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Sex Hormone Levels and Change in Left Ventricular Structure Among Men and Post-Menopausal Women: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Contributors

Vinita Subramanya and Erin D. Michos designed the research. Vinita Subramanya and Di Zhao analyzed the data under the supervision of Eliseo Guallar and Erin D. Michos. Vinita Subramanya wrote the first draft of the paper.
Pamela Ouyang and Joao A. Lima acquired the data (sex hormones and cardiac MRI, respectively).
Vinita Subramanya, Di Zhao, Pamela Ouyang, Joao A. Lima, Dhananjay Vaidya, Chiadi E. Ndumele, David A. Bluemke, Sanjiv J. Shah, Eliseo Guallar, Chike C. Nwabuo, Matthew A. Allison, Susan R. Heckbert, Wendy S. Post, and Erin D. Michos all reviewed the manuscript and provided critical scientific input.
Vinita Subramanya and Erin D. Michos had primary responsibility for final content.

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Ethical Approval Statement – Human Subjects Research

This study was conducted in concordance with the ethical principles set forth in the Declaration of Helsinki. This study was approved by the institutional review boards of each participating institution, and all participants provided written informed consent.

Declaration of Conflicts of Interest

All author conflicts-of-interest are outlined in the disclosure section of this manuscript. Dr. Michos (the Corresponding Author) reported receiving an honorarium from Siemens Healthcare Diagnostics for serving as a blinded events adjudicator for a clinical trial unrelated to the topic of this work. No other authors reported any disclosures. This study was funded by the National Institute of Health (NIH). There has been no significant financial support for this work that could have influenced its outcome.

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Abstract

Objective—Sex hormone (SH) levels may contribute to sex differences in the risk of heart failure with preserved ejection fraction (HFpEF). We examined the associations of SH levels with left ventricular mass (LVM) and mass(M):volume(V) ratio, which are risk markers for HFpEF.

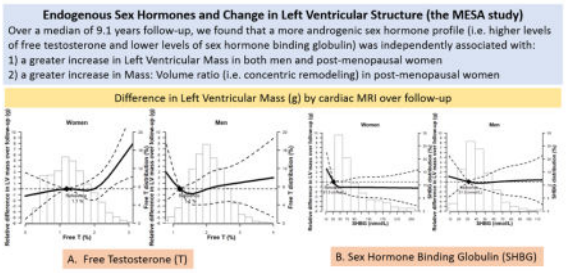
Study Design—We studied 1,941 post-menopausal women and 2,221 men, aged 45–84 years, participating in the Multi-Ethnic Study of Atherosclerosis (MESA). Serum SH levels, cardiac magnetic resonance imaging (MRI) and ejection fraction (EF) ≥50% had been recorded at baseline (2000–2002). Of these participants, 2,810 underwent repeat MRI at Exam 5 (2010–2012). Stratified by sex, linear mixed-effect models were used to test associations between SH and sex hormone binding globulin (SHBG) level [per 1 SD greater log-transformed(SH)] with baseline and change in LV structure. Models were adjusted for age, race/ethnicity, center, height, weight, education, physical activity and smoking, and, in women, for hormone therapy and years since menopause.

Main Outcome Measures—LVM and M:V ratio.

Results—After a median of 9.1 years, higher free testosterone levels were independently associated with a modest increase in LVM (g/yr) in women [β=0.05 (95%CI 0.01, 0.10)] and men [0.16 (0.03, 0.28)], while higher SHBG levels were associated with less LVM change (g/yr) in women [−0.07 (−0.13, −0.01)] and men [−0.15 (−0.27, −0.02)]. In men, higher dehydroepiandrosterone and estradiol levels were associated with increased LVM. Among women, free testosterone levels were positively and SHBG levels inversely associated with change in M:V ratio.

Conclusion—A more androgenic profile (higher free testosterone and lower SHBG levels) is associated with a greater increase in LVM in men and women and greater increase in M:V ratio in women over the course of 9 years.

Graphical Abstract



Keywords

Sex Hormones; Sex differences; left ventricular remodeling; Cardiac magnetic resonance imaging; Epidemiology

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1.0 Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for half of all HF cases and is more prevalent among women.[1] Changes in left ventricular (LV) structure, such as LV hypertrophy and LV concentric remodeling [i.e. increased mass-to-volume (M:V) ratio], are risk markers for incident HFpEF.[2] Treatments that reduce LV mass (LVM) are associated with a decreased risk for incident cardiovascular disease (CVD) and HF.[3] Thus, imaging indices of LV structure are important prognostic risk markers.[4]

Sex differences in LV structure have been observed. Men have a greater LV end diastolic volume (LVEDV) and LVM, even after adjusting for differences in body size.[5, 6] Sex hormones may influence LV structure differently in men vs. women. For example, a prior study in men found lower androgen levels [i.e. testosterone (T)] were associated with greater LVM.[7] However, the opposite pattern was seen in hypertensive peri-menopausal women, with higher androgen levels (free T) associated with LV diastolic dysfunction.[8]

At the menopausal transition, women experience drastic changes in the levels of endogenous sex hormones with an abrupt decrease in estradiol (E2) and sex hormone binding globulin (SHBG), as well as a concommitant but more gradual decrease in total T. In women, a more androgenic pattern of sex hormones after menopause has been associated with elevated blood pressure (BP), insulin resistance, and other CVD risk factors.[9, 10] Thus, a more androgenic profile may lead to adverse LV remodeling in post-menopausal women and potentially contribute to the female predominance of HFpEF risk at older ages.

