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Sex Hormones, Sex Hormone Binding Globulin, and Abdominal Aortic Calcification in Women and Men in the Multi-Ethnic Study of Atherosclerosis (MESA)

Erin D. Michos, MD, MHS¹, Dhananjay Vaidya, PhD², Susan M. Gapstur, PhD³, Pamela J. Schreiner, PhD⁴, Sherita H. Golden, MD, MHS⁵, Nathan D. Wong, PhD⁶, Michael H. Criqui, MD, MPH⁷, and Pamela Ouyang, MBBS¹

¹Division of Cardiology, Johns Hopkins School of Medicine, Baltimore, MD

²Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD

³Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

⁴Department of Epidemiology, University of Minnesota School of Public Health, Minneapolis, MN

⁵Division of Endocrinology, Johns Hopkins School of Medicine, Baltimore, MD

⁶Heart Disease Prevention Program, University of California Irvine School of Medicine, Irvine, CA

⁷Department of Family and Preventive Medicine and Department of Medicine, University of California San Diego School of Medicine, La Jolla, CA

Abstract

Background—Conflicting findings exist regarding the associations of sex hormones with subclinical atherosclerosis.

Methods—This is a substudy from MESA of 881 postmenopausal women and 978 men who had both abdominal aortic calcification (AAC) quantified by computed tomography and sex hormone levels assessed [Testosterone (T), estradiol (E2), dehydroepiandrosterone (DHEA), and sex hormone binding globulin (SHBG)]. We examined the association of sex hormones with presence and extent of AAC.

Results—For women, SHBG was inversely associated with both AAC presence [OR=0.62, 95% CI 0.42 to 0.91 for 1 unit greater log(SHBG) level] and extent [0.29 lower log(AAC) for 1 unit greater log(SHBG) level, $\beta = -0.29$ (95% CI -0.57 to -0.006)] adjusting for age, race, hypertension, smoking, diabetes, BMI, physical activity, and other sex hormones. After further adjustment for total and HDL-cholesterol, SHBG was not associated with AAC presence or extent. In men, there was no association between SHBG and AAC. In both men and women, neither T, E2, nor DHEA was associated with AAC presence or extent.

Reprints and Correspondence: Erin D. Michos, MD, MHS, Division of Cardiology, Johns Hopkins School of Medicine, Carnegie 568, 600 N. Wolfe Street, Baltimore, MD 21287, Phone: 410-502-6813, Fax: 410-502-0231, edonnell@jhmi.edu.

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Conclusion—After adjustment for non-lipid cardiovascular risk factors, SHBG levels are inversely associated with both the presence and severity of AAC in women but not in men, which may be accounted for by HDL.

Keywords

sex hormone binding globulin; abdominal aortic calcification; sex hormones; subclinical atherosclerosis

Introduction

Differences in the prevalence of cardiovascular disease (CVD) between men and women across age groups suggest that sex hormones may influence the development of subclinical atherosclerosis. However, prior studies evaluating the association of sex hormones with subclinical atherosclerosis report conflicting results. Some studies found that total testosterone (T) levels are inversely associated with carotid intimal medial thickness (cIMT) in both postmenopausal women¹ and men² suggesting a protective effect. However a more recent analysis found both total T and bioavailable testosterone (bioT) were positively associated with cIMT in postmenopausal women after adjustment for risk factors, but no association was found for estradiol (E2) or dehydroepiandrosterone (DHEA).³ Several studies also found an inverse association of sex hormone binding globulin (SHBG) on cIMT.^{1,3}

In women, estrogen replacement has been reported to be associated with less coronary artery calcification (CAC) progression⁴ despite the lack of clinical benefit (and possible increased harm) of hormone therapy (HT) with CVD events.⁵ Among women with polycystic ovarian syndrome, those with prevalent CAC had higher levels of free T and lower levels of SHBG compared to those without CAC suggesting that increased androgens may promote calcification in women.⁶

Abdominal aortic calcification (AAC), another measure of subclinical atherosclerosis, is relatively common in older women even in the presence of low levels of coronary calcification. There is less of a gender difference between men and women with AAC than there is with CAC⁷ but the relationship of sex hormones with AAC is unclear. We sought to characterize the relationship with AAC and to evaluate whether any association differed by gender or race.

