Lack of Pleiotropic Genetic Effects Between Adiposity and Sex Hormone–Binding Globulin Concentrations Before and After 20 Weeks of Exercise Training: The HERITAGE Family Study

Mary F. Feitosa, Ingrid B. Borecki, Tuomo Rankinen, Arthur S. Leon, James S. Skinner, Jack H. Wilmore, Claude Bouchard, and D.C. Rao

The relationship between sex hormone–binding globulin (SHBG) concentrations and body fat accumulation and distribution is governed by complex dynamic factors, which may involve common genetic and/or environmental factors. The current study investigated the genetic and environmental basis for the correlation between SHBG and body fat. Several measures of adiposity were investigated including body mass index (BMI) and a trunk to extremity skinfold thickness ratio (TER) assessed by anthropometry, body composition measured by hydrostatic weighing (total body fat mass [FM], fat-free mass [FFM], and percent body fat [%BF]), and abdominal fat measured by computerized tomography scanning (abdominal visceral fat [AVF]). The study comprised 501 white subjects from 99 families and 277 black subjects from 117 families participating in the HERITAGE Family Study. Familial correlations between traits and their cosegregation were investigated both at baseline and in response to endurance exercise training. Significant inverse phenotypic correlations were detected in both races between SHBG and adiposity measures at baseline and also in response to training. Significant cross-trait familial resemblance was found between SHBG and both BMI and FFM at baseline that accounted for 11% and 4% of maximal heritability, respectively, in white families. However, a joint segregation analysis of the traits failed to implicate shared genetic effects. Specifically, neither a pleiotropic major locus nor pleiotropic polygenic effects were detected between SHBG and BMI or FFM. A maximal cross-trait heritability of 45% was obtained for SHBG and TER at baseline in black families. However, no firm conclusions as to the etiology of this relationship could be drawn because of the limitations of small sample size. For the training response phenotypes, there was no significant cross-trait correlation between SHBG and any adiposity measures studied here, suggesting that their correlation may have an environmental basis. Therefore, this study fails to support the hypothesis of genetic pleiotropy between SHBG concentrations and body fat phenotypes, and suggests an environmental basis for the correlation, ie, SHBG concentrations are genetically independent of body composition and abdominal adiposity phenotypes.

SEX HORMONE–binding globulin (SHBG) is a steroid-binding plasma glycoprotein with high affinity for testosterone and dihydrotestosterone and lower affinity for estradiol. SHBG is produced by hepatocytes, and its plasma concentrations are important in the regulation of plasma free and albumin-bound androgens and estrogens.[1,2] SHBG also has a specific receptor (SHBG-R) located on membranes of sex steroid responsive cells. Low SHBG concentrations are associated with insulin resistance, hyperinsulinemia, type 2 diabetes, and increased risk for cardiovascular disease.[3-6] Obesity, in general, and visceral obesity in particular, are also associated with alterations in the pituitary-adrenal and pituitary-gonadal functions.[7] Visceral fat accumulation is associated with decreases in testosterone concentrations in males and reduces SHBG concentrations in both sexes.[2,8-10]

Conflicting results have been reported in studies of variation of SHBG concentrations in response to training.[11-13] No systematic changes in the means of SHBG concentrations were observed in middle-aged and elderly men and women after 6 months of strength training.[13] The response in young men to 3 consecutive days of heavy-resistance exercise with or without protein-carbohydrate supplementation showed that serum SHBG concentrations tended to increase in the first day of exercise and then decline. By the third day of exercise, the SHBG concentrations were below resting values. The SHBG concentrations in subjects receiving placebo were significantly higher at several time points compared with those during supplementation.[12] However, adolescent wrestlers who consumed a high-carbohydrate and low-fat diet during 3.5 to 4 months of wrestling season showed significant elevations in SHBG concentrations from preseason to late season, but returned to baseline concentrations postseason.[11] The SHBG mean change in response to training was significantly different between fathers and mothers (but not significant between sons and daughters) and between mothers and daughters (but not significant between fathers and sons) in the HERITAGE study.[14] Thus, the variability of the responses in SHBG concentrations to training may reflect complex interactions involving gender, age, nutritional deprivation, and the combination of training and energy restriction.

