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Objective and self-reported measures of physical activity and sex hormones: Women's Lifestyle Validation Study.

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Abstract

BACKGROUND: The relationship between specific characteristics of physical activity (PA) (e.g., intensity, type, frequency) with sex hormones is uncertain. We evaluated the association between characteristics of PA and circulating sex hormones.

METHODS: This was a cross-sectional analysis of the Women's Lifestyle Validation Study (n=493). Total PA (TPA), light-intensity PA (LPA), and moderate-vigorous PA (MVPA) were assessed by accelerometry (a) and self-report (sr). Self-report was used to assess PA type (i.e., aerobic, weight training) and exercise frequency. Dehydroepiandrosterone sulfate (DHEAS), testosterone, and sex hormone binding globulin (SHBG) were assayed among all women; estradiol was assayed in postmenopausal women not currently on hormone therapy.

RESULTS: Estradiol was inversely associated and SHBG positively associated with MVPA and LPA (estradiol: $\beta = -0.15$ per standard deviation [SD] increase, $p < 0.01$ for a-MVPA and a-LPA; SHBG: a-MVPA $\beta = 0.20$ per SD increase, $p < 0.01$, a-LPA $\beta = 0.15$, $p < 0.01$). By type, aerobic activity and weight training were each independently associated with estradiol and SHBG. Controlling for BMI attenuated all associations for estradiol, and to a lesser extent SHBG. PA was not associated with testosterone levels.

CONCLUSIONS: Multiple aspects of PA were independently associated with sex hormones; associations varied some by activity intensity and type, and were attenuated after accounting for BMI.

INTRODUCTION

Physical activity (PA) has been associated with a reduced risk of developing breast cancer. Indeed, physical inactivity has been attributed to an estimated 10% of breast cancer cases worldwide.¹ The relationship between PA and breast cancer risk may be mediated through its effects on sex hormones.² High levels of endogenous sex hormones and lower levels of sex-hormone-binding-globulin (SHBG) are associated with increased breast cancer risk in women.³

Previous studies examining the association between PA and circulating sex hormones have produced conflicting results. For example, among 2,082 postmenopausal women not on hormone replacement therapy participating in the EPIC study, women in the 4th vs. 1st quartile of self-reported total PA had 10% higher SHBG, 6% lower estradiol, and 19% lower testosterone.⁴ In contrast, Liedtke et al. found no associations between self-reported total PA and sex hormones or SHBG among 1,260 postmenopausal women.⁵ However, women in the 5th vs. 1st quintile of sports activities had 16% lower testosterone levels.

Prior studies were limited by the reliance on self-reported measures of PA, which have limited ability to capture light intensity PA,^{6,7} and primarily focusing on total or leisure time PA (LTPA). Therefore, little is known about how specific types (e.g., aerobic, weight training) or intensities of PA relate to sex hormones levels. A better understanding of these relationships can inform intervention approaches. Therefore, we evaluated the association of PA intensity and type, using objective and self-reported measures of PA, with circulating sex hormones in pre- and postmenopausal women.

METHODS

Study Population

The Women's Lifestyle Validation Study (WLVS) is an observational study among a subset of participants from the Nurses' Health Study (NHS) and NHS II cohorts. As previously described in detail,⁸ we sampled 5,509 women aged 45–80 years, from all geographical regions of the United States, who had completed a 2006/2007-cohort semi-quantitative food frequency questionnaire, had previously provided blood samples, had access to broadband internet, and were not planning to make substantial changes in their diet or their physical activity. We excluded women with a history of coronary heart disease, stroke, cancer, or major neurological disease. Of these women, 796 provided written informed consent and were eligible for the current study. This study was approved by the Human Subjects Committees of the Harvard T.H. Chan School of Public Health and Brigham and Women's Hospital.

