Population Differences in the Pattern of Familial Aggregation for Sex Hormone-Binding Globulin and Its Response to Exercise Training: The HERITAGE Family Study

PING AN,[1]* TREVA RICE,[1] JACQUES GAGNON,[2] INGRID B. BORECKI,[1,3]
TUOMO RANKINEN,[4] CHI GU,[1] ARTHUR S. LEON,[5] JAMES S. SKINNER,[6]
JACK H. WILMORE,[7] CLAUDE BOUCHARD,[4] AND D.C. RAO[1,3,8]
[1]*Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri*
[2]*Laboratory of Molecular Endocrinology, CHUL Research Center, Ste-Foy, Québec, Canada*
[3]*Department of Genetics, Washington University School of Medicine, St. Louis, Missouri*
[4]*Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana*
[5]*School of Kinesiology and Leisure Studies, University of Minnesota, Minneapolis, Minnesota*
[6]*Department of Kinesiology, Indiana University, Bloomington, Indiana*
[7]*Department of Health and Kinesiology, Texas A&M University, College Station, Texas*
[8]*Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri*

ABSTRACT Familial influences were investigated for baseline sex hormone-binding globulin (SHBG) and its response (post-training minus baseline) to a 20-week endurance exercise training program. One hundred, eighty-four participants from 85 Black families in the HERITAGE Family Study (HERITAGE) were analyzed using a familial correlation model. Baseline SHBG values and the training response were adjusted for the effects of age, baseline BMI, testosterone, estradiol, and fasting insulin levels (plus baseline SHBG values for the training response) within four sex-by-generation groups prior to genetic analysis. Baseline SHBG levels were influenced by appreciable familial effects (maximum heritability $h^2 = 54\%$) with neither spouse resemblance nor sex and generation differences in the correlations. This estimate is only slightly, but not significantly, smaller than the heritability of 64% reported previously in 428 participants from 99 White families in HERITAGE. In contrast to the modest familial effects for the training response in White participants in HERITAGE ($h^2 = 25\%$), there were no evidence of familial resemblance in Blacks in the current study. Furthermore, there was heterogeneity for both baseline SHBG and the training response between Blacks and Whites in the pattern of familial aggregation. In conclusion, baseline SHBG levels are influenced by significant familial effects in both Blacks and Whites, independent of the effects of age, sex, and baseline values of BMI, testosterone, estradiol, and fasting insulin levels. Whereas modest familial effects were detected for the training response in Whites, the lack of similar effects in Blacks may be due to the smaller sample size. Am. J. Hum. Biol. 13:832–837, 2001.

Decreased levels of human sex hormone-binding globulin (SHBG) are associated with cardiovascular disease risk factors, including obesity and low levels of high-density lipoprotein cholesterol (Kopelman et al., 1980; Krotkiewski et al., 1981; Hämäläinen et al., 1986; Haffner et al., 1989; Tomova et al., 1995). A handful of previous studies suggest that SHBG is influenced by genetic as well as non-genetic familial components. Genetic heritabilities for SHBG levels vary widely in twin studies (Meikle et al., 1982, 1987, 1997; Bishop et al., 1988). The estimates were 31% in Mexican Americans in the San Antonio Family Heart Study (Jaquish et al., 1997), and reached 64% in White participants in the HERITAGE Family Study (HERITAGE) (An et al., 2000). In the current study, baseline SHBG levels as well as their changes (post-training minus baseline) in response to a 20-week endurance exercise training program obtained on Black participants in HERITAGE are analyzed, and the heritability in Blacks is contrasted with previous observations in White participants (An et al., 2000). Differences in the patterns of familial

