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Prospective study of endogenous hormones and incidence of venous thromboembolism: the Atherosclerosis Risk in Communities Study

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Summary

Exogenous hormone treatments in women [oral contraceptives and hormone replacement therapy (HRT)] are established risk factors for venous thromboembolism (VTE), but less is known about associations between plasma levels of endogenous hormones and VTE risk. We examined the association of baseline dehydroepiandrosterone sulfate (DHEAS), testosterone, and sex hormone-binding globulin (SHBG) with risk of future VTE in men and postmenopausal women in the Atherosclerosis Risk in Communities (ARIC) Study. Testosterone, DHEAS, and SHBG were measured in plasma samples collected in 1996–98. Cox proportional hazards models were used to estimate hazard ratios (HRs) for incident VTE adjusting for age, race/ethnicity, body mass index, height, smoking, estimated glomerular filtration rate, and C-reactive protein. All analyses were stratified by sex and by current HRT use in women. Among 3,051 non HRT-using women, 1,414 HRT-using women, and 3,925 men at risk at baseline, 184, 62, and 206 experienced incident VTE after a median follow-up of 17.6 years. Plasma hormones were not associated with incidence of VTE among men and non HRT-using women, although lower plasma DHEAS, when modeled using quartiles or restricted cubic splines, was associated with higher risk of VTE among HRT-using women. This study does not support the existence of an important association between

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Conflicts of Interest

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plasma concentrations of endogenous testosterone, DHEAS, or SHBG with risk of VTE in middle-aged to older men or postmenopausal women not using HRT.

Keywords

deep vein thrombosis; pulmonary embolism; epidemiologic studies; risk factors; hormones

Introduction

It is well-established that exogenous hormones treatments in women, including oral contraceptives and hormone replacement therapy, are risk factors for venous thromboembolism (VTE) in women.(1) Less is known regarding the associations between endogenous levels of steroid hormones and the risk of VTE in postmenopausal women and men, with only a few studies available on levels of two androgenic hormones, testosterone and dehydroepiandrosterone sulfate (DHEAS), and the transporter protein sex-hormone binding globulin (SHBG).

There is good mechanistic reasoning to hypothesize that these endogenous hormone levels would be associated with the development of VTE. In men, low endogenous testosterone was associated with higher von Willebrand factor (vWF)(2) and lower tissue factor pathway inhibitor (TFPI),(3) both of which are VTE risk factors.(4,5) In men, low endogenous testosterone was also associated with higher levels of factor VII activity,(6) fibrinogen,(7) plasminogen activator inhibitor 1 (PAI-1),(8,9) and α_2 -antiplasmin,(6) suggesting a generalized hypercoagulable state with low endogenous testosterone. The relationship between endogenous testosterone and hemostasis is less clear in women (who have low testosterone concentrations); one study reported higher endogenous testosterone was associated with higher PAI-1 and tissue plasminogen activator (tPA) antigen,(10) possibly reflective of hypofibrinolysis.(11)

High endogenous DHEAS is associated with a variety of biomarkers that may not be specifically relevant to the etiology of VTE, including lower thrombin generation,(12) higher fibrinogen,(13,14) and higher tPA antigen and PAI-1(10) in women and lower fibrinogen in men.(7) Nevertheless, DHEAS levels decline substantially with age in women and men(15) and may represent an inverse marker of mortality risk.(16) Because VTE risk is also age related, it is possible that lower DHEAS is associated with the incidence of VTE.

In women, high endogenous SHBG was associated with higher D-dimer, vWF, and factor VIII,(14) all of which are risk factors for VTE.(4,17–19) High SHBG was also associated with lower PAI-1 and tPA antigen, possibly reflective of increased fibrinolytic activity, but also with lower factor VIIc.(10,14) Oral contraceptive formulations that lead to greater increases in SHBG are associated with greater VTE risk than other oral contraceptives.(20,21) An explanation for this association may be that the oral contraceptive-related increase in SHBG correlates positively with changes in activated protein C resistance,(22) a risk factor for VTE.(23) Studies involving SHBG and hemostatic factors in men are limited; one study found that high endogenous SHBG was associated with lower PAI-1.(9)

Only two prospective studies(24,25) and one small case-control study in women(26) have examined endogenous testosterone and SHBG, respectively, as risk factors for VTE. We are not aware of any studies on the relationship between endogenous DHEAS and VTE. Given all of the above, in the present study, we used data from the Atherosclerosis Risk in Communities Study (ARIC) to investigate whether testosterone, DHEAS, and SHBG are associated with risk of incident VTE. We hypothesized that lower DHEAS and testosterone concentrations and higher SHBG concentration would be associated with higher risk of VTE.