The function of SHBG is relatively well understood. How-

From the Division of Biostatistics, Departments of Genetics and Psychiatry, Washington University School of Medicine, St Louis, MO; Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA; School of Kinesiology and Leisure Studies, University of Minnesota, Minneapolis, MN; Department of Kinesiology, Indiana University, Bloomington, IN; and the Department of Health and Kinesiology, Texas A & M University, College Station, TX.

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Address reprint requests to Mary Furlan Feitosa, PhD, Division of Biostatistics, Campus Box 8067, Washington University School of Medicine, 660 S. Euclid, St Louis, MO 63110-1093.

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ever, little is known about genetic factors contributing to the normal variation of SHBG or about the factors leading to its relationship with body fat phenotypes. A heritability of 31% for SHBG concentrations was reported in the San Antonio Family Heart Study.[15] Also in the same study, significant genetic and environmental correlations between SHBG and measures of body fat were observed.[16] An et al[14] have investigated the inheritance patterns of SHBG in the HERITAGE Family Study. Their results suggested that baseline SHBG concentrations were influenced by a multifactorial component with a heritability of 29%, while the presence of both a multifactorial component and a major gene was detected in the response to training. In the current study, we tested the hypothesis that the correlation between SHBG concentrations and body fat measures has a genetic basis in HERITAGE white and black families. If present, genetic pleiotropy can be usefully exploited for gene discovery and mapping.

SUBJECTS AND METHODS

Sample

The HERITAGE Family Study is a large multicenter study designed to investigate the contributions of regular exercise to changes in cardiovascular disease and diabetes risk factors and to determine the role of genetic factors in cardiovascular, metabolic, and hormonal responses to endurance exercise training. The specific aims, design, and measurements of the study have been described in detail elsewhere.[17] In summary, families were recruited and studied in 4 clinical centers. Subjects were required to be sedentary at baseline, ie, participants had not engaged in regular vigorous physical activity over the previous 6 months. Subjects were required to be between 17 to 65 years old and in good health. The body mass index (BMI) had to be less than 40 kg/m^2; however, subjects with a BMI greater than 40 kg/m^2 were allowed into the study if certified by a physician. Subjects with blood pressure greater than 159 mm Hg for systolic and/or greater than 99 mm Hg for diastolic or taking antihypertensive or lipid-lowering drugs were excluded. The study was approved by the Institutional Review Board at each center, and written informed consent was obtained from each subject.

Endurance Training Program

Each subject was exercise-trained under supervision on a cycle ergometer 3 times a week for 20 weeks using the same standardized training protocol in each of the 4 clinical centers. The intensity and duration of the training program were adjusted every 2 weeks beginning at a heart rate (HR) corresponding to 55% of subject's baseline maximal oxygen uptake ($\dot{V}O_{2max}$) for 30 minutes per session and increasing gradually until the training HR was associated with 75% of the subject's $\dot{V}O_{2max}$ for 50 minutes during the last 6 weeks. The power output of the cycle ergometer was adjusted by computer to match the subject's actual HR with the programmed training HR.[18]

Measures

Blood samples were obtained from an antecubital vein into vacutainer tubes with no anticoagulant in the morning, after a 12-hour fast, with participants in a semirecumbent position. Samples were collected twice at baseline (drawn at least 24 hours apart) and twice after the endurance training program (1 sample drawn 24 hours and the other 72 hours posttraining). The present study is based on mean values from these 2 samples obtained at baseline and 2 samples obtained after the endurance training program. For eumenorrheic women, all samples were obtained in the early follicular phase of the menstrual cycle. Fasting serum was prepared according to a standard protocol. After centrifugation of blood at 2,000 × *g* for 15 minutes at 4°C, 2 aliquots of 2 mL in cryogenic tubes were frozen at -80°C until shipment within a month. Serum samples from the 3 United States HERITAGE Clinical Centers were shipped in the frozen state to the HERITAGE Steroid Core Laboratory in the Molecular Endocrinology Laboratory at the Laval University Medical Center in Québec City. SHBG quantitative measurements were determined with a IRMA-count immunoradiometric assay iodine 125 (Diagnosis System Laboratories, Webster, TX). The reproducibility of the baseline SHBG concentrations was very high. For day-to-day variation in baseline SHBG levels, the technical error (TE) was 4.1 nmol/L, the intraclass correlation coefficient (ICC) was 0.97, and the coefficient of variation (CV) was 11% in 325 males, while a TE of 11.7 nmol/L, an ICC of 0.97, and a CV of 15% were obtained in 420 females.[19,20]

