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Physical Activity and Sex Hormone Levels in Estradiol- and Placebo-Treated Postmenopausal Women

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Abstract

Objective—Postmenopausal changes in the hormonal milieu in women with or without hormone therapy (HT) are hypothesized to be the pathway for a number of menopause-associated modifications in physiology and disease risk. Physical activity may modify these changes in women's hormone profiles. The crucial yet complex relationship between physical activity and physiologic and pharmacologic sex hormone levels in postmenopausal women has not been investigated sufficiently.

Methods—Using structured recall, physical activity was assessed longitudinally over two years in 194 postmenopausal women (90 randomized to daily 1 mg 17β-estradiol and 104 to placebo) in the Estrogen in the Prevention of Atherosclerosis Trial. Levels of physical activity were correlated to serum sex hormone and serum hormone-binding globulin (SHBG) levels in each treatment group.

Results—In placebo-treated women, total energy expenditure was positively associated with sex hormone-binding globulin (SHBG) ($p<0.001$) and inversely associated with testosterones (total, bioavailable, free) and androstenedione ($p<0.001$ for all), as well as with estradiol ($p=0.02$). In estradiol-treated women, estradiol levels were inversely associated with total energy expenditure ($p=0.002$) and weekly hours spent in moderate or more vigorous physical activity ($p=0.001$).

Conclusion—Physical activity is associated with lower serum levels of estradiol in both HT-treated and untreated women. In placebo-treated women only, physical activity is associated with reduced androgen levels and elevated SHBG levels.

Keywords

Physical activity; sex hormones; estradiol; menopause

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INTRODUCTION

Menopause results in considerable physical and psychological changes and has been associated with risk for cardiovascular disease, breast cancer and osteoporosis[1–4]. Some of these associations are hypothesized to be related to menopause-associated metabolic and hormonal changes[5,6]. While hormone therapy (HT) has been the focus of intervention in menopause, its risk-benefit ratio is still debated[7–9].

Low levels of physical activity are associated with elevated cardiovascular disease risk in postmenopausal women [10,11] and numerous studies report an inverse association between physical activity and breast cancer risk in postmenopausal women [12,13]. A plausible mechanism by which physical activity may modulate disease risk is through hormone-related pathways[14]. However, observational studies have yielded inconsistent associations between physical activity and sex hormone levels[14,15]. The effect of physical activity on endogenous hormone levels in women not using hormone therapy versus women exposed to exogenous sex hormones post-menopause remains largely unexplored [15,16].

We utilized data from the Estrogen in the Prevention of Atherosclerosis Trial (EPAT; clinicaltrials.gov NCT00115024) to determine the association between physical activity and sex hormone levels in postmenopausal women randomized to estrogen therapy (ET) and women randomized to placebo.

METHODS

This study uses a post hoc data analysis from EPAT, a randomized, double-blind, placebo-controlled trial conducted among postmenopausal women free of preexisting cardiovascular disease. Detailed EPAT methods have been described elsewhere[17]. The trial tested the primary hypothesis that unopposed ET reduces the progression of subclinical atherosclerosis in this population [17].

Potential participants were prescreened by telephone and attended three screening visits 2 to 4 weeks apart to collect baseline data and to determine study eligibility. Eligible women were postmenopausal (serum estradiol<20 pg/mL), 45 years of age or older, not current smokers, and had a low-density lipoprotein (LDL) cholesterol level of 130 mg/dL or greater. Women were excluded if breast or gynecologic cancer had been diagnosed in the past 5 years or if these cancers were identi ed during screening, if they had previously used HRT for more than 10 years or had used HRT within 1 month of the rst screening visit, if they had ve or more hot ushes daily that interfered with daily activity and precluded randomization, diastolic blood pressure greater than 110 mm Hg, untreated thyroid disease, life-threatening disease with a survival prognosis of less than 5 years, total triglyceride level of 4.52 mmol/L or greater (400 mg/dL), high-density lipoprotein (HDL) cholesterol level less than 0.78 mmol/L (<30 mg/dL), serum creatinine concentration greater than 221 mmol/L (>2.5 mg/dL), or if they were current smokers. All women, including those with diabetes mellitus, were included provided their fasting blood glucose level was less than 11.1 mmol/L (<200 mg/dL). A total of 222 women (111 per group) were randomly assigned to unopposed estradiol or placebo in one of eight strata defined by LDL cholesterol (<4.15 mmol/L [<160 mg/dL] or ≥4.15 mmol/L), previous duration of HRT use (<5 years or ≥5 years), and diabetes mellitus (yes or no). Participants were followed every month for the first 6 months and every other month thereafter for two years. The study protocol was approved by the Institutional Review Board of the University of Southern California; all participants gave written informed consent[17].