Materials and Methods

Study Population.

ARIC is a prospective multi-center population-based study of the causes of atherosclerosis and its clinical outcomes in a cohort of 15,792 adults from four U.S. communities (Washington County, MD; Forsyth County, NC; Jackson, MS; and Minneapolis, MN).(27) The cohort consists of mostly whites (73%) and African Americans (27%), with slightly more women (55%) than men (45%). The baseline examination (visit 1) occurred in 1987–89 when participants were 45–64 years old, and there have been five re-examinations [visit 2 (1990–92), visit 3 (1993–95), visit 4 (1996–98), visit 5 (2011–13), and visit 6 (2016–2017)] with semiannual to annual telephone contact between and after the examinations. The study was approved by the institutional review board at each site, and all participants provided written informed consent. Participants eligible for this analysis included all men and postmenopausal women who attended visit 4 (1996–98; response rate: 81%) and had stored plasma samples available for the measurement of endogenous hormones.

VTE ascertainment.

During telephone contact, ARIC staff asked participants about all hospitalizations over the previous year. Additional hospitalizations were ascertained via surveillance of local hospital discharge lists, and all International Classification of Diseases (ICD) discharge codes were recorded. Hospital records for possible VTE events were retrieved through 2015. Two physicians independently reviewed the records using standardized criteria and required positive imaging tests for diagnosis of deep vein thrombosis (DVT) and pulmonary embolism, which together comprise VTE.(28) For this study, we restricted DVTs to those occurring in the lower extremity or vena cava, because upper extremity DVTs are rare and have a unique pathophysiology.

Hormone Measurements.

Using EDTA plasma samples stored at -70°C since being collected in 1996–98, endogenous DHEAS, testosterone, and SHBG were measured in 2015–16 in a central laboratory via chemiluminescent microparticle immunoassay on the Architect *i*2000sr instrument (Abbott Laboratories, Abbott Park, IL) according to the manufacturer's specifications. Approximately 396 plasma samples were split at the time of blood draw and then were processed, stored, and analyzed separately as blind duplicates. The inter-assay reliability was fair for DHEAS (coefficient of variation [CV]: 17.0%; Pearson r : 0.95) and testosterone (CV: 19.6%; Pearson r : 0.96) but somewhat less for SHBG (CV: 23.6%; Pearson r : 0.90).

After removal of outlier pairs (difference >3 standard deviations from the mean), inter-assay reliability was good for DHEAS (pairs removed: 8; CV: 6.9%; Pearson R: 0.99), testosterone (pairs removed: 11; CV: 9.3%; Pearson R: 0.99), and SHBG (pairs removed: 8, CV: 15.0%; Pearson R: 0.96). Further details regarding assay validity are provided in Supplementary Methods.

Postmenopausal Status and Hormone Therapy Use.

At visit 4, a trained interview asked questions related to menopause and HRT. Women who reported that they had not menstruated within the two years prior to the visit were identified as postmenopausal, with the exception of women still <55 years old who had a hysterectomy without bilateral oophorectomy that was not preceded by natural menopause (menopausal status could not be determined for these women). Any women who reported that they had a bilateral oophorectomy were also identified as postmenopausal. Women reporting that they had a period within the past two years and that they had not yet reached menopause were identified as premenopausal. Women reporting that they had a period within the past two years and that they had already reached menopause were identified as perimenopausal. Given that few women were premenopausal or perimenopausal (all women were 53 years by visit 4), the analysis in women was limited to those who were postmenopausal at the time of visit 4. Women reporting that they were currently taking oral estrogen or estrogen and progestin medications at visit 4 were identified as HRT users. All other women, including those reporting current use of transdermal estrogen, were identified as non-users of HRT.

Other Covariates.

At visit 4, weight and height were measured by trained technicians, and BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Smoking status was self-reported, and participants were identified as current, former, or never smokers. Glomerular filtration rate (eGFR) was calculated based on serum creatinine.⁽²⁹⁾ Plasma C-reactive protein (CRP) was measured using the CRP-Latex (II) high sensitivity assay from Denka Seiken (Tokyo, Japan).