Methods

Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study investigating subclinical atherosclerosis in 6814 individuals aged 45–84 years without clinical CVD at baseline. Individuals were excluded if they had clinical CVD, including physician-diagnosed myocardial infarction, angina, stroke, transient ischemic attack, or heart failure, use of nitroglycerine, current atrial fibrillation, or had undergone a procedure related to CVD (coronary artery bypass surgery, angioplasty, valve replacement, pacemaker or defibrillator implantation, any surgery on the heart or arteries).

This report includes a random sample of MESA participants who also participated in the MESA Abdominal Aortic Calcium Study (MESA-AACS). MESA-AACS participants were recruited during follow-up visits between August 2002 and September 2005 from five MESA field centers: Chicago, Illinois, Forsyth County, North Carolina, Los Angeles County, California, Columbia University, and St. Paul, Minnesota. Of 2202 MESA participants recruited, 2172 agreed to participate, and 1990 satisfied eligibility criteria. Ten individuals had missing or

incomplete scans for a total of 1980 participants with completed computed tomography scanning of their abdominal aorta.

We further restricted our analyses to postmenopausal women (n=881) and men (n=978) who participated in overlapping ancillary studies evaluating both AAC and serum sex hormone levels. The present analysis was based on data obtained at the baseline visit. Further details about the MESA study design have been published elsewhere⁸ and are available on the World Wide Web at www.mesa-nhlbi.org.

Risk Factor Assessment

Standardized questionnaires at the baseline examination were used to obtain information about participant demographics, medical history, and medication usage including current HT and cholesterol-lowering medications. Height, weight, and blood pressure were measured at the baseline examination. Body mass index (BMI) was calculated as weight (kg)/ height (m²). Resting blood pressure (BP) was measured three times in the seated position using a Dinamap automated sphygmomanometer, and the average of the 2nd and 3rd readings was used. Blood samples were obtained after a 12-hour fast to measure glucose, total cholesterol, HDL-cholesterol (HDLc), triglycerides, T, bioT, E2, DHEA, and SHBG. LDL-cholesterol (LDLc) was calculated using the Friedewald equation.

Hypertension was defined as systolic BP $\geq$ 140 mm Hg, and/or diastolic BP $\geq$ 90 mm Hg, and/or use of anti-hypertensive medications. Diabetes was classified as having a fasting blood glucose $\geq$ 126 mg/dl and/or the self-reported use of hypoglycemic medications. Smoking was classified by never, former, or current use of cigarettes. Physical activity was calculated as the total minutes of all moderate and vigorous activity multiplied by their respective metabolic equivalents (METs).

Sex Hormone Assessment

Serum hormone concentrations (nmol/L) were measured from stored samples in the Steroid Hormone laboratory at the University of Massachusetts Medical Center in Worcester, MA. Total T and DHEA were measured directly using radioimmunoassay kits, and SHBG was measured by chemiluminescent enzyme immunometric assay using Immulite kits obtained from Diagnostic Products Corporation (Los Angeles, CA). E2 was measured by use of an ultra-sensitive radioimmunoassay kit from Diagnostic System Laboratories (Webster, TX). Percent bioT was calculated according to the method of Södergard et al⁹, and bioT concentration was calculated as (total T $\times$ (percent free T $\times$ 0.01)). Assay variability was monitored by including approximately 5% blind quality control samples in each batch of samples analyzed. The quality control serum was obtained from a large pool that was aliquoted into storage vials and labeled identical to MESA participant samples. The overall coefficients of variation for total T, SHBG, DHEA, and E2 were 12.3%, 9.0%, 11.2%, and 10.5%, respectively.

