 91	6 – 87	12 – 69	6 – 109
Estradiol (pg/mL)	N	39	209	323	284	204	95	31	1186
	Mean (SD)	12 (7)	10 (2)	9 (2)	10 (5)	11 (6)	11 (7)	10 (6)	11 (6)
	Reference range	3 – 33	3 – 32	3 – 25	3 – 23	3 – 27	3 – 29	3 – 24	3 – 27
	Min-Max	4 – 28	3 – 56	3 – 36	3 – 32	4 – 37	4 – 35	3 – 31	3 – 56
Testosterone (ng/dL)	N	38	198	313	268	190	88	27	1123
	Mean (SD)	19.9 (8.1)	22.2 (9.8)	23.3 (11.3)	24.1 (12.3)	24.8 (12.7)	26.2 (15.6)	24.2 (13.7)	23.7 (11.9)
	Reference range	7.7 – 43.4	8.7 – 47.7	8.4 – 52.6	8.0 – 57.2	8.2 – 59.1	8.2 – 63.7	7.4 – 60.4	8.2 – 54.6
	Min-Max	7.4 – 42.2	6.0 – 60.2	5.8 – 71.6	6.3 – 85.2	4.2 – 77.5	8.4 – 91	8.2 – 61.6	4.2 – 91.0
SHBG (nmol/L)	N	39	210	322	281	203	95	31	1182
	Mean (SD)	43 (23)	45 (22)	47 (23)	49 (24)	49 (22)	54 (28)	68 (29)	48 (24)
	Reference range	13 – 110	15 – 106	16 – 112	17 – 115	18 – 110	18 – 127	24 – 157	16 – 115
	Min-Max	13 – 99	13 – 121	8 – 124	8 – 139	10 – 130	13 – 173	21 – 120	8 – 173
FT (pg/mL)	N	38	198	311	268	189	88	27	1120
	Mean (SD)	3.9 (1.3)	4.4 (2.3)	4.5 (2.2)	4.4 (2.2)	4.6 (2.4)	4.6 (2.8)	3.7 (1.9)	4.4 (2.3)
	Reference range	1.8 – 7.3	1.5 – 10.0	1.5 – 10.7	1.4 – 10.8	1.5 – 10.7	1.3 – 12.1	1.1 – 9.4	1.5 – 10.5
	Min-Max	1.8 – 6.4	1.1 – 13.7	0.8 – 14.7	0.9 – 12.6	0.7 – 16.2	0.8 – 14.8	1.1 – 7.9	0.7 – 16.2

FT = free testosterone.

Table 3.

Estimated mean of sex steroid hormones and SHBG in association with demographic characteristics.

		Estrone (pg/mL)		Estradiol (pg/mL)		Testosterone (ng/dL)		SHBG (nmol/L)		FT (pg/mL)	
		Mean [95% CI]	**p**	**Mean [95% CI]**	**p**	**Mean [95% CI]**	**p**	**Mean [95% CI]**	**p**	**Mean [95% CI]**	**p**
Race/Ethnicity	White non-Hispanic	31 [30–32]	0.001	9 [9–9]	<0.0001	21.6 [20.9–22.4]	0.002	46 [45–48]	<0.0001	3.9 [3.8–4.0]	0.009
	Black non-Hispanic	34 [31–36]		11 [10–12]		23.3 [21.2–25.6]		39 [36–43]		4.5 [4.1–5.0]	
	Hispanic	32 [30–34]		10 [10–11]		19.7 [18.4–21.1]		36 [34–39]		4.0 [3.7–4.2]	
	Asian/Pacific Islander	27 [25–29]		8 [7–9]		18.7 [17.1–20.4]		40 [36–43]		3.6 [3.3–3.9]	
	Other	35 [28–43]		10 [8–13]		22.8 [17.5–29.8]		35 [27–45]		4.6 [3.5–6.1]	
BMI (kg/m2)	< 24.9	27 [26–28]	<0.0001	7 [7–8]	<0.0001	20.9 [20.0–21.9]	<0.0001	56 [54–59]	<0.0001	3.4 [3.2–3.6]	<0.0001
	25–29.9	30 [29–32]		9 [9–10]		21.0 [20.0–21.9]		41 [39–43]		4.0 [3.8–4.2]	
	≥30	37 [35–38]		13 [12–13]		21.7 [20.6–22.9]		32 [31–34]		4.6 [4.4–4.9]	
Type of menopause	Natural	31 [30–31]	<0.0001	9 [9–9]	<0.0001	21.8[21.2–22.4]	<0.0001	44 [43–45]	<0.0001	4.0[3.1–3.6]	<0.0001
	Surgical	33 [31–35]		11 [10–12]		17.5 [16.3–18.9]		38 [35–41]		3.3 [3.1–3.6]	
Years since menopause	<6	31 [30–32]	<0.0001	9 [9–10]	<0.0001	20.7 [19.7–21.6]	<0.0001	42 [40–44]	<0.0001	3.9 [3.7–4.1]	<0.0001
	6-<10	33 [30–36]		10 [9–11]		22.1 [19.8–24.7]		39 [35–43]		4.1 [3.7–4.6]	
	≥10	31 [30–31]		9 [9–10]		21.4[20.6–22.2]		44 [43–46]		3.9 [3.8–4.1]	
Smoking	Never smoker	31 [30–32]	<0.0001	9 [9–10]	<0.0001	21.3[20.5–22.1]	<0.0001	43 [41–44]	<0.0001	4.0[3.8–4.1]	<0.0001
	Past smoker	31 [30–32]		9 [9–10]		21.0 [20.1–22.0]		43 [42–45]		3.9 [3.7–4.0]	
	Current smoker	30 [26–35]		8 [7–10]		20.5 [17.1–24.6]		42 [35–50]		3.9 [3.2–4.7]	
Alcohol (drinks per day)	Never	31 [30–33]	<0.0001	9 [9–10]	<0.0001	21.5 [20.7–22.4]	<0.0001	43 [41–45]	<0.0001	4.0 [3.9–4.2]	<0.0001
	0 to 1	31 [30–32]		10 [9–10]		20.8[19.9–21.7]		43 [41–44]		3.8 [3.6–4.0]	
	1 to 2	29 [27–32]		8 [8–9]		22.4[20.4–24.6]		46 [42–50]		4.1 [3.7–4.5]	
	>2	29 [25–33]		9 [8–11]		17.6 [15.0–20.8]		46 [39–54]		3.1 [2.6–3.7]	

Generalized linear regression models used log-transformed values of the sex steroids and SHBG as the outcome.

Estimated means and 95% confidence intervals (CI) were back-transformed.

FT = free testosterone.