Exclusions.

From the 11,656 participants who attended visit 4, we iteratively excluded 985 who did not have sex hormone measurements; 30 non-black or non-white participants; 492 pre- or perimenopausal women; 346 users of antineoplastic, corticosteroid, or androgen medications; 286 with a history of VTE; 167 anticoagulant users; 958 with a history of cancer; and 2 without follow-up beyond visit 4, leaving a final analytic sample of 8,390 participants.

Statistical Analysis.

Because of hormonal differences between women and men and between exogenous hormone users and nonusers, analyses were stratified into three groups: postmenopausal women not taking exogenous hormones, postmenopausal women taking exogenous hormones, and men. For descriptive purposes and to identify potential confounding variables, we explored whether DHEAS, testosterone, and SHBG were associated cross-sectionally with other VTE risk factors measured at visit 4 (age, race/ethnicity, BMI, height, smoking, eGFR, and CRP).

We categorized the hormone exposures into quartiles and compared crude means or prevalences of the VTE risk factors across these categories.

We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between hormone exposures and incidence of VTE, separately by each hormone variable and stratum of gender and HRT use. The hormone variables were modeled using restricted cubic splines (with knots at the 5th, 50th, and 95th percentiles of the distributions) and in quartiles. For restricted cubic splines models, statistical significance of the association between hormone concentrations and VTE incidence was determined using a 2 degree of freedom overall test of association. In the quartiles models, we tested for linear trend by including an ordinal variable representing the median of each category. To check whether VTE risk was higher in those with extremely low or high values, we also modeled the hormones using an extreme deciles approach, with groups defined by the 0–10th, 11–90th (reference group), and 91–100th percentiles. We verified the proportional hazards assumption by including an interaction term between the hormone exposures and log-time. For the quartile and extreme decile models, model 1 was adjusted for age and race/ethnicity, and model 2 was additionally adjusted for BMI, height, smoking, eGFR, and CRP.

Given the biological connection between SHBG and testosterone (SHBG regulates the bioavailability of testosterone), we used tensor product splines to assess for potential interactive effects between testosterone and SHBG on the incidence of VTE. Tensor product regression parameters were created by including the one-dimensional restricted cubic spline functions for each hormone variable and cross-product terms between all of the spline components.⁽³⁰⁾ Evidence for interaction was assessed using a 4 degree of freedom general test of interaction.

Results

This analysis included 3,051 non HRT-using women, 1,414 HRT-using women, and 3,925 men who experienced 184, 62, and 206 incident VTE events, respectively, over a median of 17.6 years of follow-up. Black participants comprised 31%, 21%, and 18% of these groups, and the mean baseline ages were 64, 61, and 63 years, respectively.

Means, medians, or prevalences of baseline characteristics are shown across quartiles of endogenous sex hormones separately by sex and HRT status in Tables 1a, 1b, and 1c. All endogenous hormones were positively correlated with current smoking (except for SHBG in HRT-using women). Endogenous testosterone was positively associated with BMI in women, but negatively associated in men. Endogenous SHBG was negatively correlated with BMI in all groups. Endogenous DHEAS was negatively correlated with age and positively correlated with eGFR in all groups. In non-HRT using women, endogenous testosterone and DHEAS were positively (and SHBG was negatively) associated with black race/ethnicity, but these patterns were not consistent among HRT-using women and men.

The associations between plasma concentrations of each hormone, modeled using restricted cubic splines, and the log-hazard of VTE with adjustment for age, race/ethnicity, BMI,

height, smoking, eGFR, and CRP are shown in Figure 1. Results provide little evidence of association between any of the endogenous hormones and risk of VTE, except possibly an association between lower plasma DHEAS and higher plasma SHBG concentrations and increased risk of VTE in HRT-using women. Results when modeling the endogenous hormones using quartiles are shown in Table 2. Compared to women HRT-users in the fourth quartile of DHEAS, VTE risk was 2.5-fold higher among those with DHEAS below the median in the fully adjusted model (P -value for linear trend=0.005). Compared to women HRT-users in the first quartile of SHBG, VTE risk was 2-fold higher among those with in the fourth quartile of SHBG (P -value for linear trend=0.07). When modeling endogenous hormones using an extreme deciles approach, we found no associations with VTE risk, except possibly for an increased risk of VTE among women not using HRT in the upper 10 percent of SHBG compared to those in the middle 80 percent [HR (95% CI): 1.6 (1.0, 2.6); Table 3]. Finally, there was no evidence of interaction in the association between plasma concentrations of testosterone and SHBG with risk of VTE in tensor product spline models (all interaction P -values > 0.44).