Subclinical Vascular Disease Assessment

Computed tomography of the abdomen was performed a single time for each individual in the MESA-AACS ancillary study. For electron-beam computed tomography (Chicago and Los Angeles; Imatron C-150), scanners were set as follows: scan collimation of 3mm; slice thickness of 6mm; reconstruction using 25 6mm slices with 35cm field of view and normal kernel. For multi-detector computed tomography mode (New York, Forsyth County, and St. Paul field centers; Sensation 64, GE Lightspeed, Siemens S4+ Volume Zoom and Siemens Sensation 16), images were reconstructed in a 35cm field of view with 5mm slice thickness. All scans were brightness adjusted with a standard phantom.

Scans were read centrally by the MESA CT Reading Center, and calcium in an 8cm segment of the distal abdominal aorta ending at the aortic bifurcation was scored. Calcification was identified as a plaque of $\geq 1\text{mm}^2$ with a density of ≥ 130 Hounsfield units and quantified using the previously described Agatston scoring method.¹⁰ This scoring method has previously shown to be highly reproducible for CAC.^{11,12}

Statistical methods

For all analyses, we evaluated men and women separately because sex hormone levels differ by gender and there is insufficient overlap in levels to test for differences; thus the association of sex hormones on AAC may also differ by gender. Sex hormone levels did not follow a normal distribution, so they were log-transformed to make the distribution more symmetric.

We tabulated the distribution of the clinical characteristics of the study participants by the presence or absence of AAC, and tested differences between groups using chi-squared tests for categorical variables and t-tests for normally distributed variables or log-transformed variables. Using the direct age-standardization method, we also age-adjusted the baseline characteristics by presence or absence of AAC using the whole MESA study population's age distribution as the standard population.¹³

We used regression methods to determine the association of each sex hormone with both the presence of AAC and the extent of AAC for those in whom AAC was present. The association of each log(sex hormone) variable with presence and extent of AAC was analyzed singly and then in models including all sex hormones. Because bioT is a calculated value based on total T, it was not included in models including all sex hormones.

For the presence of AAC, we used logistic regression to determine the odds of having any prevalent detectable aortic calcium (Agatston score >0) vs the absence of aortic calcium (Agatston score $=0$) for each 1 unit greater log(sex hormone) level. This was repeated in multivariate regression after adjusting for covariates of age, race/ethnicity, BMI, former and current smoking, systolic BP, diastolic BP, use of BP medications, diabetes, HT use (women only), and physical activity [Model 1] and after additionally adjusting for total cholesterol, HDLc, and cholesterol-lowering medication use [Model 2].

For the severity of aortic calcium among those that have detectable AAC (>0), non-zero calcium levels were log-transformed, and the association of log(AAC) with log(sex-hormones) was analyzed using linear regression both unadjusted and then adjusted for covariates in Models 1 and 2. We also examined whether the associations between sex hormones and AAC differed by race/ethnicity or HT in models with terms for interaction effects

Scatterplots were created between log(sex hormones) and log(AAC) to verify that the linearity assumption of our models was not violated. Since sex hormones are known to be correlated with each other, variance inflation factors (VIF) and tolerances were tested to ensure that none of the models had VIFs that approached a level of concern (i.e. $\text{VIF} > 10$ or tolerances $< 10\%$). Stata 9.0 (Stata Corp., College Station, TX) was used for all analyses.

Results

Abdominal aortic calcium was present in 73.1% of men and 73.8% of the women ($p=0.74$ for the comparison of prevalent AAC between gender). Mean age in women without and with AAC was 58 ± 7 and 66 ± 9 years respectively ($p < 0.001$). Mean age in men without and with AAC was 54 ± 8 and 64 ± 10 years respectively ($p < 0.001$). Because age is so strongly associated with the prevalence of AAC, age-adjusted clinical characteristics are presented in Table I. After adjusting for age, men and women without AAC were less likely to have hypertension, diabetes,

ever-smoked, or used cholesterol-lowering medications, had higher HDLc and lower total cholesterol, LDLc, and triglycerides. There were 301 women on current HT, but HT use did not differ significantly between those without AAC and those with prevalent AAC. Age-adjusted geometric mean sex hormone levels by gender and presence of AAC are shown in Table 2. After adjusting for age only, there was a trend for higher SHBG levels among the women without AAC.

