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Age, Body Mass, Usage of Exogenous Estrogen, and Lifestyle Factors in Relation to Circulating Sex Hormone–Binding Globulin Concentrations in Postmenopausal Women

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BACKGROUND: Circulating concentrations of sex hormone–binding globulin (SHBG) have been associated with cardiovascular diseases, type 2 diabetes, metabolic syndrome, and hormone-dependent cancers; however, correlates of SHBG concentrations are not well understood.

METHODS: We comprehensively investigated correlates of SHBG concentrations among 13 547 women who participated in the Women's Health Initiative and who had SHBG measurements. We estimated study- and ethnicity-specific associations of age, reproductive history, usage of exogenous estrogen, body mass index (BMI), and lifestyle factors such as physical activity, smoking, alcohol consumption, coffee intake, and dietary factors with SHBG concentrations. These estimates were pooled using random-effects models. We also examined potential nonlinear associations using spline analyses.

RESULTS: There was no significant ethnic difference in the age-adjusted mean concentrations of SHBG. Age, exogenous estrogen use, physical activity, and regular coffee intake were positively associated with SHBG concentrations, whereas BMI was inversely associated with SHBG concentrations after adjustment for potential confounding factors. Similar patterns were observed among both ever users and never users of exogenous estrogen. The spline analysis indicated nonlinear relations of regular intake of coffee, age, and BMI with SHBG concentrations. Two or more cups/day of regular coffee consumption and age of 60 years or older were associated with higher SHBG concentrations; the inverse BMI–SHBG relation was especially strong among women whose BMI was below 30.

CONCLUSIONS: In this large sample of postmenopausal women, age, exogenous estrogen use, physical activity, regular coffee intake, and BMI were significant correlates of SHBG concentrations, presenting potential targets for interventions.

Sex hormone–binding globulin (SHBG)[16] is synthesized primarily in the liver and binds with high affinity to androgens and with low affinity to estrogens *(1)*. Emerging evidence indicates that SHBG is associated with the development of hormone-dependent cancers *(2, 3)*, cardiovascular diseases *(4)*, type 2 diabetes *(5)*, and hip fracture *(6)*.

Both genetic and environmental factors have been hypothesized to determine SHBG concentrations *(7)*. Earlier studies have evaluated the potential environmental correlates of circulating SHBG concentrations *(8–14)*. However, sample sizes were small, and the precision was therefore limited. Furthermore, the differ-

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[16] Nonstandard abbreviations: SHBG, sex hormone–binding globulin; WHI-CT, Women's Health Initiative Clinical Trial; WHI-OS, WHI Observational Study; BMI, body mass index; MET-h/week, metabolic equivalent-hours per week.

ent factors have often been examined separately; this limits the evaluation of the relative importance of each factor. Therefore, we comprehensively investigated the relation of potential environmental correlates, both separately and jointly, with circulating SHBG concentrations in a large cross-sectional study among participants in the Women's Health Initiative Clinical Trial (WHI-CT) and the WHI Observational Study (WHI-OS).

Materials and Methods

STUDY POPULATION

The WHI included 161 808 postmenopausal women enrolled between 1993 and 1998. The WHI has 2 major components, the WHI-CT and WHI-OS, conducted at 40 clinical centers in the US. The WHI-CT enrolled 68 132 postmenopausal women aged 50–79 years. The WHI-OS included 93 676 women not participating in the WHI-CT. The institutional review boards at all participating institutions approved the study protocols and procedures. Each participant provided written informed consent to participate in the study. A series of substudies within the WHI with various study designs (e.g., case-control study, case-cohort study, and cross-sectional study) have measured a variety of biomarkers *(15)*, and 11 of them have measured plasma SHBG concentrations at baseline (see Table 1 in the Data Supplement that accompanies the online version of this report at http://www.clinchem.org/content/vol60/issue1). In total, 13 547 women with SHBG measurements were included in the current analysis. Because 1023 women were included in multiple substudies, they had multiple SHBG measurements. We compared SHBG concentrations measured using different assays on the same blood sample in these women. The median (interquartile range) intraindividual CV was 6.3% (2.9%–12.3%), suggesting that SHBG concentrations were comparable between the assays. Thus, we randomly selected one measurement for each woman. Women with missing information regarding covariates or exposures were excluded. Because stratification by disease status such as diabetes did not materially alter the estimates, participants were included in the analyses regardless of disease status at baseline. The assignment of hormone therapy in the WHI-CT was not used as a covariate in the main analyses. Sensitivity analyses with covariate adjustment for treatment assignment in the WHI-CT did not materially change the estimates.

MEASUREMENTS OF SHBG CONCENTRATIONS

Blood samples were collected at baseline after at least a 12-h fast and stored at −80 °C to −70 °C. Plasma SHBG concentrations were measured using an electrochemiluminescence immunoassay (Roche Diagnostics), a solid-phase 2-site chemiluminescent immunoassay (Diagnostic Products, Siemens Healthcare Diagnostics, Siemens Medical Solutions Diagnostics, or Siemens Medical Solutions Diagnostics), or an immunoradiometric assay (Esoterix Laboratory Services) (see online Supplemental Table 1). The inter- and intraassay CVs ranged from 3.7% to17.7% and 2.5% to 7.7%, respectively.