Prior studies evaluating sex hormones and LV structure have been limitated by cross-sectional designs and smaller sample sizes.[7, 8] It is still uncertain how sex hormone levels may influence cardiac structure over time after accounting for changes in established CVD risk factors. Therefore, we studied the cross-sectional and longitudinal associations of sex hormone levels with LV structure in a multi-ethnic population without clinical CVD at baseline. We hypothesized that a more androgenic sex hormone profile at baseline (i.e. lower E2, higher free T, and lower SHBG) would be longitudinally associated with increased LVM and increased M:V ratio (i.e. concentric remodeling) among post-menopausal women but not men.

2.0 Methods

2.1 Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is an ongoing prospective cohort investigating subclinical CVD in a community-based sample of 6,814 men and women aged between 45–84yrs at baseline. Participants were recruited from four race/ethnicities across six U.S. centers, as described previously.[11] MESA exclusion criteria included a history of clinical CVD or HF (assessed by self-reported questionnaire), weight >300lb, and any restriction to participation. For our analysis, we excluded pre-menopausal women, as sex hormone levels substantially change after menopause.

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Our study had two components (Figure 1): 1) cross-sectional analyses (N=4,162) of participants at baseline (2000–2002) who had available sex hormone and cardiac MRI data, and a preserved ejection fraction (EF ≥50%) and 2) longitudinal analyses (N=2,810) that included participants with an additional follow-up MRI at Exam 5 (2010–2012). The protocols of MESA were approved by the institutional review boards of all collaborating institutions; all participants provided written informed consent.

2.2 Exposure variables

Baseline serum sex hormones were measured from an early morning fasting blood sample and stored at −70°C. Hormone assays were performed at the University of Massachusetts Medical Center in Worcester, MA. E2 was measured using an ultrasensitive radioimmunoassay kit (Diagnostic System Laboratories, Webster, TX). Total T and dehydroepiandrosterone (DHEA) were measured using radioimmunoassay kits, and SHBG was measured by chemiluminescence enzyme immunometric assay using Immulite kits (Diagnostic Products Corporation, Los Angeles, CA).[9] Free T was calculated using the Sodergard method[12] and reported as percent of total T. The intra-assay coefficients of variation for total T, SHBG, DHEA, and E2 were 12.3%, 9.0%, 11.2%, and 10.5%, respectively.

2.3 Outcome variables

LV parameters (LVM, LVEDV, and M:V ratio) were measured by cardiac MRI at baseline and Exam 5. Left atrial size parameters were not measured from the MRIs and thus not available for analysis. The cardiac MRI was performed using 1.5T magnets with a phased array surface coil placed both anteriorly and posteriorly with ECG gating. The MRI consisted of long and short axis images taken during short breath holding at resting lung volume. Further details of the MRI protocol have been described previously.[6, 13] MRI images were analyzed at the central reading center at the Johns Hopkins Hospital, Baltimore, MD.

LVM was measured at end-diastole. Papillary muscles were included in the LVEDV measurement and excluded from LVM. Interventricular septum was included in the LVM. The intraclass correlation was 0.98 for LVM and 0.98 for LVEDV for baseline MRI data.[13] The overall interobserver intraclass correlation coefficients for LVM and LVEDV were 0.95 and 0.96.[6]

2.4 Covariates

Standard questionnaires assessed race/ethnicity, education level, smoking status, and physical activity (defined as intentional exercise in METS*min/week). Medications were determined by an inventory. Menopausal status was determined by an algorithm incorporating self-reported status, age, age at menopause/hysterectomy/ovariectomy, and hormone therapy (HT) use.[14] Only post-menopausal women were included.

Height and weight were measured per standardized procedures.[11] Resting BP was measured three times in the seated position using a Dinamap automated sphygmomanometer, and average of the 2nd and 3rd readings was used. Diabetes was

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determined by self-reported physician diagnosis, a fasting glucose level of ≥126 mg/dl, or the use of hypoglycemic medication. Covariates were assessed at Exams 1 and 5.

2.5 Statistical analysis

Baseline characteristics were stratified by sex and summarized using means (standard deviations (SD)), medians (interquartile interval), or percentages. The sex hormone levels were postively skewed and thus were logarithmically-transformed and analyzed per 1 SD of their natural log. LV measures were used as continuous variables.

To assess the longitudinal associations between baseline sex hormones and LV structure changes over time, we used multivariable-adjusted linear mixed effect models, and allowed for random variations in baseline sex hormones and longitudinal slopes of sex hormones across participants. Independent covariance structure between random intercept and random slope was used. The longitudinal effect was estimated by the coefficient of interactions between sex hormones and time since baseline. The cross-sectional effect was estimated by the coefficient of sex hormones, which corresponds to difference of LV structure when time since baseline=0.