SHBG levels were correlated with the other sex hormones of total T, E2, and DHEA in women (age-adjusted correlation coefficient [r] of -0.15 , 0.37 , -0.31 , respectively, $p < 0.0001$ for all) and with testosterone in men ($r = 0.42$, $p < 0.0001$). Because sex hormone levels are correlated with each other, but are not collinear, we also examined the independent effects of each sex hormone in models adjusted for all of the other sex hormones in addition to covariates. Scatterplots showed no non-linearity in the association between $\log(\text{sex hormones})$ and $\log(\text{AAC})$.

For postmenopausal women, Model 1 (adjusted for age, race/ethnicity, BMI, former and current smoking, systolic and diastolic BP, use of hypertension medications, diabetes, physical activity, and HT use) showed a significant inverse association of SHBG with AAC presence (Table 3a) and an inverse trend with AAC extent (Table 4a). There also was a statistically significant inverse association of SHBG with both AAC presence and extent in models additionally adjusted for the other sex hormones [OR 0.62 (95% CI 0.42 to 0.91) for each 1 unit greater $\log(\text{SHBG})$ level] [Table 3a] and extent [0.29 lower $\log(\text{AAC})$ for every 1 unit greater $\log(\text{SHBG})$ level, $\beta = -0.29$ (95% CI -0.57 to -0.006)] [Table 4b]. However, after further adjustment for the total cholesterol, HDLc, and lipid medication use (Model 2), SHBG was no longer independently associated with either presence [Table 3a] or extent [Table 4b] of AAC in women. Also, the associations of any sex hormones with AAC were not significantly heterogeneous across race/ethnicity strata, nor was there heterogeneity for the relationship between SHBG and AAC by HT status in women.

In men, we found no association of SHBG with either presence or severity of AAC in Models 1 or 2. There were no independent associations of T, E2, or DHEA with presence or extent of AAC in either men or women in Models 1 or 2 [Table 3&Table 4]. No significant interactions were found between any of the sex hormones and race/ethnicity with AAC in men either.

Serum SHBG levels were directly associated with HDLc levels (age-adjusted correlation coefficient [r] = 0.44 in women, $r = 0.24$ in men, $p < 0.0001$ for both). Greater total cholesterol, lower HDLc, and use of cholesterol medications were all strongly significantly associated with both the presence of AAC and extent of AAC in both women and men in our multivariate model. The lack of association of SHBG with AAC in women after adjusting for lipids seems predominantly mediated by HDLc. After adjustment for total cholesterol only (plus Model 1 variables but not HDLc or lipid medication usage), SHBG was still significantly associated with a reduced presence (OR 0.63, $p = 0.018$) and severity ($\beta = -0.29$, $p = 0.044$) of AAC in women. However, after adjusting for HDLc only (plus Model 1 variables but not total cholesterol or cholesterol-medication usage), SHBG was no longer significantly associated with AAC in women, although direction was still the same (OR 0.76, $p = 0.19$ for presence and $\beta = -0.24$, $p = 0.10$) for severity. This suggests that HDLc levels may have accounted for the association between SHBG and AAC in women.

Discussion

Unlike the gender differences seen with CAC, our study confirms prior findings⁷ that there is no significant difference in prevalence of AAC between men and women of similar ages in this multi-ethnic cohort of individuals free of clinical CVD. Abdominal aortic calcification is

common in these asymptomatic individuals, and is associated with traditional CVD risk factors such as age, smoking, hypertension, diabetes, and adverse lipid profiles.

We did not find an association of T, E2, or DHEA levels with either presence or extent of AAC in either men or women. However, in postmenopausal women only, there were inverse associations of serum SHBG level with both the presence of AAC and with AAC severity. While the inverse association of SHBG with AAC severity did not quite meet statistical significance in Model 1 when the sex hormones were analyzed separately, the magnitude and direction of the SHBG coefficient, which is the best measure of association strength, was almost identical to the SHBG coefficient in the models adjusted for the other sex hormones. Then, the inverse associations of SHBG with AAC presence and severity were confirmed to be statistically-significantly independent of T and the other sex hormones in fully-adjusted models including diabetes and BMI (which both correlate with SHBG), as well as other major non-lipid CVD risk factors. However, after adjusting for HDLc, there was no significant association of SHBG with either the presence or extent of AAC, suggesting that HDLc levels may explain or confound the protective association of SHBG with AAC.

