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Sex Hormones are Associated with Right Ventricular Structure and Function: The MESA-Right Ventricle Study

Corey E. Ventetuolo, MD[1], Pamela Ouyang, MBBS[4], David A. Bluemke, MD, PhD[5], Harikrishna Tandri, MD, PhD[4], R. Graham Barr, MD, DrPH[1,2], Emilia Bagiella, PhD[3], Anne R. Cappola, MD, ScM[6], Michael R. Bristow, MD, PhD[7], Craig Johnson, MS[8], Richard A. Kronmal, PhD[8], Jorge R. Kizer, MD, MS[9], Joao A.C. Lima, MD[4], and Steven M. Kawut, MD, MS[6,10,11]

Authors' affiliations:

[1]Department of Medicine, College of Physicians and Surgeons, and the Departments of [2]Epidemiology and [3]Biostatistics, Mailman School of Public Health, Columbia University, New York, NY

[4]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

[5]Radiology and Imaging Sciences, National Institutes of Health/Clinical Center, National Institute for Biomedical Imaging and Bioengineering, Bethesda, MD

[6]Department of Medicine, [10]Penn Cardiovascular Institute, and the [11]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA

[7]Department of Medicine, Anschutz Medical Center, University of Colorado Denver, Aurora, CO

[8]Department of Biostatistics, University of Washington, Seattle, WA

[9]Departments of Medicine and Public Health, Weill-Cornell Medical College, New York, NY

Correspondence and requests for reprints:

Steven M. Kawut, MD, MS

University of Pennsylvania School of Medicine

711 Blockley Hall

423 Guardian Dr.

Philadelphia, PA 19104

kawut@mail.med.upenn.edu

Ph: 215-573-0258

Fax: 215-573-5325

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At a Glance Commentary

Scientific Knowledge on the Subject: Female gender is a risk factor for the development of pulmonary hypertension (PH), yet women appear to have better right ventricular (RV) function and improved survival compared to men with PH. While sex hormones have been well-studied in left heart failure, the role of sex hormones in RV structure and function is largely unknown.

What This Study Adds to the Field: We have shown that higher levels of estradiol are associated with better RV systolic function in post-menopausal women using hormone therapy. Higher levels of androgens (both testosterone and dehydroepiandrosterone) are associated with greater RV mass and larger RV volumes in men and post-menopausal women, respectively, in a large cohort of cardiovascular disease-free participants.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT

Rationale: Sex hormones have effects on the left ventricle, but hormonal influences on the right ventricle (RV) are unknown.

Objectives: We hypothesized that sex hormones would be associated with RV morphology in a large cohort free of cardiovascular disease.

Methods: Sex hormones were measured by immunoassay and RV ejection fraction (RVEF), stroke volume (RVSV), mass, end-diastolic volume, and end-systolic volume (RVESV) were measured by cardiac magnetic resonance imaging in 1957 men and 1738 post-menopausal women. The relationship between each hormone and RV parameter was assessed with multivariable linear regression.

Measurements and Main Results: Higher estradiol levels were associated with higher RVEF (beta per 1 ln[nmol/L] 0.88, 95% Confidence Interval [CI] 0.32 – 1.43, p = 0.002) and lower RVESV (beta per 1 ln[nmol/L] -0.87, 95% CI -1.67 – -0.08, p = 0.03) in women using hormone therapy (HT) . In men, higher bioavailable testosterone levels were associated with higher RVSV (beta per 1 ln[nmol/L] 1.97, 95% CI 0.20 – 3.73, p = 0.03) and greater RV mass and volumes ($p \leq 0.01$). Higher dehydroepiandrosterone levels were associated with higher RVSV (beta per 1 ln[nmol/L] 1.37, 95% CI 0.15 – 2.59, p = 0.03) and greater RV mass (beta per 1 ln[nmol/L] 0.25, 95% CI 0.00 – 0.49, p = 0.05) and volumes ($p \leq 0.001$) in women.

Conclusions: Higher estradiol levels were associated with better RV systolic function in women using HT. Higher levels of androgens were associated with greater RV mass and volumes in both genders.

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INTRODUCTION

Gender differences in atherosclerosis and congestive heart failure (CHF) have been well-described, with women experiencing a significant lag in the onset of coronary artery disease and lower rates of CHF compared to men (1). Estrogen, testosterone, dehydroepiandrosterone (DHEA), and sex hormone binding globulin (SHBG) have important, albeit controversial, roles in left ventricular (LV) function and systemic vascular disease, whereas the effects of sex hormones on right ventricular (RV) and pulmonary vascular function are unknown.

Estrogen has protective effects on the pulmonary vasculature and improves RV contractility in animals (2-4). Testosterone has been shown to be a pulmonary vasodilator, yet has unclear effects on pulmonary endothelium (5, 6). Treatment with DHEA prevents pulmonary vascular changes, RV hypertrophy, and prolongs survival in animal models of pulmonary hypertension (PH) (7, 8). SHBG is expressed in myocytes of failing human hearts and in murine fetal lung epithelium, but its role in pulmonary vascular function has not been studied (9, 10).

Despite the beneficial effects of estrogen on the pulmonary vasculature, female gender is the best established clinical risk factor for idiopathic pulmonary arterial hypertension (PAH) (11). Yet, women have higher RV ejection fraction (RVEF) and improved survival compared to men with PAH (12-14). In systemic cardiovascular disease, an individual's estrogen:testosterone balance may be more predictive of disease risk than either hormone alone (15, 16). Finally, it is unknown how sex hormones affect the interaction of the RV with the pulmonary vasculature, particularly in individuals with no known (or subclinical) PH.

We examined the cross-sectional association of serum estradiol (E2), bioavailable testosterone (bioT), DHEA, SHBG, and the E2:testosterone ratio (E2:T) with RV structure and function assessed by cardiac magnetic resonance imaging (MRI) in a large cohort of men and

post-menopausal women without clinical cardiovascular disease. We hypothesized that higher E2, DHEA, and E2:T and lower testosterone and SHBG levels would be associated with higher RVEF and RV stroke volume (RVSV) and lower RV mass, RV end-diastolic volume (RVEDV), and RV end-systolic volume (RVESV). Preliminary results from this study have been published in abstract form (17).

METHODS

Study Sample

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter prospective cohort study to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease in Caucasians, African-Americans, Hispanics, and Chinese (18). In 2000-2002, MESA recruited 6,814 subjects aged 45-84 years old from six U.S. communities: Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles, CA. Exclusion criteria included clinical cardiovascular disease, weight > 300 lbs, pregnancy, or impediment to long-term participation. The presence of clinical cardiovascular disease was determined at participant screening by questionnaire. Participants were excluded if they answered "yes" to having been diagnosed by a physician with heart attack, stroke, transient ischemic attack, heart failure, angina, current atrial fibrillation, and/or to having undergone any prior cardiovascular procedure. The protocols of MESA and studies described herein were approved by the Institutional Review Boards of all collaborating institutions and the National Heart Lung and Blood Institute. The MESA-Right Ventricle Study measured RV morphology in participants eligible for MRI (without metal implants, device or

fragment). We included all subjects from MESA-RV with interpretable cardiac MRIs and available sex hormone levels.

Cardiac Magnetic Resonance Imaging Measures

The cardiac MRI protocol has been described elsewhere (19). All imaging was performed on 1.5 T magnets with a 4-element phased-array surface coil positioned anteriorly and posteriorly and electrocardiographic gating. Imaging consisted of fast gradient echo cine images of the LV with temporal resolution $\leqslant$50 ms.