MEASUREMENTS OF DEMOGRAPHIC FACTORS, REPRODUCTIVE HISTORY, AND LIFESTYLE FACTORS

Height was measured by use of a wall-mounted stadiometer, and weight was measured with the women dressed in light clothing. The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Baseline information on medical history, marital status, and reproductive history was collected via several self-administered questionnaires. To assess exogenous estrogen and oral contraceptive use, a detailed interview was conducted at baseline.

As previously reported *(16, 17)*, participants completed a standardized, self-administered food frequency questionnaire developed for the WHI to estimate average daily dietary intake over the previous 3-month period. This food frequency questionnaire has demonstrated reasonably good validity as a measurement of dietary intake compared with 24-h dietary recall interviews and food records *(18)*. Alcohol intake (g/day) was calculated from the intake of beer, wine, and liquor, as well as foods. The validated physical activity questionnaire collected data on the frequency, duration, and pace of recreational walking and frequency and duration of other recreational activities or exercises (mild, moderate, and strenuous) and household and yard activities *(19)*. Metabolic equivalent–h per week (MET-h/week) were calculated from the questionnaire.

STATISTICAL ANALYSIS

Biomarker concentrations were log-transformed to improve normality assumptions in all analyses. First, we compared baseline characteristics across quintiles of the SHBG concentrations using ANOVA for continuous variables or χ^2 test for categorical variables (Table 1). Then, we cross-sectionally examined the association of each lifestyle factor separately with SHBG concentrations (Tables 2 through 4 and online Supplemental Table 2). The lifestyle factors examined were physical activity, alcohol intake, cigarette smoking, and intake of coffee, decaffeinated coffee, tea, and dietary factors. Dietary factors examined were consumptions of red meat (beef, pork, or lamb), fish, eggs, soy, fruits, vegetables, whole grains, refined grains, potatoes, and sweets. After categorizing lifestyle factors into 5 groups,

Table 1. Baseline characteristics according to quintiles (Q) of plasma SHBG concentrations in the WHI, 1993–1998.

	Q1 (lowest) (n = 2756)	Q2 (n = 2668)	Q3 (n = 2711)	Q4 (n = 2707)	Q5 (highest) (n = 2705)	P[a]
Plasma SHBG concentrations, nmol/L[b]	22.9 (18.7–26.0)	34.4 (31.8–36.9)	45.1 (42.1–48.2)	60.0 (55.8–65.4)	93.2 (80.0–122.0)	
Age, years[c]	63.3 (7.0)	65.1 (7.3)	65.7 (7.3)	66.5 (7.4)	65.9 (7.8)	<0.001
Ethnicity, % European American	67.0	68.9	70.2	71.4	61.1	<0.001
Ethnicity, % African American	19.3	18.3	17.7	16.5	22.5	
Ethnicity, % Hispanic	8.0	7.3	6.5	7.0	8.3	
Ethnicity, % Asian/Pacific Islander	3.8	3.7	3.7	3.7	7.0	
Ethnicity, % Native American	1.3	1.0	1.3	0.7	0.5	
BMI, kg/m^2[c]	32.3 (6.1)	30.4 (5.9)	28.9 (5.9)	27.1 (5.5)	25.8 (5.5)	<0.001
Waist circumference, cm[c]	97.7 (12.5)	93.0 (12.9)	89.0 (12.6)	84.1 (12.1)	80.7 (12.2)	<0.001
Alcohol consumption, g/day[b]	0.06 (0.01–1.98)	0.12 (0.01–3.52)	0.50 (0.01–4.60)	0.51 (0.01–6.00)	0.12 (0.01–2.76)	<0.001
Current smoking, %	6.9	8.0	8.7	9.7	10.7	<0.001
Physical activity, total MET-h/week[b]	4.5 (0.5–12.1)	5.3 (1.3–14.0)	7.5 (1.5–16.3)	8.3 (2.5–17.8)	8.8 (2.5–19.2)	<0.001
Past postmenopausal hormone use, %	27.0	30.2	29.4	31.3	40.5	<0.001
Ever oral contraceptive use, %	40.1	34.9	32.2	31.5	30.6	<0.001
Age at menopause, years[c]	46.6 (6.8)	46.9 (6.7)	47.0 (6.7)	47.6 (6.5)	47.0 (6.5)	0.009
Time since menopause, years[c]	16.9 (9.0)	18.5 (9.3)	19.0 (9.4)	19.2 (9.1)	19.1 (9.4)	<0.001
Age at menarche, ≥13years old, %	50.6	49.9	51.9	54.4	56.2	<0.001
Age at first pregnancy of ≥6 months, <20 years, %	20.9	20.5	17.7	16.8	17.9	<0.001
History of hypertension, %	49.0	42.2	39.1	34.8	33.1	<0.001
Pregnancies, ≥5, %	20.9	20.8	19.6	17.5	16.9	<0.001
Marital status,% currently married	56.5	55.1	51.8	52.7	51.3	<0.001
Education, % college graduates	30.5	30.7	31.2	35.6	36.0	<0.001
Total estradiol, pg/mL[b]	12.6 (8.8–18.1) (n = 2730)	11.4 (8.0–16.5) (n = 2625)	10.3 (7.3–15.0) (n = 2666)	9.4 (6.8–14.0) (n = 2641)	10.1 (6.8–21.0) (n = 2584)	<0.001
Total testosterone, ng/dL[b]	18.3 (12.1–25.5) (n = 1464)	20.2 (13.1–28.4) (n = 1414)	20.5 (13.2–29.8) (n = 1530)	21.2 (13.4–31.5) (n = 1575)	16.0 (0.1–28.0) (n = 1803)	<0.001

[a] Baseline characteristics were compared between groups using ANOVA for continuous variables or chi-squared test for categorical variable.
[b] Values are medians (interquartile range).
[c] Values are means (SD).

