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ENDOGENOUS SEX HORMONES, BLOOD PRESSURE CHANGE, AND RISK OF HYPERTENSION IN POSTMENOPAUSAL WOMEN: THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

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Abstract

Objective—Sex steroid hormones have been postulated to involve in blood pressure (BP) regulation. We examine the association of endogenous sex hormone levels with longitudinal change of BP and risk of developing hypertension in initially normotensive postmenopausal women.

Methods—We conducted prospective analysis among 619 postmenopausal women free of hypertension at baseline in the Multi-Ethnic Study of Atherosclerosis (MESA). Change of BP and development of incident hypertension were assessed during a mean of 4.8 years follow-up.

Results—After adjusting for age, race/ethnicity, and lifestyle factors, baseline serum estradiol (E₂), total and bioavailable testosterone (T), dehydroepiandrosterone (DHEA) were each positively and sex- hormone binding globulin (SHBG) was inversely associated with risk of hypertension. Additional adjustment for body mass index eliminated the associations for E₂ and T

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None.

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but only attenuated the associations for DHEA and SHBG. The corresponding multivariable hazard ratios (95% CIs) in the highest quartile were 1.28 (0.83–1.97) for E₂, 1.38 (0.89–2.14) for total T, 1.42 (0.90–2.23) for bioavailable T, 1.54 (1.02–2.31) for DHEA, and 0.48 (0.30–0.76) for SHBG. Adjustment for fasting glucose, insulin, and C-reactive protein further attenuated the association for DHEA but not SHBG. Associations of sex hormones with longitudinal BP change were similar.

Conclusion—In postmenopausal women, higher endogenous E₂, T, and DHEA and lower SHBG were associated with higher incidence of hypertension and greater longitudinal rise in BP. The associations for E₂, T, and DHEA were mostly explained by adiposity, while the association for SHBG was independent of measures of adiposity, insulin resistance, and systemic inflammation.

Keywords

sex steroid hormones; hypertension; blood pressure; postmenopausal women; prospective study; epidemiology

Introduction

High blood pressure (BP) is one of the largest contributors to death in the U.S. and worldwide [1]. BP differs by sex [2], which may be explained partly by endogenous sex steroid hormones. Evidence from laboratory studies shows that both estrogens and androgens can affect BP. Estrogens can promote vasodilation and lower BP [3]; whereas estrogens may also cause impairment in insulin signaling pathway [4], affect normal immune function [5], and induce cytokine activities [6], subsequently raise BP. Androgens also have been shown to activate both vasoconstricting [7] and vasorelaxing [8] mechanisms.

Epidemiologic studies that examined the relations between circulating sex hormone levels and BP or hypertension status are largely confined to cross-sectional studies and retrospective case-control studies, with inconsistent results. In women, higher estradiol (E₂) levels were found among those with elevated BP or hypertension than those with normal BP in some [9], but not all [10, 11] studies. Similarly, total or free testosterone (T) concentrations were positively correlated with BP among postmenopausal women in some studies [11, 12] but not in others [13]. Sex-hormone binding globulin (SHBG), a serum protein that affects free circulating sex hormone levels [14], has been shown either not associated [9, 10] or inversely associated [12] with BP in women.

To further evaluate the possible role of sex steroid hormones in BP regulation and development of hypertension, we examined the prospective associations of baseline serum concentrations of endogenous sex hormones, including E₂, T, dehydroepiandrosterone (DHEA, a pre-androgen), and SHBG, with the subsequent change of BP and the incidence of hypertension among postmenopausal women free of baseline hypertension.