Sex steroid hormones

Prior to randomization and every 6 months during trial follow-up, fasting blood was drawn; serum was stored at −70°C. Sex hormone levels were measured from stored samples. All samples for each participant were processed in the same batch. Radioimmunoassay (RIA) was used to quantify serum levels of androstenedione, dehydroepiandrosterone (DHEA), testosterone, estrone and estradiol. Prior to RIA, steroids were extracted from serum with hexane:ethyl acetate (3:2). Androstenedione, DHEA, total testosterone, estrone and estradiol were then separated by Celite column partition chromatography [18]. Sex hormone-binding globulin (SHBG) was quantified by direct immunoassay using the Immulite analyzer (Diagnostic Products Corporation, Inglewood, CA). Free testosterone and free estradiol were calculated using total testosterone and total estradiol concentrations, respectively, SHBG concentrations and an assumed constant for albumin in a validated algorithm [19]. Intra-assay and inter-assay coefficients of variation ranged from 4 to 8% and 8 to 13%, respectively. The assay sensitivities for estradiol, estrone, testosterone, DHEA, androstenedione and SHBG were 3 pg/ml, 4 pg/ml, 1.5 ng/ml, 0.04 ng/ml, 0.03 ng/ml and 1 nmol/L, respectively.

Assessment of physical activity—The Stanford Seven-Day Physical Activity Recall was completed at baseline and every 6 months[20]. This questionnaire is a self-report recall instrument assessing physical activity over the previous week [21]. Each reported activity was coded for its metabolic equivalents of energy expenditure (METs) using the coding scheme provided by Ainsworth, et al [22]. For each week recalled, the energy expenditure of each activity was calculated by multiplying hours of participation by the activity's MET. Any self-reported activity that required 3–6 METs was considered moderate-intensity and any that required more than 6 METs was considered vigorous-intensity physical activity. Energy expenditure in sleep was calculated by multiplying sleep time with 1 MET. Time spent in light activity was computed by subtracting the sum of time spent in sleep, moderate and vigorous activity from the total 168 weekly hours. The metabolic cost of light activity was computed by multiplying the number of hours spent in light activities by 1.5 MET [23]. Total energy expenditure was the sum of energy expenditure (MET-hours) in sleep, light, moderate, and vigorous activities.

Other reproductive and anthropometric measures—Reproductive and smoking history and demographic factors including age, race, income, and education were assessed by structured questionnaires completed at baseline. Reproductive history included age at menarche, age at last menstrual period and history of hysterectomy and oophorectomy. For women without a hysterectomy/oophorectomy, age at last menstrual period was considered their age at natural menopause. For women with bilateral oophorectomy, age at surgery was considered the age of menopause. For 15 participants with hysterectomy and unilateral oophorectomy and 26 participants with hysterectomy without oophorectomy, the mean age at natural menopause of the sample was imputed as their menopause age. Menopausal status was validated by levels of serum estradiol (less than 20pg/ml). Height and weight were measured with a free-standing stadiometer and calibrated digital scale (Salter) to the nearest 0.1 cm and 100 g, respectively. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

Statistical analysis

This post hoc analysis included 104 of 111 participants in the placebo group and 90 of 111 participants in the estradiol group, who had data available for both physical activity and hormone levels. Demographic characteristics between treatment groups were compared using independent t-tests (means) or chi-square tests (proportions). Baseline and average on-trial levels of sex hormones were compared between the treatment groups using independent

t-tests. As total estradiol and estrone levels were not normally distributed, these variables were log-transformed for analysis and back-transformed for summarizing results.

We computed the average value (averaged over the trial) of each sex hormone, SHBG and physical activity levels for each participant. Thus, each participant contributed one observation to the analysis. All measurements (baseline and on-trial) were used to calculate the per-participant means of sex hormones and SHBG for the placebo group. For the estradiol-treated group, only the on-trial measurements were used to calculate these per-participant means. Since assessment of physical activity in EPAT began nearly a year after the initial participant recruitment, a number of participants did not have baseline physical activity data (71 in placebo group and 68 in the estradiol group). All available measurements (baseline and/or on-trial) were used to calculate the per-subject means of physical activity for both placebo- and estradiol-treated women.