Table 2. Adjusted geometric mean plasma concentrations of SHBG by physical activity, alcohol, and smoking in the WHI, 1993–1998.

	SHBG concentrations, nmol/L											
	(Lowest)								(Highest)			
	Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI	*P* for linear trend[a]	*P* for quadratic trend[a]
Physical activity	Q1		Q2		Q3		Q4		Q5			
MET-h/week, median (n)	0 (2544)		2.5 (2540)		7.0 (2665)		13.7 (2409)		27.8 (2538)			
MET-h/week, range	0–0.5		0.8–4.2		4.2–10.0		10.0–18.8		18.8–134.2			
Model 1[b]	46.9	42.2–52.1	44.7	41.5–48.1	46.7	42.5–51.4	47.8	43.6–52.5	49.3	45.3–53.6	<0.001	0.95
Model 2[c]	46.6	41.8–52.0	44.9	41.6–48.4	46.7	42.4–51.5	47.7	43.2–52.6	49.1	45.1–53.5	<0.001	0.95
Alcohol	Q1		Q2		Q3		Q4		Q5			
Median (g/day) (n)	0.00 (2,708)		0.02 (2699)		0.13 (2701)		1.99 (2703)		13.9 (2702)			
Range	0.00–0.01		0.01–0.03		0.03–0.99		0.99–6.49		6.49–191.9			
Model 1[b]	45.8	41.8–50.2	46.5	42.2–51.3	47.3	43.1–51.8	48.5	44.2–53.3	46.5	43.0–50.3	0.33	0.04
Model 2[c]	45.8	41.5–50.6	46.4	41.9–51.3	47.2	42.9–52.0	48.3	44.0–53.1	46.4	43.0–50.0	0.27	0.04
Years of smoking (n)	Never (6997)		<10 years (1301)		10–29 years (2545)		30–49 years (2048)		≥50 years (301)			
Model 1[b]	47.0	42.9–51.5	47.8	44.3–51.5	47.5	43.2–52.2	46.4	42.6–50.5	45.6	41.5–50.2	0.29	0.48
Model 2[c]	47.0	42.8–51.6	48.0	44.1–52.1	47.1	42.7–52.0	46.5	42.6–50.7	46.3	41.6–51.6	0.35	0.67
Cigarettes per day (n)	Never or past (4918)		<5 (196)		5–24 (786)		25–34 (127)		≥35 (63)			
Model 1[b]	46.5	42.6–50.8	44.8	41.6–48.3	49.1	45.2–53.3	50.8	45.7–56.6	41.8	37.1–47.2	0.002	0.001
Model 2[c]	46.5	42.5–50.8	45.5	42.2–49.0	49.6	45.1–54.4	50.4	46.2–55.0	47.6	45.3–50.0	0.002	0.002

[a] Based on median values in categories of the participants with the exception of smoking. For increasing categories of years of smoking, 0, 5, 20, 40, and 60 years of smoking were assigned, and for increasing categories of cigarettes per day, 0, 1, 15, 30, and 45 cigarettes per day were assigned to compute *P* values for trend.

[b] Model 1, geometric mean and CI of SHBG concentrations and *P* values for linear trend and quadratic trend were estimated using a random-effects model with adjustment for age (continuous), ethnicity (categorical), BMI (continuous), cigarette smoking (never, past, or current), alcohol consumption (none/past drinkers, <1 drink/week, or ≥1 drink/week), physical activity (MET-h/week) (continuous), and total energy intake (continuous) that were not examined as the primary independent variable.

[c] Model 2, further adjusted for reproductive history: use of exogenous estrogen, use of oral contraceptives, age of menarche (<13 vs ≥13 years), age of first pregnancy (<20 vs ≥20 years), parity (<5 vs ≥5 live births), and marital status (currently married vs not married).

Table 3. Adjusted geometric mean plasma concentrations of SHBG by regular coffee, decaffeinated coffee, and tea intakes in the WHI, 1993–1998.