Materials and Methods

Study Subjects

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter, prospective cohort study of subclinical cardiovascular disease (CVD). Study design has been described in detail elsewhere [15]. In brief, 6,814 men and women from 4 ethnic origins (Caucasian, African American, Hispanic, and Asian American), aged 45–84 years and free of clinically diagnosed CVD, were enrolled from 6 US field centers. The baseline, second, third, and fourth clinic examination took place from 2000 through 2002, 2002 through 2004, 2004

through 2005, and 2005 through 2007, respectively. The study procedures were approved by Institutional Review Boards at all participating sites. All participants provided written consent. For the current study, we considered 3199 postmenopausal female participants in the MESA, excluding those with baseline hypertension (n=1,556) and those who had ever used hormone replacement therapy (n=1,526), had no sex hormone measurements (n=303), or had insufficient information to ascertain incident hypertension status during follow-up (n=222). As a result, 619 postmenopausal women remained for analyses, of whom 595, 570, and 558 attended the second, third, and fourth examination, respectively.

Measurement of Blood Pressure and Ascertainment of Hypertension

At baseline and each follow-up examination, physician diagnosis of hypertension was obtained from self-report, use of BP-lowering medications was assessed by reviewing participants' medications brought to clinic, and resting seated BP was measured three times in the right arm using a Dinamap model Pro 100 automated sphygmomanometer (Critikon, Tampa, FL), with average of the last two readings used for analysis. Hypertension was defined as measured systolic BP (SBP) ≥ 140 mmHg, or diastolic BP (DBP) ≥ 90 mmHg, or using medications for physician diagnosed hypertension. Incident hypertension was defined as newly developed hypertension during follow-up among those free of hypertension at baseline. Time of event was assigned to the mid-point between the last visit without hypertension and the first visit with hypertension.

Measurement of Sex Hormones

Fasting blood samples were obtained from participants between 7:30 and 10:30 AM at baseline examination. Serum samples were extracted by centrifugation at $2000 \times g$ for 15 min or $3000 \times g$ for 10 min, immediately frozen at -70°C , and then shipped to the University of Vermont for long-term storage and future analyses. Serum sex hormone concentrations were measured in the Sex Hormone Laboratory at the University of Massachusetts Medical Center in Worcester, MA. Total E_2 was measured using an ultrasensitive RIA kit from Diagnostic Systems Laboratory (Webster, TX). Total T and DHEA were measured directly using RIA kits. SHBG was measured by chemiluminescent enzyme immunoassay using Immulite kits from Diagnostic Products Corp. (Los Angeles, CA). Concentrations of free T, SHBG-bound T, and albumin-bound T were calculated according to the method of Södergard *et al* [16]. Bioavailable T was determined as total T minus SHBG-bound T. Calculated bioavailable T has been shown to be comparable to free T concentration obtained by equilibrium dialysis [17]. Assay quality was blindly monitored by assessing 5% randomly selected duplicate participant samples and quality control sera included with the kits. The overall coefficients of variation for total E_2 , total T, DHEA, and SHBG were 10.5, 12.3, 11.2 and 9.0%, respectively.

Assessment of Other Covariates at Baseline

Participants came to clinic examinations after an 8- to 12-h overnight fast. Information on demographics, lifestyle factors, reproductive history, and medical history were collected from standardized questionnaires. Physical activity was assessed using the MESA Typical Week Physical Activity Survey, which was adapted from the Cross-Culture Activity Participation Study [18] and designed to assess the time spent in and frequency of various physical activities during a typical week in the past month. [19] Smoking and alcohol consumption were self-reported. Anthropometrics including weight, height, and waist circumference were measured using standard protocols as described previously [15]. Body mass index (BMI) was calculated. Serum concentrations of fasting glucose (by the glucose oxidase method using a Vitros 950 analyzer, Johnson & Johnson Ortho-Clinical Diagnostics, Rochester, NY), fasting insulin (by a radioimmunoassay method using the Linco Human Insulin Specific RIA kit, Linco Research, Inc., St. Charles, MO), and C-reactive protein

(CRP) (using the BNII nephelometer, N High-Sensitivity CRP, Dade Behring Inc., Deerfield, IL) were measured at central laboratory.