Results were stratified by sex. In our primary model (Model 1), we adjusted for potential confounders of age, race/ethnicity, center, height, weight, education, physical activity, and smoking status. Additionally, in women, we adjusted for HT use and years since menopause. An additional model (Model 2) further adjusted for CVD risk factors that may be in the causal pathway between sex hormone levels and LV structure including systolic BP, anti-hypertensive medication use, total and HDL cholesterol, lipid lowering medication use, and diabetes. For the longitudinal analyses, time-varying changes of these covariates were included in the models.

To evaluate for possible non-linear dose-response associations between sex hormones and LVM, we used restricted cubic splines of sex hormones with knots at the 5th, 35th, 65th and 95th percentiles of their sample distributions. The *p*-values for the nonlinear spline components were not significant, indicating that the associations were approximately linear.

We performed some supplementary analyses. We repeated analyses among women not taking HT at baseline. We repeated analyses excluding individuals with an incident CVD event between Exams 1 and 5. We also performed regression analysis with all sex hormones mutually adjusted for each other in one model, from which we excluded free T, as free T is mathematically derived from total T and SHBG.

Statistical significance was defined as a p value of <0.05. All analyses were conducted on Stata version 14 (StataCorp, College Station, TX, USA).

3.0 Results

3.1 Participant characteristics

The baseline characteristics of the cross-sectional study sample (N=4,162) stratified by sex are depicted in Table 1. Men were slightly younger than women, had higher physical activity

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levels, were more likely current smokers, had lower systolic BP, and were less likely to be taking anti-hypertensive medications. Among women, 34% were current HT users. As expected, baseline sex hormone levels varied between men and women such that men had higher total T, free T, DHEA and E2, while women had higher SHBG levels. As anticipated, men had greater LVM and LVEDV, that persisted after indexing to body surface area.

The baseline characteristics of the cross-sectional sample were further stratified by those who had a follow-up MRI (N=2,810) vs. those with a baseline MRI only (N=1,352) and presented in Supplemental Table 1. The participant characteristics at Exam 5 are shown in Supplemental Table 2. Among those who underwent a repeat MRI, there was an increase in the use of antihypertensive and cholesterol-lowering medications, fewer participants had normal glucose levels; however the prevalence of current smokers decreased.

3.2 Cross-sectional analysis

Among 1,941 women at the baseline exam (Table 2A), after adjusting for demographics and HT use (Model 1), per 1 SD higher log(sex hormone), DHEA was associated with greater LVM (g) [β=0.78 (95% CI 0.14, 1.42)]. Free T was associated with higher [1.34 (0.90, 1.77)] and SHBG with lower [−1.58 (−2.09, −1.07)] average difference in M:V ratio (%). Higher free T and lower SHBG were also associated with lower LVEDV (ml). After adjustment for additional CVD risk factors (Model 2), the associations of free T and SHBG with M:V ratio and LVEDV remained statistically significant.

Among 2,221 men (Table 2B), greater free T [1.29 (0.46, 2.11)] and E2 [0.76 (0.01, 1.52)] were positively associated, while total T [−0.83 (−1.56, −0.10)] and SHBG [1.37 (−2.20, −0.54)] were inversely associated, with higher M:V ratio. Conversely, higher free T and E2, as well as lower total T and SHBG, were associated with lower LVEDV. After adjustment for additional CVD risk factors, higher E2 was also associated with lower LVM and LVEDV, and total T associated with greater LVEDV.

3.3 Longitudinal analyses

After a median follow-up of 9.1 years, a more androgenic pattern of higher free T and lower SHBG was associated with greater LVM in both sexes (depicted in Figures 2 and 3, respectively).

Among 1,304 women (Table 3A), higher free T was associated with a modest increase in LVM (g/yr) [0.05 (0.01, 0.10)] and M:V ratio (%/yr) [0.07 (0.01, 0.13)], while higher SHBG was associated with less change in LVM [−0.07 (−0.13, −0.01)] and M:V ratio −0.09 (−0.16, −0.02). There was no association of sex hormones with change in LVEDV. Findings for M:V ratio remained consistent after adjustment for additional CVD risk factors (Model 2).

Among women not taking HT (N=836), findings for the associations with LVM remained statistically significant (Supplemental Table 3). In this smaller subgroup of non-users of HT, the findings for M:V ratio did not reach statistical significance, but the direction and magnitude of the associations were similar to the overall cohort of women.

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Among 1,506 men (Table 3B), higher E2 [0.20 (0.08, 0.33)], DHEA [0.14 (0.01, 0.27)], and free T [0.16 (0.03, 0.28)], were associated with increased LVM and higher SHBG [−0.15 (−0.27, −0.02)] with less change in LVM (Model 1), which remained statistically significant after adjustment for additional CVD risk factors. There were no significant associations between any hormones and LVEDV or M:V ratio.