The serum levels of the different sex hormones and SHBG were modeled separately as continuous variables in all analyses. Within each treatment group, we fitted general linear models to assess the continuous relationship between average physical activity and average sex hormone levels. Analysis of variance was used to compare the means of hormone levels across categorical levels of physical activity. We also tested for a trend in average hormone/SHBG levels across categories of physical activity by fitting the median value for each physical activity category.

We modeled physical activity in different ways to assess the qualitative and quantitative associations with hormone levels. Total weekly MET expenditure (total MET-hours) was the sum of energy expenditure as detailed above; total MET-hours was modeled as a continuous variable and as a categorical variable (four quartiles of total MET-hours). Physical activity was also modeled as total time (in hours per week) spent in moderate or higher intensity physical activity (total hours spent in activities with MET estimates 3 or greater) and hours per week spent in vigorous-intensity physical activity (total hours spent in activities with MET estimates greater than 6). Time in moderate or vigorous physical activity was categorized into three levels based on the tertile distribution of the total sample. Time in vigorous physical activity was also categorized into three levels; the lowest levels represented women reporting no vigorous activity, while the upper two levels were determined by a median split of weekly hours of vigorous activity (among participants reporting at least one vigorous activity).

Hormone and SHBG levels were initially modeled as dependent variables without covariate adjustment. Age at randomization, race, BMI, age at menopause, type of menopause (natural, surgical), smoking status (ever, never smoked regularly) and years since menopause were evaluated as possible confounders. Confounding was assessed by comparing the unadjusted to the covariate-adjusted change in the beta-estimate (15% or more) of the main effect of physical activity. Wald's tests were used to assess possible effect modification by these covariates testing product interaction terms in the multivariate model. Due to high correlation between age at randomization and age at menopause (r=0.86), we included only age at randomization in the multivariate analyses. Smoking status and years since menopause were not included in the multivariate model as neither variable altered the impact of physical activity on sex hormones. None of the interaction tests were statistically significant (all P>0.10). Our final models included adjustment for age at randomization, race, BMI and type of menopause. All statistical analysis used SAS software 9.13 (SAS, Inc, Cary, North Carolina) and all tests for significance were conducted at a 2-sided 0.05 level.

RESULTS

Baseline characteristics

Baseline characteristics of the 194 participants included in the analysis are summarized in Table 1. Compared to placebo recipients, more estradiol recipients had a history of hysterectomy or surgical menopause (p=0.03). The groups did not significantly differ on other demographic and reproductive characteristics. The physical activity levels were generally comparable between treatment groups. However, estradiol-treated women spent more time in vigorous physical activity than placebo-treated women (p=0.04).

Treatment group comparisons on hormone levels

Women in the placebo and estradiol groups had different levels of estrone at baseline (p=0.02) but were comparable on all other hormone levels (Table 2). During the trial, the estradiol group had statistically significantly higher mean levels of estradiol, estrone, bioavailable estradiol, free estradiol and SHBG, and statistically significantly lower mean levels of bioavailable testosterone and free testosterone (p<0.001 for all) and DHEA (p=0.02) compared to placebo participants.

Associations of physical activity with sex hormone levels (placebo-treated group)

The relationships between average total weekly MET expenditure and hormone and SHBG levels among 104 placebo-treated women are summarized in Table 3. Adjusting for age at randomization, race, BMI, and type of menopause, continuous measures of total energy expenditure were positively associated with SHBG level (p<0.001) and inversely associated with total testosterone (p<0.001), bioavailable testosterone (p<0.001), free testosterone (p<0.001), androstenedione (p<0.001), bioavailable estradiol (p=0.02) and free estradiol (p=0.02). Results analyzed by quartile of total energy expenditure were consistent with the continuous analysis.