Methods for interpretation of LV and RV parameters have been previously reported (19, 20). Briefly, RV image analysis was performed by two independent analysts on Windows workstations using QMASS software (v4.2, Medis, the Netherlands). The endocardial and epicardial borders of the RV were traced manually on short axis cine images at the end-diastolic and end-systolic phase. Papillary muscles and trabeculae were included in the RV volumes and excluded from RV mass (21). RVEDV and RVESV were calculated using Simpson's rule by summation of areas on each slice multiplied by the sum of slice thickness and image gap. RV mass was determined at the end-diastole phase as the difference between end-diastolic epicardial and endocardial volumes multiplied by the specific gravity of the heart (1.05 g/cm^3) (19). RVSV was calculated by subtracting RVESV from RVEDV. RVEF was calculated by dividing RVSV by RVEDV. The intra-reader intraclass correlation coefficient (ICC) from random, blinded re-reads of 229 scans for RV mass was 0.94 and for 230 scans was 0.99, 0.95, and 0.89 for RVEDV, RVESV, and RVEF, respectively. The ICC was 0.96 for RVSV. The inter-reader ICC from

random, blinded re-reads of 240 scans for RV mass, RVEDV, RVESV, and RVEF was 0.89, 0.96, 0.94 and 0.80, respectively. The ICC for RVSV was 0.93.

Serum Sex Hormones

Fasting morning blood samples were drawn and stored using standardized procedures (22). Serum hormone concentrations (nmol/L) were measured in the Steroid Hormone Laboratory at the University of Massachusetts Medical Center in Worcester, MA. E2 was measured via an ultra-sensitive radioimmunoassay kit (Diagnostic System Laboratories, Webster, TX). Total testosterone (total T) and DHEA were measured directly with radioimmunoassay kits and SHBG was measured by chemiluminescent enzyme immunometric assay using Immulite kits (Diagnostic Products Corporation, Los Angeles, CA). BioT was calculated from total T and SHBG, using the method described by Södergård (23). Assay quality control has been described elsewhere (24). The intra-assay coefficients of variation for E2, total T, DHEA, and SHBG were 10.5%, 12.3%, 11.2%, and 9.0%, respectively.

Other Covariates

Race/ethnicity was self-reported during the baseline exam according to 2000 US Census criteria as race (Caucasian, African-American, etc) and ethnicity (Hispanic or non-Hispanic). Standard questionnaires were used to ascertain smoking status and level of education. Medication use, including current post-menopausal hormone therapy (HT), testosterone therapy, and DHEA supplement use, was ascertained by medication inventory (25). Self-report was used to determine pre-, peri-, or post-menopausal status. Intentional exercise (MET-min/wk) was assessed by survey. Height was measured to the nearest 0.1 cm with the participant in stocking

feet and weight was measured to the nearest pound with the participant in light clothing using a balanced scale. Resting blood pressure was measured using the Dinamap Monitor PRO 100 (Critikon, Tampa, FL) automated oscillometric device. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or current use of anti-hypertension medication. Fasting blood samples were drawn and sent to a central laboratory for measurement of glucose and lipids. Presence of diabetes mellitus was based on self-reported physician diagnosis or a fasting glucose value ≥126 mg/dL, the latter measured by rate reflectance spectrophotometry (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY). Fasting glucose of 100-125 mg/dL was considered impaired fasting glucose. Spirometry, urine cotinine, and computed tomographic (CT) lung density (percentage of emphysema-like lung) measures were available for 2406 participants (26, 27).

Statistical Analysis

Continuous variables were expressed as means and standard deviations. Categorical variables were expressed as percentages. Sex hormones were logarithmically transformed, except in the case of E2:T.

Multivariate linear regression was used to assess the relationship of each hormone with RV parameter. Initial models included age, race/ethnicity, height, weight, waist circumference, and current hormone supplementation. Adjustment for height and weight avoided the assumptions made in indexing the RV measures to certain parameters of body size (e.g., body surface area), while accounting for differences in body size between participants. Models were further adjusted for smoking, diabetes mellitus, impaired glucose tolerance, hypertension and use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high-density lipoprotein levels, statin

use, intentional exercise, education level, and respective LV parameters (e.g., the model for RVEF was adjusted for LV ejection fraction, the model for RV mass for LV mass, and so forth). Adjustment for LV parameters was performed to account for the contribution of LV abnormalities to RV changes (for example, increased LV mass causing pulmonary venous hypertension leading to increased RV mass), to account for body size differences, and to examine RV-specific associations. RVSV was not adjusted for LV stroke volume considering the significant inter-dependence of these measures.

We performed adjustments for lung function in the subgroup with available lung function measures (N = 2406). Statistical significance was defined as $P < 0.05$. As each hormone analysis was considered an independent hypothesis, there was no correction made for multiple comparisons (28). Analyses were performed using STATA 10.0 (StataCorp, College Station, TX).

RESULTS

MESA enrolled 6814 participants of whom 5098 had cardiac MRIs and 5004 had interpretable scans (Figure 1). Of these, 4634 were selected for RV interpretation, and 4204 had RV measures completed. We excluded women missing HT data (N = 221), those who reported pre- (N = 146), unknown (N = 60), or missing (N =1) menopausal status, and participants with missing data for covariates (N = 81). The final study sample of 3695 participants included 1957 men and 1738 postmenopausal women, of whom 61 were missing E2 levels, 66 were missing bioT levels, 61 were missing DHEA levels, and 60 were missing SHBG levels.

Participant characteristics are shown in Table 1 and Table E1 of the Supplemental Material. One-third of women reported current HT use. Women tended to have higher RVEF (72.6 ± 6.0% vs. 68.2 ± 6.2%) and lower RVSV (77.5 ± 16.3 mL vs. 95.9 ± 20.7 mL), RV mass

(18.9 ± 3.6 g vs. 23.1 ± 4.4 g), RVEDV (107.2 ± 22.5 mL vs. 140.9 ± 29.7 mL) and RVESV (29.7 ± 10.0 mL vs. 45.1 ± 14.1 mL) than men.

Estradiol

Among women, there were significant or borderline significant interactions between E2 and HT for several RV measures (RVEF p = 0.02, RV mass p = 0.09, RVESV p = 0.10); the E2 analyses were therefore stratified by HT use. Higher levels of E2 were associated with higher RVEF in women using HT (Figure 2 and Table 2). This association persisted in the fully adjusted model and after adjustment for LVEF, suggesting that exogenous E2 was associated with RV systolic function independent of any effects on the LV. There was a 2% difference in RVEF across quintiles of E2 levels (data not shown). There was no association between E2 and RVEF in HT non-users or in men (Table 2).

Similarly, a higher E2 level was associated with lower RVESV in HT users, corresponding to a 6% difference across quintiles of E2 levels (data not shown), but not in HT non-users or in men. This association persisted after adjustment for LVESV (Table 2). In the subset of women with available lung function (N = 1072), adjustment for lung function variables did not affect the results (Table E2, Supplemental Material).

Bioavailable Testosterone

Higher levels of bioT were associated with larger RVSV, greater RV mass, and larger RVEDV and RVESV in men but not in women (Table 3). There was a 4% difference in RVSV, a 3% difference in RV mass, and a 1% and 3% difference in RVEDV and RVESV respectively across quintiles of bioT levels (data not shown). These associations persisted after adjustment for

respective LV measures (Table 3), and after adjustment for lung function (N = 1303) (Table E3, Supplemental Material). Similar associations were seen between total T and RVSV, RV mass, and RV volumes, and results were unchanged when participants taking testosterone supplementation (N = 27) were excluded from analysis (data not shown).