Accelerometer

The participants were mailed an ActiGraph GT3X accelerometer (Actigraph Corporation, Pensacola, FL), detailed instructions on how to wear the monitor, and a wear time diary at baseline and six months' follow-up. Participants were instructed to wear the monitor on the hip for seven days during all waking hours, except for water-based activities, and record the days the monitor was worn. After the wear period, participants shipped the accelerometer and wear time diary back to the study center where it was processed using standard methods.^{9,10}

The accelerometer measures the duration and intensity of PA by determining the magnitude of acceleration (intensity) and summing those magnitudes (counts) within a specified time interval (epoch). We used a one-second epoch with the low-frequency extension to allow us to capture low-frequency activities. Non-wear time was defined as any block of time with 60 minutes or more of consecutive zero counts, allowing for two-minute interruptions with limited movement (<200 counts/min). Daily wear time was determined by subtracting non-wear time from 24 hours. The wear time diary was used to identify wear days to avoid counting spurious PA while monitors were in transit. We included participants in this analysis with 4 days of 10 hours of wear for at least one measurement period. Approximately 95% of women had data at each measurement period. We present the average of each assessment period, ignoring missing values. The women provided on average 6.8 (standard deviation [SD]=0.44) valid wear days, with approximately 73% wearing the monitor for 7 days at each assessment. The mean wear time was 15.1 (SD=1.1) hours per day.

The GT3X accelerometer estimates PA using triaxial counts, which combines the vector magnitude from three individual orthogonal planes. Total PA (TPA) was estimated by summing the total counts per day (CPD). We estimated time spent in light intensity (LPA) and moderate-vigorous intensity PA (MVPA) using the following cutpoints: LPA = 200 to <2690 counts, MVPA = 2690 counts.^{11,12} The cutpoints used in the present study were similar to cutpoints (>2751) developed by Santos-Lozano et al. among older participants (aged 65 – 80 years), using Artificial Neural Networks.¹³ We selected a cutpoint of 2690 for MVPA because it is more commonly used and will allow for comparisons with other studies.

Time spent in activity of a defined intensity (i.e., LPA and MVPA) was determined by summing the minutes per day where the count met the criterion for that intensity, then averaging it across the number of valid wear days. Time spent in PA is presented for every minute that meets the specific criterion. For MVPA, we additionally presented time spent in modified 10-min activity bouts (MVPA_{bouts}), as described previously.⁹

Physical Activity Questionnaire

A modified Paffenbarger PA questionnaire (PAQ) was administered on two separate occasions, at baseline and one-year follow-up. The PAQ was described in more detail elsewhere.¹⁴ Briefly, the questionnaire assesses the average time per week in the past year that participants spent engaged in leisure time (e.g., jogging, biking, weight training), occupational (e.g., standing at work), or household activities (e.g., yard work, digging,

standing at home). The duration of each activity was multiplied by its metabolic equivalent (MET) to estimate its energy expenditure.¹⁵ Total MET-hrs/wk was computed as the sum of all activities. LPA was estimated as the sum of time spent walking at an easy or normal walking pace and standing at home or work. MVPA was the sum of walking at a brisk or very brisk pace, biking, swimming, or playing tennis at a moderate or vigorous intensity level, moderate or heavy outdoor work, and weight training. We subtracted weight training from total MET-hr/wk to distinguish between weight training and aerobic activity. Approximately 94% of women had data at each measurement period. We present the average of two assessment periods whenever possible, otherwise responses from one assessment were used.

Assessment of Sex Hormones

Plasma samples were collected from 796 WLVS participants at two assessment periods, baseline and 6 months follow-up; however, sex hormones were only measured on a subset of women during the first assessment due to budgetary constraints. We selected 692 women with data on both PA measures. From this group, we selected all postmenopausal (n=433) and premenopausal (n=73) women not currently using exogenous hormones (i.e., oral contraception or postmenopausal hormone therapy). To maximize statistical power, we included 31 additional women whose menopausal status was unknown or was known and using exogenous hormones.

Dehydroepiandrosterone sulfate (DHEAS), testosterone, and SHBG were assayed among all participants; estradiol was assayed only in postmenopausal women not currently on hormone therapy. Four hundred ninety-two, 493, and 435 women had data on testosterone, SHBG, and DHEAS respectively. Four hundred ninety-five women had data on at least one sex hormone. Estradiol was available for 393 of the subsample of postmenopausal women not currently on hormones.