Time spent in moderate or more intense physical activity among placebo group participants was statistically significantly positively associated with SHBG level (p<0.001) and was inversely associated with serum levels of total testosterone (p=0.006), bioavailable testosterone (p<0.001) and free testosterone (p<0.001) (Table 4). Only 36% of the placebo participants reported some time spent in vigorous physical activity; only 9% reported more than one hour weekly of vigorous activity on average over the trial period. Relationships of hormone levels with vigorous physical activity as a continuous measure and as three categories (0 weekly hours, more than 0 to 0.3 weekly hours, more than 0.3 weekly hours) are summarized in Table 5. All continuous and categorical measures of testosterone (total, bioavailable and free) were statistically significantly inversely associated (all p<0.001), while serum DHEA level was positively associated (p=0.002) with time spent in vigorous physical activity. SHBG levels were positively associated with vigorous physical activity only when analyzed on a categorical scale (p=0.04). The mean (SD) SHBG level was 33.0 (1.3), 39.4 (1.9), and 39.0 (2.1) nmol/l for women with no vigorous physical activity, up to 0.3 weekly hours of vigorous activity, and more than 0.3 weekly hours of vigorous activity, respectively.

Associations of physical activity with hormone levels (estradiol-treated group)

The relationships between total weekly MET expenditure and hormone and SHBG levels in 90 estradiol-treated women are summarized in Table 3. None of the hormones nor SHBG was statistically significantly associated with continuous measures of total weekly energy expenditure after adjusting for age at randomization, race, BMI and type of menopause. However, total estradiol level decreased with increasing quartiles of energy expenditure (p=0.04). There was evidence of decreasing trends in bioavailable estradiol and free

estradiol levels, although these associations did not achieve statistical significance (p=0.06 for both). Associations of total MET quartiles with other hormones were consistent with the continuous analyses.

Total estradiol (p=0.001), bioavailable estradiol (p=0.01) and free estradiol (p=0.01) levels were inversely associated with the continuous measure of weekly hours spent in moderate or more intense physical activity (Table 4). Androgen levels were not statistically significantly associated with weekly hours spent in moderate or vigorous activities. Serum DHEA (p=0.001) and androstenedione (p=0.005) levels increased with increasing tertiles of time spent in moderate or vigorous activity.

Relationships of the hormones to vigorous physical activity, defined as a continuous measure and as a categorical measure are summarized in Table 5. All estrogen measures were inversely associated with time spent in vigorous physical activity (p-value <0.001 to 0.01), while mean DHEA was positively associated with time spent in vigorous physical activity (p-value <0.001). Serum androstenedione levels were inversely associated with time in vigorous physical activity only when analyzed in three categories of vigorous physical activity.

DISCUSSION

In this cohort of postmenopausal women participating in a randomized controlled clinical trial, physical activity levels were associated with sex steroid hormone levels in both placebo-treated and estradiol-treated women. Among the estradiol-treated women, total energy expenditure on a continuous scale was not associated with alterations in any hormone or SHBG level. However, in a categorical analysis estradiol levels decreased with increasing quartiles of total energy expenditure. All measures of serum estradiol were inversely associated with total hours spent in moderate or vigorous physical activity. There was also a statistically significant increasing trend in serum DHEA and androstenedione level with increasing tertiles of weekly hours spent in moderate or vigorous physical activity. Among placebo-treated women, total energy expenditure was inversely associated with circulating concentrations of most androgens and bioavailable and free estradiol. Total hours spent in moderate or more physical activity as well as time spent in vigorous physical activities was negatively associated with all measures of serum testosterone. SHBG was positively associated with total energy expenditure and time spent in moderate and vigorous activity. The majority of our findings are consistent with the results from other studies[14,24–26].

While the relationship of physical activity and sex hormone levels in postmenopausal women taking exogenous female steroid hormones is a crucial topic there exists a paucity of data. Our EPAT data represent the first report on the relationship of physical activity and sex hormone levels in postmenopausal women taking estradiol or any exogenous female steroid hormones. The statistically significant inverse trend of female sex hormones with increasing time spent in moderate or vigorous physical activities may be beneficial in the presence of an added risk of breast cancer associated with estrogen therapy in some studies [8,27,28. 27]. These observations in with estrogen therapy are consistent with and extend previously reported relationships between physical activity and endogenous estrogen levels.[29–32]

A reduction in female sex hormones with higher physical activity may impact breast cancer risk in postmenopausal women. High endogenous estrogen levels are associated with elevated breast cancer risk in postmenopausal women[28]. Cumulative exposure to estrogen is particularly relevant to breast cancer risk and is determined by factors such as age at menarche, age at menopause, pregnancy, lactation and postmenopausal obesity[1]. Physical activity itself has been associated with reduced breast cancer risk. Numerous reports have

investigated the relationship of physical activity and breast cancer risk. Of 10 of these studies reporting results separately for postmenopausal women, 9 found an inverse association [29]. The mechanisms by which physical activity exerts its beneficial effects are still being explored and debated [30,31,32]