Sensitivity analyses

Excluding individuals with incident CVD between Exams 1 and 5 (N=175) yielded similar results to main findings (Supplemental Table 4). Although all primary analyses adjusted for height and weight, both cross-sectional and longitudinal associations were similar when using LVM indexed to body surface area instead (Supplemental Table 5). When all sex hormones were included in the same model, among women, lower SHBG was significantly associated with a longitudinal increase in LVM and M:V ratio in fully-adjusted model (Supplemental Table 6). Among men, greater E2 was associated with an increase in LVM and M:V ratio (Supplemental Table 7). There were no statistically significant associations for the other sex hormones in this mutally-adjusted model.

4.0 Discussion

In a well-characterized multi-ethnic cohort of men and women followed for approximately 9yrs, we found that the more androgenic pattern of higher free T and lower SHBG was associated with greater LVM in both sexes, but was associated with increased M:V ratio (indicative of concentric remodeling) only in women. The increase in LVM in men, without an increase in M:V ratio, could represent more physiologic remodeling, while the increase in M:V ratio, reflective of concentric remodeling, related to this hormone pattern seen in women, is a more pathologic precursor to HFpEF. As temporal relationships can not be ascertained from cross-sectional studies, our longitudinal evaluation of sex hormones with change in LV structure is a key strength of our study.

4.1 Testosterone

As a possible mechanism for the increased prevalence of HFpEF seen in women, we hypothesized that higher androgen levels would be associated with increased concentric remodeling in women, but not in men. Indeed, prior animal studies have shown opposite effects of T on LV structure by sex as seen in post-myocardial infarction rat models, with T associated with adverse cardiac remodeling in female rats, which is accentuated in the presence of reduced E2 levels,[15] while the opposite was true in post-myocardial infarction male rats.[16, 17]

Among men, prior epidemiological studies have shown that low T is associated with worse CVD and HF outcomes, as well as worse functional capacity,[18, 19] suggesting that low T may be a marker of a poorer health state. Consistent with this, a prior study found that low total T was associated with increased LVM among men.[7] While we could not confirm the associations with low *total* T and LVM change in men in our study, we did find that *free* T was associated with increased LVM longitudinally in men. Among women, free T had previously been implicated in LV diastolic dysfunction.[8] Our study findings were

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consistent with this (and with our hypothesis), as we found free T was associated with increased LVM and M:V ratio longitudinally in women.

4.2 Estradiol

There are several mechanisms by which E2 may antagonize the concentric remodeling caused by androgens. Estrogen can down-regulate angiotensin receptors, improve vascular endothelium function, protect against vascular injury, and inhibit adverse remodeling processes.[20] Thus the abrupt loss of E2 at menopause (which men do not experience) may be an important contributor to the concentric LV remodeling and increased HFpEF risk seen in older women.

Animal studies of female rats have shown that lower E2 levels result in an increase in LV remodeling, which can be prevented by 17beta-estradiol supplementation.[21] Similarly, in a small clinical trial, 17beta-estradiol treatment in post-menopausal hypertensive women resulted in a decrease in LVM in the presence of anti-hypertensive medications.[22] Some observational studies have shown similar improvements in LVM in women receiving HT.[23]

Thus, we hypothesized that higher E2 levels would be protective against concentric remodeling, but this was not the case in our study. Specifically, in men, greater E2 levels were actually associated with increased LVM longitudinally. The reason for this is uncertain, but we speculate greater E2 in men may be a marker of more adiposity, although we adjusted for baseline weight and changes in weight.

In women, we did not find any association of E2 with markers of LV structural change, but E2 levels were very low, even lower than in men, in this sample of post-menopausal women. Women on HT had a slightly higher E2 than those who were not on HT but we adjusted for this variable (and excluded HT users in sensitivity analyses).

4.3 Sex hormone binding globulin

SHBG binds 17-β-hydroxysteroids such as T (with high affinity) and E2 (with lower affinity).[24] Thus, higher SHBG levels result in more T in the bound state. We found greater SHBG was longitudinally associated with less increase in LVM for both men and women, and for women, this was independent of the other sex hormone levels. Low SHBG has been implicated in impaired LV performance in young women with obesity[25] and with increased LVM among men[7], which is consistent with our findings.

4.4 DHEA

We found that higher DHEA was longitudinally associated with increased LVM among men, with no longitudinal associations seen among women. We did not have any *a priori* hypotheses related to DHEA and LV structure, as animal studies of DHEA have shown conflicting results.[26, 27] Previous epidemiological studies have shown that reduced DHEA is associated with greater cardiovascular risk in men.[28]

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4.5 Strengths and limitations

The strengths of our study include the ability to conduct longitudinal analyses relating baseline sex hormone levels to change in MRI-assessed LV structure in a well-characterized, multi-ethnic cohort, after adjustment for baseline and change in CVD risk factors. We analyzed changes in LV structure as a surrogate subclinical marker of HFpEF risk to gain insight into pathophysiologic mechanisms.