Sex hormones and sex hormone binding globulin (SHBG) (referred to collectively as sex hormones throughout) were measured in plasma samples in 4 batches. All assays were conducted at the Clinical Laboratory at the Mayo Clinic (Rochester, MN). Estradiol and testosterone were assayed by liquid chromatography tandem-MS (Thermo-Fisher Scientific, Franklin, MA; Applied Biosystems-MDS Sciex, Foster City, CA). Limits of detection are 1.25 pg/ml for estradiol and 1 ng/dL for testosterone. SHBG was assayed using a chemiluminescent enzyme immunometric assay (Immunlite 2000; DPC, Inc). DHEAS was measured by a solid-phase, competitive chemiluminescent enzyme immunoassay (Siemens Healthcare Diagnostics, Deerfield, IL). The overall within-batch coefficient of variability (CV) from masked samples embedded with study samples for DHEAS ranged between 5.2–8.6%, with a 1% CV in one of the batches. The CVs for estradiol and SHBG ranged between 6.4–11.1% and 2.1–5.6% respectively. The CVs for testosterone ranged between 0–4.8%, with a 10.9% CV for one of the batches.

Covariates

We assessed socio-demographic, behavioral, anthropometric, and medical history characteristics that may be associated with PA or sex hormones at or around the time of the

blood draw. Age, body mass index (BMI, kg/m²) and alcohol intake, menopausal status, current hormone use, oophorectomy status, and age at menarche were assessed by self-report at the blood draw visit. Caucasian race/ethnicity, age at menopause and parity were ascertained from previous NHS and NHS II questionnaires.

Statistical Analysis

SAS version 9.3 for UNIX (SAS Institute Inc) was used for all statistical analysis. Chi-square tests were used to compare the distribution of categorical descriptive, behavioral, and medical history characteristics by quartiles of CPD. Analysis of variance was used to compare mean levels across quartiles of CPD for continuous variables.

Multivariable linear regression was used to examine the associations between each measure of PA and sex hormones. PA was treated as both a continuous and categorical variable. For continuous analysis, we reported standardized estimates to show differences in sex hormones by standard deviation differences in PA. We further reported the percent difference in hormone levels per standard deviation differences in PA using the following formula: $[(1 - \exp^{\beta}) * 100]$. Consistent with other studies,^{4,5,16,17} we further compared differences in sex hormone levels between the least and most active participants by categorizing each PA variable. Specifically, we grouped participants into quartiles of PA for each PA variable, with the exception of weight training and exercise frequency, with the lowest quartile serving as the reference group. Participants who reported any weight training were grouped into high and low categories using a median split. Individuals that reported no weight training served as the reference. Exercise frequency was only treated as a categorical variable and was categorized as zero (6.3%), 1–3 (50.1%), 4+ days per week (43.6%). We treated zero days per week as the reference group. All biomarkers were logarithmically transformed to normalize the distribution. For the categorical analysis, we report the geometric mean (95% CI) hormone level in each PA category and the percent difference in hormone levels between the lowest and highest categories. Model 1 was adjusted for age (continuous), Caucasian race (yes/no), age at menopause (premenopausal, <45, 45 to <50, 50 to 52, >52 yrs), age at menarche (<12, 12, >12 yrs), parity (nulliparous, 1–2 children, 3+ children), oophorectomy (yes/no), and alcohol intake (continuous). To examine the independence of intensity-specific PA and PA type, we additionally included other PA intensities or type in the model. For example, models examining the relationship between aerobic activity and sex hormones also included weight training. Model 2 adjusted for BMI (continuous) as it is hypothesized to be in the causal pathway. Smoking status was not included in the final models because of its low prevalence in this population (2.5% current smokers). Next, since we previously observed a U-shaped relationship between PA and sex hormones,¹⁶ we used polynomial regression to identify possible non-linear associations.

RESULTS

The mean age of the sample population was 63.5 (SD = 9.4) years. Women that were the most physically active were on average younger (58.7 vs. 68.3, $p < 0.001$) and had a lower BMI (23.9 vs. 30.1, $p < 0.001$) than the least active women. More active women were also less likely to be postmenopausal (84% vs. 85%, $p < 0.01$), to have had an oophorectomy (13%

vs. 33%, $p<0.01$), more likely to be nulliparous (15% vs. 6%, $p<0.01$), and more likely to have age at first menarche 12 years or older (40% vs. 35%; $p<0.01$) than the least active women. Race, age at menopause, current hormone use, alcohol intake, and smoking status were similar across activity groups (Table 1).