The direct association of physical activity with serum SHBG levels may also have implications for reduced breast cancer risk. SHBG binds estradiol, reducing the bioavailability of this hormone. Postmenopausal women with low serum SHBG have increased risk of breast cancer[14]. The statistically significant negative associations of physical activity with androgens in the placebo group may imply a beneficial effect on cardiovascular disease. A large body of observational evidence suggests a positive association between menopause and cardiovascular disease risk [33,34]. Some studies suggest that an increase in androgens relative to estrogen in healthy postmenopausal women is associated with an unfavorable cardiovascular risk profile [35].

In EPAT placebo-treated women, androgen levels were affected by as little as 2 hours of weekly moderate or vigorous physical activity, which, might be explained partially by the positive association of physical activity with serum SHBG. SHBG is known to regulate the concentration of bioavailable estrogen and androgens and has a greater affinity for androgens, especially testosterone [36]. Therefore, physical activity may benefit postmenopausal women not taking any hormonal intervention by contributing to a reduction in androgen excess.

Most of our other findings on non hormone users are consistent with the majority of current literature.[14,32]. The first randomized controlled trial to address the relationship between physical activity and endogenous sex hormone levels in postmenopausal women investigated the effects of a 12-month moderate-intensity physical activity intervention compared to a control group who performed only stretching exercises [25,26,37]. After 3 months, exercisers (n=87) experienced statistically significant declines in estrone, estradiol, and free estradiol compared to controls (n=86). At 12 months, the direction of effect remained the same, although the differences were no longer statistically significant[26]. Also at 12 months, women in the exercise intervention group showed reductions in total testosterone and free testosterone compared to control intervention. However, the associations were statistically significant only in women who lost more than 2% of body fat. The trial also noted a statistically significant increase in SHBG levels in the moderate exercise intervention group at 3 months; however, this was not maintained at 12 months.

In a recent cross-sectional population-based study, 2082 postmenopausal women not using exogenous hormones demonstrated inverse relationships between usual physical activity levels and circulating concentrations of estradiol and testosterone[14]. Consistent with our findings, physical activity was also positively associated with SHBG concentrations[14]. Another cross-sectional study on 806 post-menopausal women reported a similar inverse association between estradiol levels and physical activity and positive association between physical activity and SHBG [38]. In a longitudinal study following participants for 8 years, endurance-trained postmenopausal women had lower estrogen, specifically estrone levels compared to sedentary women [39].

Strengths and limitations

There are several strengths of the current analysis from EPAT. This post hoc analysis was performed in the setting of a randomized trial of hormone therapy, separately examine women taking exogenous estradiol and women without any exogenous hormones. Hence, we had a unique opportunity to observe the influence of physical activity in postmenopausal women at both physiologic and pharmacologic levels of hormones, free of selection biases

associated with self-selected hormone use. A comprehensive panel of hormones was measured, enabling us to investigate a large part of the hormonal milieu in these postmenopausal women. Moreover, repeated measures of hormone and physical activity allowed us to obtain a more representative measure of a woman's average hormone and physical activity profiles over time than is achieved by a single measurement.

The major limitation of the study is the post hoc nature of the analysis, in that EPAT was not designed to address the relationship of physical activity and sex hormone levels in postmenopausal women randomized to ET versus placebo. Hence, physical activity was not a study intervention, but rather represented self-selected activities. We also could not assess longitudinal changes in physical activity as no recommendations were made regarding physical activity; in fact, physical activity remained quite stable over the trial (within-participant coefficient of variation was 2.6% in placebo-treated and 3.7% in estradiol-treated participants).

The relatively small sample size may have compromised our statistical power in testing physical activity and hormone associations. For example, in the 90 participants receiving HT there were marginally statistically significant decreasing trends in bioavailable and free estradiol levels with increasing quartiles of total energy expenditure. In addition, the small sample reduced the statistical power to test interactions, including possible interactions with BMI and race. The cohort had a high BMI with a mean of 29 kg/m^2. As adipose tissue is a major source of estrogens in postmenopausal women, the amount of physical activity might not have been sufficient to reduce the hormones to a great extent in this relatively overweight population of postmenopausal women. This may explain the lack of inverse association of serum levels of estradiol and estrone with time spent in moderate or vigorous activity in the placebo group, where only 36% of the participants reported some time spent in vigorous physical activity and only 9% reported more than one hour of weekly vigorous physical activity.