Discussion

In this prospective study of postmenopausal women and men, plasma concentrations of endogenous testosterone, DHEAS, and SHBG were generally not associated with incidence of VTE. Some exceptions included possible signals of association between lower plasma DHEAS and higher plasma SHBG with higher VTE risk among HRT-using women. Also, we found no evidence of an interaction in the association between plasma testosterone and SHBG with risk of VTE.

Our null findings on testosterone and VTE risk agree with two prospective studies, one including men and pre- and postmenopausal women not using exogenous hormones(25) and the other including only men,(24) that found no association between endogenous testosterone and future risk of VTE. Our study adds to the literature by also showing no association between endogenous testosterone and VTE risk among HRT-using postmenopausal women. A small case-control study among premenopausal women not using exogenous hormones found no association between endogenous SHBG and VTE risk, (26) and no previous studies have reported on the association of endogenous DHEAS and VTE risk. Therefore, our study is the first to report on the prospective association of endogenous SHBG and DHEAS with risk of VTE among men and postmenopausal women using and not using HRT.

Our findings among HRT-using women that lower plasma DHEAS and higher plasma SHBG were potentially associated with higher risk of VTE is consistent with the hypothesized directions (i.e., consistent with lower DHEAS being associated with increased risk of death in men(16) and with higher SHBG possibly reflecting the estrogenic effect of the HRT and thereby serving as a marker of thrombosis risk, as has been hypothesized for oral contraceptives(20,21,31)). However, there are possible alternative explanations. First, there may be residual confounding and/or misclassification with respect to HRT therapy, because we were unable to account for heterogeneity by drug type and dose, nor for HRT therapy after visit 4, an era when HRT use in the U.S. declined. Second, the apparent

findings may also be due to chance; there were a small number of VTE events among HRT-using women, and we tested multiple hypotheses, so it is possible that these are false positive results.

Our findings suggest that endogenous testosterone, DHEAS, and SHBG are not relevant to the development of VTE among men and postmenopausal women not using HRT, at least with respect to the basal concentrations measured in this study. However, it is still possible that these hormones, particularly testosterone, may play a role in the etiology of VTE at non-physiologic levels (e.g., among exogenous hormone users). In a meta-analysis of three randomized trials with only five VTE events combined, use of exogenous testosterone therapy was associated with increased risk of VTE (OR: 5.94, 95% CI: 1.00, 35.30) compared to placebo.(32) Also, an observational study found a transiently higher risk of VTE in the first six months of starting testosterone therapy (relative risk: 1.63, 95% CI: 1.12, 2.37).(33) Two other observational studies did not find an association between testosterone therapy and VTE risk.(34,35) Given the recent increases in testosterone therapy prescriptions,(36) additional studies are needed to verify a potential association between exogenous testosterone and VTE risk.

One limitation of this study is the single, rather than repeated, measurement of endogenous hormones, especially given higher analytical CVs than might be desired for these analytes. We would have been able to get a more accurate representation of the steady-state mean hormone concentrations of participants if we had taken the average of multiple serum measurements taken a few days apart; an earlier study in men found that day-to-day variation accounts for the largest component of within-person variability in sex hormones.(37) Another year-long study in men found that the month-to-month within-subject CVs for serum testosterone and SHBG were 12.1% and 10.9%, respectively.(38) A second limitation is the use of a direct immunoassay to measure endogenous testosterone, which has poorer specificity and accuracy than liquid chromatography-tandem mass spectrometry.(39) A third limitation is that VTE events were only ascertained by inspection of hospitalization records, meaning sudden fatal VTEs and VTEs treated in the outpatient setting were missed. This could lead to biased results, although pilot data indicate that most ARIC participants with incident VTE occurring between 1999 and 2011 were hospitalized. Third, our power may have been limited to detect weak associations, in part because of our analysis, by necessity, was stratified by sex and HRT use.