Dehydroepiandrosterone

In women, higher levels of DHEA were associated with increased RVEF, RVSV, greater RV mass, and larger volumes (Table 4). There was a 3% difference in RVEF, a 1% difference in RV mass, and 3% and 6% differences in RVEDV and RVESV, respectively, across quintiles of DHEA (data not shown). There appeared to be similar associations between DHEA and RVEF, RV mass, and RVESV in men, although these were not statistically significant. Similar associations were seen in the subset of participants with available measures of lung function (Table E4, Supplemental Material). Results were unchanged when participants taking DHEA supplementation (N = 36) were excluded and, among women, effect estimates were unchanged when adjusted for HT (data not shown).

Sex Hormone Binding Globulin

Among women and possibly men, higher levels of SHBG were associated with higher RVSV in limited models, but these associations were attenuated and not statistically significant when fully adjusted for all covariates (Table 5). Similarly, among men there was an association between higher SHBG levels and greater RV mass ($p = 0.05$) that did not persist in multivariate analysis. Results were unchanged when adjusted for HT (in women) and testosterone supplementation (in men). In the smaller subgroup of participants with lung function measures,

there were no significant associations seen in men or women but effect estimates were unchanged after adjustment for these measures (Table E5, Supplemental Material).

Estradiol:Testosterone Ratio

There was a suggestion of an association between higher E2:T and lower RV volumes in men only (Table E6, Supplemental material). For example, a 1 unit increase in E2:T was associated with an 18.98 mL decrement in RVESV after multivariate adjustment (95% CI -37.19 – -0.77 mL, p = 0.04), although this association was attenuated after adjustment for LVESV (-15.08, 95% CI -31.22 – 1.07 mL, p = 0.07). Similar associations were seen in the models for RVEDV and while not significant, among men with available lung function measures (Table E7, Supplemental Material).

DISCUSSION

Serum sex hormones were associated with RV structure and function in an ethnically and racially diverse cohort without clinical cardiovascular disease. Higher levels of E2 were associated with higher RVEF and lower RVESV in post-menopausal women using HT (but not in HT non-users or men), and higher testosterone levels were associated with greater RV mass and larger RV volumes in men (but not in women). Contrary to our hypothesis, higher levels of DHEA were associated with greater RV mass and larger volumes in women and possibly in men. These associations were similar to those seen with testosterone in men, suggesting an androgenic effect. Higher levels of SHBG may have been associated with higher RVSV among women and possibly men in limited models only. With E2, bioT, and DHEA, most of the results remained significant after adjustment for the respective LV measures, implying RV-specific or RV-

disproportionate associations, as well as after adjustment for measures of lung function (in a smaller subset), implying unique associations between sex hormones and the RV independent of respiratory effects. To our knowledge, this is the only study of sex hormones and RV structure and function assessed by cardiac MRI.

While some of the effect sizes seem small, they are comparable to those seen in the LV related to active smoking and diabetes mellitus (29). In severe PAH, intravenous epoprostenol improves RVEF by only 4% while leading to significant improvements in exercise capacity, functional status, and survival (30, 31). In the normal RV (with a lower "signal:noise ratio" compared to that seen in disease), similar or smaller differences may have important physiologic effects.

We have shown that higher E2 levels in HT users were associated with higher RVEF and lower RVESV. In men, higher E2:T was possibly associated with lower RV volumes. High estrogen:low testosterone states have been associated with a lower risk of cardiovascular disease in aging men (15, 16). Estrogen has been associated with elevated markers of angiogenesis and heart neovascularization, and human ventricular myocardium contains functional estrogen receptors (ER) (32, 33). Cardiac neovascularization promotes collateral blood flow, which may promote beneficial remodeling and improve RV systolic function (34). There are several possible explanations as to why these associations (in women) were demonstrated only in HT users. A 1 ln increment in E2 in HT users may have different biologic implications than a 1 ln increment in a non-user, either due to greater E2 levels (as seen here) or variance in HT users, altered or unmeasured metabolites, or protein/receptor interactions. HT upregulates ER tissue expression and may lead to altered E2 sensitivity among HT users (35). The appearance of this association

in HT users only may be explained by unmeasured differences between users and non-users, although they had similar baseline characteristics (36).

We have shown that bioT levels were associated with greater RV mass and larger RV volumes, independent of these LV measures. Testosterone increases the myocardial inflammatory response, promotes cardiac remodeling, and increases LV mass in animals (37, 38). On the other hand, epidemiologic studies suggest testosterone *deficiency* is associated with worse cardiovascular outcomes among men, and there is some evidence that testosterone supplementation improves functional capacity in androgen-deficient men with CHF (39, 40). The association between androgens (both bioT and DHEA) and greater RV mass and volumes here may not be detrimental *per se*, as has been proposed with exercise-induced increases in LV mass in trained athletes and in RV mass in MESA participants (41). In fact, higher levels of both bioT (in men) and DHEA (in women) were associated with higher RVSV. Ultimately, maintaining androgen balance may be most important for cardiopulmonary health.

The associations of DHEA with greater RV mass and volumes contradict extensive animal and preclinical data demonstrating that DHEA prevents or reverses PH and improves vascular remodeling (7, 8, 42). Similarly, previous epidemiologic studies have shown lower levels of DHEA associated with increased cardiovascular risk (43). It has been proposed that DHEA may have important intracellular signaling effects independent of hormonal or steroid action (42). DHEA stimulates both nitric oxide and endothelin-1, two important but antagonistic mediators in PH (44). As such, DHEA may have more complex effects on the pulmonary vasculature and RV than previously appreciated. As our findings relate to RV morphology, it is possible that DHEA has pleiotropic effects on the pulmonary vasculature and the RV. Recently, it has been shown that extremes (low or high levels) and variability in serum DHEA predict

mortality in older adults more-so than a single measurement (45). Thus, it is possible that baseline measurement may not accurately capture DHEA trajectory and therefore disease risk. The sulfate ester of DHEA (DHEA-S), known to have higher and more stable serum levels than DHEA, was not measured in this study and may have been more informative.

While the effects were modest, there was a suggestion that higher levels of SHBG were associated with higher RVSV. In left heart failure, higher levels of SHBG are associated with poor outcomes and we have found associations with subclinical atherosclerosis (46, 47). Whether SHBG has unique effects on the pulmonary vasculature and the RV is unknown.

Our study has several limitations. Since this is a cross-sectional observational study, no conclusions can be drawn about causality. However, the MESA cohort offers a unique opportunity to generate hypotheses about hormonal influences on the RV given 1) it is population-based, 2) it includes female and minority participants, and 3) to our knowledge, it is the largest study of RV structure and function assessed by cardiac MRI to date. Cardiac MRI is considered the "gold standard" for assessment of the RV, and RV measures have been found to be highly accurate and reproducible in normal individuals (and in those with heart failure) (48). We included post-menopausal women; the results may not apply to younger, premenopausal women. Measurement of hormones was performed only at baseline, although single measurements of sex hormones are reliable and reproducible over several years in post-menopausal women (49). While hemodynamic data would have allowed for hypothesis-generation about the associations between sex hormones and pulmonary vascular function specifically, these measurements were not available nor would they have been feasible in a cohort of this size.

We included women taking HT given 1) the potential for selection bias if excluded, as it has been well-documented that women taking HT are fundamentally different (e.g. lower cardiovascular risk, higher socioeconomic status) than those who are not (36), 2) E2 levels regardless of source (i.e. endogenous or exogenous) may directly affect RV structure and function, and 3) available data on HT use and related covariates allowed for adjustment for potential unmeasured confounders. A small number of individuals were receiving either testosterone or DHEA supplementation; analyses excluding such individuals provided identical results. The relationship of E2 with RV measures depended on HT use, justifying this approach and indicating an important interaction for further study. Unmeasured or residual confounding of our results is still possible.