Conclusions

This study adds to the limited evidence on the relationship between physical activity and sex hormone levels in postmenopausal women. The reduction in physical activity with increasing age and/ or increasing weight in postmenopause can potentially impact sex hormones levels contributing to increased disease risks. Given the fact that this was a post hoc cross-sectional analysis, we cannot infer a causal relationship between physical activity and hormone levels. Despite that, the implications of the results warrant further exploration. To our knowledge, no study has examined the relationship of physical activity with such a large panel of hormones at both physiologic and pharmacologic states. Further longitudinal interventional studies with a larger sample size might help to further understand the uncertain, largely unexplored yet intriguing relationship between physical activity and sex hormone levels in this population.

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Table 1

Distribution of Study Variables by Treatment Group in EPAT

	Placebo group (N=104)	Estradiol group (N=90)	P-value*
Age at Menarche			
<= 13	59 (53.6%)	56 (52.8%)	0.91
>13	51 (46.4%)	50 (47.2%)	
Race			
Non-Hispanic White	65 (59.1%)	56 (52.8%)	0.62
Black	10 (9.1%)	15 (14.2%)	
Hispanic	24 (21.8%)	23 (21.7%)	
Asian	11 (10.0%)	11 (10.4%)	
Others	0 (0.0%)	1 (0.9%)	
Annual family Income			
<29,900	45 (45.4%)	47 (49.0%)	0.60
30,000–59,900	33 (33.3%)	34 (35.4%)	
>60,000	21 (21.2%)	15 (15.6%)	
Education level			
High school or less	4 (3.6%)	2 (1.9 %)	0.60
Trade or business school, some college	69 (62.7%)	19 (59.4 %)	
Bachelors degree or more	37 (33.6%)	85 (38.7%)	
Parity			
0	18 (16.4%)	12 (11.3%)	0.38
1–3	47 (42.7%)	42 (39.6%)	
>3	45 (40.9%)	52 (49.1%)	
Type of menopause			
Natural	74 (67.3%)	56 (52.8%)	0.03
Surgical	36 (32.7%)	50 (47.2%)	
Proportion of surgical menopause with bilateral oophorectomy	19 (57.1%)	31 (72%)	0.15
Age at randomization	61.5 (7.2)	60.5 (6.6)	0.28
BMI (kg/m^2)	29.0 (5.4)	28.9 (5.9)	0.76
Years since menopause	13.9 (9.7)	13.5 (8.9)	0.84
Total energy expenditure (MET-hours/ week)	237.5 (25.4)	238.0 (16.2)	0.90
Moderate (>3 MET)physical activity (Hrs/Week)	4.1 (6.9)	4.3 (4.1)	0.90
Vigorous (>6 MET) physical activity (Hrs/Week)	0.2 (0.7)	0.6 (1.2)	0.04

* Chi-square test (categorical variables) and independent t-test (continuous variables)

N (%) for categorical and mean (SD) for continuous variables; EPAT: Estrogen in the Prevention of Atherosclerosis Trial; MET: Metabolic Equivalent