Contract grant sponsor: National Heart, Lung, and Blood Institute; Contract grant numbers: HL45670 (C. Bouchard, PI), HL47323 (A.S. Leon, PI), HL47317 (D.C. Rao, PI), HL 47327 (J.S. Skinner, PI), and HL47321 (J. H. Wilmore, PI). Contract grant sponsor: The National Institutes of Health.
*Correspondence to: P. An, Division of Biostatistics, Campus Box 8067, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110-1093.
E-mail: anping@wubios.wustl.edu
Received 11 April 2001; Revision received 9 July 2001; Accepted 11 July 2001

TABLE 1. Means and SD of unadjusted baseline SHBG and its training response

Variables	No.	Means	SD	No.	Means	SD
Blacks						
		Fathers			*Mothers*	
Age (years)	20	50.0*#	7.3	21	43.5*#	4.3
BMI (kg/m^2)	20	25.9*	3.4	21	28.6*	4.7
Testosterone (nmol/L)	20	14.9*	5.9	21	1.2*#	0.6
Estradiol (pmol/L)	20	66.2*#	40.8	19	112.9*	79.7
Fasting insulin (pmol/L)	17	55.7#	41.1	21	92.0	107.0
Baseline SHBG (nmo/L)	20	48.7*#	18.3	21	58.3$^\delta$	32.1
Response SHBG (nmol/L)	20	2.1	5.7	21	−0.5	10.4
		Sons			*Daughters*	
Age (years)	58	28.5*#	7.2	85	26.8#	7.4
BMI (kg/m^2)	58	27.2	5.3	85	28.0	6.6
Testosterone (nmol/L)	58	17.0*	6.2	85	1.5*#	0.5
Estradiol (pmol/L)	58	86.9*#	38.1	85	136.7*	132.6
Fasting insulin(pmol/L)	58	83.6#	66.1	79	79.9	64.0
Baseline SHBG(nmol/L)	58	33.6*#	14.0	85	67.9*$^\delta$	44.0
Response SHBG (nmol/L)	58	1.3	8.2	85	3.0	25.8
Whites						
		Fathers			*Mothers*	
Age (years)	93	53.5*#	5.4	46	48.6*#	2.6
BMI (kg/m^2)	93	28.3#	4.5	46	27.0#	5.1
Testosterone (nmol/L)	93	13.3*#	5.7	46	1.1*#	0.5
Estradiol (pmol/L)	93	61.7*	40.0	46	206.0*#	258.9
Fasting insulin (pmol/L)	92	81.2*	66.2	46	55.9*	34.1
Baseline SHBG (nmol/L)	93	44.4*#	17.6	46	83.8*$^\delta$	45.3
Response SHBG (nmol/L)	93	−0.1*	8.3	46	−7.9*#	25.3
		Sons			*Daughters*	
Age (years)	136	25.4#	6.2	153	25.5#	6.4
BMI (kg/m^2)	136	25.7*#	4.9	153	23.5*#	4.3
Testosterone (nmol/L)	136	15.7*#	5.8	153	1.4*#	0.6
Estradiol (pmol/L)	136	71.1*	45.5	147	98.2*#	107.5
Fasting insulin (pmol/L)	136	66.1*	47.7	151	54.9*	27.7
Baseline SHBG (nmol/L)	136	35.1*#	15.0	153	87.6*$^\delta$	47.4
Response SHBG (nmol/L)	136	0.1	8.0	153	3.4#	43.5

*Significant ($P < 0.05$) mean differences for father-mother or son-daughter (within generation) comparisons.
#Significant ($P < 0.05$) mean differences for father-son or mother-daughter (within sex) comparisons.
$^\delta$Significant ($P < 0.05$) mean differences between the Black and White samples for mother-mother and daughter-daughter comparisons for the baseline.

aggregation in Blacks and whites are also assessed.