	SHBG concentrations, nmol/L											
	(Lowest)								(Highest)			
	Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI	*P* for linear trend[a]	*P* for quadratic trend[a]
Regular coffee, n	1646		2135		4175		1245		393			
Range, cups/day, n	0		1		2–3		4–5		≥6			
Model 1[b]	47.7	43.3–52.6	46.2	41.9–50.9	47.2	43.7–51.0	50.4	46.3–54.8	52.8	47.7–58.5	<0.001	0.002
Model 2[c]	47.4	43.0–52.3	45.9	41.5–50.8	47.3	43.6–51.3	50.9	46.6–55.5	53.1	47.8–58.9	<0.001	0.002
Decaffeinated coffee, n	2215		859		645		121		22			
Range, cups/day, n	0		1		2–3		4–5		≥6			
Model 1[b]	51.5	44.3–60.0	50.9	43.2–60.1	52.0	45.2–59.9	49.4	43.4–56.3	51.6	41.4–64.3	0.62	0.82
Model 2[c]	51.6	44.0–60.4	50.8	42.5–60.6	51.8	44.9–59.7	49.3	43.4–55.9	53.2	42.4–66.7	0.64	0.57
Tea, n	4444		706		581		98		28			
Range, cups/day, n	0		1		2–3		4–5		≥6			
Model 1[b]	51.1	43.5–59.9	49.5	43.9–55.8	50.2	44.6–56.5	52.6	42.7–64.8	51.1	41.2–63.3	0.70	0.47
Model 2[c]	50.9	43.2–60.0	49.9	43.5–57.2	50.2	44.2–56.9	54.6	42.6–70.1	51.5	41.8–63.3	0.46	0.44

[a] For increasing categories, 0, 1, 2.5, 4.5, and 6 cups/day were assigned to compute *P* values for trend.

[b] Model 1, geometric mean and CI of SHBG concentrations and *P* values for linear trend and quadratic trend were estimated using the random-effects model with adjustment for age (continuous), ethnicity (categorical), BMI (continuous), cigarette smoking (never, past, or current), alcohol consumption (none/past drinkers, <1 drink/week, or ≥1 drink/week), physical activity (MET-h/week) (continuous), and total energy intake (continuous).

[c] Model 2, further adjusted for reproductive history: use of exogenous estrogen, use of oral contraceptives, age of menarche (<13 vs ≥13 years), age of first pregnancy (<20 vs ≥20 years), parity (<5 vs ≥5 live births), and marital status (currently married vs not married).

Table 4. Adjusted geometric mean plasma concentrations of SHBG by categories of red meat, fish, egg, dairy, and soy intakes in the WHI, 1993–1998.

	SHBG concentrations, nmol/L											
	(Lowest)								(Highest)		*P* for linear trend[a]	*P* for quadratic trend[a]
	Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI	Geometric mean	95% CI		
Red meat												
Median, servings/week (n)	0 (1974)		0.5 (7588)		2.0 (2027)		3.5 (1718)		7.6 (206)			
Range, servings/week	0		<1		1–2		2–7		≥7			
Model 2[b]	48.2	44.6–53.4	47.4	43.3–51.9	46.2	42.4–50.4	44.7	40.3–49.6	46.6	39.3–55.2	0.04	0.03
Fish												
Median, servings/week (n)	0 (725)		0.6 (4748)		1.5 (3825)		3.0 (3925)		8.5 (290)			
Range, servings/week	0		<1		1–2		2–7		≥7			
Model 2[b]	46.9	42.3–51.8	47.1	43.2–51.4	47.2	42.6–52.2	46.9	42.8–51.3	48.4	43.1–54.5	0.44	0.14
Egg												
Median, servings/week (n)	0 (2368)		0.5 (7919)		2.0 (2042)		3.4 (1074)		3.5 (110)			
Range, servings/week	0		<1		1–2		2–7		≥7			
Model 2[b]	47.3	42.7–52.3	47.2	43.3–51.5	47.0	42.2–52.4	45.9	41.5–50.7	44.9	38.9–51.8	0.03	0.57
Dairy												
Median, servings/week (n)	0.5 (419)		1.6 (590)		4.6 (3750)		11.9 (6803)		26.7 (1951)			
Range, servings/week	<1		1–2		2–7		7–21		≥21			
Model 2[b]	51.2	44.3–59.2	48.2	43.0–53.9	47.1	42.6–52.2	47.3	43.5–51.3	45.5	41.3–50.0	0.11	0.56
Soy												
Median, servings/week (n)	0 (11 397)		0.3 (1526)		2.0 (247)		3.5 (268)		7.6 (75)			
Range, servings/week	0		<1		1–2		2–7		≥7			
Model 2[b]	46.8	43.0–50.9	47.4	42.7–52.6	49.4	43.0–56.8	53.4	46.2–61.7	47.9	39.2–58.5	0.007	0.18

[a] Based on median values in categories of the participants.

[b] Model 2, geometric mean and CI of SHBG concentrations and *P* values for linear trend and quadratic trend were estimated using the random-effects model with adjustment for age (continuous), ethnicity (categorical), BMI (continuous), cigarette smoking (never, past, or current), alcohol consumption (none/past drinkers, <1 drink/week, or ≥1 drink/week), physical activity (metabolic equivalent (MET)-hours per week) (continuous), total energy intake (continuous), and reproductive history: use of exogenous estrogen, use of oral contraceptives, age of menarche (<13 vs ≥13 years), age of first pregnancy (<20 vs ≥20 years), parity (<5 vs ≥5 live births), and marital status (currently married vs not married).

we calculated geometric means and SEs of SHBG concentrations according to lifestyle factor categories. We categorized physical activity and alcohol consumption into quintiles, and we grouped other variables into meaningful categories to maintain a gradient of exposure.