We have shown that serum E2 in the setting of HT is associated with better RV systolic function in post-menopausal women and that higher levels of androgens (bioT and DHEA) are associated with larger RVs in men and post-menopausal women without cardiovascular disease. Estrogen: testosterone balance may be particularly informative in men and further study is needed to define the role of SHBG in pulmonary vascular and RV function. The associations seen for E2 and DHEA, in particular, contradict what is known about pulmonary vascular disease, suggesting that certain hormones may have pleiotropic actions for the RV and the pulmonary vasculature.

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Figure Legends

Figure 1: Study sample

Figure 2: Ln(E2) parameter estimates with 95% Confidence Intervals for RVEF stratified by hormone therapy use in limited, adjusted, and fully adjusted regression models (women only)

Table 1. Participant characteristics

	Gender	
	Men	Women
Number of Participants	1957	1738
Demographics		
Age, years	61.5 ± 10.1	64.0 ± 9.1
Race/ethnicity, %		
Caucasian	38.6	40.2
African-American	25.2	26.2
Hispanic	23.5	21.1
Chinese	12.8	12.4
Education, %		
< High school	15.5	18.9
High school	15.7	22.0
< College, (> high school)	26.0	30.3
≥ College	42.8	28.8
Anthropomorphics		
Height, cm	173.4 ± 7.7	159.7 ± 7.1
Weight, kg	83.0 ± 14.8	71.8 ± 15.3
Body mass index, kg/m^2	27.5 ± 4.1	28.1 ± 5.5
Waist circumference, cm	98.2 ± 11.4	96.1 ± 14.5
Disease Prevalence		
Hypertension, %	40.9	49.8
Systolic blood pressure, mm Hg	125.1 ± 18.9	128.3 ± 23.1
Diastolic blood pressure, mm Hg	74.9 ± 9.3	69.3 ± 10.4
Diabetes mellitus, %		
Normal	71.6	76.6
Impaired fasting glucose	15.7	12.0
Untreated diabetes	2.9	2.2
Treated diabetes	9.8	9.2
Total cholesterol, mg/dl	188.1 ± 33.8	202.1 ± 35.2
High-density lipoprotein, mg/dl	45.0 ± 11.5	57.1 ± 15.6
Statin use, %	13.8	17.6
Smoking Status		
Never-smoker, %	42.6	60.8

Former smoker, %	43.4	28.7
Current smoker, %	14.1	10.6
Pack years, among ever-smokers	15.4 ± 26.7	13.1 ± 21.9
Serum sex hormone levels		
Estradiol, nmol/L	0.1 ± 0.0	0.1 ± 0.2
Hormone therapy Users		0.3 ± 0.2
Hormone therapy Non-Users		0.1 ± 0.1
Bioavailable testosterone, nmol/L	5.5 ± 2.1	0.3 ± 0.3
DHEA, nmol/L	14.2 ± 7.3	11.6 ± 6.4
Sex hormone binding globulin, nmol/L	43.9 ± 18.7	77.6 ± 55.2
Estradiol: testosterone ratio	0.01 ± 0.03	0.23 ± 0.63
Hormone therapy User		0.50 ± 1.01
Hormone therapy Non-User		0.10 ± 0.16
Hormone supplementation		
Hormone therapy, %	0.0	33.1
Testosterone compounds, %	0.7	0.0
DHEA supplement, %	0.01	0.01
RV measures		
RVEF, %	68.2 ± 6.2	72.6 ± 6.0
RVSV, mL	95.9 ± 20.7	77.5 ± 16.3
RV mass, g	23.1 ± 4.4	18.9 ± 3.6
RVEDV, mL	140.9 ± 29.7	107.2 ± 22.5
RVESV, mL	45.1 ± 14.1	29.7 ± 10.0

Data shown as mean ± standard deviation or %.

Table 2. Associations between estradiol and RV measures in limited and adjusted models among men and women (based on hormone therapy [HT] use)

	Men		Women HT Users		Women HT Non-Users	
Number	1927		567		1140	
	Beta (95% CI)*	**P value**	**Beta (95% CI)**	**P value**	**Beta (95% CI)**	**P value**
RVEF, %						
Limited†	-0.23 (-0.97 – 0.50)	0.54	1.07 (0.49 – 1.65)	< 0.001	0.15 (-0.39 – 0.69)	0.58
Adjusted‡	-0.26 (-1.00 – 0.48)	0.49	0.91 (0.32 – 1.50)	0.003	0.13 (-0.41 – 0.67)	0.65
Adjusted + LVEF	-0.35 (-1.02 – 0.32)	0.30	0.88 (0.32 – 1.43)	0.002	0.05 (-0.46 – 0.55)	0.86
RVSV, mL						
Limited	-1.72 (-3.92 – 0.47)	0.12	1.04 (-0.29 – 2.37)	0.13	-0.31 (-1.53 – 0.91)	0.61
Adjusted	-1.25 (-3.43 – 0.93)	0.26	0.57 (-0.76 – 1.90)	0.40	-0.29 (-1.50 – 0.93)	0.40
RV mass, g						
Limited	-0.16 (-0.60 – 0.29)	0.49	0.08 (-0.20 – 0.37)	0.57	-0.25 (-0.51 – 0.01)	0.06
Adjusted	-0.08 (-0.53 – 0.37)	0.72	0.02 (-0.27 – 0.30)	0.90	-0.24 (-0.50 – 0.02)	0.07
Adjusted + LV mass	-0.02 (-0.44 – 0.39)	0.91	0.11 (-0.16 – 0.38)	0.42	-0.20 (-0.44 – 0.05)	0.12
RVEDV, mL						
Limited	-2.21 (-5.20 – 0.76)	0.15	-0.08 (-1.83 – 1.67)	0.93	-0.71 (-2.31 – 0.89)	0.38
Adjusted	-1.47 (-4.44 – 1.50)	0.33	-0.50 (-2.26 – 1.25)	0.57	-0.64 (-2.24 – 0.96)	0.43
Adjusted + LVEDV	1.17 (-1.03 – 3.38)	0.30	0.17 (-1.13 – 1.47)	0.80	0.57 (-0.62 – 1.76)	0.35
RVESV, mL						
Limited	-0.49 (-1.99 – 1.01)	0.52	-1.12 (-1.99 – -0.26)	0.01	-0.40 (-1.19 – 0.39)	0.32
Adjusted	-0.22 (-1.73 – 1.29)	0.77	-1.07 (-1.94 – -0.21)	0.02	-0.36 (-1.15 – 0.44)	0.38
Adjusted + LVESV	0.50 (-0.84 – 1.83)	0.47	-0.87 (-1.67 – -0.08)	0.03	0.02 (-0.71 – 0.75)	0.95

*Per ln(nmol/L) increase in estradiol

†Adjusted for age, race/ethnicity, height, weight, waist circumference.

‡Adjusted for age, race/ethnicity, height, weight, waist circumference, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education.