Sex hormone binding globulin is a glycoprotein synthesized in the liver that binds 17- β -hydroxysteroids such as T and E2 with high affinity.¹⁴ SHBG levels are strongly correlated with T levels; however SHBG is negatively correlated with glucose and insulin levels independently of T levels.^{15,16,17} Low levels of SHBG has been shown to be strongly and consistently related to elevated CVD risk factors of higher insulin, glucose, hemostatic and inflammatory markers, and adverse lipids even after controlling for BMI,¹⁸ but not associated with systolic or diastolic blood pressure.¹⁹ Low SHBG levels have been shown to be associated with the metabolic syndrome in postmenopausal women.²⁰ Levels of SHBG in the lowest quartile were also associated with a 2-fold age-adjusted risk of CVD; yet this association was no longer seen after adjustment for obesity, hypertension, diabetes, and lipids, suggesting that the increased CVD risk associated with low SHBG was attributable to the metabolic syndrome.²⁰ Racial differences between Caucasians and African Americans in the association of SHBG with adverse metabolic profile have been reported,²¹ although our study did not find any racial interactions between SHBG and the presence or severity of AAC.

Many prior cross-sectional studies have found an independent association of SHBG with lipoprotein levels in both men and postmenopausal women with the most consistent finding of a positive association between SHBG and HDLc.^{22,23,24,25} We also found that SHBG is directly associated with HDLc. Hepatic production of SHBG is regulated by many influences including sex steroid levels, thyroid hormones, cortisol, and growth factors and is inhibited by insulin.^{14,26,27} Many of these metabolic factors may also influence HDLc levels. For example, hyperinsulinism might negatively regulate both SHBG and HDLc levels. Also, physical activity and HDLc are positively correlated.

SHBG has been postulated to influence atherogenesis through metabolism and/or production of HDLc either directly or indirectly through the estrogen-testosterone balance.²⁸ Increasing levels of HDL are associated with less subclinical atherosclerosis independent of LDL levels,²⁹ and the positive association of SHBG levels with HDLc may be one mechanism that explains the inverse relationship of SHBG with subclinical atherosclerosis. To our knowledge, there are no current prospective studies that document SHBG increases HDL in a causal fashion, but such a pathway is now well established for alcohol which reduces CVD risk through HDLc (in addition to other factors) as a mediator.³⁰ Our study is limited by the cross-sectional design, thus the causality and temporality of the association of SHBG with HDLc and AAC cannot be determined.

In conclusion, SHBG levels are inversely associated with both the presence and severity of AAC in women but not in men after adjustment for non-lipid CVD risk factors. Levels of T, E2, and DHEA, however, do not appear associated with AAC in either gender. The association of SHBG with AAC in women was largely accounted for by HDLc levels. Further prospective studies with baseline measures of SHBG and serial measurements of AAC and/or serum lipids are needed to determine the temporal relationship of SHBG with HDLc and subclinical atherosclerosis.

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Age-Adjusted Baseline Characteristics by Gender and Presence of AAC, the Multi-Ethnic Study of Atherosclerosis, 2000–2002