Statistical Analyses

Analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC). Distribution of each biomarker was checked for outliers, and logarithmic transformation was used to normalize skewed distributions for computation of means. Hypertension risk factors and sex hormone concentrations at baseline were compared between women who developed incident hypertension and those who did not. Cox regression was performed to calculate hazard ratios (HRs) and 95% CIs of incident hypertension according to quartiles of sex hormones. Covariates, including age, race/ethnicity, age at menopause, smoking status, alcohol use, physical activity, and BMI, were sequentially controlled for. Fasting glucose, fasting insulin, and CRP were added lastly as potential explanatory factors. Analyses were also stratified by race/ethnicity, baseline BMI, baseline BP, and interactions by these factors were tested.

In addition, longitudinal change of BP from baseline to each follow-up examination was compared across quartiles of sex hormone variables, using PROC MIXED models with an unstructured covariance matrix for repeated measures. For women who started anti-hypertensive treatment, we imputed the untreated BP at the first visit when hypertension was detected by adding 15 mmHg and 10 mmHg to the measured SBP and DBP, respectively, and assigned BP at all following examinations to missing. Previous simulation studies have demonstrated that addition of a sensible constant to the observed BP is an appropriate method to adjust for the underlying BP in treated subjects [20].

Sensitivity analyses were performed. First, we included women who had previously used hormone replacement therapy but had stopped for 1 year; second, we excluded women with baseline diabetes; third, we substituted waist circumference for BMI as a measure of adiposity; fourth, we adjusted for BMI or waist circumference with quadratic terms; fifth, we added a constant of other values to impute untreated BP; finally, we additionally adjusted for baseline BP. All sensitivity analyses obtained results generally similar to main analyses, and therefore are not presented.

Results

The mean (SD) age of 619 postmenopausal women free of hypertension at baseline was 63.5 (9.1) years. The time after menopause was 10 years for 63.5% and 20 years for 34.1% of women. Over a mean of 4.8 (maximum: 6.7) years follow-up, 194 women developed incident hypertension. As expected, women who developed hypertension were significantly older, more likely in the late postmenopausal period, and had higher BP at baseline than those who remained free of hypertension. (Table 1) Hypertension cases also had higher baseline BMI, waist circumference, fasting glucose, fasting insulin, and CRP. In univariate analyses, compared with women who did not develop incident hypertension, those who developed hypertension had similar baseline concentrations of E₂ and DHEA, significantly higher total T and bioavailable T, and significantly lower SHBG. (Table 1)

The characteristics of baseline hypertension risk factors according to quartiles of sex hormone variables are shown in Supplement Table. Women were on average younger, presumably closer to menopause, in higher quartiles of E₂, bioavailable T, and DHEA, but were older in higher quartiles of SHBG. BMI was greater with higher E₂, total T, and bioavailable T, while lower with higher SHBG. E₂, total T and DHEA seem to have a graded, positive relation with smoking; a similar trend was seen for alcohol in relation to E₂. No other consistent relations were found for smoking, alcohol, and physical activity. Without adjustment, E₂, bioavailable T, and DHEA were positively related to fasting

glucose, fasting insulin, and CRP, while SHBG was strongly and inversely related to these biomarkers.

After adjusting for age and race/ethnicity, E₂, total T, bioavailable T, and DHEA were each positively associated, while SHBG was inversely associated with risk of hypertension. (Table 2) Adjustment for hypertension-related lifestyle factors including cigarette smoking, alcohol use, and physical activity (multivariable model 1) did not materially change these associations. Additional adjustment for BMI eliminated the associations for E₂, total T, and bioavailable T, but not for DHEA and SHBG. The corresponding multivariable-adjusted HRs and 95% CIs in the highest versus the lowest quartile were 1.28 (0.83–1.97) for E₂, 1.38 (0.89–2.14) for total T, 1.42 (0.90–2.23) for bioavailable T, 1.54 (1.02–2.31) for DHEA, and 0.48 (0.30–0.76) for SHBG. Adjustment for fasting glucose, fasting insulin, and CRP (multivariable model 2) further attenuated the HR in the highest quartile of DHEA, while the inverse association for SHBG remained strong, graded, and significant.