Two-sided *P* values for linear trend were computed by assigning a category score for each category and including the variables as continuous variables in the models. We also computed 2-sided *P* values for quadratic trends by further including a quadratic term in each linear trend model. In model 1, the study-specific geometric means and SEs of SHBG concentrations were estimated using a generalized linear model with adjustment for age (continuous), ethnicity (categorical), BMI (continuous), cigarette smoking (never, past, or current), alcohol consumption (non-/past drinkers, <1 drink/week, or ≥1 drink/week), physical activity (MET-h/week) (continuous), and total energy intake (continuous). Then, we pooled estimates using the DerSimonian and Laird random-effects model *(20)*. In model 2, we further adjusted for reproductive history: hormone use, oral contraceptive use, age of menarche (categorical, ≥13 years old or not), age of first pregnancy (categorical, ≥20 years old or not), parity (categorical, ≥5 or not), and marital status (categorical, currently married or not). To examine a possible bias introduced by pooling studies with different study designs, we further examined the associations after excluding participants who served as cases in the studies included in the analysis.

To jointly examine the associations between age, BMI, and lifestyle factors and SHBG concentrations, we further included these factors in the model simultaneously (model 3, Table 5) (n = 8712). We estimated study- and ethnicity-specific means and SEs of log-transformed SHBG concentrations per 5-year increment in age, BMI unit, 7.5 MET-h/week for physical activity (e.g., brisk walking for 30 min, 5 days per week), 10 cigarettes smoked/day, 10 g alcohol ingested/day, 1 serving/day for each dietary factor with adjustment for total energy intake (continuous), and reproductive history [use of exogenous estrogen, use of oral contraceptives, age of menarche (<13 vs ≥13 years), age of first pregnancy (<20 vs ≥20 years), parity (<5 vs ≥5 live births), and marital status (currently married vs not married)]. Then we pooled the results using the DerSimonian and Laird random-effects model. We also examined the associations between those factors and SHBG concentrations according to ethnicity. Heterogeneity between studies and ethnicity was evaluated using the χ^2 test *(21)*. We further stratified studies according to SHBG assay types and study outcomes (cardiovascular diseases or type 2 diabetes, cancer, fractures, and others). Additionally, because sex hormones are also considered to regulate SHBG synthesis in the liver *(22)*, we further stratified according to exogenous estrogen use. To provide a visual representation of the dose–response curve, we fitted unrestricted quadratic spline models by including transformed variables of each factor to the regression models (with knots at the 20th, 40th, 60th, and 80th percentiles) *(23)*.

Finally, we estimated pooled means and SEs of log-transformed SHBG concentrations according to exogenous estrogen use, oral contraceptive use, years since menopause (per 5-year interval), menarche age (≥13 vs <13 years), number of parities (≥5 vs <5), and marital status (currently married vs not married) using the same model (model 3, Table 5) (n = 8712). We conducted statistical analyses using SAS (version 9.3; SAS institute) and Stata (version 11.2; StataCorp).

Results

BASELINE CHARACTERISTICS

The baseline characteristics according to quintiles of SHBG concentrations are presented in Table 1. Compared to women with lower SHBG concentrations, women with higher SHBG concentrations tended to be older, have low adiposity measures, be current smokers, engage in physical activity, and have higher education levels, but less likely to have a history of hypertension. Furthermore, they tended to be past users of postmenopausal hormones and never users of oral contraceptives, had more years since menopause, and underwent menarche at an older age. African-Americans or Asians/Pacific Islanders appeared to have higher SHBG concentrations in the crude model (Table 1). However, there was no significant ethnic difference in the age-adjusted geometric mean concentrations of SHBG (*P* for heterogeneity = 0.35; European Americans, mean, 46.4 nmol/L, 95% CI, 43.0–50.2; African-Americans, mean, 45.0, 95% CI, 39.6–51.3; Hispanics, mean, 40.4, 95% CI, 33.7–48.4; Asians/Pacific Islanders, mean, 50.4, 95% CI, 42.6–59.6) (not shown).

PHYSICAL ACTIVITY

Physical activity was positively associated with SHBG concentrations. In model 2, compared with women in the lowest quintile of physical activity, women in the highest quintile had 5.4% higher SHBG concentrations (*P* for linear trend <0.001; Table 2). In model 3, the pooled adjusted mean difference in log-SHBG concentrations per increment of 7.5 MET-h/week was 0.034 (log-transformed SD, 0.061; 95% CI, 0.012–0.056; Table 5). Physical activity was positively associated with SHBG concentrations regardless of exogenous estro-

Table 5. Adjusted mean difference in log-transformed plasma SHBG concentrations in relation to age, BMI, lifestyle factors, reproductive history, and use of exogenous estrogen in the WHI, 1993–1998.