Table 3. Associations between bioavailable testosterone and RV measures in limited and adjusted models, by gender

	Men		Women	
Number	1925		1696	
	Beta (95% CI)*	**P value**	**Beta (95% CI)**	**P value**
RVEF, %				
Limited†	-0.37 (-0.97 – 0.23)	0.23	-0.15 (-0.51 – 0.20)	0.40
Adjusted‡	-0.36 (-0.95 – 0.24)	0.25	-0.01 (-0.38 – 0.36)	0.97
Adjusted + LVEF	-0.40 (-0.94 – 0.14)	0.15	0.02 (-0.33 – 0.37)	0.92
RVSV, mL				
Limited	1.42 (-0.37 – 3.21)	0.12	-0.66 (-1.47 – 0.14)	0.11
Adjusted	1.97 (0.20 – 3.73)	0.03	-0.04 (-0.88 – 0.79)	0.92
RV mass, g				
Limited	0.40 (0.03 – 0.76)	0.03	-0.03 (-0.20 – 0.15)	0.77
Adjusted	0.49 (0.13 – 0.85)	0.01	0.08 (-0.10 – 0.26)	0.38
Adjusted + LV mass	0.44 (0.10 – 0.77)	0.01	0.04 (-0.13 – 0.21)	0.66
RVEDV, mL				
Limited	2.90 (0.47 – 5.33)	0.02	-0.70 (-1.75 – 0.36)	0.20
Adjusted	3.71 (1.31 – 6.11)	0.001	-0.05 (-1.15 – 1.06)	0.93
Adjusted + LVEDV	2.43 (0.64 – 4.21)	0.01	0.13 (-0.69 – 0.94)	0.78
RVESV, mL				
Limited	1.48 (0.26 – 2.70)	0.02	-0.03 (-0.55 – 0.49)	0.91
Adjusted	1.74 (0.53 – 2.96)	0.01	-0.01 (-0.55 – 0.54)	0.98
Adjusted + LVESV	1.63 (0.55 – 2.71)	0.001	-0.01 (-0.51 – 0.49)	0.96

*Per ln(nmol/L) increase in bioavailable testosterone
†Adjusted for age, race/ethnicity, height, weight, waist circumference, and testosterone supplementation (in men).
‡Adjusted for age, race/ethnicity, height, weight, waist circumference, testosterone supplementation (in men), smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education.

Table 4: Associations between DHEA and RV measures in limited and adjusted models, by gender

	Men		Women	
Number	1927		1696	
	Beta (95% CI)*	**P value**	**Beta (95% CI)**	**P value**
RVEF, %				
Limited†	-0.19 (-0.83 – 0.44)	0.55	-0.54 (-1.07 – -0.01)	0.05
Adjusted‡	-0.19 (-0.82 – 0.45)	0.56	-0.54 (-1.08 – 0.00)	0.05
Adjusted + LVEF	-0.24 (-0.82 – 0.33)	0.40	-0.44 (-0.94 – 0.07)	0.09
RVSV, mL				
Limited	0.16 (-1.73 – 2.05)	0.87	0.77 (-0.42 – 1.97)	0.21
Adjusted	0.55 (-1.32 – 2.42)	0.56	1.37 (0.15 – 2.59)	0.03
RV mass, g				
Limited	0.08 (-0.30 – 0.47)	0.67	0.21 (-0.04 – 0.47)	0.10
Adjusted	0.13 (-0.25 – 0.52)	0.51	0.36 (0.10 – 0.62)	0.01
Adjusted + LV mass	0.19 (-0.17 – 0.55)	0.31	0.25 (0.00 – 0.49)	0.05
RVEDV, mL				
Limited	0.87 (-1.69 – 3.43)	0.51	2.00 (0.43 – 3.57)	0.01
Adjusted	1.39 (-1.16 – 3.94)	0.29	2.80 (1.20 – 4.40)	0.001
Adjusted + LVEDV	1.30 (-0.59 – 3.19)	0.18	2.28 (1.09 – 3.46)	<0.001
RVESV, mL				
Limited	0.71 (-0.57 – 2.00)	0.28	1.23 (0.45 – 2.01)	0.001
Adjusted	0.84 (-0.45 – 2.13)	0.20	1.43 (0.63 – 2.22)	<0.001
Adjusted + LVESV	0.92 (-0.23 – 2.10)	0.12	1.28 (0.55 – 2.00)	0.001

*Per ln(nmol/L) increase in DHEA

†Adjusted for age, race/ethnicity, height, weight, waist circumference, and DHEA supplementation

‡Adjusted for age, race/ethnicity, height, weight, waist circumference, DHEA supplementation, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education.

Table 5. Associations between sex hormone binding globulin and RV measures in limited and adjusted models, by gender

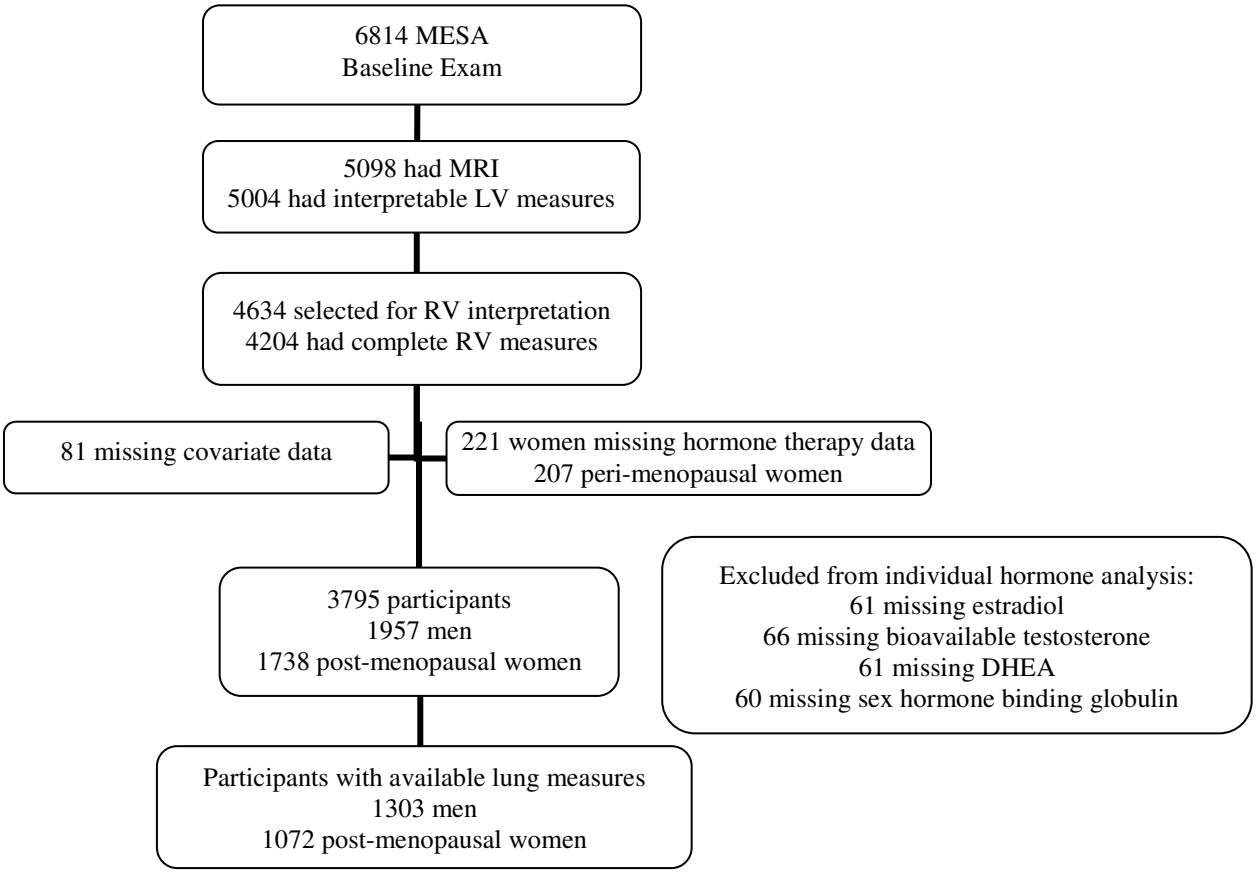
	Men		Women	
Number	1928		1707	
	Beta (95% CI)*	**P value**	**Beta (95% CI)**	**P value**
RVEF, %				
Limited†	0.08 (-0.69 – 0.85)	0.85	0.38 (-0.12 – 0.87)	0.14
Adjusted‡	0.12 (-0.68 – 0.91)	0.78	0.20 (-0.34 – 0.75)	0.47
Adjusted + LVEF	0.03 (-0.68 – 0.74)	0.93	0.09 (-0.42 – 0.60)	0.73
RVSV, mL				
Limited	1.96 (-0.34 – 4.25)	0.09	1.16 (0.05 – 2.27)	0.04
Adjusted	0.64 (-1.69 – 2.97)	0.59	0.08 (-1.15 – 1.31)	0.90
RV mass, g				
Limited	0.46 (-0.01 – 0.93)	0.05	0.09 (-0.14 – 0.33)	0.44
Adjusted	0.17 (-0.31 – 0.65)	0.48	-0.09 (-0.35 – 0.17)	0.51
Adjusted + LV mass	0.16 (-0.28 – 0.61)	0.47	-0.03 (-0.28 – 0.21)	0.78
RVEDV, mL				
Limited	2.90 (-0.20 – 6.01)	0.07	1.03 (-0.43 – 2.50)	0.17
Adjusted	0.78 (-2.40 – 3.95)	0.63	-0.18 (-1.80 – 1.44)	0.83
Adjusted + LVEDV	-0.13 (-2.47 – 2.22)	0.92	-0.42 (-1.62 – 0.77)	0.49
RVESV, mL				
Limited	0.95 (-0.61 – 2.51)	0.23	-0.13 (-0.85 – 0.60)	0.73
Adjusted	0.14 (-1.47 – 1.75)	0.86	-0.26 (-1.07 – 0.54)	0.52
Adjusted + LVESV	-0.07 (-1.49 – 1.36)	0.93	-0.09 (-0.82 – 0.65)	0.82