SUBJECTS AND METHODS

A total of 184 individuals from 85 Black families (78 men, 106 women) and 428 individuals from 99 White families (229 men, 199 women) completed the training program in HERITAGE. Post-menopausal mothers (17 Blacks, 44 Whites) and participants with incomplete pre- and post-training SHBG measurements were excluded. Table 1 gives the sample sizes within four sex-by-generation groups (fathers [*f*], mothers [*m*], sons [*s*], daughters [*d*]) by race. Baseline SHBG was determined by averaging the two pre-training measurements. The training response was determined by a simple difference of the averaged two post-training and the averaged two pre-training values. Technical errors for repeated measurements were 4.1 nmol/L in 325 men and 11.7 nmol/L in 420 women. Intra-class correlations for repeated measurements were greater than 0.97 in men and women. Coefficients of variation (CV) for repeated measurements were 11% and 15% in men and women, respectively. The moderately high CV values appear to be accounted for by a few outliers, which were defined as more than 3 standard deviations (SD) and at least 1 SD away from the nearest value in the current study. HERITAGE protocol, population, inclusion and exclusion criteria, and the training program have been described previously (Bouchard et al., 1995; Skinner et al., 2000). Descriptions of SHBG measurements and data adjustments were given in our previous report on Whites in HERITAGE (An et al., 2000).

A sex-specific familial correlation model was used to assess familial effects underly-

ing the variation in baseline SHBG and the training response in Blacks. The likelihood ratio test (LRT) and Akaike's Information Criterion (AIC) were used to compare models (Akaike, 1974; Province and Rao, 1995). Several different hypotheses were addressed including the presence of familial resemblance, the presence of sex and/or generation differences in the correlations, and the presence of spouse resemblance. A parsimonious model was determined by combining the non-rejected hypotheses into a single test. Maximal heritability was computed using the following equation: $(r_{sibling} + r_{parent\text{-}offspring})(1 + r_{spouse})/(1 + r_{spouse} + 2 \times r_{spouse} \times r_{parent\text{-}offspring})$, where $r_{sibling}$, $r_{parent\text{-}offspring}$, and r_{spouse} denote sibling (ss, dd, and sd), parent-offspring (*fs*, *fd*, *ms*, and *md*), and spouse (*fm*) correlations, respectively. (Rice et al., 1997) Heterogeneity between Blacks and Whites was assessed under a 16-correlation model. This model is a simple extension of the 8-correlation model and allows for race-specific correlations (fm_1, fs_1, fd_1, ms_1, md_1, ss_1, dd_1, sd_1 in Blacks, and fm_2, fs_2, fd_2, ms_2, md_2, ss_2, dd_2, sd_2 in Whites). Since means and variances are estimated separately for each race, this procedure not only allows testing for overall heterogeneity but also enables a determination of the sources of heterogeneity.

RESULTS AND DISCUSSION

Means and SD of unadjusted baseline SHBG and the training response for Blacks are presented in Table 1. Corresponding same descriptive statistics for Whites are also given for comparison. Sex differences in the means were noted with higher baseline SHBG levels in women than in men in both generations although not strictly significant in the father-mother comparison. Whereas there was no significant generation difference in the means between mothers and daughters, baseline SHBG was significantly higher in fathers than in sons. No sex and generation difference in the means for the training response was significant. No mean differences between the races within any of the sex-by-generation groups for baseline SHBG in men and the training response in both sexes were noted except that baseline SHBG in women was significantly higher in Whites than in Blacks in both generations. The percentages of the variance accounted for by the covariates in baseline SHBG for Blacks were 48% (testosterone, age^3), 52% (estradiol, insulin), 65% (testosterone, insulin, BMI), and 36% (insulin, age) in fathers, mothers, sons, and daughters, respectively. For the training response, testosterone accounted for 8% of the variance in sons, whereas no other covariate effects were significant in parents and daughters.