Table 1

Mean values ± standard error or percent distribution

	Women No AAC (N=231)	Women AAC >0 (N=650)	p-value	Men No AAC (N=263)	Men AAC >0 (N=715)	p-value
Race/Ethnicity (%)						
Caucasian	26.9	42.4		23.7	46.6	
Chinese	12.3	13.4	0.002	8.9	14.1	<0.001
African-American	30.4	19.6		35.7	14.6	
Hispanic	30.5	24.6		31.7	24.7	
BMI (kg/m ²)	28.0±0.4	28.6±0.23	0.27	27.6±0.3	28.0±0.2	0.31
Hypertension (%)	35.6	55.1	<0.001	29.3	45.8	0.002
Systolic BP (mm Hg)	125.0 ±1.5	129.6 ±0.9	0.011	122.7 ±1.3	127.6 ±0.7	0.001
Diastolic BP (mm Hg)	68.7 ±0.7	69.3 ±0.4	0.49	74.3 ±0.6	76.0 ±0.4	0.019
Use of BP meds (%)	23.5	44.5	<0.001	21.7	35.9	0.009
Diabetes (%)	10.5	13.4	0.03	11.9	14.5	0.43
Never Smoker (%)	68.9	54.3	<0.001	58.8	34.6	<0.001
Former Smoker	24.0	31.2		34.6	48.5	
Current Smoker	7.1	14.6		6.6	16.9	
Total cholesterol (mg/dl)	193.8±2.3	204.6±1.3	<0.001	186.1±2.2	192.3±1.3	0.02
HDLc (mg/dl)	61.1±1.1	55.0±0.6	<0.001	47.3±0.8	44.5±0.5	0.003
LDLc (mg/dl)	110.8±2.1	120.9±1.2	<0.001	114.7±2.0	120.2±1.2	0.023
Triglycerides (mg/dl)	110.7±5.4	143.7±3.1	<0.001	122.0±5.4	141.3±3.2	0.003
Use of cholesterol medications (%)	7.9	22.2	<0.001	6.6	15.1	0.03
Use of HT (%)	32.7	35.4	0.38	N/A	N/A	N/A
Physical activity (MET min/week) *	3248.5 (2834.3–3723.1)	3422.1 (3163.8–3701.6)	0.527	4730.9 (4137.8–5408.9)	3992.2 (3694.9–4313.4)	0.039

* Geometric mean after log transformation, 95% CI

Table 2
Age-Adjusted Geometric Mean Levels (95% CI) of Sex Hormones by Gender and Presence of AAC, the Multi-Ethnic Study of Atherosclerosis, 2000–2002

	Women No AAC (N=231)	Women AAC >0 (N=650)	p-value	Men No AAC (N=263)	Men AAC >0 (N=715)	p-value
Total T (nmol/L)	0.84 (0.77–0.92)	0.86 (0.82–0.91)	0.69	14.09 (13.29–14.94)	13.79 (13.33–14.27)	0.55
BioT (nmol/L)	0.19 (0.17–0.21)	0.20 (0.19–0.22)	0.21	5.22 (4.93–5.54)	5.10 (4.93–5.27)	0.50
E2 (nmol/L)	0.089 (0.078–0.10)	0.088 (0.082–0.095)	0.94	0.11 (0.10–0.12)	0.108 (0.104–0.110)	0.50
DHEA (nmol/L)	10.49 (9.70–11.34)	9.89 (9.45–10.34)	0.21	12.97 (12.26–13.72)	12.33 (11.94–12.74)	0.14
SHBG (nmol/L)	67.15 (61.57–73.24)	61.03 (58.05–64.16)	0.07	40.63 (38.73–42.62)	40.18 (39.08–41.30)	0.70

Prevalence Odds of AAC by Sex Hormones in Women (3A) and Men (3B): The Multi-Ethnic Study of Atherosclerosis 2000–2002
Per 1 unit greater log(sex hormone) level