*Per ln(nmol/L) increase in sex hormone binding globulin

†Adjusted for age, race/ethnicity, height, weight, and waist circumference

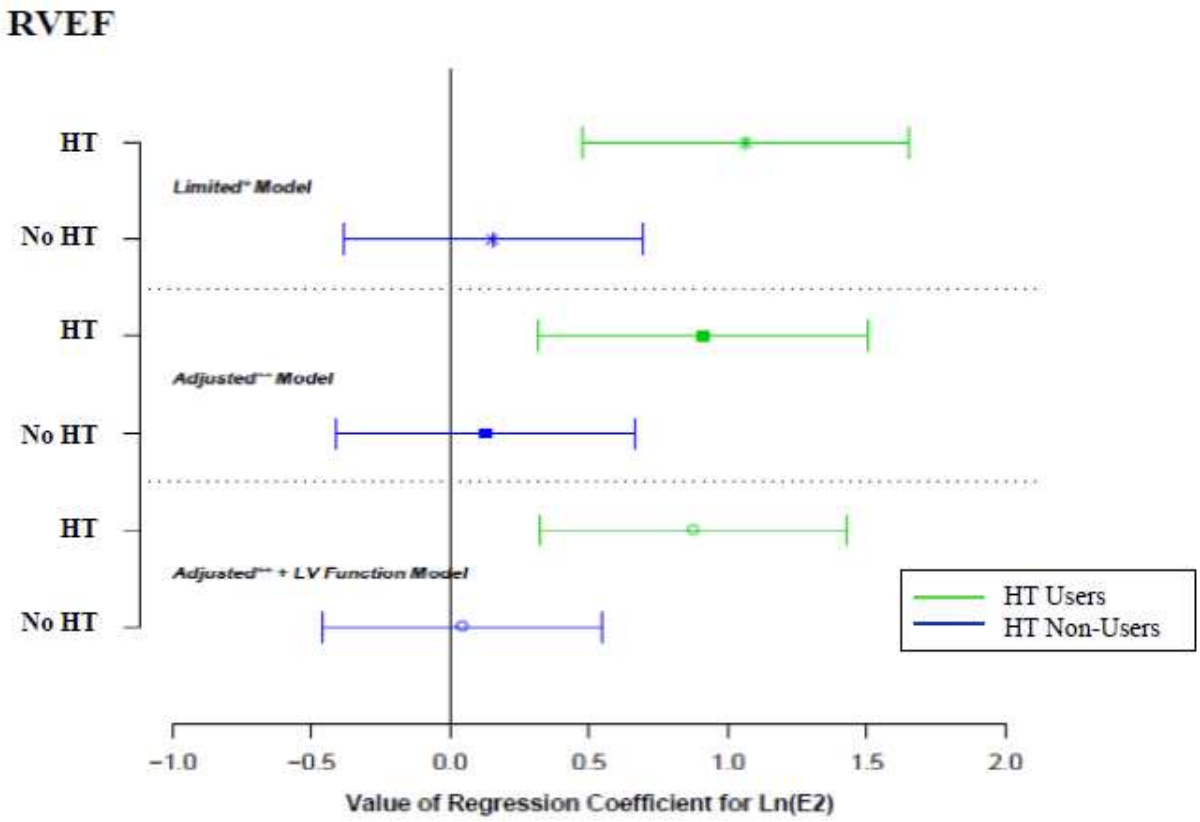
‡Adjusted for age, race/ethnicity, height, weight, waist circumference, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education.

Figure 1. Study sample



MESA: Multi-Ethnic Study of Atherosclerosis; MRI: Magnetic Resonance Imaging; RV: right ventricle

Figure 2. Ln(E2) parameter estimates with 95% Confidence Intervals for RVEF stratified by hormone therapy use in limited, adjusted, and fully adjusted regression models (women only)



*Adjusted for age, race/ethnicity, height, weight, waist circumference
**Adjusted for age, race/ethnicity, height, weight, waist circumference, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education.
LV function: left ventricular ejection fraction; E2: estradiol; RVEF: right ventricular ejection fraction; HT: hormone therapy

Sex Hormones are Associated with Right Ventricular Structure and Function: The MESA-Right Ventricle Study

Corey E. Ventetuolo, MD, Pamela Ouyang, MBBS, David A. Bluemke, MD, PhD, Harikrishna Tandri, MD, PhD, R. Graham Barr, MD, DrPH, Emilia Bagiella, PhD, Anne R. Cappola, MD, ScM, Michael R. Bristow, MD, PhD, Craig Johnson, MS, Richard A. Kronmal, PhD, Jorge R. Kizer, MD, MS, Joao A.C. Lima, MD, and Steven M. Kawut, MD, MS

Online Data Supplement

Table E1. Transformed serum sex hormone levels and RV measures, by hormone therapy use

	Gender	
	Men	Women
Number of Participants	1957	1738
Serum sex hormone levels		
Estradiol, ln(nmol/L)	-2.2 ± 0.4	-2.5 ± 0.9
Hormone therapy Users		-1.6 ± 0.8
Hormone therapy Non-Users		-2.9 ± 0.7
Bioavailable testosterone, ln(nmol/L)	1.6 ± 0.5	-1.6 ± 0.8
DHEA, ln(nmol/L)	2.5 ± 0.5	2.3 ± 0.6
Sex hormone binding globulin, ln(nmol/L)	0.5 ± 0.5	0.5 ± 0.5
RV measures		
RVEF, %	68.2 ± 6.2	72.6 ± 6.0
Hormone therapy Users		72.8 ± 5.7
Hormone therapy Non-Users		72.5 ± 6.2
RVSV, mL	95.9 ± 20.7	77.5 ± 16.3
Hormone therapy Users		78.3 ± 16.7
Hormone therapy Non-Users		77.2 ± 16.1
RV mass, g	23.1 ± 4.4	18.9 ± 3.6
Hormone therapy Users		19.0 ± 3.5
Hormone therapy Non-Users		18.9 ± 3.6
RVEDV, mL	140.9 ± 29.7	107.2 ± 22.5
Hormone therapy Users		107.8 ± 22.7
Hormone therapy Non-Users		106.9 ± 22.5
RVESV, mL	45.1 ± 14.1	29.7 ± 10.0
Hormone therapy Users		29.5 ± 9.4
Hormone therapy Non-Users		29.7 ± 10.2

Data shown as mean ± standard deviation or %.