The mean accelerometer estimated LPA was 202.9 min/day (SD = 56.1). The mean accelerometer estimated total MVPA and MVPA_{bouts} was 34.1 min/day (SD=34.1) and 10.3 min/day (SD=20.1) respectively. The mean self-reported total activity and LPA was 114.8 (SD = 61.8) MET-hr/wk and 42.9 (SD = 43.2) MET-hr/wk respectively. The median self-reported MVPA was 21.0 (IQR = 32.3) MET-hr/wk, which is approximately 51 min/day. By type, the majority of the reported activity was from aerobic activity (median = 67.3, IQR = 58.2 MET-hr/wk) as opposed to weight training. Approximately 47.1% of the women reporting not engaging in any weight training. Among the women that reported any weight training, they reported a median of 2.98 MET-hr/wk, approximately 51 min/week. Finally, only 6.3% of women reported not exercising in the past year, with 43.6% reporting exercising on 4 days per week.

PA and estradiol

Overall, we observed statistically significant inverse associations between most measures of PA with estradiol in non-BMI adjusted models. These observed associations were attenuated and no longer statistically significant after BMI adjustment. By total PA, each standard deviation increase in CPD and self-reported TPA was associated with 23.2% ($p<0.01$) and 12.9% ($p=0.01$) lower estradiol levels respectively (Table 2). After BMI adjustment, the associations were substantially attenuated with each standard deviation increase associated with 9.6% and 5.7% lower estradiol levels ($p=0.06$) respectively.

By intensity, we observed similar linear associations between MVPA and LPA with estradiol for both accelerometer and self-report (Table 2). Specifically, each standard deviation increase in accelerometer estimated MVPA, MVPA_{bouts}, and LPA was associated with approximately 14% lower estradiol levels ($p<0.01$). Each standard deviation increase in self-reported MVPA and LPA was associated with approximately 10% lower estradiol levels ($p=0.02$). However, differences between the most and least active participants varied by intensity (Supplemental Table 2). Women in the 4th vs. 1st quartile of accelerometer estimated, MVPA, MVPA_{bouts}, and LPA had 30.6% ($p<0.01$), 35.0% ($p<0.01$) and 21.6% ($p=0.02$) lower estradiol levels, respectively. Women in the 4th vs. 1st quartile of self-reported MVPA and LPA had 26.3% ($p<0.01$) and 12.2% ($p=0.20$) lower estradiol levels. These observed associations were attenuated and no longer statistically significant after BMI adjustment.

By type, aerobic activity had slightly stronger linear associations with estradiol than weight training (Table 2). Specifically, each standard deviation increase in aerobic activity was associated with 12.7% ($p<0.01$) lower estradiol levels. There was no statistically significant linear association between weight training and estradiol, after adjusting for aerobic activity levels. However, the women reporting the highest levels of weight training had 25.0% lower estradiol levels ($p<0.01$) than women reporting no weight training after adjusting for aerobic activity (Supplemental Table 3). Lastly, women who reported exercising 4 or more days per

week vs. none had 35.3% lower estradiol levels. All of the observed associations were attenuated and no longer statistically significant after BMI adjustment.

PA and testosterone

There were no consistent associations between PA, by intensity, type, or frequency with testosterone, except for a significant non-linear association of accelerometer estimated CPD and MVPA with testosterone (data not shown). Specifically, for CPD, women in the 1st and 4th quartile had lower testosterone levels than women in the 2nd and 3rd quartiles ($p=0.02$). For MVPA, the pattern was less clear, as women in the 2nd and 4th quartiles had slightly higher testosterone levels than women in the 1st and 3rd quartiles ($p<0.03$).

PA and DHEAS

PA was not associated with DHEAS, with the exception of positive associations with accelerometer estimated CPD and MVPA (Table 2). Specifically, each standard deviation increase in MPVA was associated with 13.0% higher DHEAS levels in non-BMI adjusted models. The relationships of CPD (12.1%, $p=0.04$) and MVPA (14.6%, $p=0.01$) with DHEAS levels were slightly stronger after BMI adjustment.