We also examined the longitudinal change of BP from baseline through the last follow-up in relation to sex hormone levels. (Table 3) After adjusting for age and race/ethnicity, the increment of SBP and/or DBP over time tended to be greater in the higher quartiles of E₂, total T, bioavailable T, and DHEA while the BP increase was smaller across increasing quartiles of SHBG. Adjustment for BMI eliminated the associations for E₂, total T, and bioavailable T, but not for DHEA and SHBG. Further adjustment for fasting glucose, fasting insulin, and CRP continued attenuating the association for DHEA, while the association for SHBG remained strong and highly significant. When BP levels at baseline and at each follow-up examination were compared between quartiles of SHBG, a consistent, graded pattern was observed, i.e. the increment of SBP and DBP over time was smaller with higher concentrations of baseline SHBG. (Figure 1)

When we stratified analyses by race/ethnicity, we found only modest differences in concentrations of sex hormones between 4 race/ethnicity groups (data not shown). The inverse association between SHBG and risk of hypertension was generally consistent in all race/ethnicity groups, except for Asian Americans for whom the number of cases was small. (Figure 2) The association of E₂ with risk of hypertension appeared to differ by race/ethnicity, but the test for interaction was not statistically significant after considering multiple comparisons. No association differed significantly by baseline BMI or baseline BP (all *p* for interaction > 0.05).

Discussion

In this prospective study among postmenopausal women without baseline hypertension, higher baseline concentrations of endogenous E₂, total and bioavailable T, and DHEA and lower concentration of SHBG were associated with a higher incidence of hypertension and a greater increase in BP during follow-up. The associations for E₂ and T were eliminated and the association for DHEA was attenuated by adjustment for BMI, whereas the association for SHBG remained strong and significant after adjusting for BMI, fasting glucose, fasting insulin, and CRP.

The observation of BP variation during episodes of estrogen level change in women has led to the hypothesis that estrogens are involved in BP regulation. Data from *in vivo* and *in vitro* studies have provided evidence for E₂ – the most potent estrogen in humans – being a vasodilator [3], which will potentially lower BP. However, E₂ may also induce insulin resistance and thereafter tend to raise BP. High levels of E₂ in physiological states, such as puberty, luteal phase of menstrual cycle, and late pregnancy, are associated with insulin resistance [4]. There are epidemiologic studies [21, 22], including MESA [21], showing a

strong association between E_2 and measures of insulin resistance in postmenopausal women, independent of adiposity. Estrogen may also increase BP through pro-inflammatory activities. Metabolism of estrogens is altered in patients with systemic immune disease such as lupus erythematosus.[5] In postmenopausal women that received hormone replacement therapy, estrogen therapy increased mononuclear cell secretion of tumor necrosis factor alpha (TNF- α).[6] In at least one population-based study, estrone levels were positively associated with inflammatory markers in postmenopausal women [23]. Previous studies on circulating estrogens in relation to BP have mainly used cross-sectional design. One study found higher plasma E_2 in 24 hypertensive men and women compared with 24 normotensive controls [9]. However, other studies found no such associations in premenopausal [10] and postmenopausal women [11]. Our study showed that postmenopausal women with higher baseline E_2 had increased risk of hypertension and greater BP rise with aging, whereas the association was eliminated by adjustment for BMI. The relation between estrogens and adiposity is likely bidirectional. E_2 can be synthesized from aromatization of T in adipocytes. In postmenopausal women, the major source of circulating E_2 is derived from the extragonadal conversion of androgen precursors in adipose tissue, with the degree of conversion increasing with the growth of fat mass.[24] On the other hand, some animal studies showed that E_2 has direct effects on adipocyte enlargement and weight gain [25]. Because of this bidirectional relation, obesity could be either a confounder or a mediating factor in the link between estrogens and hypertension.