Table E2. Associations between estradiol and RV measures in limited and adjusted models among men and women (based on hormone therapy [HT] use) with available measures of lung function

	Men		Women HT Users		Women HT Non-Users	
Number	1303		370		702	
Mean, ln nmol/L ± SD	-2.2 ± 0.4		-1.61 ± 0.9		-2.88 ± 0.7	
	Beta (95% CI)*	**P value**	**Beta (95% CI)**	**P value**	**Beta (95% CI)**	**P value**
RVEF, %						
Adjusted†	-0.37 (-1.18 - 0.43)	0.36	0.78 (0.11 – 1.45)	0.02	0.03 (-0.60 – 0.67)	0.92
Adjusted + lung function‡	-0.40 (-1.21 – 0.40)	0.33	0.79 (0.12 – 1.47)	0.02	0.00 (-0.64 – 0.63)	0.99
RVSV, mL						
Adjusted	-1.84 (-4.45 – 0.76)	0.17	0.50 (-1.08 – 2.07)	0.54	0.38 (-1.12 – 1.87)	0.62
Adjusted + lung function	-1.76 (-4.32 – 0.80)	0.18	0.50 (-1.08 – 2.07)	0.54	0.41 (-1.08 – 1.89)	0.59
RV mass, g						
Adjusted	-0.05 (-0.54 – 0.44)	0.84	0.07 (-0.25 – 0.38)	0.69	-0.07 (-0.37 – 0.22)	0.63
Adjusted + lung function	-0.05 (-0.53 – 0.44)	0.85	0.03 (-0.28 – 0.35)	0.83	-0.07 (-0.36 – 0.23)	0.66
RVEDV, mL						
Adjusted	-0.35 (-2.98 – 2.28)	0.79	0.20 (-1.31 – 1.70)	0.80	0.93 (-0.49 – 2.35)	0.20
Adjusted + lung function	-0.27 (-2.90 – 2.35)	0.84	0.10 (-1.40 – 1.61)	0.89	1.00 (-1.40 – 1.61)	0.17
RVESV, mL						
Adjusted	0.12 (-1.52 – 1.77)	0.88	-0.79 (-1.74 – -0.15)	0.10	0.22 (-0.67 – 1.12)	0.62
Adjusted + lung function	0.20 (-1.44 – 1.84)	0.81	-0.86 (-1.80 – 0.08)	0.08	0.28 (-0.61 – 1.17)	0.54

*Per ln(1nmol/L) increase in estradiol

†Adjusted for age, race/ethnicity, height, weight, waist circumference, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education. RVEF adjusted for LVEF, RV mass adjusted for LV end-diastolic mass, RVEDV and RVESV adjusted for LVEDV and LVESV, respectively.

‡ FEV1, FVC, FEV1/FVC, urine cotinine concentration, and CT lung density.

Table E3. Associations between bioavailable testosterone and RV measures in limited and adjusted models among men and women with available measures of lung function

	Men		Women	
Number	1302		1066	
Mean, ln nmol/L ± SD	1.7 ± 0.4		-1.7 ± 0.8	
	Beta (95% CI)*	**P value**	**Beta (95% CI)**	**P value**
RVEF, %				
Adjusted†	-0.60 (-1.33 – 0.13)	0.11	-0.06 (-0.50 – 0.38)	0.78
Adjusted + lung function‡	-0.65 (-1.37 – 0.08)	0.08	-0.06 (-0.50 – 0.38)	0.80
RVSV, mL				
Adjusted	1.82 (-0.54 – 4.19)	0.13	-0.26 (-1.30 – 0.78)	0.63
Adjusted + lung function	1.69 (-0.64 – 4.01)	0.16	-0.35 (-1.39 – 0.69)	0.51
RV mass, g				
Adjusted	0.64 (0.19 – 1.08)	0.01	0.05 (-0.15 – 0.26)	0.63
Adjusted + lung function	0.63 (0.19 – 1.08)	0.01	0.04 (-0.17 – 0.24)	0.71
RVEDV, mL				
Adjusted	2.14 (-0.24 – 4.52)	0.08	0.51 (-0.48 – 1.50)	0.31
Adjusted + lung function	2.21 (-0.17 – 4.59)	0.07	0.49 (-0.50 – 1.48)	0.34
RVESV, mL				
Adjusted	1.85 (0.36 – 3.34)	0.02	0.13 (-0.49 – 0.75)	0.68
Adjusted + lung function	1.92 (0.44 – 3.41)	0.01	0.11 (-0.52 – 0.73)	0.74

*Per ln(1nmol/L) increase in bioavailable testosterone

†Adjusted for age, race/ethnicity, height, weight, waist circumference, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, level of education, and testosterone supplementation (in men). RVEF adjusted for LVEF, RV mass adjusted for LV end-diastolic mass, RVEDV and RVESV adjusted for LVEDV and LVESV, respectively.

‡ FEV1, FVC, FEV1/FVC, urine cotinine concentration, and CT lung density.

Table E4. Associations between DHEA and RV measures in limited and adjusted models among men and women with available measures of lung function

	Men		Women	
Number	1303		1072	
Mean, ln nmol/L ± SD	2.6 ± 0.5		2.3 ± 0.5	
	Beta (95% CI)*	**P value**	**Beta (95% CI)**	**P value**
RVEF, %				
Adjusted†	-0.64 (-1.33 – 0.05)	0.07	-0.52 (-1.17 – 0.12)	0.11
Adjusted + lung function‡	-0.61 (-1.30 – 0.08)	0.08	-0.60 (-1.26 – 0.06)	0.07
RVSV, mL				
Adjusted	-0.17 (-2.40 – 2.07)	0.88	1.67 (0.13 – 3.20)	0.03
Adjusted + lung function	-0.16 (-2.36 – 2.03)	0.88	1.53 (0.01 – 3.06)	0.05
RV mass, g				
Adjusted	0.29 (-0.13 – 0.71)	0.18	0.34 (0.04 – 0.64)	0.03
Adjusted + lung function	0.29 (-0.13 – 0.71)	0.18	0.33 (0.03 – 0.63)	0.03
RVEDV, mL				
Adjusted	0.36 (-1.89 – 2.61)	0.76	2.44 (0.99 – 3.90)	0.001
Adjusted + lung function	0.27 (-1.98 – 2.52)	0.82	2.46 (1.00 – 3.91)	0.001
RVESV, mL				
Adjusted	1.08 (-0.33 – 2.49)	0.13	1.41 (0.50 – 2.32)	0.001
Adjusted +lung function	1.02 (-0.38 – 2.43)	0.15	1.38 (0.47 – 2.29)	0.001

*Per ln(1nmol/L) increase in DHEA

†Adjusted for age, race/ethnicity, height, weight, waist circumference, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, level of education, and DHEA supplementation. RVEF adjusted for LVEF, RV mass adjusted for LV end-diastolic mass, RVEDV and RVESV adjusted for LVEDV and LVESV, respectively.

‡ FEV1, FVC, FEV1/FVC, urine cotinine concentration, and CT lung density.