	Difference in log-SHBG concentrations (n = 8712)	
Variable	Pooled mean[a]	95% CI[a]
Age, per 5-year increment	0.037	0.026–0.047
BMI, per unit	−0.028	−0.033 to −0.024
Physical activity, per 7.5 MET-h/week	0.034	0.012 to 0.056
Alcohol, per 10 g/day	−0.0003	−0.0008 to 0.0003
Cigarettes, per 10/day	−0.010	−0.021 to 0.000
Regular coffee, per cup/day	0.025	0.018 to 0.032
Red meat, per serving/day	−0.077	−0.171 to 0.016
Fish, per serving/day	0.026	−0.032 to 0.085
Eggs, per serving/day	0.000	−0.201 to 0.202
Dairy, per serving/day	−0.016	−0.036 to 0.003
Soy, per serving/day	−0.013	−0.018 to 0.082
Fruits, per serving/day	0.011	−0.021 to 0.043
Vegetables, per serving/day	0.002	−0.010 to 0.013
Whole grains, per serving/day	0.001	−0.014 to 0.017
Refined grains, per serving/day	−0.009	−0.017 to 0.000
Potatoes, per serving/day	−0.015	−0.053 to 0.024
Sweets, per serving/day	0.013	−0.002 to 0.027
Oral contraceptive use, ever vs never	−0.013	−0.037 to 0.011
Exogenous estrogen use, current vs past/never	0.225	0.043 to 0.408
Exogenous estrogen use, ever vs never	0.083	0.012 to 0.153
Years since menopause, per 5-year increment	0.001	−0.007 to 0.010
Menarche age, ≥13 vs <13 years	−0.000	−0.021 to 0.021
Number of parities, ≥5 vs <5	−0.028	−0.062 to 0.006
Marital status, currently married vs not married	−0.033	−0.062 to −0.003

[a] Random-effects models were used to estimate adjusted means and CIs of log-transformed SHBG concentrations per 5-year age increment, BMI unit, 7.5 MET-h/week for physical activity, 10 cigarettes smoked/day, 10 grams of alcohol ingested/day, and 1 serving/day for dietary factors and according to exogenous estrogen use, oral contraceptive use, and reproductive history (years since menopause, menarche age, number of parities, and marital status) with adjustment for age (continuous), BMI (continuous), physical activity [MET-h/week (continuous)], cigarettes smoked per day (continuous), alcohol ingestion per day [in grams (continuous)], total energy intake (continuous), and all dietary factors and indices of reproductive history listed in the table that were not examined as the primary independent variable.

gen use (not shown). Further excluding the case subjects resulted in similar findings (not shown). Stratification according to the study outcome or SHBG assay type did not explain the heterogeneity across studies (not shown).

ALCOHOL CONSUMPTION

After multivariable adjustment, we did not observe a clear linear association between alcohol consumption and SHBG concentrations (P for linear trend = 0.27), but a nonlinear association was suggested in models 1 and 2 (P for quadratic trend = 0.04; Table 2). However, model 3 (Table 5) and spline curves (not shown) did not indicate any clear alcohol–SHBG association.

CIGARETTE SMOKING

Although we did not observe any significant association between years of smoking and SHBG concentrations, a weak positive association between number of cigarettes smoked per day and SHBG concentrations was suggested in models 1 and 2 (Table 2). However, in model 3, no apparent association was observed (Table 5). Moreover, spline curves for number of cigarettes smoked indicated no clear association (not shown).

REGULAR COFFEE, DECAFFEINATED COFFEE, AND TEA CONSUMPTION

Higher regular coffee intake, but not decaffeinated coffee or tea intake, was associated with higher SHBG concentrations. In model 2, compared with no cups of coffee per day, intake of 6 or more cups of regular coffee per day was associated with 12.0% higher SHBG concentrations (P for linear trend <0.001; P for quadratic trend $= 0.002$; Table 3). Further excluding the case subjects did not materially change the results (not shown). Model 3 also indicated that regular coffee intake was moderately and positively associated with SHBG concentrations [log-SHBG concentrations per cup/day = 0.025 (SD, 0.045); 95% CI, 0.018–0.032; Table 5]. Similar patterns were observed among both ever users and never users of exogenous estrogen (not shown). We did not observe any substantial heterogeneity across the studies or ethnicities (not shown). Spline curves suggested that heavy drinkers of regular coffee (>2 cups/day) had higher concentrations of plasma SHBG (Fig. 1C).

RED MEAT, FISH, EGG, DAIRY, AND SOY INTAKES

In model 2, red meat and egg intakes appeared to be inversely associated with SHBG concentrations (Table 4), while after simultaneous adjustment for other lifestyle factors, we did not find any apparent association in model 3 (Table 5) or spline curves (not shown). In addition, a weak positive association between soy intake and SHBG concentrations was suggested in model 2 (Table 4), but model 3 (Table 5) and a spline model (not shown) did not indicate any clear soy–SHBG association. Fish and dairy intakes were not associated with SHBG concentrations (Tables 4 and 5).

FRUIT, VEGETABLE, GRAIN, POTATO, AND SWEET INTAKES

We did not observe any significant association of fruit, vegetable, whole grain, refined grain, or potato intake with SHBG concentrations (Table 5 and online Supplemental Table 2). A moderate positive association between sweets and SHBG concentrations was suggested in model 2 (see online Supplemental Table 2), but we observed no clear association in model 3 (Table 5) or a spline model (not shown).

AGE

In model 3, age was moderately and positively associated with SHBG concentrations; log-SHBG concentration per 5-year increment in age was 0.037 (SD, 0.066; 95% CI in log-SHBG concentrations, 0.026–0.047; Table 5). The association was observed regardless of the use of exogenous estrogen. No substantial heterogeneity was seen across studies or ethnicities (not shown). Spline curves indicated that age of 60 years or older was associated with higher SHBG concentrations (Fig. 1A).