BMI was computed as the weight in kilograms divided by height in meters squared. The trunk to extremity skinfold thickness ratio (TER) was calculated as the ratio on the sum of the trunk (abdominal, subscapular, suprailiac, and midaxillary) to the sum of the extremity (biceps, triceps, thigh, and medial calf) skinfold thicknesses. Body density was measured by the hydrostatic weighing technique.[21] The mean of the highest 3 (of 10) measurements was used to calculate percent body fat (%BF) from body density.[22] Fat mass (FM) and fat-free mass (FFM) (in kilograms) were calculated from %BF and body weight. Abdominal fat area (in square centimeters) was assessed by computerized tomography scanning.[23] The abdominal scan was obtained between the fourth and fifth lumbar vertebrae. The abdominal visceral fat (AVF) was defined by drawing a line within the muscle wall surrounding the abdominal cavity. More details about these measures can be found in Wilmore et al.[22]

Data Adjustments

Baseline SHBG concentrations, BMI, and AVF were transformed using natural logarithms to improve distributional properties. All adjustments before genetic analysis were performed separately within each of 8 sex by generation by race groups, using stepwise multiple regression. Extreme outliers (> 4 standard deviations from the mean) were temporarily set aside so that they would not unduly influence the regression models. Baseline SHBG concentrations (as well as the adiposity measures, BMI, TER, AVF, FM, FFM, and %BF) were individually adjusted for the effects of a polynomial in age (age, age^2, age^3), retaining the terms significant at the 5% level in the stepwise regression analysis. The residual variances were also examined for age effects (heteroscedasticity) by regressing the squared residual from the mean age regression on another cubic polynomial in age in a stepwise manner and retaining significant terms. The final phenotypes for all subjects (including the outliers) were computed using the best regression models and were finally standardized to a mean of 0 and a standard deviation of 1. Similar procedures were applied to the training responses (baseline – post values), which were also adjusted for baseline values.

Correlation Analysis

Pearson correlation coefficients between SHBG and the adiposity phenotypes were calculated using Statistical Analysis System (SAS), ignoring familial dependencies. Sex-specific familial correlation models were used to investigate the extent of familial variation in each trait and the covariation between 2 traits in a bivariate analysis. The model accounts for 4 types of subjects (f, fathers; m, mothers; s, sons; d, daughters) leading to 8 interindividual correlations (fm, fs, fd, ms, md, ss, dd, sd). In the bivariate extension, in addition to estimating the interindividual correlations for each trait, the inter- and intraindividual cross-trait correlations also are estimated leading to a total of 34 estimated correlations.[24] Thus, for the general bivariate model, the

Table 1. Number of Subjects, Means, and Standard Deviations of Unadjusted Variables for White and Black Samples