Findings that BP is reduced in male animal models by castration suggest that androgens also control BP, at least in men [26]. Experimental studies show that the most potent androgen – T – can activate both vasoconstriction [7] and vasorelaxation [8]. The balance between the two mechanisms determines the net effect on vascular tone and BP. T may also stimulate cardiac hypertrophy [27], impair insulin sensitivity [28], and increase central adiposity [29]. These effects tilt the cardiovascular system toward a pro-hypertensive state. Previous studies of circulating androgens in relation to BP have also been cross-sectional. Among postmenopausal women, serum T was elevated in hypertensive participants [9, 11, 12], and total T, free T, and DHEA were positively correlated with SBP [11, 12]. Our study extends prior cross-sectional findings to a prospective setting. Similar to E_2 , the associations for T and DHEA were attenuated by adjustment for BMI, reflecting either a confounding or a mediating effect of obesity.

SHBG, produced by the liver, is the major circulating protein that binds to and transports steroid sex hormones. According to the free-hormone hypothesis, SHBG-bound sex hormone is unavailable to the target tissues. Because the affinity of SHBG to T is higher than to E_2 , SHBG is conventionally considered an indirect indicator of androgenicity, with its concentrations mainly inversely correlated with free T [14]. Evidence emerged recently for low SHBG as an independent predictor of adverse cardiometabolic outcomes. Compared with the accumulating findings on metabolic syndrome [30] and type 2 diabetes [31], the relation of SHBG with risk of hypertension has not been well studied. Previous cross-sectional studies showed either null [9–11] or inverse [12] association between SHBG and BP among men and women. In the current prospective study of postmenopausal women, we found that SHBG concentration was inversely associated with risk of hypertension and longitudinal rise of BP over time. These associations were strong, monotonic, and independent of known hypertension risk factors including measures of obesity.

The exact biologic mechanisms underlying the association between SHBG and cardiometabolic disorders remain largely unknown. In addition to a direct impact on the bioavailability of E_2 and T, SHBG has been postulated as a marker for insulin resistance. *In vitro* studies showed that insulin inhibits SHBG production from hepatoma cells [32]. In intervention studies, successful weight loss and weight maintenance increased SHBG in men

with obesity [33]; suppression of insulin secretion by diazoxide treatment led to increased SHBG levels in both non-diabetic obese men and normal weight men [34]. These findings support a down-regulating effect of insulin on SHBG production. SHBG also inversely correlates with inflammatory markers [35], indicating that a suppressive effect of cytokines on hepatic SHBG synthesis is possible. Consistent with previous observations, our study found inverse relations of SHBG with measures of obesity, insulin resistance, and inflammation. However, adjustment for these factors only slightly attenuated the strong relation between SHBG and hypertension risk, which suggest an independent role of SHBG in the prevention of hypertension.

Several limitations of this study deserve considerations. First, we had only a single baseline measurement of sex hormones, and we lacked information on BP or hypertension status between follow-up examinations. Any random misclassification in these measurements would tend to bias the associations towards null. Second, our study is observational, and thus, although we have adjusted for many covariates, residual confounding cannot be ruled out. Third, since we simultaneously examined several sex hormone variables, false positive findings due to multiple testing are possible. Finally, our study results apply only to postmenopausal women not on hormone therapy. The age range of MESA participants (45–84 years) does not provide us with enough power to assess the association of interest in premenopausal women, which may be different from postmenopausal women.

In conclusion, we found that in a prospective cohort of postmenopausal women without baseline hypertension, higher serum concentrations of endogenous E_2 , total and bioavailable T, and DHEA and lower concentration of SHBG were each associated with increased risk of hypertension and greater BP rise over time. The associations with E_2 , T, and DHEA were mostly explained by adiposity, while the association with SHBG was independent of measures of adiposity, insulin resistance, and systemic inflammation. Further studies are needed to identify direct biological effect of SHBG on hypertension and other atherosclerotic disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Higher endogenous sex hormones were associated with higher risk of hypertension
- Lower sex-hormone binding globulin was associated with higher risk of hypertension
- Associations for sex hormones were mostly explained by adiposity
- Association for sex-hormone binding globulin was independent of adiposity

Figure 1.