Familial correlation model-fitting results in Blacks are presented in Table 2. For baseline SHBG, the hypothesis of no familial resemblance was rejected (model 2), providing evidence that there are familial effects. There were no sex and generation differences in the familial correlations

TABLE 2. Model-fitting summary for baseline SHBG and the training response in Blacks

Model	d.f.	χ^2	*P*	AIC
Baseline SHBG				
1. General model *(fm, fs, fd, ms, md, ss, dd, sd)*	–	–	–	16.00
2. No familial correlations *(fm = fs = fd = ms = md = ss = dd = sd = 0)*	8	19.13	0.01	19.13
3. No sex differences in offspring *(fm, fs = fd, ms = md, ss = dd = sd)*	4	6.18	0.19	14.18
4. No sex differences in parents and offspring *(fm, fs = fd = ms = md, ss = dd = sd)*	5	6.18	0.29	12.18
5. No sex and generation differences *(fm, fs = fd = ms = md = ss = dd = sd)*	6	6.18	0.40	10.18
6. No spouse resemblance* *(fm = 0, fs = fd = ms = md = ss = dd = sd)*	7	6.63	0.47	8.63
SHBG training response				
1. General model *(fm, fs, fd, ms, md, ss, dd, sd)*	–	–	–	16.00
2. No familial correlations *(fm = fs = fd = ms = md = ss = dd = sd = 0)*	8	5.47	0.71	5.47

*Parsimonious model: $fm = 0$, $fs = fd = ms = md = ss = dd = sd = 0.27 \pm 0.08$; general model: $fm = -0.02 \pm 0.19$, $fs = 0.60 \pm 0.14$, $ms = 0.27 \pm 0.15$, $fd = 0.11 \pm 0.18$, $md = 0.24 \pm 0.14$, $sd = 0.43 \pm 0.13$, $ss = 0.38 \pm 0.22$, $dd = 0.09 \pm 0.16$.

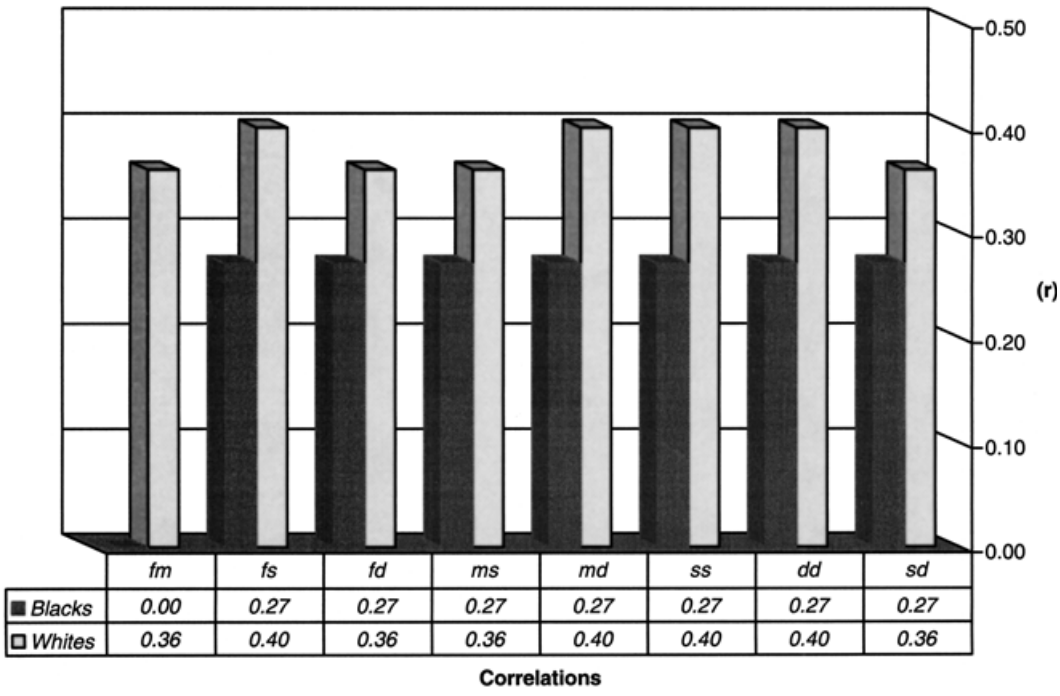

Fig. 1. Differences in familial correlations for baseline SHBG between Blacks and Whites in the HERITAGE Family Study.