	Father		Mother		Son		Daughter	
Variable	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
White sample								
SBHG (nmol/L)	98	44.2 ± 17.5	93	86.4 ± 49.3	156	36.0 ± 15.2	168	88.8 ± 50.3
BMI (kg/m^2)	98	28.4 ± 4.4	94	27.6 ± 5.0	160	25.6 ± 4.9	167	23.7 ± 4.5
AVF (cm^2)	98	158.6 ± 61.5	93	120.1 ± 59.0	157	77.6 ± 43.2	166	52.7 ± 29.8
FM (kg)	92	24.6 ± 9.0	85	27.0 ± 10.4	147	17.1 ± 10.9	167	18.0 ± 9.8
FFM (kg)	92	62.3 ± 7.5	85	44.5 ± 5.0	147	64.3 ± 8.1	167	46.1 ± 5.2
%BF	92	27.6 ± 6.4	85	36.6 ± 7.9	147	19.7 ± 9.1	167	26.7 ± 9.0
Black sample								
SBHG (nmol/L)	28	47.3 ± 19.5	57	65.5 ± 34.1	84	34.3 ± 13.3	139	68.5 ± 43.1
BMI (kg/m^2)	29	29.5 ± 5.2	59	29.4 ± 5.2	86	27.4 ± 5.8	147	27.9 ± 7.0
AVF (cm^2)	29	105.9 ± 69.3	57	95.7 ± 43.8	83	67.6 ± 50.4	145	59.7 ± 36.0
FM (kg)	25	21.3 ± 8.7	39	31.1 ± 10.3	81	20.7 ± 12.6	121	27.1 ± 13.4
FFM (kg)	25	60.2 ± 5.9	39	46.3 ± 5.1	81	65.5 ± 9.5	121	46.3 ± 6.6
%BF	25	25.3 ± 6.0	39	39.2 ± 7.3	81	22.3 ± 8.9	121	35.1 ± 9.1

estimated interindividual cross-trait correlations are 4 sibling (s_1s_2, d_1d_2, s_1d_2, s_2d_1), 8 parent-offspring (f_1s_2, f_1d_2, m_1s_2, m_1d_2, f_2s_1, f_2d_1, m_2s_1, m_2d_1), and 2 spouse (f_1m_2, f_2m_1); 4 intraindividual cross-trait correlations (s_{12}, d_{12}, f_{12}, m_{12}); and 16 interindividual correlations within trait (trait 1: f_1m_1, f_1s_1, f_1d_1, m_1s_1, m_1d_1, s_1s_1, d_1d_1, s_1d_1; trait 2: f_2m_2, f_2s_2, f_2d_2, m_2s_2, m_2d_2, s_2s_2, d_2d_2, s_2d_2), where the subscripts refer to phenotype 1 and 2. Familial correlations were estimated by maximum likelihood under the assumption of multivariate normality of the family data using the computer program SEGPATH.[25] Reduced models testing certain hypotheses were evaluated using the likelihood ratio test (LRT), which is the difference in minus twice the log-likelihoods (-2 ln L) between a reduced model and a more general model. The LRT is asymptotically distributed as a χ^2, with the degrees of freedom being given by the difference in the number of parameters estimated in the 2 models. Non-nested models were compared by Akaike's[26] Information Criterion (AIC), which is computed as minus twice the log likelihood of the model plus twice the number of estimated parameters. The model with the lowest AIC indicates the most parsimonious fit to the observed data. The maximal heritability (h^2) is computed from the most parsimonious model according to the following equation[27]:

$$h^2 = (r_{\text{sibling}} + r_{\text{parent-offspring}})(1 + r_{\text{spouse}})/(1 + r_{\text{spouse}} + 2 \cdot r_{\text{spouse}} \cdot r_{\text{parent-offspring}}), \quad (1)$$

where r represents the respective correlations. This represents the *maximal* cross-trait heritability because both genetic and shared environmental sources of variation are reflected in the familial correlations.

Segregation Model

Segregation analysis was performed using the Pedigree Analysis Package (PAP), version 4.0.[28] The phenotype is assumed to be influenced by the independent and additive contributions from a major gene, a polygenic/multifactorial background, and a non-transmitted environmental component. The major gene is modeled to have 2 alleles (A, a), in which the upper case allele is associated with lower phenotypic values and its frequency is denoted by p. The other parameters in the model are: the mean values for the 3 genotypes (μ_{AA}, μ_{Aa}, μ_{aa}, in which the order of the means is constrained to be $\mu_{AA} \leq \mu_{Aa} \leq \mu_{aa}$); the common standard deviation within major locus genotypes (σ); the polygenic heritability (H), after accounting for the major gene effect; and parent-to-offspring transmission probabilities for the 3 genotypes (τ_{AA}, τ_{Aa}, and τ_{aa}). For a single diallelic locus, the 3 τ's denote the probability of transmitting allele *A* for genotypes *AA*, *Aa*, and *aa*, with Mendelian expectations of 1, 1/2, and 0, respectively; while under an environmental (no transmission) model, $p = \tau_{AA} = \tau_{Aa} = \tau_{aa}$. Recessive ($\mu_{AA} = \mu_{Aa}$) and dominant ($\mu_{Aa} = \mu_{aa}$) modes of transmission were tested.