The limitations of our study include only a single measurement of sex hormones at baseline. The cross-sectional analysis may have been subject to temporal bias while the longitudinal analysis to selection bias. The associations of log(sex hormones) with annual change in the LV parameters were modest, and the clinical significance of these findings is uncertain. We also performed multiple comparisons, however findings were generally consistent with our *a priori* hypotheses and similar among men and women for LVM. Our study population included post-menopausal women. Exploring these relationships in a younger cohort could help better understand the role of sex hormones and LV structure during the menopausal transition specifically.

5.0 Conclusions

In summary, we found that higher levels of free T and lower levels of SHBG [i.e. a more androgenic milieu] are associated with increased LVM, independent of potentially mediating CVD risk factors, but this more androgenic pattern was associated with concentric remodeling (M:V ratio) only in women. This may be related to the change in sex hormone levels that occur in women around menopause that is absent in men and may go toward understanding the female preponderance of HFpEF. However, the best interventions to mitigate this risk is uncertain, as clinical trials of HT after menopause have not been shown to reduce CVD (or HF) risk, although this may have been related to timing of HT.[29] Nonetheless, an androgenic sex hormone profile may identify women at risk for concentric remodeling who might benefit from other risk-reducing stragies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

HFpEF	Heart Failure with Preserved Ejection Fraction
CVD	Cardiovascular Disease
MRI	Magnetic Resonance Imaging
RV	Right ventricle
LV	Left ventricle
LVM	Left ventricular mass
LVEDV	Left ventricular end diastolic volume
M	V ratio, Left ventricular Mass to Volume ratio
SBP	Systolic blood pressure
SH	Sex Hormones
T	Testosterone
E2	Estradiol
DHEA	Dehydroepiandrosterone
SHBG	Sex Hormone Binding Globulin

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Highlights

- There may be sex differences in the way that sex hormones influence cardiac structural change.
- We studied hormones and change in the left ventricle mass (LVM) and mass:volume ratio.
- A more androgenic profile was associated with a greater increase in left ventricle mass in men.
- An androgenic profile was associated with increased left ventricle mass and mass:volume ratio in women.

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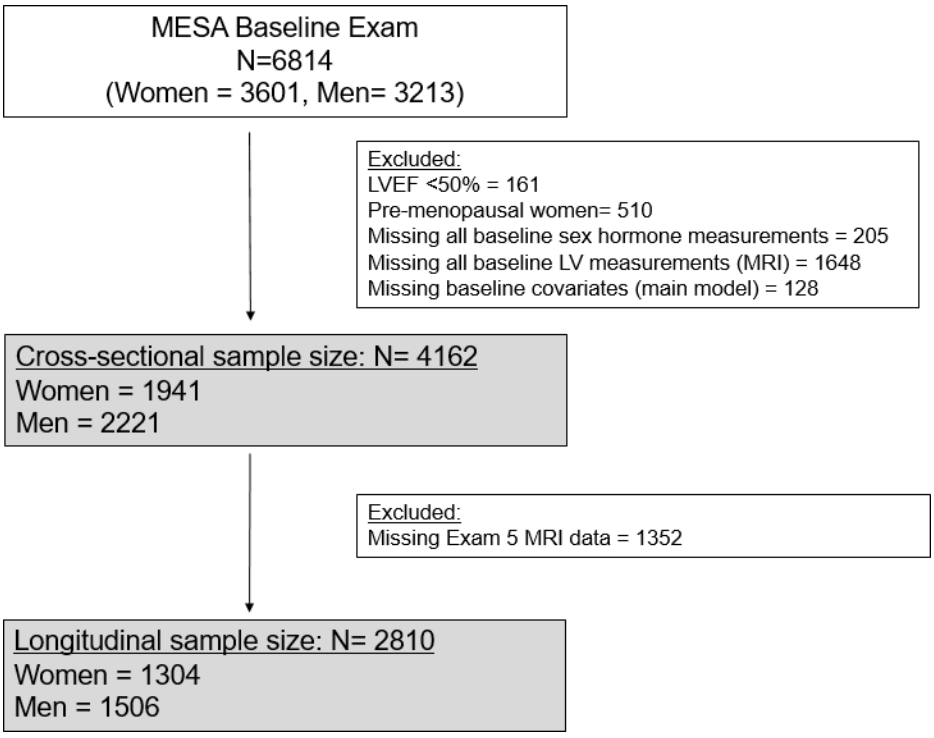