(models 3–5), and there was no spouse resemblance (model 6). According to the AIC, the hypothesis of equal sibling and parent-offspring correlations in the absence of spouse resemblance was the most parsimonious (model 6). The maximum likelihood familial correlation estimates under the most parsimonious hypothesis for baseline SHBG were $fm = 0$ and $fs = fd = ms = md = ss = dd = sd = 0.27 \pm 0.08$ (see Table 2 footnote). Baseline SHBG was influenced by appreciable familial factors, and the maximal heritability reached 54% with the 95% confidence interval of approximately 40% to 70%). For the training response, the hypothesis of no familial correlations was not rejected (model 2). No significant familial effects were found.

Figure 1 presents familial correlation estimates for baseline SHBG in the Black and White participants. For Whites, familial correlations were 0.40 for father-son, mother-daughter, son-son, and daughter-daughter pairs and 0.36 for the remaining familial correlations (An et al., 2000). For the training response in Blacks, familial correlations were not significantly different from zero. Therefore, the maximal heritability was negligible in Blacks. By contrast the heritability of the training response in Whites was 25%. These observed differences in familial correlations between Blacks and Whites were significant for both baseline SHBG and the training response phenotypes. The heterogeneity model allowed investigation of specific sources of heterogeneity with 16 correlations. Detailed analyses suggested that heterogeneity by race was possibly due to differences in parent-offspring and sibling correlations for baseline SHBG (Table 3). Heterogeneity by race for the training response also was observed because of the presence of familial resemblance in Whites but not in Blacks. The small sample size in Blacks yields a power of only 48% to detect heritability of approximately 20% in contrast to a power of 92% for the relatively larger sample size of Whites in HERITAGE. Therefore, although a significant heritability was not found here, a familial component of low magnitude for the training response in Blacks cannot be

TABLE 3. Heterogeneity tests for baseline SHBG between the two populations in HERITAGE