In conclusion, this study, along with evidence from a few prior studies,(24–26) does not support the existence of an important association between plasma concentrations of endogenous testosterone, DHEAS, or SHBG with risk of VTE in middle-aged to older men or postmenopausal women not using HRT. Researchers should continue to explore the reasons why VTE risk is increased at non-physiological levels of hormones, including among women taking exogenous estrogen and men using testosterone therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is known on this topic

- Use of exogenous hormones, including oral contraceptives and hormone replacement therapy, is a well-recognized risk factor for VTE in women.
- Plasma concentrations of endogenous hormones, such as testosterone, DHEAS, and SHBG, may also play a role in the development of VTE; however, evidence from prospective studies is limited.

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What this paper adds

- Plasma concentrations of testosterone, SHBG, and DHEAS were not associated with VTE risk in men or women not using hormone replacement therapy.
- This is the first study to report on the prospective association of endogenous SHBG and DHEAS with risk of VTE.
- In women using hormone replacement therapy, lower plasma DHEAS and higher plasma SHBG were potentially associated with higher VTE risk, although these findings need to be confirmed by other studies.

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Figure 1. Associations between hormones (restricted cubic splines) and VTE.

Log hazard ratios (HRs) and 95% confidence intervals of VTE in relation to plasma sex hormone concentrations, adjusted for age, race/ethnicity, body mass index, height, smoking, estimated glomerular filtration rate, and C-reactive protein. Sex hormones are modeled using restricted cubic splines with knots at the 5th, 50th, and 95th percentiles of the distributions. The plots are truncated at the 97.5th percentile. P -values represent the 2 degree of freedom overall test of association between hormones and incidence of VTE.

Table 1a.
Participant characteristics by testosterone.

Characteristics of participants (mean [SD], median [IQR], or %) in relation to quartiles of plasma testosterone concentrations, ARIC, 1996–98.

	Testosterone			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Women (no HRT)	<i>18 ng/dL</i>	<i>18–24 ng/dL</i>	<i>24–33 ng/dL</i>	<i>33+ ng/dL</i>
<i>N</i>	762	762	765	761
Age, years	64 (5)	63 (6)	63 (5)	64 (5)
African American, %	27%	31%	29%	37%
BMI, kg/m ²	28 (6)	29 (6)	30 (7)	31 (7)
Height, cm	161 (6)	161 (6)	161 (6)	161 (6)
Current smoker, %	13%	13%	16%	18%
eGFR, mL/min/1.73 m ²	87 (17)	87 (17)	86 (17)	85 (17)
C-reactive protein, mg/L	2.3 (1.0, 5.1)	2.8 (1.2, 5.9)	2.8 (1.3, 5.6)	3.0 (1.4, 6.6)
Women (HRT)	<i>16 ng/dL</i>	<i>16–22 ng/dL</i>	<i>22–29 ng/dL</i>	<i>29+ ng/dL</i>
<i>N</i>	353	353	354	353
Age, years	62 (5)	61 (5)	61 (5)	61 (5)
African American, %	24%	22%	22%	18%
BMI, kg/m ²	28 (6)	29 (6)	29 (6)	28 (6)
Height, cm	162 (6)	162 (6)	162 (6)	161 (6)
Current smoker, %	9%	11%	13%	15%
eGFR, mL/min/1.73 m ²	89 (16)	90 (15)	89 (15)	88 (15)
C-reactive protein, mg/L	4.7 (2.1, 8.0)	4.6 (2.1, 8.6)	4.1 (2.0, 7.6)	4.2 (2.0, 8.0)
Men	<i>390 ng/dL</i>	<i>391–513 ng/dL</i>	<i>513–663 ng/dL</i>	<i>663+ ng/dL</i>
<i>N</i>	980	981	981	980
Age, years	63 (6)	63 (6)	63 (6)	63 (6)
African American, %	19%	17%	17%	21%
BMI, kg/m ²	31 (5)	29 (4)	28 (4)	26 (4)
Height, cm	175 (6)	175 (7)	176 (6)	176 (7)
Current smoker, %	10%	11%	17%	23%
eGFR, mL/min/1.73 m ²	85 (16)	86 (16)	86 (15)	85 (15)
C-reactive protein, mg/L	2.4 (1.2, 4.9)	1.9 (1.0, 3.8)	1.5 (0.8, 3.0)	1.3 (0.7, 2.8)

SD: standard deviation, IQR: interquartile range, eGFR: estimated glomerular filtration rate

Table 1b.
Participant characteristics by DHEAS.