PA and SHBG

Overall, we observed a consistent positive linear relationship between accelerometer estimated and self-reported PA with SHBG, the majority of which were attenuated but remained statistically significant after BMI adjustment (Table 2). Specifically, each standard deviation increase in CPD and TPA was associated with 24.3% and 20.8% higher SHBG levels respectively. After BMI adjustment, the relationship between CPD and SHBG was no longer statistically significant. However, the positive relationship between self-reported TPA and SHBG remained statistically significant in BMI adjusted models.

By intensity, each standard deviation increase in accelerometer estimated MVPA, MVPA_{bouts}, and LPA was associated with 19.2%, 22.6%, and 16.5% higher SHBG levels respectively ($p<0.01$). After BMI adjustment, the relationship between MVPA_{bouts} and estradiol was attenuated but remained statistically significant ($p=0.04$). Each standard deviation increase in self-reported MVPA and LPA was associated with 17.3% and 15.8% higher SHBG levels ($p<0.01$). The statistically significant relationship between self-reported LPA and estradiol persisted after BMI adjustment.

By type, aerobic activity had slightly stronger linear associations with SHBG than weight training in non-BMI adjusted models. Specifically, each standard deviation increase in aerobic activity and weight training was associated with 20.0% ($p<0.01$) and 13.3% ($p<0.01$) higher SHBG levels respectively. After BMI adjustment, the observed relationships were attenuated but remained statistically significant. Lastly, women who exercised four or more days per week had 21.3% higher SHBG levels than women who reported not exercising in non-BMI adjusted models. This observed association was attenuated and no longer statistically significant after BMI adjustment (Supplemental Table 3).

DISCUSSION

In this sample of pre- and postmenopausal women from the NHS and NHS II cohorts, we examined the relationship between PA intensity and type with sex hormones using both objective and self-reported measures of PA. We observed modest but consistent inverse associations for accelerometer estimated and self-reported PA with estradiol and positive associations between accelerometer estimated and self-reported PA with SHBG. Further, accelerometer estimated PA was positively associated with DHEAS. The majority of the observed associations were entirely or substantially attenuated after accounting for BMI, however, the relationships between PA and DHEAS largely persisted in BMI adjusted models.

This manuscript extends the findings of prior studies, which largely examined the relationship between total and leisure-time PA and sex hormones. A better understanding of how specific types or intensities of PA relate to sex hormones levels could inform the development of intervention strategies. Overall, the relationship between PA and sex hormones varied relatively little by intensity. The only exceptions were the relationship between PA and DHEAS, where MVPA, but not LPA, had positive associations, and several comparisons between the most and least active women (e.g., 4th vs. 1st quartile of estradiol for sr-MVPA and sr-LPA). In general, these findings support the benefits of encouraging movement regardless of intensity. However, randomized controlled trials that directly compare similar PA interventions with varying intensity levels are needed to further elucidate the relationship between intensity and sex hormones.

By type, aerobic activity was more strongly associated with sex hormones than weight training. However, nearly half of the participants reported not engaging in any weight training. Among the women that reported some weight training, it was typically performed approximately 51 minutes per week. Women reporting weight training above this level had lower estradiol levels and higher SHBG levels than women not engaging in this activity, independent of the amount of aerobic activity they reported. Although confirmation is needed, our findings suggest greater attention should be given to encouraging women to perform weight training, in addition to aerobic activity.

This manuscript additionally fills a research gap by examining the relationships between PA and sex hormones using both objective and self-reported measures of PA. We observed similar patterns with each assessment tool, particularly when examining intensity-specific associations. However, consistent with prior studies,^{18,19} the accelerometer showed slightly stronger associations with PA and sex hormones. For example, each standard deviation increase in CPD was associated with a 23% lower estradiol compared to only 13% lower estradiol with self-report. Therefore, while the general trends were similar, associations may be attenuated and hence no longer statistically significant if using self-reported measures of PA.