The bivariate segregation model assumes that the single locus potentially influences both of the quantitative traits. The major locus is parameterized identically to the univariate model, however, distinct genotypic means and residual variances are estimated for each quantitative trait (e.g., BMI and SHBG), with a single allele frequency and set of transmission probabilities. Thus, the phenotypic correlation between the 2 phenotypes can be attributed to 3 potential sources: a pleiotropic major gene, a correlation between the respective polygenic components for each trait (r_G), or a correlation between the non-transmitted environmental components (r_U).

RESULTS

Table 1 presents the sample sizes, means and standard deviations for unadjusted baseline phenotypes within each of the 4 sex by generation groups in white and black subjects. Based on a comparison of means, there were significant differences in the measures across sex, generation, and race for all baseline phenotypes. Age was a significant predictor of all phenotypes. Particularly for SHBG, age for white fathers and black daughters was a significant predictor of baseline values accounting for 6.3% and 3.8% of the variance, respectively. For the SHBG training response, baseline SHBG accounted for 82%, 79%, 75%, and 46% of the variance in white fathers, mothers, sons, and daughters, respectively, while baseline SHBG accounted for 89%, 88%, 74%, 70%, of the response variance in black fathers, mothers, sons, and daughters, respectively.

Significant negative Pearson correlations between SHBG concentrations and fat body phenotypes at baseline were found in both white (-0.21 to -0.39, $P < .001$) and black (-0.26 to -0.44, $P < .001$) samples. For the training response, significant negative correlations were observed for SHBG with FM, %BF in the white sample alone, and with BMI in both white and black samples (-0.13 to -0.11, $0.01 < P < .04$). Bivariate analysis was performed to investigate whether there was a familial basis for the observed phenotypic correlations. Table 2 gives the summary of *P* values for various models testing cross-trait correlations between SHBG and body fat measures at baseline in white and black families. There was evidence of

Table 2. Summary of *P* Values for Cross-Trait Hypothesis Tests Model Between SHBG and Body Fat Measures at Baseline

Hypothesis	BMI	AVF	FM	FFM	%BF
White sample					
No cross-trait-sibling	0.321	0.224	0.287	0.021	0.648
No cross-trait-parent-offspring	0.013	0.434	0.432	0.049	0.597
No cross-trait-sibling and parent-offspring	0.040	0.424	0.395	0.015	0.604
No cross-trait-spouse	0.075	0.178	0.699	0.405	0.856
No cross-trait-intraindividual	<.001	<.001	<.001	0.003	<.001
No cross-trait-interindividual	0.016	0.374	0.313	0.004	0.718
Black sample					
No cross-trait-sibling	0.888	0.752	0.286	0.647	0.250
No cross-trait-parent-offspring	0.237	0.325	0.261	0.326	0.494
No cross-trait-sibling and parent-offspring	0.410	0.501	0.369	0.495	0.401
No cross-trait-spouse	0.694	0.586	0.535	0.395	0.604
No cross-trait-intraindividual	0.008	<.001	<.001	<.001	<.001
No cross-trait-interindividual	0.571	0.645	0.616	0.535	0.589

common familial factors at baseline for SHBG with both BMI and FFM in white families, as well as between SHBG and TER in black families. There was no significant cross-trait correlation involving SBHG with body composition or abdominal fat measurements for the training responses in either race (results not shown).