Characteristics of participants (mean [SD], median [IQR], or %) in relation to quartiles of plasma dehydroepiandrosterone sulfate (DHEAS) concentrations, ARIC, 1996–98.

	DHEAS			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Women (no HRT)	<i>39 µg/dL</i>	<i>39–63 µg/dL</i>	<i>63–95 µg/dL</i>	<i>95+ µg/dL</i>
<i>N</i>	761	761	764	763
Age, years	65 (5)	64 (5)	63 (5)	62 (5)
African American, %	27%	31%	33%	33%
BMI, kg/m ²	29 (6)	30 (7)	30 (6)	30 (7)
Height, cm	160 (6)	161 (6)	162 (6)	162 (6)
Current smoker, %	12%	12%	17%	18%
eGFR, mL/min/1.73 m ²	85 (17)	87 (17)	87 (17)	88 (17)
C-reactive protein, mg/L	2.4 (1.1, 5.3)	2.7 (1.2, 5.4)	2.8 (1.3, 5.7)	3.1 (1.3, 6.6)
Women (HRT)	<i>33 µg/dL</i>	<i>33–52 µg/dL</i>	<i>52–86 µg/dL</i>	<i>87+ µg/dL</i>
<i>N</i>	353	353	354	353
Age, years	63 (5)	61 (5)	61 (5)	60 (5)
African American, %	20%	23%	19%	22%
BMI, kg/m ²	28 (6)	29 (6)	28 (6)	29 (6)
Height, cm	162 (6)	162 (6)	162 (6)	162 (6)
Current smoker, %	8%	11%	12%	16%
eGFR, mL/min/1.73 m ²	87 (17)	89 (15)	89 (14)	91 (15)
C-reactive protein, mg/L	4.7 (2.4, 8.3)	4.4 (2.2, 7.6)	4.0 (1.7, 8.1)	4.7 (2.1, 8.2)
Men	<i>70 µg/dL</i>	<i>70–103 µg/dL</i>	<i>103–152 µg/dL</i>	<i>152+ µg/dL</i>
<i>N</i>	979	979	980	980
Age, years	65 (6)	63 (6)	62 (5)	61 (5)
African American, %	15%	17%	19%	22%
BMI, kg/m ²	29 (5)	28 (4)	28 (4)	28 (4)
Height, cm	175 (6)	175 (7)	176 (7)	176 (7)
Current smoker, %	11%	13%	17%	20%
eGFR, mL/min/1.73 m ²	83 (16)	85 (15)	86 (16)	87 (15)
C-reactive protein, mg/L	1.7 (0.9, 3.8)	1.7 (0.9, 3.6)	1.7 (0.9, 3.8)	1.7 (0.9, 3.7)

SD: standard deviation, IQR: interquartile range, eGFR: estimated glomerular filtration rate

Table 1c.
Participant characteristics by SHBG.

Characteristics of participants (mean [SD], median [IQR], or %) in relation to quartiles of plasma sex hormone-binding globulin (SHBG) concentrations, ARIC, 1996–98.

	SHBG			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Women (no HRT)	<i>23 nmol/L</i>	<i>23–33 nmol/L</i>	<i>33–51 nmol/L</i>	<i>51+ nmol/L</i>
<i>N</i>	756	758	760	757
Age, years	63 (5)	64 (5)	64 (5)	64 (5)
African American, %	34%	38%	32%	21%
BMI, kg/m ²	33 (6)	31 (6)	29 (6)	26 (5)
Height, cm	161 (6)	161 (6)	161 (6)	161 (6)
Current smoker, %	10%	14%	17%	21%
eGFR, mL/min/1.73 m ²	88 (17)	87 (18)	86 (17)	86 (16)
C-reactive protein, mg/L	4.4 (2.1, 7.8)	3.1 (1.4, 5.9)	2.3 (1.0, 5.2)	1.6 (0.7, 3.9)
Women (HRT)	<i>48 nmol/L</i>	<i>48–79 nmol/L</i>	<i>79–117 nmol/L</i>	<i>117+ nmol/L</i>
<i>N</i>	350	351	350	351
Age, years	61 (5)	61 (5)	61 (5)	62 (5)
African American, %	33%	24%	16%	11%
BMI, kg/m ²	31 (6)	29 (5)	28 (6)	26 (5)
Height, cm	162 (6)	162 (6)	162 (6)	162 (6)
Current smoker, %	12%	12%	11%	12%
eGFR, mL/min/1.73 m ²	91 (16)	89 (14)	89 (15)	86 (15)
C-reactive protein, mg/L	4.5 (2.1, 7.9)	4.1 (1.8, 8.0)	4.6 (2.2, 8.2)	4.9 (2.3, 8.3)
Men	<i>23 nmol/L</i>	<i>23–31 nmol/L</i>	<i>31–41 nmol/L</i>	<i>41+ nmol/L</i>
<i>N</i>	972	975	976	968
Age, years	62 (6)	62 (5)	63 (6)	64 (6)
African American, %	19%	20%	17%	18%
BMI, kg/m ²	30 (4)	29 (4)	28 (4)	26 (4)
Height, cm	176 (7)	176 (6)	175 (7)	175 (6)
Current smoker, %	9%	14%	14%	23%
eGFR, mL/min/1.73 m ²	85 (16)	87 (16)	85 (15)	86 (15)
C-reactive protein, mg/L	2.2 (1.1, 4.5)	1.8 (1.0, 3.7)	1.6 (0.8, 3.2)	1.4 (0.7, 3.2)