Table 3

A.	Women (Model 1)				Women (Model 2)			
	Sex Hormones analyzed separately plus covariates				Sex Hormones analyzed separately plus covariates			
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI
T	0.96	0.73–1.28	0.80	1.01	0.75–1.36	0.95		
E2	0.84	0.66–1.07	0.15	0.83	0.65–1.08	0.17		
DHEA	0.76	0.54–1.08	0.13	0.76	0.53–1.10	0.14		
SHBG	0.63	0.44–0.92	0.016	0.91	0.61–1.37	0.66		
Sex Hormones adjusted for each other plus covariates								
T	1.07	0.78–1.45	0.69	1.10	0.80–1.52	0.55		
E2	0.92	0.71–1.19	0.54	0.88	0.67–1.15	0.34		
DHEA	0.72	0.49–1.06	0.10	0.75	0.50–1.12	0.17		
SHBG	0.62	0.42–0.91	0.014	0.90	0.59–1.37	0.63		
B.	Men (Model 1)				Men (Model 2)			
	Sex Hormones analyzed separately plus covariates				Sex Hormones analyzed separately plus covariates			
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI
T	0.93	0.59–1.46	0.76	1.04	0.66–1.62	0.87		
E2	0.89	0.56–1.43	0.64	0.86	0.53–1.39	0.54		
DHEA	0.93	0.62–1.41	0.75	0.97	0.64–1.48	0.88		
SHBG	1.03	0.62–1.70	0.91	1.33	0.79–2.25	0.28		
Sex Hormones adjusted for each other plus covariates								
T	0.95	0.56–1.61	0.84	0.98	0.57–1.69	0.94		
E2	0.92	0.56–1.52	0.75	0.86	0.51–1.43	0.56		
DHEA	0.97	0.63–1.48	0.88	1.04	0.67–1.60	0.87		
SHBG	1.07	0.61–1.89	0.80	1.39	0.77–2.52	0.27		

*Model 1: adjusted for age, race, BMI, systolic BP, diastolic BP, use of BP medications, diabetes, former and current smoking, HT use (women only), and physical activity

*Model 2: adjusted for all Model 1 variables, total cholesterol, HDL-c, and use of cholesterol-lowering medications

Severity of AAC by Sex Hormones in Women (4A) and Men (4B): The Multi-Ethnic Study of Atherosclerosis, 2000–2002
 β =log-unit difference in AAC per 1 log-unit greater sex hormone level

A.	Women (Model 1)				Women (Model 2)			
	Sex Hormones analyzed separately plus covariates				Sex Hormones analyzed separately plus covariates			
	β	95% CI	p-value	β	95% CI	p-value	β	p-value
T	-0.101	-0.31-0.11	0.35	-0.081	-0.29-0.13	0.44		
E2	-0.071	-0.26-0.11	0.45	-0.091	-0.27-0.09	0.32		
DHEA	-0.153	-0.39-0.085	0.21	-0.167	-0.40-0.07	0.17		
SHBG	-0.26	-0.53-0.015	0.064	-0.155	-0.44-0.13	0.28		
Sex Hormones adjusted for each other plus covariates								
T	-0.048	-0.27-0.18	0.67	-0.026	-0.25-0.20	0.82		
E2	-0.027	-0.21-0.17	0.79	-0.054	-0.24-0.14	0.58		
DHEA	-0.17	-0.43-0.099	0.22	-0.16	-0.43-0.10	0.23		
SHBG	-0.29	-0.57- -0.006	0.045	-0.18	-0.46-0.11	0.23		
B.	Men (Model 1)				Men (Model 2)			
	Sex Hormones analyzed separately plus covariates				Sex Hormones analyzed separately plus covariates			
	β	95% CI	p-value	β	95% CI	p-value	β	p-value
T	-0.112	-0.36-0.14	0.38	-0.064	-0.32-0.18	0.61		
E2	-0.092	-0.38-0.19	0.53	-0.119	-0.40-0.16	0.41		
DHEA	-0.0005	-0.28-0.27	0.997	0.0322	-0.24-0.30	0.82		
SHBG	-0.061	-0.39-0.27	0.72	0.0478	-0.28-0.38	0.78		
Sex Hormones adjusted for each other plus covariates								
T	-0.095	-0.38-0.18	0.50	-0.06	-0.34-0.22	0.67		
E2	-0.043	-0.35-0.26	0.78	-0.096	-0.40-0.21	0.53		
DHEA	0.0093	-0.27-0.29	0.95	0.055	-0.22-0.33	0.70		
SHBG	-0.021	-0.37-0.33	0.91	0.081	-0.27-0.44	0.65		

*Model 1: adjusted for age, race, BMI, systolic BP, diastolic BP, use of BP meds, diabetes, former and current smoking, HT use (women only), and physical activity

*Model 2: adjusted for all Model 1 variables, total cholesterol, HDL-c, and use of cholesterol-lowering medications