For SHBG and BMI (Table 2), the hypotheses of no intraindividual cross-trait correlations ($P < .001$) and no interindividual cross-trait correlations ($P = .016$) were rejected. The hypothesis of no spouse cross-trait correlation was of marginal significance ($P = .075$), while the hypothesis of no parent-offspring cross-trait correlations ($P = .013$) was rejected. There was no suggestion of sibling cross-trait correlations between SHBG and BMI ($P = .321$); this hypothesis was the most parsimonious model. The estimated interindividual cross-trait correlations ranged from 0.04 to 0.23 and from -0.23 to -0.45 for intraindividual cross-trait correlations. Assuming no sex differences in the cross-trait correlations in parents and offspring, we estimate the maximal cross-trait heritability at 11%. The significant spouse cross-trait correlations suggest that the heritability is due, at least in part, to familial environmental factors. Furthermore, we observed a telling pattern in which the absolute values of the cross-trait correlations between SHBG concentrations and BMI were stronger within individuals than across individuals. If genetic factors were the basis of the correlation between traits, we would expect to see appreciable interindividual cross-trait resemblance among family members. Thus, this pattern also is suggestive of a primarily environmental basis for the cross-trait correlations. For SHBG and FFM at baseline, the parsimonious model involved parent-offspring and sibling cross-trait correlations. The estimated interindividual cross-trait correlations ranged from -0.05 to 0.27 and from -0.11 to -0.28 for intraindividual cross-trait correlations. However, assuming no sex differences in cross-trait correlations, we estimated the maximal cross-trait heritability to be very small (4%). Nonetheless, there were significant inverse correlations between SHBG concentrations and adiposity phenotypes, but no evidence of any cross-trait correlations, suggesting that there was no familial basis for the relationship between SHBG concentrations and BMI and FFM. Therefore, the correlations between SHBG and body composition phenotypes are probably due to common environmental factors in white families. For SHBG and TER in black families, the parsimonious model, as indicated by the AIC, suggested no sex or generation differences ($P = .499$, result not shown) and 45% maximal cross-trait heritability. The interindividual and intraindividual cross-trait correlation estimates were -0.25 and -0.21, respectively.

Segregation analysis of SHBG was previously reported by An et al.[14] They concluded that there was a multifactorial basis for SHBG family resemblance at baseline. However, SHBG was adjusted for BMI in addition to age and sex. Since our interest was specifically in the relationship between SHBG and BMI, we performed another segregation analysis in the white families of SHBG adjusted only for age and sex (results not shown). In summary, we obtained suggestive, but not significant, evidence of a major gene effect associated with baseline SHBG, although the multifactorial model also provided a comparable parsimonious fit to the data. We repeated the analysis adjusting SHBG for menopausal status and hormonal replacement therapy to see if these adjustments would alter our conclusions, and they did not.

Segregation analysis of BMI at baseline in white families (Table 3) confirmed the evidence of a major gene, as previously described in the literature. The hypothesis of no major gene model was rejected [model 3] ($P < .001$), while the recessive [model 5] and dominant [model 6] models did not fit the data ($P < .001$ for both models). The Mendelian transmission hypothesis was not rejected [model 7] ($P = .371$), while the no-transmission of the major effect model was rejected [model 8] ($P < .001$). The mixed Mendelian hypothesis [model 1], involving a major gene and a multifactorial component, was the parsimonious model by the AIC. The major gene accounted for 40% of the variance, with an additional 16% of the variance attributed to a multifactorial component.

Table 4 shows the bivariate segregation results for BMI and SHBG at baseline in white families. The general model solution we obtained had 1 parameter (the polygenic correlation, r_G) estimated at the boundary value of 1.0. Although, in this case, this does not actually reflect a strong polygenic component because the multifactorial effect for the BMI was almost zero (H = 0.037). In model 2, we tested the null hypothesis that

Table 3. Univariate Segregation Analysis Results for BMI at Baseline in White Families