Adjusted mean systolic and diastolic blood pressure (BP) at baseline (1) and follow-up (2, 3, 4) visits by quartiles of sex hormone binding globulin (SHBG) were computed using PROC MIXED models with an unstructured covariance matrix for repeated measures. For women who started anti-hypertensive treatment, the untreated BP at the first visit when hypertension was detected was imputed by adding 15 mmHg and 10 mmHg to the measured systolic and diastolic BP, respectively, and BPs at all following visits were assigned to missing. Model adjusted for age, race/ethnicity, age at menopause, cigarette smoking, alcohol use, physical activity, and body mass index.

Figure 2.

Hazard ratio and 95% CI of hypertension across quartiles of sex hormone binding globulin (SHBG) in 4 race/ethnicity groups. N shown in parentheses indicates the numbers of cases/total participants at risk. P, trend was tested using the median value in each quartile of SHBG as ordinal variable. Multivariable model in Figure 1 without race/ethnicity was used.

Table 1

Baseline characteristics of postmenopausal women who developed incident hypertension compared to those who remained free of hypertension, MESA 2000–2007.

Characteristics	Incident HTN (N=194)	No HTN (N=425)	P ^a
Systolic blood pressure, mmHg	125.2±0.77 ^b	111.3±0.61	< 0.0001
Diastolic blood pressure, mmHg	68.6±0.57	63.7±0.39	< 0.0001
Age, years	66.0±0.62	62.3±0.44	< 0.0001
Age at menopause, years	47.8±0.47	48.1±0.29	0.59
Years after menopause, %			< 0.0001
<5 years	10.8	24.7	
5–<10 years	15.0	16.7	
10–<20 years	27.8	30.1	
≥20 years	46.4	28.5	
Race/ethnicity, %			0.35
Caucasian	32	32	
African American	25	20	
Hispanic	28	28	
Asian American	15	20	
Cigarette smoking, %			0.97
Current	12.4	12.5	
Former	24.7	23.8	
Never	62.9	63.7	
Alcohol use, %			0.60
Current	43.8	45.3	
Former	22.2	18.7	
Never	34.0	36.0	
Physical activity, MET-min/week	1208±116.2	1354±100.1	0.34
Adiposity			
Body mass index, kg/m ²	29.2±0.43	27.4±0.27	0.0002
Waist circumference, cm	98.3±1.07	93.9±0.69	0.0005
Metabolic and inflammatory markers ^c			
Fasting glucose, mg/dL ^d	97.3 (85, 101)	90.7 (81, 94)	0.001
Fasting insulin, mU/L	5.90 (3.90, 8.60)	4.95 (3.40, 7.40)	0.0006
C-reactive protein, mg/L ^e	2.39 (1.09, 5.58)	1.76 (0.72, 3.97)	0.003
Sex hormone variables ^c			
E ₂ , nmol/L	0.053 (0.040, 0.081)	0.054 (0.037, 0.081)	0.75
Total T, nmol/L	0.98 (0.73, 1.35)	0.88 (0.59, 1.28)	0.03
Bioavailable T, nmol/L	0.28 (0.17, 0.42)	0.23 (0.14, 0.38)	0.002
DHEA, nmol/L	11.2 (7.84, 16.2)	10.9 (7.95, 15.5)	0.57
SHBG, nmol/L	46.8 (35.1–62.3)	52.5 (36.7, 72.4)	0.005

^aP values are derived from *t*-test for continuous variables and χ^2 test for categorical variables.

^bMean±standard error and all such values

^cGeometric means (interquartile range) are shown for all biomarkers because of the skewed distribution.

Table 2

Hazard ratios and 95% confidence intervals (CI) of incident hypertension according to quartiles of baseline sex hormone variables, MESA 2000–2007.