Models	−2 ln L	d.f.	χ^2	*P*
Baseline SHBG				
1. Homogeneous *($fm_1=fm_2$, $fs_1=fs_2$, $fd_1=fd_2$, $ms_1=ms_2$, $md_1=md_2$, $ss_1=ss_2$, $dd_1=dd_2$, $sd_1=sd_2$)*	1,418.06	0	–	–
2. Heterogeneous spouse correlations *(fm_1, fm_2, $fs_1=fs_2$, $fd_1=fd_2$, $ms_1=ms_2$, $md_1=md_2$, $ss_1=ss_2$, $dd_1=dd_2$, $sd_1=sd_2$)*	1,815.57	1	2.49	0.11
3. Heterogeneous parent-offspring correlations (P-O)* *($fm_1=fm_2$, fs_1, fs_2, fd_1, fd_2, ms_1, ms_2, md_1, md_2, $ss_1=ss_2$, $dd_1=dd_2$, $sd_1=sd_2$)*	1,806.46	4	11.60	0.02
(3a) Homogeneity with no sex differences in P-O *($fm_1=fm_2$, $fs_1=fs_2$, $fd_1=fd_2$, $=ms_1=ms_2=md_1=md_2$, $ss_1=ss_2$, $dd_1=dd_2$, $sd_1=sd_2$)*	1,825.51	3	7.45	0.06
(3b) Heterogeneous P-O with no sex differences in Blacks *($fm_1= fm_2$, $fs_1=fd_1=ms_1=md_1$, fs_2, fd_2, ms_2, md_2, $ss_1=ss_2$, $dd_1=dd_2$, $sd_1=sd_2$)*	1,818.51	4	7.00	0.14
(3c) Heterogeneous P-O with no sex differences in *Whites** ($fm_1=fm_2$, fs_1, fd_1, ms_1, md_1, $fs_2=fd_2=ms_2=md_2$, $ss_1=ss_2$, $dd_1=dd_2$, $sd_1=sd_2$)*	–	4	–	–
4. Heterogeneous sibling correlations (SIB) *($fm_1=fm_2$, $fs_1=fs_2$, $fd_1=fd_2$, $ms_1=ms_2$, $md_1=md_2$, ss_1, ss_2, dd_1, dd_2, sd_1, sd_2)*	1,811.56	3	6.50	0.09
SHBG training response				
1. Homogeneous	2,169.46	0	–	–
2. Heterogeneous spouse correlations	2,169.20	1	0.26	0.61
3. Heterogeneous P-O	2,163.51	4	5.95	0.20
4. Heterogeneous SIB*	2,164.02	3	5.44	0.14
(4a) Homogeneity with no sex differences in SIB *($fm_1=fm_2$, $fs_1=fs_2$, $fd_1=fd_2$, $ms_1=ms_2$, $md_1=md_2$, $ss_1=ss_2=dd_1=dd_2=sd_1=sd_2$,)*	2,172.44	2	2.98	0.23
(4b) Heterogeneous SIB with no sex differences in *Blacks ($fm_1=fm_2$, $fs_1=fs_2$, $fd_1=fd_2$, $ms_1=ms_2$, $md_1=md_2$, $ss_1=dd_1=sd_1$, ss_2, dd_2,sd_2,)*	2,168.52	3	3.92	0.27
(4c) Heterogeneous SIB with no sex differences in *Whites ($fm_1=fm_2$, $fs_1=fs_2$, $fd_1=fd_2$, $ms_1=ms_2$, $md_1=md_2$, ss_1,dd_1, sd_1, $ss_2=dd_2=sd_2$)*	2,180.05	3	7.61	<0.05

*Models were not appropriately converged.

ruled out. This is supported by the previous finding of low magnitude, but significant, heritability of 25% for the training response in Whites (An et al., 2000). The participants from the 85 Black families were healthy in general, non-diabetic, non-hypertensive, but sedentary. The current report conveys new information, representing the first study of its kind in Blacks.

Previous family studies on the heritability of SHBG include one report in Mexican Americans (h^2 = 31%) (Jaquish et al., 1997) and the recent report in HERITAGE Whites (h^2 = 64%) (An et al., 2000). The current estimate of 54% in Blacks for baseline SHBG was significantly ($P < 0.05$) higher than that in the Mexican Americans (Jaquish et al., 1997), which would suggest stronger and/or additional familial components in Blacks (just as in Whites) in HERITAGE. Differences in characteristics of the samples such as inactivity in HERITAGE along with other distinctively shared familial environmental factors may account for this observation. For baseline SHBG, the estimate of 54% in Blacks was slightly but not significantly lower than the estimate of 64% in Whites (An et al., 2000). It was also noted that, for the training response, the modest familial component in Whites, with a heritability of 25%, was not replicated in Blacks and was estimated to be near zero (An et al., 2000).

Spouse resemblance for both baseline SHBG and its training response was nonsignificant in Blacks but significant in Whites (0.36 ± 0.06 for baseline SHBG and 0.13 ± 0.05 for the training response) (An et al., 2000). The small number of spouse pairs (N = 19) in Blacks, obtained after excluding postmenopausal mothers and those with incomplete training response information from the current analysis, yields a large standard error that would render a corre-

lation of up to approximately 0.40 not significantly different from zero.

In conclusion, moderate genetic as well as non-genetic familial factors influence baseline SHBG levels in both the races. Familial resemblance for SHBG training response was non-significant in Blacks, whereas it was modest, but significant, in Whites. The observed patterns of familial resemblance were significantly heterogeneous comparing the races for both the baseline and training response phenotypes.