Figure 1.
Flowchart of study sample

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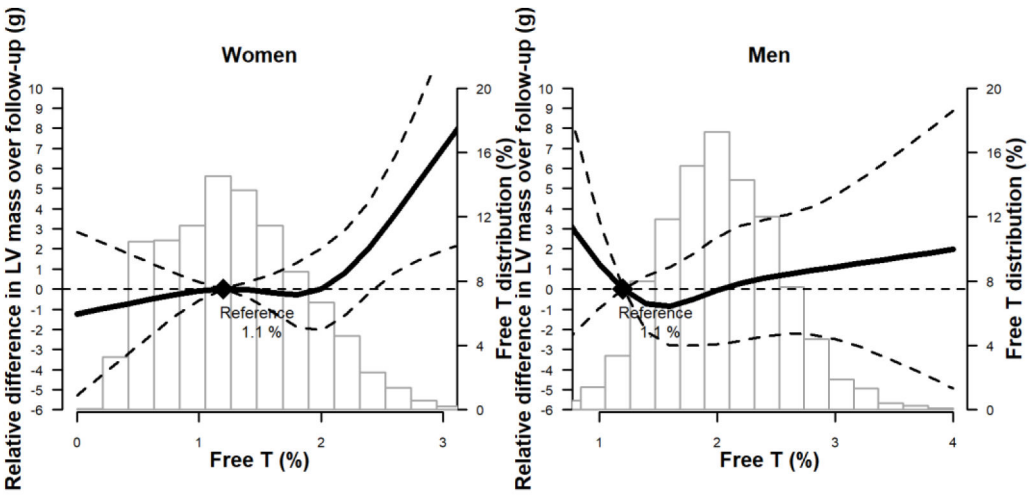

Figure 2.

Adjusted longitudinal association between free testosterone levels and LVM over median 9.1 years follow-up in women and men*,†

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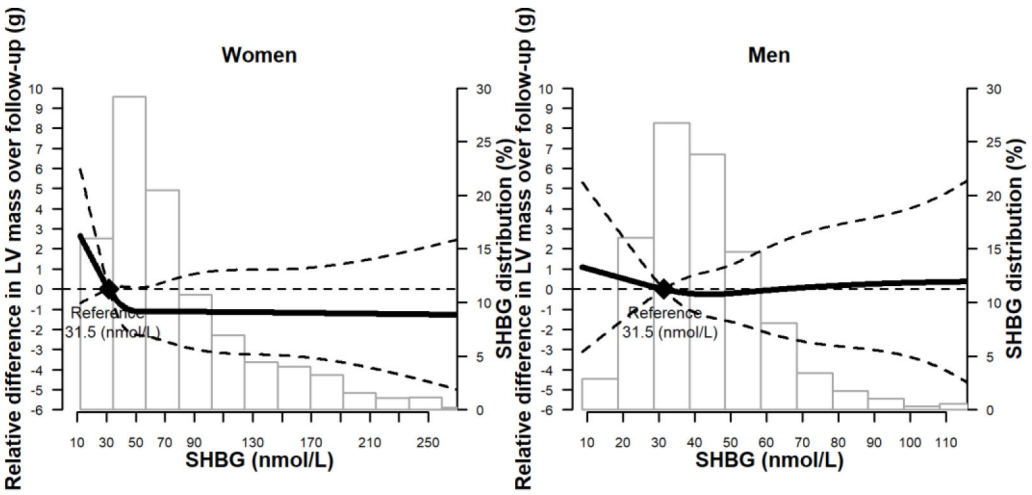

Figure 3.

Adjusted longitudinal association between SHBG levels and LVM over median 9.1 years follow-up in women and men*,†

* Adjusted for Model 1 variables

†Curves represent adjusted average difference (solid lines) and their 95% confidence intervals (dashed lines) of LVM (g) over median 9.1 years of follow-up based on restricted cubic splines for free T (Figure 2) or SHBG (Figure 3) with knots at the 5th, 35th, 65th and 95th percentiles of their sample distributions. The reference values (diamond dots) were set at 20th percentile (1.1 % for free T and 31.5 nmol/L for SHBG)

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Table 1

Characteristics of Participants (N=4,162) at MESA baseline exam (2000–2002)[a, b]

Characteristic	Women (n= 1,941)	Men (n= 2,221)	p-value
Demographic factors			
Age (years)	65 (8.9)	61 (10.1)	<0.001
Race/Ethnicity			0.51
White, Caucasian	40	39	
Chinese American	13.8	14.1	
Black, African-American	24.3	23.3	
Hispanic	21.8	22.8	
Education			<0.001
< high school	19.8	15.4	
high school	21.4	14.6	
< college	28.4	25.9	
≥ college	30.3	44.1	
Lifestyle Factors			
Physical activity (METS*min/wk)	3660 (1815, 6540)	4500 (2205, 8460)	<0.001
Smoking status			<0.001
Never	60	42.9	
Former	30.3	43.2	
Current	9.7	13.9	
Cardiovascular Risk factors			
Height (cm)	159.5 (7.0)	173.5 (7.7)	<0.001
Weight (lb)	156.5 (33.6)	182.1 (32.2)	<0.001
Body Mass Index (kg/m2)	27.9 (5.4)	27.4 (4.1)	<0.01
Hypertension	48.3	40.25	<0.001
Systolic Blood Pressure (mm Hg)	128.0 (23.4)	125.1 (19.2)	<0.001
Diastolic Blood pressure (mm Hg)	68.9 (10.3)	74.8 (9.3)	<0.001
Anti-hypertensive medication	40.5	33.6	<0.001
Total cholesterol (mg/dl)[c]	202.1 (35.9)	186 (165, 209)	<0.001
HDL cholesterol (mg/dl)[c]	57.4 (15.7)	43 (37, 51)	<0.001
Cholesterol lowering meds	19.7	15.4	<0.001
Diabetes mellitus status			<0.01
Normal	76.9	72.5	
Impaired fasting glucose	11.9	15.3	
Diabetes	11.3	12.2	
eGFR	75.7 (15.6)	78.6 (15.6)	p <0.001
Current HT (n=651)	33.5		<0.001
Sex Hormones			
Total T (nmol/L)	0.9 (0.6, 1.3)	14.4 (11.6, 17.9)	<0.001
Free T (%)	1.3 (0.9, 1.7)	2.0 (1.7, 2.4)	<0.001