Sex Hormones	N of case/total	Hazard ratios (95% CI)			
		Age, race/ethnicity adjusted		Multivariable model 1 ^a + BMI	
		Multivariable model 1 ^a	Multivariable model 2 ^b	Multivariable model 1 ^a	Multivariable model 2 ^b
E2					
Q1	46/121	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	50/103	1.28 (0.86–1.92)	1.27 (0.85–1.92)	1.28 (0.85–1.92)	1.20 (0.79–1.81)
Q3	47/89	1.51 (1.00–2.29)	1.53 (1.01–2.32)	1.39 (0.91–2.13)	1.34 (0.87–2.05)
Q4	51/112	1.50 (1.00–2.25)	1.51 (0.99–2.29)	1.28 (0.83–1.97)	1.14 (0.74–1.77)
P, trend ^c		0.047	0.046	0.29	0.58
Total T					
Q1	36/120	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	46/100	1.48 (0.96–2.30)	1.37 (0.88–2.14)	1.26 (0.81–1.99)	1.29 (0.82–2.03)
Q3	61/105	1.87 (1.24–2.84)	1.74 (1.15–2.64)	1.62 (1.06–2.46)	1.64 (1.08–2.51)
Q4	51/100	1.60 (1.04–2.47)	1.51 (0.97–2.33)	1.38 (0.89–2.14)	1.33 (0.86–2.08)
P, trend ^c		0.04	0.07	0.16	0.22
Bioavailable T					
Q1	36/113	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	50/119	1.25 (0.82–1.92)	1.21 (0.78–1.87)	1.12 (0.72–1.75)	1.08 (0.69–1.69)
Q3	57/102	1.71 (1.13–2.61)	1.66 (1.08–2.55)	1.49 (0.97–2.31)	1.42 (0.92–2.20)
Q4	51/91	1.76 (1.15–2.71)	1.67 (1.08–2.58)	1.42 (0.90–2.23)	1.27 (0.80–2.02)
P, trend ^c		0.007	0.01	0.11	0.27
DHEA					
Q1	50/104	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	46/110	1.04 (0.69–1.56)	0.94 (0.62–1.43)	0.91 (0.60–1.38)	0.83 (0.54–1.26)
Q3	41/112	1.07 (0.69–1.64)	1.00 (0.65–1.55)	0.93 (0.60–1.44)	0.87 (0.56–1.34)
Q4	57/99	1.68 (1.12–2.51)	1.59 (1.06–2.38)	1.54 (1.02–2.31)	1.38 (0.92–2.08)
P, trend ^c		0.01	0.02	0.02	0.07
SHBG					
Q1	54/101	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	63/92	1.05 (0.72–1.51)	1.03 (0.71–1.50)	1.05 (0.72–1.52)	1.16 (0.79–1.70)

Sex Hormones	N of case/total	Hazard ratios (95% CI)			
		Age, race/ethnicity adjusted	Multivariable model 1 ^a	Multivariable model 1 ^a + BMI	Multivariable model 2 ^b
Q3	42/111	0.59 (0.39–0.89)	0.57 (0.37–0.86)	0.60 (0.39–0.91)	0.67 (0.43–1.03)
Q4	35/121	0.43 (0.28–0.67)	0.42 (0.27–0.66)	0.48 (0.30–0.76)	0.54 (0.33–0.88)
P, trend ^c		< 0.0001	< 0.0001	0.0003	0.002

^aMultivariable model 1 adjusted for age (continuous), race/ethnicity (Caucasian, African American, Hispanic, Asian American), age at menopause (continuous), cigarette smoking (current, former, never), alcohol use (current, former, never), physical activity (quartiles).

^bMultivariable model 2 adjusted for variables in model 1 plus BMI and serum concentrations of fasting glucose, fasting insulin, and C-reactive protein (all continuous).

^cP, trend was tested using the median value in each quartile of the sex hormone variables as ordinal variables.