Parameter	Model 1	2	3	4	5	6	7	8
p	0.694	[1]	[1]	0.699	0.660	0.930	0.682	0.770
τ_{AA}	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[p]
τ_{Aa}	[0.5]	[0.5]	[0.5]	[0.5]	[0.5]	[0.5]	0.556	[p]
τ_{aa}	[0]	[0]	[0]	[0]	[0]	[0]	[0]	[p]
μ_{AA}	.346	0.026	0.023	−.531	−.205	−.198	−.542	−.560
μ_{Aa}	0.028	[μ_{AA}]	[μ_{AA}]	0.249	[μ_{AA}]	1.519	0.241	0.635
μ_{aa}	2.027	[μ_{AA}]	[μ_{AA}]	2.066	1.839	[1.519]	2.041	2.459
σ	0.808	1.040	1.032	0.738	0.814	0.864	0.732	0.641
H	0.261	[0]	0.414	[0]	[0]	[0]	[0]	[0]
−21nL	1,434.20	1,513.69	1,471.03	1,436.78	1,455.02	1,463.99	1,435.98	1,466.94
test	—	2-1	3-1	4-1	5-4	6-4	7-4	8-7
df	—	4	3	1	1	3	3	3
χ^2		79.49	36.83	2.58	18.24	27.21	0.80	30.96
P	—	<0.001	<0.001	0.108	<0.001	<0.001	0.371	<0.001
AIC	13.64*	85.13	44.47	14.22	30.46	39.43	15.42	44.38

NOTE. [] The parameter was constrained to the value shown.
(1) Mixed Mendelian ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$).
(2) Sporadic ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $\mu_{AA} = \mu_{Aa} = \mu_{aa}$, p = 1, H = 0).
(3) No major gene ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $\mu_{AA} = \mu_{Aa} = \mu_{aa}$, p = 1).
(4) No multifactorial component ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, H = 0).
(5) Recessive ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $\mu_{AA} = \mu_{Aa}$, H = 0).
(6) Dominant ($\tau_{AA} = 1$, $\tau_{Aa} = 0.5$, $\tau_{aa} = 0$, $\mu_{Aa} = \mu_{aa}$, H = 0).
(7) Free transmission probabilities (τ_{aa} bounded to 0 value; H = 0).
(8) Environmental ($\tau_{AA} = \tau_{Aa} = \tau_{aa}$ = p, H = 0).
*The parsimonious model.

Table 4. Bivariate Segregation Analysis Results for BMI and SHBG at Baseline in White Families

Parameter	Model 1	2	3	4
p	0.731	0.734	0.728	0.752
$r_{genetic}$	1.0*	.652	[0]	1.0*
$r_{environmental}$	−.533	−.583	−.602	[0]
BMI				
μ_{AA}	−.509	−.484	−.493	−.458
μ_{Aa}	0.371	0.350	0.343	0.389
μ_{aa}	2.148	2.124	2.082	2.165
σ	0.743	0.761	0.753	0.808
H	0.033	0.032	[0]	0.359
SHBG				
μ_{AA}	−.025	−.018	−.018	−.017
μ_{Aa}	−.018	[μ_{AA}]	[μ_{AA}]	[μ_{AA}]
μ_{aa}	−.018	[μ_{AA}]	[μ_{AA}]	[μ_{AA}]
σ	0.998	1.001	0.990	1.053
H	0.417	0.396	0.360	0.626
−21nL + c	0.00	0.02	0.67	56.31
test		2-1	3-1	4-1
df		2	4	3
χ^2		0.02	0.67	56.31
P		0.990	0.955	<.001
AIC	26.00	22.02	18.67†	66.31

NOTE. c = 2,749.00. [] The parameter was constrained to the value shown.
*The parameter reached the bound value.
†The parsimonious model.

there is no effect of the putative BMI locus on SHBG concentrations. This hypothesis was not rejected ($P = .990$). We further tested whether there was evidence of correlation between the polygenic components ([model 3], $r_G = 0$), and this hypothesis also was not rejected ($P = .955$). Finally, the test of zero correlation between the non-transmitted environmental components ([model 4], $r_E = 0$) was strongly rejected ($P < .001$) suggesting that, again, the likely basis of the inverse relationships between SHBG and BMI stems from common environmental determinants.