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Characteristic	Women (n= 1,941)	Men (n= 2,221)	p-value
Estradiol (nmol/L)	0.07 (0.04, 0.17)	0.1 (0.1, 0.1)	<0.001
DHEA (nmol/L)	10.2 (7.0, 14.4)	12.7 (9.2, 17.2)	<0.001
SHBG (nmol/L)	60.6 (41.2, 98.2)	40.4 (31, 52.4)	<0.001
LV measures			
LV EF (%)	64.0 (5.2)	61.9 (5.3)	<0.001
LV EDV (ml) (indexed to BSA)	66.0 (10.4)	72.0 (13.3)	<0.001
LV mass (g) (indexed to BSA)	59.8 (9.2)	69.8 (11.2)	<0.001
LV ESV (ml) (indexed to BSA)	23.7 (5.0)	27.4 (6.4)	<0.001

[a]Data are mean (SD), for normally distributed variables, median (25^{th}, 75^{th} percentiles) for skewed variables, or (%) for categorical variables. P values were obtained using t-test or the chi-square test.

[b]Abbreviations: MESA, Multi-Ethnic Study of Atherosclerosis; HDL, high density lipoprotein; eGFR, estimated glomerular fibrillation rate; HT, hormone therapy; T, testosterone; DHEA, dehydroepiandrosterone; SHBG, sex hormone binding globulin; LV, left ventricular; EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume, BSA; body surface area

[c]To convert Total and HDL cholesterol from mg/dl to mmol/L, divide by 38.67

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Table 2

The cross-sectional associations of sex hormone levels with adjusted difference in LV parameters at the MESA baseline exam (2000–2002) [N=4,162][a,b]

Sex hormones	Model 1[c]			Model 2[c]		
	LV Mass (g)	LV EDV (ml)	M: V ratio (%)	LV Mass (g)	LV EDV (ml)	M: V ratio (%)
A. Women (N= 1,941)						
Total T	0.42 (−0.004, 0.84)	0.02 (−0.44, 0.48)	0.37 (−0.03, 0.77)	0.31 (−0.08, 0.71)	0.01 (−0.44, 0.46)	0.29 (−0.10, 0.68)
E2	−0.04 (−0.41, 0.32)	−0.12 (−0.51, 0.27)	0.12 (−0.23, 0.46)	−0.20 (−0.54, 0.14)	−0.23 (−0.62, 0.15)	0.07 (−0.27, 0.40)
DHEA	**0.78 (0.14, 1.42)**	0.31 (−0.38, 1.00)	0.55 (−0.06, 1.16)	**0.69 (0.09, 1.29)**	0.31 (−0.37, 0.99)	0.49 (−0.10, 1.08)
Free T	0.16 (−0.30, 0.63)	**−1.19 (−1.68, −0.69)**	**1.34 (0.90, 1.77)**	−0.03 (−0.49, 0.43)	**−0.88 (−1.40, −0.37)**	**0.92 (0.47, 1.37)**
SHBG	−0.16 (−0.71, 0.39)	**1.43 (0.85, 2.01)**	**−1.58 (−2.09, −1.07)**	0.08 (−0.46, 0.62)	**1.08 (0.47, 1.69)**	**−1.08 (−1.62, −0.55)**
B. Men (N= 2,221)						
Total T	0.69 (−0.17, 1.55)	**1.85 (0.85, 2.85)**	**−0.83 (−1.56, −0.10)**	0.75 (−0.07, 1.56)	**1.68 (0.69, 2.67)**	−0.65 (−1.37, 0.07)
E2	−0.79 (−1.68, 0.09)	**−1.56 (−2.59, −0.52)**	**0.76 (0.01, 1.52)**	**−0.94 (−1.78, −0.10)**	**−1.36 (−2.38, −0.34)**	0.50 (−0.25, 1.24)
DHEA	−0.44 (−1.45, 0.57)	−0.22 (−1.39, 0.95)	−0.24 (−1.09, 0.62)	−0.20 (−1.16, 0.76)	−0.04 (−1.20, 1.12)	−0.21 (−1.06, 0.64)
Free T	0.08 (−0.90, 1.06)	**−1.17 (−2.30, −0.04)**	**1.29 (0.46, 2.11)**	−0.05 (−1.00, 0.90)	−0.47 (−1.61, 0.67)	0.65 (−0.18, 1.49)
SHBG	0.12 (−0.87, 1.10)	**1.56 (0.42, 2.69)**	**−1.37 (−2.20, −0.54)**	0.27 (−0.69, 1.22)	0.87 (−0.27, 2.02)	−0.73 (−1.57, 0.11)