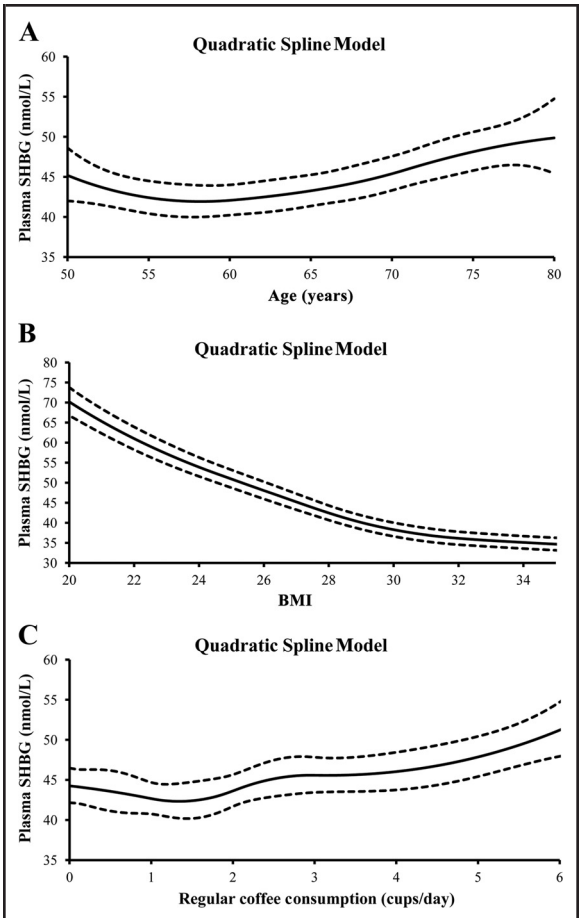

Fig. 1. Estimated plasma SHBG concentrations using spline analyses according to age (A), BMI (B), and regular coffee consumption (C).

Unrestricted quadratic spline models with the inclusion of transformed variables for each factor in the regression models (with knots at the 20th, 40th, 60th, and 80th percentiles) with adjustment for age (continuous), BMI (continuous), physical activity [MET-h/week (continuous)], cigarettes smoked per day (continuous), alcohol ingestion per day [in grams (continuous)], total energy intake (continuous), and all dietary factors and indices of reproductive history included in Table 5 that were not examined as the primary independent variable were used to plot curves (solid curve, point estimates; dashed curves, point-wise 95% confidence limits).

BODY MASS INDEX

In model 3, BMI was inversely associated with SHBG concentrations [log-SHBG concentrations per 1-U increase in BMI, −0.028 (SD, −0.050); 95% CI, −0.033 to −0.024; Table 5]. Similar patterns were observed for the association between waist circumference and SHBG concentrations (not shown). The BMI–SHBG

association was observed among both ever users and never users of exogenous estrogen (not shown). Heterogeneity was suggested across studies, but stratification according to SHBG assay type or study outcomes did not explain the heterogeneity across studies (not shown). Spline curves indicated an inverse association of BMI with SHBG concentrations, especially at BMIs below 30 (Fig. 1B).

EXOGENOUS ESTROGEN USE AND REPRODUCTIVE HISTORY

The use of exogenous estrogen was positively associated with SHBG concentrations. Current estrogen users had higher SHBG concentrations than past or never users of exogenous estrogen [log-SHBG, 0.225 (SD, 0.401); 95% CI, 0.043–0.408; Table 5]. Heterogeneity was suggested across studies, but stratification according to SHBG assay type or according to study outcomes did not explain the heterogeneity (not shown). In addition, compared with never users of exogenous estrogen, ever users had higher SHBG concentrations [log-SHBG, 0.083 (SD, 0.149); 95% CI, 0.012–0.153; Table 5]. In addition, compared with women who were never or previously married, women who were currently married had lower concentrations of SHBG [log-SHBG, −0.033 (SD, −0.059), 95% CI, −0.062 to −0.003; Table 5].

Discussion

In this large cross-sectional study of postmenopausal women, positive associations with SHBG concentrations were observed for age, use of exogenous estrogen, physical activity, and regular coffee intake, whereas BMI was inversely associated with SHBG concentrations. Our comprehensive assessment supports the notion that in addition to sex hormones, age, adiposity, physical activity, and regular coffee intake may be associated with SHBG concentrations.

Regular coffee intake, but not decaffeinated coffee or tea intake, was positively associated with SHBG concentrations. These findings are in line with the findings of earlier studies *(11, 24)*. One recent study found that caffeinated coffee and caffeine intakes, but not decaffeinated coffee intake, were positively associated with SHBG concentrations *(11)*. Because few decaffeinated coffee or tea drinkers were included in our study, we lacked statistical power to detect an association with SHBG concentrations. The molecular mechanisms underlying the relation between coffee and SHBG are largely unknown. Caffeine and other major components of coffee (cafestol and kahweol) alter liver enzyme expression and activity *(25)*. Because SHBG is synthesized and metabolized primarily in the liver *(1)*, coffee intake may affect SHBG metabolism in the liver to influence SHBG concentrations *(24)*. Importantly, caffeine increases the resting metabolic rate *(26)*, and SHBG production is regulated by the metabolic state of the liver via hepatocyte nuclear factor-4α *(27)*.