However, other aspects of activity may be important to consider in addition to time and intensity characteristics of movement. Accelerometers are unable to measure specific behaviors, like weight training. Thus, it may be important to incorporate self-reported

measures of PA if a primary interest is to understand how contextual or behavior characteristics relate to sex hormones. Prior studies mostly focused on TPA or activities accumulated within specific domains (e.g., LTPA). Thus, aerobic activities were not examined separately from resistance activities. Although aerobic activity had stronger linear associations with sex hormones than weight training, weight training had somewhat stronger associations when specifically comparing the highest vs. the least active groups. These findings may be relevant for the design of interventions aimed at impacting sex hormones levels. Given that most of the existing interventions have focused on aerobic activity,²⁰ intervention studies that directly compare aerobic and resistance training interventions are needed to further elucidate the relationship between activity type and breast cancer risk.

The findings of the current study were similar to some prior studies^{17,21–23} and conflict with others.^{4,5,16} For example, van Gils et al examined the association between self-reported PA in the past year and several sex hormones in 806 postmenopausal women not on hormone replacement therapy.²³ In this study, women self-reporting the most (vs. least) PA had nearly 22% higher SHBG levels. In contrast, Liedtke et al found no association between self-reported PA and SHBG among 1260 postmenopausal women.⁵ These studies used a variety of self-reported measures, which measured PA during different time frames (e.g., typical, past week, past year). No real patterns emerged regarding the characteristics of PA assessment and its relationship between sex hormones.

Consistent with reports by others, the association between PA and sex hormones were substantially attenuated and mostly non-significant after controlling for BMI. BMI is well confirmed to be positively associated with plasma estrogens, through aromatization of androgens to estrogens in adipose tissue,²⁴ and inversely associated with SHBG.^{25,26} These results suggest that the relationship between PA and sex hormones are largely mediated through BMI. In the instances where associations remained after accounting for BMI (e.g., MVPA, weight training), it is unclear if this is due to additional mechanisms for physical activities' influence on hormone levels or inadequate control for adiposity.

Strengths of our study include the use of both subjective and objective PA assessments in the same relatively large population, state-of-the-art hormone assessments with excellent laboratory coefficients of variation, and detailed information on potential covariates. However, there also are several limitations worth noting. First, while the value of accelerometers for measuring PA in free-living settings is well recognized, they are not true gold standards of PA assessment. However, accelerometers are more practical to use in large observational studies than true measures of free-living PA, direct observation. Also, we relied on cut-point based methods to estimate the intensity of PA, which can misclassify the intensity of some activities of daily living. However, the cut-points used have been utilized by many previous studies and have been considered to be valid estimates of MVPA.^{11,12} Lastly, the data is cross-sectional, which prevents evaluation of a temporal association between PA and sex hormones.

In conclusion, multiple aspects of PA measured via both accelerometer and self-report were independently associated with plasma levels of several sex hormones in pre- and postmenopausal women. The magnitude of the associations may vary somewhat by intensity