Table 3

Mean±standard error of systolic blood pressure (SBP) / diastolic blood pressure (DBP) change from baseline to the last follow-up visit according to quartiles of baseline sex hormone variables, MESA 2000–2007

Sex Hormones	SBP change ^a			DBP change ^a		
	Age, race/ethnicity adjusted	Multivariable model 1 ^b + BMI	Multivariable model 2 ^c	Age, race/ethnicity adjusted	Multivariable model 1 ^b + BMI	Multivariable model 2 ^c
E2						
Q1	5.71±1.34	6.40±1.38	6.71±1.36	0.68±0.62	0.85±0.64	0.95±0.64
Q2	8.19±1.43	8.22±1.44	8.10±1.42	1.76±0.66	1.75±0.67	1.71±0.66
Q3	7.09±1.51	7.23±1.52	7.11±1.50	2.49±0.70	2.53±0.71	2.53±0.70
Q4	7.18±1.38	6.67±1.44	6.33±1.42	1.78±0.64	1.62±0.67	1.47±0.66
P, trend ^d	0.59	0.97	0.73	0.23	0.40	0.57
Total T						
Q1	5.76±1.34	6.35±1.39	6.25±1.36	0.69±0.62	0.86±0.64	0.88±0.64
Q2	7.49±1.45	7.39±1.48	7.31±1.46	1.82±0.68	1.81±0.69	1.79±0.68
Q3	8.04±1.39	8.14±1.40	8.08±1.38	2.19±0.65	2.22±0.65	2.20±0.65
Q4	6.77±1.44	6.54±1.45	6.50±1.44	1.85±0.67	1.67±0.68	1.63±0.68
P, trend ^d	0.66	0.95	0.92	0.23	0.43	0.46
Bioavailable T						
Q1	5.58±1.40	6.66±1.47	6.77±1.45	0.68±0.65	1.09±0.68	1.18±0.68
Q2	7.43±1.32	7.51±1.33	7.44±1.31	2.06±0.61	1.99±0.62	1.99±0.61
Q3	7.24±1.43	7.22±1.45	6.94±1.43	1.50±0.67	1.46±0.68	1.30±0.67
Q4	7.75±1.48	6.98±1.50	6.96±1.50	2.20±0.69	1.93±0.70	1.96±0.70
P, trend ^d	0.37	0.98	0.97	0.21	0.56	0.60
DHEA						
Q1	5.21±1.46	5.44±1.50	5.76±1.48	0.31±0.68	0.49±0.69	0.63±0.69
Q2	7.13±1.40	7.25±1.43	7.00±1.41	1.59±0.65	1.48±0.66	1.36±0.66
Q3	5.73±1.37	5.84±1.38	5.74±1.36	1.02±0.63	0.99±0.64	0.97±0.64
Q4	9.66±1.40	9.52±1.40	9.35±1.38	3.48±0.65	3.44±0.65	3.37±0.65
P, trend ^d	0.05	0.08	0.11	0.002	0.004	0.006
SHBG						

Sex Hormones	SBP change ^d		DBP change ^d	
	Age, race/ethnicity adjusted		Age, race/ethnicity adjusted	
	Multivariable model 1 ^b + BMI	Multivariable model 2 ^c	Multivariable model 1 ^b + BMI	Multivariable model 2 ^c
Q1	11.36±1.41	10.74±1.46	3.39±0.66	3.15±0.69
Q2	6.66±1.44	6.80±1.47	1.52±0.68	1.62±0.69
Q3	7.15±1.34	7.21±1.35	1.54±0.63	1.58±0.63
Q4	2.67±1.35	3.50±1.43	0.085±0.63	0.22±0.68
P, trend ^d	< 0.0001	0.001	0.0009	0.006
		0.002		0.007

^aLongitudinal change of BP from baseline to each follow-up visit was computed using PROC MIXED models with an unstructured covariance matrix for repeated measures. For women who developed incident hypertension and were on anti-hypertensive treatment, the untreated BP at the first visit when hypertension was detected was imputed by adding 15 mmHg for SBP and 10 mmHg for DBP to the measured BP, and BP at all following visits were assigned to missing.

^bMultivariable model 1 in Table 2 was used.

^cMultivariable model 2 in Table 2 was used.

^dP, trend was tested using the median value in each quartile of the sex hormone variables as ordinal variables.