The positive association between age and SHBG concentrations observed in this study is in line with earlier findings *(8, 28)*; several mechanisms have been proposed to explain this association. The age-related decrease in growth hormone and insulin-like growth factor 1 concentrations may be responsible for the apparent age-associated increase in SHBG concentrations. In addition, the age-related decline in insulin secretion or insulin sensitivity may result in increased SHBG concentrations. The age-related weight change may also explain the age-associated increase in SHBG concentrations *(8)*. However, there is as yet no conclusive mechanistic understanding of the apparent positive age–SHBG association.

Our findings indicated that exogenous estrogen use was positively associated with SHBG concentrations. This observation is consistent with the findings from clinical studies that exogenous estrogen administration increases SHBG concentrations *(29–31)*. Our results did not indicate a relation between oral contraceptive use and SHBG concentrations among postmenopausal women, suggesting that past use of oral contraceptives may have little impact on SHBG concentrations later in life, whereas exogenous estrogen use may influence the regulation of SHBG in postmenopausal women.

Additionally, our findings indicated that currently married women had lower SHBG concentrations than single women, whereas an earlier study reported that married nulliparous postmenopausal women had higher SHBG concentrations than single nulliparous postmenopausal women *(14)*. Because few nulliparous women were included in our study, future work is needed to better understand this relation. Consistent with previous studies, we observed little or no association between number of parities or age of menarche and SHBG concentrations *(14)*. Number of parities and age of menarche have been associated with SHBG concentrations among premenopausal but not among postmenopausal women. Although previous research reported that the number of years since menopause was positively associated with SHBG concentrations *(14)*, we observed no association between years since menopause and SHBG concentrations after multivariable adjustment for potential confounding factors including age. However, this finding is not surprising in light of the fact that age and years since menopause are highly correlated ($r = 0.71$ in our study). In fact, we observed a positive association between age and SHBG concentrations even after adjustment for the number of years since menopause. This finding suggests that

age, but not years since menopause, may be an important predictor of SHBG concentrations.

The positive association between physical activity and SHBG concentrations is consistent with earlier reports *(32, 33)*. In a post hoc analysis of the Estrogen in the Prevention of Atherosclerosis Trial examining the effect of estradiol vs placebo on atherosclerosis among postmenopausal women, the mean levels (averaged over the trial) of physical activity were positively associated with mean SHBG concentrations *(32)*. Also, a randomized clinical trial of 170 sedentary, overweight, postmenopausal women showed a greater increase in SHBG concentrations among exercisers compared with a control group *(33)*. However, little is known about the mechanisms underlying the possible effect of exercise on SHBG metabolism. Improved insulin sensitivity or loss of adiposity induced by physical activity may influence SHBG production in the liver.

The inverse association between BMI and SHBG concentrations observed in this study is consistent with previous studies *(34–36)*. The Study of Women's Health Across Nation reported inverse associations of BMI, waist circumference *(35)*, and visceral fat *(36)* with SHBG concentrations in premenopausal and early perimenopausal women. The mechanisms responsible for the BMI-SHBG association are not well understood. Decreased SHBG concentrations have been associated with insulin resistance *(37)*. Adiposity is also known to be associated with higher blood insulin concentrations resulting from insulin resistance, and insulin has been reported to inhibit SHBG production in hepatoma cells *(38)*. These findings may suggest that compensatory hyperinsulinemia in women with higher BMI levels can lead to lower SHBG concentrations. Alternatively, insulin resistance itself might play a major role in the regulation of SHBG concentrations.

No clear association was seen between soy intake and SHBG concentrations in this study. Our results are consistent with findings from a recent metaanalysis, suggesting that soy or isoflavone intake may not play a major role in SHBG metabolism *(39)*.

The strengths of our study include its large sample size and multiethnic study design, with detailed measurement of variables. However, several limitations of this study should be recognized. First, the major limitation is its inability to establish a temporal relationship between exposure (e.g., lifestyle factors) and SHBG concentrations, although SHBG concentrations are unlikely to alter exposure. Second, the studies pooled in the current investigation differed in their SHBG measurement methods, the laboratories where the measurements were performed, and the study outcomes that were selected, which may have introduced sources of heterogeneity. Third, although SHBG is produced by the liver, we were unable to examine the relation between liver function and SHBG concentrations. Fourth, we cannot exclude the possibility of residual confounding arising from incompletely measured or unmeasured covariates. Finally, biases due to measurement errors in exposure variables, covariates, and SHBG concentrations may exist and may vary across the studies. However, because such biases are likely to be nondifferential, the estimates would tend to attenuate toward the null.

In conclusion, in this large multiethnic study of postmenopausal women, we identified age, exogenous estrogen use, physical activity, and regular coffee intake to be positively associated with SHBG concentrations, whereas BMI was inversely associated with SHBG concentrations. Based on the emerging significance of SHBG as an early biomarker for vascular outcomes, some cancers, and fracture risk, these findings may have important implications for developing preventive measures against various diseases.

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