and type but confirmation in larger studies is needed. BMI largely explained the relationship between some measures of PA and sex hormones. These results may inform the design (i.e. by intensity and type) of interventions aimed at reducing breast cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*. 2012;380(9838):219–229. [PubMed: 22818936]
2. Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. *J Nutr*. 2002;132(11 Suppl):3456S–3464S. [PubMed: 12421870]
3. Zhang X, Tworoger SS, Eliassen AH, Hankinson SE. Postmenopausal plasma sex hormone levels and breast cancer risk over 20 years of follow-up. *Breast Cancer Res Treat*. 2013;137(3):883–892. [PubMed: 23283524]
4. Chan MF, Dowsett M, Folkard E, et al. Usual physical activity and endogenous sex hormones in postmenopausal women: the European prospective investigation into cancer-norfolk population study. *Cancer Epidemiol Biomarkers Prev*. 2007;16(5):900–905. [PubMed: 17507613]
5. Liedtke S, Schmidt ME, Becker S, et al. Physical activity and endogenous sex hormones in postmenopausal women: to what extent are observed associations confounded or modified by BMI? *Cancer causes & control : CCC*. 2011;22(1):81–89. [PubMed: 21052816]
6. Petree Gabriel K, Morrow JJ, Woolsey A. Framework for Physical Activity as a Complex and Multidimensional Behavior. *Journal of physical activity & health*. 2012;9(Suppl 1):S11–18. [PubMed: 22287443]
7. Troiano RP, Petree Gabriel KK, Welk GJ, Owen N, Sternfeld B. Reported physical activity and sedentary behavior: why do you ask? *Journal of physical activity & health*. 2012;9 Suppl 1:S68–75. [PubMed: 22287450]
8. Yuan C, Spiegelman D, Rimm EB, et al. Validity of a Dietary Questionnaire Assessed by Comparison With Multiple Weighed Dietary Records or 24-Hour Recalls. *Am J Epidemiol*. 2017;185(7):570–584. [PubMed: 28338828]
9. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc*. 2008;40(1):181–188. [PubMed: 18091006]
10. Tudor-Locke C, Camhi SM, Troiano RP. A catalog of rules, variables, and definitions applied to accelerometer data in the National Health and Nutrition Examination Survey, 2003–2006. *Preventing chronic disease*. 2012;9:E113.
11. Sasaki JE, John D, Freedson PS. Validation and comparison of ActiGraph activity monitors. *Journal of science and medicine in sport / Sports Medicine Australia*. 2011;14(5):411–416.
12. Aguilar-Farias N, Brown WJ, Peeters GM. ActiGraph GT3X+ cut-points for identifying sedentary behaviour in older adults in free-living environments. *Journal of science and medicine in sport / Sports Medicine Australia*. 2014;17(3):293–299.
13. Santos-Lozano A, Santin-Medeiros F, Cardon G, et al. Actigraph GT3X: validation and determination of physical activity intensity cut points. *Int J Sports Med*. 2013;34(11):975–982. [PubMed: 23700330]

14. Winters-Hart CS, Brach JS, Storti KL, Trauth JM, Kriska AM. Validity of a questionnaire to assess historical physical activity in older women. *Med Sci Sports Exerc.* 2004;36(12):2082–2087. [PubMed: 15570143]
15. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc.* 2000;32(9 Suppl):S498–504. [PubMed: 10993420]
16. Bertone-Johnson ER, Tworoger SS, Hankinson SE. Recreational physical activity and steroid hormone levels in postmenopausal women. *Am J Epidemiol.* 2009;170(9):1095–1104. [PubMed: 19783585]
17. Schmitz KH, Lin H, Sammel MD, et al. Association of physical activity with reproductive hormones: the Penn Ovarian Aging Study. *Cancer Epidemiol Biomarkers Prev.* 2007;16(10):2042–2047. [PubMed: 17905944]
18. Aienza A, Moser R, Perna F, et al. Self-Reported and Objectively-Measured Activity Related To Biomarkers Using NHANES. *Med Sci Sports Exerc.* 2010;43(5):815–821.
19. Tucker JM, Welk GJ, Beyler NK, Kim Y. Associations Between Physical Activity and Metabolic Syndrome: Comparison Between Self-Report and Accelerometry. *American journal of health promotion : AJHP.* 2016;30(3):155–162. [PubMed: 25806568]
20. Ennour-Idrissi K, Maunsell E, Diorio C. Effect of physical activity on sex hormones in women: a systematic review and meta-analysis of randomized controlled trials. *Breast Cancer Res.* 2015;17(1):139. [PubMed: 26541144]
21. Gyllenhammer LE, Vanni AK, Byrd-Williams CE, Kalan M, Bernstein L, Davis JN. Objective habitual physical activity and estradiol levels in obese Latina adolescents. *Journal of physical activity & health.* 2013;10(5):727–733. [PubMed: 23038707]
22. Goto A, Chen BH, Song Y, et al. Age, body mass, usage of exogenous estrogen, and lifestyle factors in relation to circulating sex hormone-binding globulin concentrations in postmenopausal women. *Clin Chem.* 2014;60(1):174–185. [PubMed: 24048437]
23. van Gils CH, Peeters PH, Schoenmakers MC, et al. Physical activity and endogenous sex hormone levels in postmenopausal women: a cross-sectional study in the Prospect-EPIC Cohort. *Cancer Epidemiol Biomarkers Prev.* 2009;18(2):377–383. [PubMed: 19190137]
24. Grodin JM, Siiteri PK, MacDonald PC. Source of estrogen production in postmenopausal women. *The Journal of clinical endocrinology and metabolism.* 1973;36(2):207–214. [PubMed: 4688315]
25. Simo R, Saez-Lopez C, Barbosa-Desongles A, Hernandez C, Selva DM. Novel insights in SHBG regulation and clinical implications. *Trends Endocrinol Metab.* 2015;26(7):376–383. [PubMed: 26044465]
26. Crave JC, Lejeune H, Brebant C, Baret C, Pugeat M. Differential effects of insulin and insulin-like growth factor I on the production of plasma steroid-binding globulins by human hepatoblastoma-derived (Hep G2) cells. *The Journal of clinical endocrinology and metabolism.* 1995;80(4):1283–1289. [PubMed: 7536204]