ACKNOWLEDGMENTS

Thanks are expressed to Dr. Alain Belanger and his collaborators in the Molecular Endocrinology Laboratory at Laval University where the steroids were assayed. A.S. Leon also is supported in part by the Henry L. Taylor Professorship in Exercise Science and Health Enhancement. C. Bouchard also is partially supported by the George A. Bray Chair in Nutrition.

LITERATURE CITED

Akaike H. 1974. A new look at the statistical model identification. IEEE Trans Automat Control 19:716–723.

An P, Rice T, Gagnon J, Hong Y, Leon AS, Skinner JS, Wilmore JH, Bouchard C, Rao DC. 2000. A genetic study of sex hormone-binding globulin measured before and after a 20-week endurance exercise training program: the HERITAGE family study. Metabolism 49:1014–1020.

Bishop DT, Meikle AW, Slattery ML, Stringham JD, Ford MH, West DW. 1988. The effect of nutritional factors on sex hormone levels in male twins. Genet Epidemiol 5:43–59.

Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J. 1995. The HERITAGE family study: aims, design and measurement protocol. Med Sci Sports Exerc 276:721–729.

Haffner SM, Katz MS, Stern MP, Dunn JF. 1989. Association of decreased sex hormone binding-globulin and cardiovascular risk factors. Arteriosclerosis 9:136–143.

Hämäläinen E, Aldercruetz H, Ehnholm C, Puska P. 1986. Relationship of serum lipoproteins and apoproteins to sex hormones and to binding capacity of sex hormone binding globulin in healthy Finnish men. Metabolism 36:535–541.

Jaquish CE, Blangero J, Haffner SM, Stern MP, MacCluer JW. 1997. Quantitative genetics of serum sex hormone-binding globulin levels in participants in the San Antonio family heart study. Metabolism 46: 988–991.

Kopelman PG, Pilkington TRE, White N, Jeffcoate SL. 1980. Abnormal sex steroid secretion and binding in massively obese women. Clin Endocrinol. Oxford: 12: 363–369.

Krotkiewski M, Toss L, Björntorp, Holm G. 1981. The effect of a very low calorie diet with and without chronic exercise on thyroid and sex hormone, plasma proteins, oxygen uptake, insulin, and C-peptide concentrations in obese women. Int J Obes 5:287–293.

Meikle AW, Stanish WM, Taylor N, Edwards CQ, Bishop CT. 1982. Familial effects on plasma sex-steroid content in man: testosterone, estradiol and sex-hormone-binding globulin. Metabolism 31:6–9.

Meikle AW, Bishop DT, Stringham JD, Ford MH, West DW. 1987. Quantitating genetic and nongenetic factors that determine plasma sex steroid variation in normal male twins. Metabolism 35:1090–1095.

Meikle AW, Stephenson RA, Lewis CM, Wiebke GA, Middleton RG. 1997. Age, genetic, and nongenetic factors influencing variation in serum sex steroids and zonal volumes of the prostate and benign prostatic hyperplasia in twins. Prostate 33:105–111.

Province MA, Rao DC. 1995. General purpose model and a computer program for combined segregation and path analysis (SEGPATH): automatically creating computer programs from symbolic language model specifications. Genet Epidemiol 12:203–219.

Rice T, Després JP, Daw EW, Gagnon J, Borecki IB, Pérusse L, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bouchard C. 1997. Familial resemblance for abdominal visceral fat: the HERITAGE family study. Int J Obes 21:1024–1031.

Skinner JS, Wilmore KM, Krasnoff JB, Jaskolski A, Jaskolska A, Gagnon J, Province MA, Loen AS, Rao DC, Wilmore JH, Bouchard C. 2000. Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE family study. Med Sci Sports Exerc 32:157–161.

Tomova A, Kumanov P, Kirilov G. 1995. Factors related to sex hormone binding globulin concentrations in women with anorexia nervosa. Horm Metab Res 27:508–510.