Table 2

Baseline and On-Trial Hormone Levels by Treatment Group

Hormone	Placebo group (N=104)	Estradiol group (N=90)	P-value*
	Mean (SD)	Mean (SD)	
Estradiol (pg/ml)			
Baseline	19.1 (8.4)	20.3 (12.2)	0.53
On-trial	17.2 (12.0)	61.5 (16.2)	<0.001
Estrone (pg/ml)			
Baseline	44.3 (16.5)	48.9 (44.6)	0.02
On-trial	46.2 (39.2)	296.6 (198.1)	<0.001
Bioavailable Estradiol (pg/ml)			
Baseline	14.1 (4.7)	16.8 (14.2)	0.08
On-trial	14.7 (6.7)	39.2 (20.2)	<0.001
Free Estradiol (pg/ml)			
Baseline	0.6 (0.2)	0.7 (0.6)	0.08
On-trial	0.6 (0.3)	1.5 (0.8)	<0.001
Testosterone (ng/dl)			
Baseline	22.9 (9.5)	21.7 (10.4)	0.38
On-trial	22.6 (9.6)	23.3 (11.9)	0.46
DHEA (ng/ml)			
Baseline	2.3 (1.5)	2.2 (1.4)	0.55
On-trial	2.1 (1.3)	1.9 (1.0)	0.02
Androstenedione (pg/ml)			
Baseline	515.1 (221.3)	522.9 (247.7)	0.82
On-trial	508.4 (194.3)	515.7 (214.4)	0.64
Bioavailable testosterone (ng/ml)			
Baseline	9.4 (4.5)	8.9 (4.9)	0.50
On-trial	9.1 (4.0)	7.1 (4.0)	<0.001
Free Testosterone (pg/ml)			
Baseline	4.3 (2.0)	4.1 (2.3)	0.50
On-trial	4.1 (1.8)	3.2 (1.8)	<0.001
SHBG (nmol/l)			
Baseline	35.2 (15.1)	36.4 (21.6)	0.64
On-trial	36.3 (19.3)	57.1 (27.3)	<0.001

*P-value from independent t-test;

SHBG: Sex hormone-binding globulin; DHEA: Dehydroepiandrosterone

Table 3

Total-MET-hours and Sex Hormone Levels in EPAT Participants (n=194)

	Beta*	95% Confidence Interval	P-value (Linear trend)	P-value (Quartile Trend)
Placebo participants (n=104)				
Estradiol (pg/ml)	−2.84	−8.14, 2.45	0.30	0.91
Estrone (pg/ml)	−9.78	−27.71, 8.14	0.30	0.35
Bioavailable Estradiol (pg/ml)	−3.94	−7.20, −0.69	0.02	0.03
Free Estradiol (pg/ml)	−0.15	−0.28, −0.02	0.02	0.03
Testosterone (ng/dl)	−8.65	−14.94, −2.35	0.007	<0.001
DHEA (ng/ml)	0.11	−0.74, 0.96	0.80	0.80
Androstenedione (pg/ml)	−270.23	−401.22, −139.24	<0.001	<0.001
Bioavailable testosterone (ng/ml)	−6.51	−9.20, −3.83	<0.001	<0.001
Free Testosterone (pg/ml)	−2.99	−4.22, −1.76	<0.001	<0.001
SHBG (nmol/l)	26.52	15.32, 37.71	<0.001	<0.001
Estradiol Participants (n=90)				
Estradiol (pg/ml)	−15.56	−36.22, 5.09	0.14	0.04
Estrone (pg/ml)	−44.21	−171.43, 83.01	0.49	0.40
Bioavailable Estradiol (pg/ml)	−8.98	−21.35, 3.39	0.15	0.06
Free Estradiol (pg/ml)	−0.35	−0.84, 0.13	0.15	0.06
Testosterone (ng/dl)	−2.88	−11.47, 5.72	0.51	0.09
DHEA (ng/ml)	−0.11	−0.75, 0.53	0.73	0.86
Androstenedione (pg/ml)	−31.40	−182.11, 119.30	0.68	0.76
Bioavailable testosterone (ng/ml)	0.35	−2.46, 3.16	0.81	0.60
Free Testosterone (pg/ml)	0.14	−1.14, 1.43	0.83	0.59
SHBG (nmol/l)	−11.09	−29.02, 6.83	0.22	0.15

*Regression coefficient = mean difference in hormone/SHBG level per 100 MET-hours, adjusted for age, race, body mass index, type of menopause

EPAT: Estrogen in the Prevention of Atherosclerosis Trial; MET; Metabolic equivalents of energy expenditure;

SHBG: Sex hormone-binding globulin; DHEA: Dehydroepiandrosterone

Table 4

Moderate or More Physical Activity (hours/week) and Sex Hormone Levels in EPAT Participants (n=194)