Table E5. Associations between sex hormone binding globulin and RV measures in limited and adjusted models among men and women with available measures of lung function

	Men		Women	
Number	1304		1072	
Mean, ln nmol/L ± SD	3.7 ± 0.4		4.2 ± 0.6	
	Beta (95% CI)*	**P value**	**Beta (95% CI)**	**P value**
RVEF, %				
Adjusted†	0.25 (-0.63 – 1.12)	0.58	0.06 (-0.59 – 0.70)	0.86
Adjusted + lung function	0.30 (-0.59 – 1.18)	0.51	0.02 (-0.63 – 0.67)	0.95
RVSV, mL				
Adjusted	0.30 (-2.56 – 3.16)	0.84	0.36 (-1.17 – 1.89)	0.65
Adjusted + lung function	0.52 (-2.30 – 3.33)	0.72	0.30 (-1.22 – 1.81)	0.70
RV mass, g				
Adjusted†	0.06 (-0.48 – 0.59)	0.83	0.02 (-0.28 – 0.32)	0.90
Adjusted + lung function	0.06 (-0.48 – 0.59)	0.83	0.01 (-0.29 – 0.31)	0.94
RVEDV, mL				
Adjusted	-1.85 (-4.71 – 1.02)	0.22	-0.40 (-1.85 – 1.05)	0.59
Adjusted + lung function	-1.83 (-4.71 – 1.05)	0.21	-0.43 (-1.89 – 1.02)	0.56
RVESV, mL				
Adjusted	-0.69 (-2.48 – 1.11)	0.45	-0.07 (-0.97 – 0.84)	0.89
Adjusted + lung function	-0.64 (-2.44 – 1.16)	0.49	-0.08 (-0.99 – 0.83)	0.86

*Per ln(1nmol/L) increase in sex hormone binding globulin

†Adjusted for age, race/ethnicity, height, weight, waist circumference, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education. RVEF adjusted for LVEF, RV mass adjusted for LV end-diastolic mass, RVEDV and RVESV adjusted for LVEDV and LVESV, respectively.

‡ FEV1, FVC, FEV1/FVC, urine cotinine concentration, and CT lung density.

Table E6. Associations between estradiol:testosterone ratio and RV measures in limited and adjusted models among men and women (based on hormone therapy [HT] use)

	Men		Women HT Users		Women HT Non-Users	
Number	1924		566		1139	
	Beta (95% CI)*	**P value**	**Beta (95% CI)**	**P value**	**Beta (95% CI)**	**P value**
RVEF, %						
Limited†	4.75 (-4.25 – 13.74)	0.30	0.36 (-0.11 – 0.82)	0.13	-0.90 (-3.09 – 1.28)	0.42
Adjusted‡	4.92 (-4.04 – 13.87)	0.28	0.20 (-0.29 – 0.69)	0.43	-0.96 (-3.15 – 1.24)	0.39
Adjusted + LVEF	6.15 (-1.93 – 14.22)	0.14	0.27 (-0.19 – 0.73)	0.26	-1.13 (-3.18 – 0.93)	0.28
RVSV, mL						
Limited	-10.46 (-37.25 – 16.34)	0.44	0.10 (-1.03 – 1.22)	0.87	1.12 (-3.64 – 5.88)	0.64
Adjusted	-16.79 (-43.14 – 9.55)	0.21	-0.20 (-1.40 – 1.00)	0.74	0.41 (-4.33 – 5.14)	0.87
RV mass, g						
Limited	1.22 (-4.23 – 6.68)	0.66	0.02 (-0.21 – 0.25)	0.85	-0.07 (-1.10 – 0.97)	0.90
Adjusted	-0.18 (-5.60 – 5.24)	0.95	-0.01 (-0.25 – 0.23)	0.94	-0.25 (-1.28 – 0.78)	0.63
Adjusted + LV mass	1.31 (-3.75 – 6.37)	0.61	0.05 (-0.18 – 0.27)	0.69	-0.18 (-1.17 – 0.81)	0.72
RVEDV, mL						
Limited	-25.56 (-61.91 – 10.78)	0.17	-0.35 (-1.81 – 1.12)	0.64	2.87 (-3.40 – 9.14)	0.37
Adjusted	-35.78 (-71.68 – 0.13)	0.05	-0.50 (-2.06 – 1.06)	0.53	1.95 (-4.29 – 8.19)	0.54
Adjusted + LVEDV	-7.86 (-34.52 – 18.81)	0.56	-0.67 (-1.75 – 0.42)	0.23	3.31 (-1.47 – 8.09)	0.17
RVESV, mL						
Limited	-15.11 (-33.34 – 3.13)	0.10	-0.44 (-1.13 – 0.24)	0.21	1.75 (-1.44 – 4.94)	0.28
Adjusted	-18.98 (-37.19 – -0.77)	0.04	-0.30 (-1.02 – 0.42)	0.41	1.55 (-1.65 – 4.74)	0.34
Adjusted + LVESV	-15.08 (-31.22 – 1.07)	0.07	-0.35 (-1.00 – 0.30)	0.29	1.96 (-1.00 – 4.92)	0.19

*Per 1 unit increase in estradiol:testosterone ratio

†Adjusted for age, race/ethnicity, height, weight, and waist circumference, and testosterone supplementation (in men)

‡Adjusted for age, race/ethnicity, height, weight, waist circumference, testosterone supplementation (in men), smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, and level of education.

Table E7. Associations between estradiol:testosterone and RV measures in limited and adjusted models among men and women (based on hormone therapy [HT] use) with available measures of lung function

	Men		Women HT Users		Women HT Non-Users	
Number	1301		370		702	
Mean ± SD	0.1 ± 0.0		0.5 ± 1.2		0.1 ± 0.1	
	Beta (95% CI)*	**P value**	**Beta (95% CI)**	**P value**	**Beta (95% CI)**	**P value**
RVEF, %						
Adjusted†	16.18 (-35.23 – 67.59)	0.54	0.07 (-0.44 – 0.57)	0.79	-1.22 (-4.54 – 2.11)	0.47
Adjusted + lung function	16.71 (-34.78 – 68.21)	0.52	0.06 (-0.45 – 0.57)	0.81	-1.56 (-4.90 – 1.77)	0.36
RVSV, mL						
Adjusted	-140.94 (-307.65 – 25.77)	0.10	-0.52 (-1.84 – 0.79)	0.43	1.46 (-5.97 – 8.89)	0.70
Adjusted + lung function	-144.88 (-308.59 – 18.83)	0.08	-0.64 (-1.95 – 0.67)	0.34	1.75 (-5.69 – 9.18)	0.64
RV mass, g						
Adjusted	-19.39 (-50.76 – 11.99)	0.23	0.00 (-0.23 – 0.23)	1.00	-0.36 (-1.91 – 1.18)	0.65
Adjusted + lung function	-20.90 (-52.08 – 10.28)	0.19	-0.01 (-0.24 – 0.22)	0.92	-0.22 (-1.77 – 1.32)	0.78
RVEDV, mL						
Adjusted	-119.40 (-287.45 – 48.65)	0.16	-0.82 (-1.95 – 0.31)	0.16	4.02 (-3.42 – 11.45)	0.29
Adjusted + lung function	-118.95 (-286.79 – 48.90)	0.17	-0.85 (-1.99 – 0.29)	0.14	4.62 (-2.82 – 12.06)	0.22
RVESV, mL						
Adjusted	-76.31 (-181.65 – 29.04)	0.16	-0.21 (-0.90 – 0.48)	0.55	2.33 (-2.38 – 7.03)	0.33
Adjusted + lung function	-78.44 (-183.58 – 26.70)	0.14	-0.32 (-1.00 – 0.36)	0.36	3.58 (-1.15 – 8.31)	0.14

*Per ln(1nmol/L) increase in estradiol:testosterone ratio

†Adjusted for age, race/ethnicity, height, weight, waist circumference, smoking (status and pack-years), diabetes mellitus, impaired glucose tolerance, hypertension, use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol, high density lipoprotein levels, statin use, intentional exercise, level of education, and testosterone supplementation (in men). RVEF adjusted for LVEF, RV mass adjusted for LV end-diastolic mass, RVEDV and RVESV adjusted for LVEDV and LVESV, respectively.

‡ FEV1, FVC, FEV1/FVC, urine cotinine concentration, and CT lung density.