[a] Abbreviations: MESA, Multi-Ethnic Study of Atherosclerosis; T, testosterone; E2, estradiol; DHEA, dehydroepiandrosterone; SHBG, sex hormone binding globulin; LV, left ventricular; EDV, end-diastolic volume; M:V, Mass: Volume; HDL, high density lipoprotein

[b] Per 1 SD of log Sex Hormone (nmol/L or %). Results presented as β coefficients (95% confidence interval). Bolded results are statistically significant (p <0.05)

[c] Model 1 adjusts for age, race/ethnicity, site, education, baseline physical activity, baseline smoking, baseline height, baseline weight (women: additionally, adjusted for hormone therapy, and years since menopause)

[d] Model 2 additionally adjusts for baseline systolic blood pressure, use of anti-hypertensive medication, total cholesterol, HDL cholesterol, lipid lowering medication and diabetes mellitus.

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Table 3

The longitudinal associations of baseline sex hormone levels with adjusted annual change in LV parameters from MESA Exam 1 (2000–2002) to Exam 5 (2010–2012) [N=2,810][a,b]

Sex hormones	Model 1 [b]			Model 2 [c]		
	LV Mass (g/yr)	LV EDV (ml/yr)	M: V ratio (%/yr)	LV Mass (g/yr)	LV EDV (ml/yr)	M: V ratio (%/yr)
A. Women (N= 1,304)						
Total T	−0.00 (−0.06, 0.05)	−0.02 (−0.07, 0.04)	0.01 (−0.05, 0.08)	−0.01 (−0.06, 0.05)	−0.02 (−0.08, 0.04)	0.01 (−0.05, 0.08)
E2	−0.03 (−0.07, 0.01)	−0.01 (−0.05, 0.02)	−0.04 (−0.08, 0.00)	−0.02 (−0.05, 0.02)	−0.004 (−0.04, 0.03)	−0.03 (−0.08, 0.01)
DHEA	−0.01 (−0.10, 0.07)	−0.03 (−0.12, 0.05)	−0.02 (−0.11, 0.08)	−0.02 (−0.11, 0.06)	−0.04 (−0.13, 0.04)	−0.02 (−0.11, 0.08)
Free T	**0.05 (0.01, 0.10)**	−0.02 (−0.07, 0.03)	**0.07 (0.01, 0.13)**	0.04 (−0.01, 0.09)	−0.04 (−0.09, 0.02)	**0.08 (0.02, 0.13)**
SHBG	**−0.07 (−0.13, −0.01)**	0.02 (−0.04, 0.08)	**−0.09 (−0.16, −0.02)**	**−0.06 (−0.12, 0.00)**	0.04 (−0.02, 0.10)	**−0.10 (−0.17, −0.02)**
B. Men (N=1,506)						
Total T	−0.07 (−0.21, 0.07)	−0.06 (−0.20, 0.09)	−0.08 (−0.23, 0.07)	−0.06 (−0.20, 0.07)	−0.06 (−0.21, 0.09)	−0.07 (−0.22, 0.08)
E2	**0.20 (0.08, 0.33)**	−0.01 (−0.15, 0.13)	0.14 (0.00, 0.28)	**0.19 (0.07, 0.31)**	−0.03 (−0.16, 0.11)	0.14 (−0.00, 0.28)
DHEA	**0.14 (0.01, 0.27)**	0.04 (−0.10, 0.18)	−0.06 (−0.20, 0.09)	**0.13 (0.00, 0.25)**	0.03 (−0.11, 0.17)	−0.06 (−0.20, 0.08)
Free T	**0.16 (0.03, 0.28)**	−0.02 (−0.16, 0.12)	0.08 (−0.06, 0.22)	**0.16 (0.04, 0.28)**	−0.02 (−0.16, 0.11)	0.08 (−0.06, 0.22)
SHBG	**−0.15 (−0.27, −0.02)**	0.01 (−0.13, 0.14)	−0.08 (−0.22, 0.06)	**−0.15 (−0.27, −0.03)**	0.01 (−0.13, 0.14)	−0.08 (−0.22, 0.06)

[a]Abbreviations: MESA, Multi-Ethnic Study of Atherosclerosis; T, testosterone; E2, estradiol; DHEA, dehydroepiandrosterone; SHBG, sex hormone binding globulin; LV, left ventricular; EDV, end-diastolic volume; M:V, Mass: Volume; HDL, high density lipoprotein

[b]Per 1 SD of log sex hormone (nmol/L or %). Results presented as β coefficients (95% confidence interval). Bolded results are statistically significant ($p < 0.05$)

[c]Model 1: age, race/ethnicity, site, education, baseline physical activity, baseline smoking, baseline height, baseline weight, change of physical activity, change of smoking, change of height, change of weight, (women: additionally, adjusted for hormone therapy, and years since menopause)

[d]Model 2: additionally adjusts for baseline and change in systolic blood pressure, use of anti-hypertensive medication, total cholesterol, HDL cholesterol, lipid lowering medication, and diabetes mellitus.