	Beta*	95% Confidence Interval	P-value (Linear trend)	P-value (Tertile Trend)
Placebo participants (n=104)				
Estradiol (pg/ml)	−0.002	−0.01, 0.01	0.54	0.99
Estrone (pg/ml)	−0.002	−0.01, 0.01	0.60	0.61
Bioavailable Estradiol (pg/ml)	−0.10	−0.22, 0.02	0.09	0.09
Free Estradiol (pg/ml)	−0.004	−0.01, 0.001	0.09	0.09
Testosterone (ng/dl)	−0.31	−0.54, −0.09	0.006	0.004
DHEA (ng/ml)	0.03	−0.002, 0.06	0.07	0.11
Androstenedione (pg/ml)	−1.91	−6.75, 2.92	0.44	0.88
Bioavailable testosterone (ng/ml)	−0.21	−0.31, −0.12	<0.001	<0.001
Free Testosterone (pg/ml)	−0.10	−0.14, −0.05	<0.001	<0.001
SHBG (nmol/l)	0.82	0.41, 1.23	<0.001	<0.001
Estradiol Participants (n=90)				
Estradiol (pg/ml)	−1.38	−2.15, −0.62	<0.001	0.03
Estrone (pg/ml)	−4.02	−8.85, 0.80	0.10	0.88
Bioavailable Estradiol (pg/ml)	−0.80	−1.27, −033	<0.001	0.05
Free Estradiol (pg/ml)	−0.03	−0.05, −0.01	<0.001	0.05
Testosterone (ng/dl)	−0.04	−0.37, 0.29	0.81	0.18
DHEA (ng/ml)	0.01	−0.01, 0.04	0.33	0.001
Androstenedione (pg/ml)	1.50	−4.26, 7.23	0.61	0.005
Bioavailable testosterone (ng/ml)	−0.006	−0.11, 0.10	0.92	0.67
Free Testosterone (pg/ml)	−0.002	−0.05, 0.05	0.92	0.66
SHBG (nmol/l)	0.10	0.58, 0.77	0.80	0.33

*Regression coefficient = mean difference in hormone/SHBG level per hour of moderate or more activity, adjusted for age, race, body mass index, type of menopause

EPAT: Estrogen in the Prevention of Atherosclerosis Trial; MET; Metabolic equivalents of energy expenditure;

SHBG: Sex hormone-binding globulin; DHEA: Dehydroepiandrosterone

Table 5

Vigorous Physical Activity (hours/week) and Sex Hormone Levels in EPAT Participants (n=194)

	Beta*	95% Confidence Interval	P-value (Linear trend)	P-value (Categorical Trend)
Placebo participants (n=104)				
Estradiol (pg/ml)	−0.005	−0.03, 0.02	0.75	0.05
Estrone (pg/ml)	−0.003	−0.03, 0.03	0.88	0.62
Bioavailable Estradiol (pg/ml)	−0.25	−0.69, 0.19	0.27	0.45
Free Estradiol (pg/ml)	−0.01	−0.03, 0.01	0.27	0.45
Testosterone (ng/dl)	−1.13	−1.96, −0.30	0.008	<0.001
DHEA (ng/ml)	0.18	0.07, 0.28	0.002	0.001
Androstenedione (pg/ml)	−9.39	−27.2, 8.44	0.30	0.36
Bioavailable testosterone (ng/ml)	−0.66	−1.02, −0.30	<0.001	<0.001
Free Testosterone (pg/ml)	−0.30	−0.47, −0.14	<0.001	<0.001
SHBG (nmol/l)	0.96	−0.59, 2.52	0.22	0.04
Estradiol Participants (n=90)				
Estradiol (pg/ml)	−2.83	−4.88, −0.77	0.007	0.001
Estrone (pg/ml)	−17.00	−29.80, −4.20	0.01	0.003
Bioavailable Estradiol (pg/ml)	−2.41	−3.65, −1.17	<0.001	<0.001
Free Estradiol (pg/ml)	−0.09	−0.14, −0.04	<0.001	<0.001
Testosterone (ng/dl)	0.76	−0.11, 1.64	0.09	0.17
DHEA (ng/ml)	0.14	0.07, 0.20	<0.001	<0.001
Androstenedione (pg/ml)	11.45	−3.83, 26.73	0.14	0.01
Bioavailable testosterone (ng/ml)	0.07	−0.21, 0.36	0.61	0.87
Free Testosterone (pg/ml)	0.03	−0.10, 0.16	0.64	0.88
SHBG (nmol/l)	0.33	−1.48, 2.14	0.72	0.24

*Regression coefficient = mean difference in hormone/SHBG level per hour of vigorous physical activity, adjusted for age, race, body mass index, type of menopause

EPAT: Estrogen in the Prevention of Atherosclerosis Trial; MET; SHBG: Sex hormone-binding globulin;

DHEA: Dehydroepiandrosterone