SD: standard deviation, IQR: interquartile range, eGFR: estimated glomerular filtration rate

Table 2.

Associations between hormones (quartiles) and VTE.

Hazard ratios (HRs) and 95% confidence intervals (CIs) of VTE in relation to quartiles of plasma sex hormone concentrations, ARIC, 1996–2015.

	Testosterone				DHEAS				SHBG			
	N		HR (95% CI)		N		HR (95% CI)		N		HR (95% CI)	
	N	N VTE	Model 1	Model 2	N	N VTE	Model 1	Model 2	N	N VTE	Model 1	Model 2
<i>Women (no HRT)</i>												
Quartile 1	762	37	0.7 (0.5, 1.1)	0.8 (0.5, 1.2)	761	52	1.3 (0.8, 1.9)	1.4 (0.9, 2.1)	756	48	1 (Ref.)	1 (Ref.)
Quartile 2	762	43	0.8 (0.5, 1.2)	0.9 (0.6, 1.3)	761	42	1.0 (0.6, 1.5)	1.0 (0.6, 1.6)	758	49	1.0 (0.7, 1.5)	1.1 (0.7, 1.6)
Quartile 3	765	51	1.0 (0.7, 1.5)	1.0 (0.7, 1.5)	764	48	1.2 (0.8, 1.9)	1.3 (0.8, 2.0)	760	40	0.8 (0.5, 1.3)	1.0 (0.6, 1.5)
Quartile 4	761	53	1 (Ref.)	1 (Ref.)	763	42	1 (Ref.)	1 (Ref.)	757	46	1.1 (0.7, 1.6)	1.4 (0.9, 2.2)
<i>Test for trend</i>			<i>P=0.11</i>	<i>P=0.29</i>			<i>P=0.40</i>	<i>P=0.26</i>			<i>P=0.68</i>	<i>P=0.12</i>
<i>Women (HRT)</i>												
Quartile 1	353	14	1.2 (0.5, 2.7)	1.3 (0.6, 2.9)	353	22	2.4 (1.1, 5.3)	2.5 (1.1, 5.8)	350	13	1 (Ref.)	1 (Ref.)
Quartile 2	353	23	2.1 (1.0, 4.2)	2.1 (1.0, 4.3)	353	22	2.4 (1.1, 5.3)	2.5 (1.1, 5.4)	351	15	1.2 (0.6, 2.5)	1.5 (0.7, 3.2)
Quartile 3	354	13	1.1 (0.5, 2.5)	1.1 (0.5, 2.5)	354	9	1.0 (0.4, 2.4)	1.0 (0.4, 2.4)	350	18	1.5 (0.7, 3.1)	1.9 (0.9, 4.0)
Quartile 4	353	11	1 (Ref.)	1 (Ref.)	353	9	1 (Ref.)	1 (Ref.)	351	16	1.4 (0.7, 2.9)	2.0 (0.9, 4.5)
<i>Test for trend</i>			<i>P=0.27</i>	<i>P=0.19</i>			<i>P=0.006</i>	<i>P=0.005</i>			<i>P=0.35</i>	<i>P=0.07</i>
<i>Men</i>												
Quartile 1	980	58	1.3 (0.9, 1.9)	1.1 (0.7, 1.7)	979	57	1.2 (0.8, 1.7)	1.1 (0.8, 1.7)	972	44	1 (Ref.)	1 (Ref.)
Quartile 2	981	50	1.1 (0.7, 1.6)	1.0 (0.7, 1.6)	979	59	1.2 (0.8, 1.8)	1.2 (0.8, 1.8)	975	53	1.2 (0.8, 1.7)	1.3 (0.8, 1.9)
Quartile 3	981	50	1.1 (0.7, 1.6)	1.0 (0.7, 1.6)	980	42	0.9 (0.6, 1.3)	0.8 (0.5, 1.2)	976	51	1.1 (0.7, 1.6)	1.3 (0.8, 1.9)
Quartile 4	980	48	1 (Ref.)	1 (Ref.)	980	28	1 (Ref.)	1 (Ref.)	968	56	1.2 (0.8, 1.8)	1.4 (0.9, 2.2)
<i>Test for trend</i>			<i>P=0.21</i>	<i>P=0.76</i>			<i>P=0.27</i>	<i>P=0.34</i>			<i>P=0.52</i>	<i>P=0.16</i>