While the segregation analysis of FFM provided no evidence for a major gene (results not shown), we used the bivariate PAP model in an attempt to distinguish between polygenic and environmental sources of covariance between FFM and SHBG. The results indicated an absence of polygenic pleiotropy between these phenotypes ($P > .99$; $r_G = 0$ and $r_E = -0.436$), similar to the case above. As suggested by the cross-trait correlation analysis, it appears that in both cases, the relationships between SHBG and BMI or FFM are due to environmental factors in white families. We were not able to perform similar analyses of SHBG and TER in black families because insufficient sample size led to extensive statistical convergence problems.

DISCUSSION

Plasma SHBG concentrations have been recognized as an important correlate of obesity-related metabolic alterations in both sexes. Low SHBG concentrations are associated with an enhanced accumulation of abdominal fat, with hyperinsulinemia, insulin resistance, and increased risk for cardiovascular

disease and type 2 diabetes.[2,6,8,9] Consistent with earlier reports,[6,10,29-31] this study also showed negative phenotypic correlations between SHBG concentrations and body fat and abdominal adiposity measures at baseline, in both white and black families. Phenotypic correlations between SHBG concentrations and adiposity measures for training response were also negative, although some correlations were not significant.

The familial cross-trait correlation analysis showed evidence of common familial factors influencing baseline SHBG concentrations and BMI, which accounted for 11% of the phenotypic variance in white families. However, the significant spouse cross-trait correlations and the predominance of intraindividual correlations over those across family members strongly suggest that the heritability is due primarily to environmental factors. Similar conclusions were obtained for SHBG and FFM. Since BMI is an index of heaviness including both lean and fat mass, it seems that such familial environmental factors influence simultaneously SHBG concentrations and lean mass rather than adiposity. Nonetheless, there is a clear inverse relationship between SHBG and measures of adiposity or abdominal fat in this study, but no suggestion of common familial factors (genetic or environmental) underlying this relationship. On the other hand, the pattern of bivariate correlation results between SHBG concentrations and TER in black families was more suggestive of a genetic basis (results not shown). The maximal cross-trait heritability was about 45%, which was based on sibling and parent-offspring cross-trait correlations and the absence of significant spouse cross-trait correlations. However, we were not able to explore this relationship further due to the small sample size.

Our findings support those reported by Comuzzie et al,[16] who examined the genetic and environmental correlations among hormone concentrations and body fat distribution in Mexican-American families using a variance component decomposition approach. The investigators detected significant negative environmental correlations between SHBG concentrations and BMI (r = -.253, P = .009), subscapular/triceps ratio (r = -.201, P = .033), as well as with relative fat patterning index (r = -.201, P = .033), but no genetically-based correlations.

Regardless of the observation that BMI has been found to be the most important predictor of SHBG concentrations in the HERITAGE data,[20] there is no significant (interindividual) cross-trait correlation in relative pairs between the 2 variables. Therefore, it appears that the correlation is rather due to common environmental factors, perhaps lifestyle factors and obesity-related metabolic correlates such as insulin, glucose, leptin, triglycerides, or total cholesterol levels. However, our goal here was not predict the relationship between SHBG concentrations and these factors, but to test the hypothesis that the correlation between SHBG and body fat measures is founded in genetic pleiotropy. Neither a pleiotropic major locus nor pleiotropic polygenic effects were detected between SHBG concentrations and body composition and abdominal adiposity phenotype in white families. Moreover, there was no evidence of any genetic pleiotropy in the posttraining measures. Despite the fact that some significant changes in response to training were observed in BMI, FM, %BF,[22] and in SHBG concentrations, there was no suggestion of a genetic basis for these concurrent responses.

These conclusions apply to healthy subjects. Strict exclusion criteria were applied in the present study. Subjects with type 2 diabetes, extreme obesity, hypertension, and definite or possible coronary heart disease were not eligible, and whether the same results would be obtained in these subjects is not known. In conclusion, we found no evidence that SHBG concentrations are genetically correlated to body composition phenotypes either at baseline or in response to training in the HERITAGE Family Study.

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