Model 1: Adjusted for age and race

Model 2: Model 1 + body mass index, height, smoking, estimated glomerular filtration rate, and C-reactive protein

Table 3.

Associations between hormones (extreme deciles) and VTE.

Hazard ratios (HRs) and 95% confidence intervals (CIs) of VTE in relation to extreme deciles of plasma sex hormone concentrations, ARIC, 1996–2015.

	Testosterone						DHEAS				SHBG				
	N	N	VTE	HR (95% CI)		N	N	VTE	HR (95% CI)		N	N	VTE	HR (95% CI)	
				Model 1	Model 2				Model 1	Model 2				Model 1	Model 2
Women (no HRT)															
<10th percentile	306	15		0.8 (0.5, 1.4)	0.9 (0.5, 1.5)	303	16		0.9 (0.5, 1.5)	1.0 (0.6, 1.6)	301	16		0.9 (0.5, 1.4)	0.8 (0.4, 1.3)
10–90th percentile	2,439	149		1 (Ref.)	1 (Ref.)	2,442	146		1 (Ref.)	1 (Ref.)	2,427	146		1 (Ref.)	1 (Ref.)
>90th percentile	305	20		1.1 (0.7, 1.7)	1.0 (0.6, 1.7)	304	22		1.3 (0.8, 2.0)	1.2 (0.7, 1.9)	303	21		1.4 (0.9, 2.2)	1.6 (1.0, 2.6)
Women (HRT)															
<10th percentile	141	9		1.5 (0.7, 3.0)	1.5 (0.8, 3.1)	141	6		0.9 (0.4, 2.1)	1.0 (0.4, 2.3)	139	5		0.8 (0.3, 2.0)	0.7 (0.3, 1.8)
10–90th percentile	1,131	48		1 (Ref.)	1 (Ref.)	1,131	54		1 (Ref.)	1 (Ref.)	1,123	49		1 (Ref.)	1 (Ref.)
>90th percentile	141	4		0.7 (0.2, 1.9)	0.7 (0.3, 2.0)	141	2		0.3 (0.1, 1.3)	0.3 (0.1, 1.3)	140	8		1.4 (0.7, 2.9)	1.8 (0.8, 3.8)
Men															
<10th percentile	392	22		1.1 (0.7, 1.7)	0.9 (0.5, 1.4)	391	26		1.3 (0.9, 2.0)	1.3 (0.8, 2.0)	386	18		0.9 (0.6, 1.5)	0.9 (0.6, 1.5)
10–90th percentile	3,138	168		1 (Ref.)	1 (Ref.)	3,136	161		1 (Ref.)	1 (Ref.)	3,116	162		1 (Ref.)	1 (Ref.)
>90th percentile	392	16		0.8 (0.5, 1.3)	0.9 (0.5, 1.5)	391	19		1.0 (0.6, 1.6)	1.0 (0.6, 1.6)	389	24		1.1 (0.7, 1.8)	1.4 (0.9, 2.1)

Model 1: Adjusted for age and race

Model 2: Model 1 + body mass index, height, smoking, estimated glomerular filtration rate, and C-reactive protein