Table 1

Descriptive characteristics by accelerometer-determined physical activity: WLVS

	Quartiles of Total Counts Per Day				
	Q1 (n=123)	Q2 (n=124)	Q3 (n=124)	Q4 (n=124)	
Age, yrs *	68.3(8.2)	64.7(8.6)	62.5(9.6)	58.7(8.7)	<0.01
Body Mass Index, kg/m ²	30.1(7.0)	28.0(5.7)	25.5(4.2)	23.9(3.4)	<0.01
white, %	84	89	93	94	0.17
Postmenopausal, %	85	88	85	84	<0.01
Age at Menopause, yrs *	47.6(6.7)	48.2(5.8)	48.9(5.3)	49.0(5.8)	0.34
Current Hormone Use, %	6	6	3	6	0.85
Ovaries Removed, %	33	23	20	13	<0.01
Parity, %					
Nulliparous	6	6	9	15	0.02
1 – 2 children	50	55	46	38	
3 or more children	44	39	44	47	
Age at Menarche, %					
< 12 yrs	65	66	60	59	<0.01
12 yrs	11	14	10	17	
> 12 yrs	24	20	30	23	
Alcohol, g/d	8.1(14.5)	7.7(9.9)	9.4(13.4)	8.2(9.9)	0.84
Current Smoker, %	2	1	1	4	0.31

Values are means(SD) or percentages and are standardized to the age distribution of the study population.

* Value is not age adjusted

The linear association between accelerometer estimated and self-reported physical activity, by intensity, and type with sex hormones: Women's Lifestyle Validation Study

Table 2 -

	Estradiol (pg/ml) (n=393)			Testosterone (ng/dL) (n=492)			DHEAS (ug/dL) (n=435)			SHBG (nmol/L) (n=493)		
	β	%	p-value	β	%	p-value	β	%	p-value	β	%	p-value
Total Physical Activity												
Counts per day												
Model 1	-0.26	-23.2	<0.01	-0.02	-2.2	0.65	0.09	9.5	0.08	0.22	24.3	<0.01
Model 2	-0.10	-9.6	0.06	-0.04	-4.3	0.40	0.11	12.1	0.04	0.06	6.0	0.25
Total activity (MET hr/wk)												
Model 1	-0.14	-12.9	0.01	0.03	3.0	0.51	-0.05	-4.9	0.27	0.19	20.8	<0.01
Model 2	-0.06	-5.7	0.22	0.02	2.2	0.63	-0.05	-4.7	0.30	0.10	10.9	0.02
By Intensity												
MVPA (min/day)												
Model 1	-0.15	-14.1	<0.01	0.01	1.2	0.80	0.12	13.0	0.01	0.18	19.2	<0.01
Model 2	-0.03	-2.7	0.59	0.00	-0.4	0.93	0.14	14.6	0.01	0.06	6.1	0.20
MVPA bouts (min/day)												
Model 1	-0.15	-14.2	<0.01	0.01	0.6	0.90	0.04	4.5	0.34	0.20	22.6	<0.01
Model 2	-0.03	-3.2	0.50	-0.01	-1.1	0.81	0.05	5.3	0.28	0.09	9.4	0.04
LPA (min/day)												
Model 1	-0.15	-13.7	<0.01	-0.04	-4.1	0.33	-0.04	-3.8	0.38	0.15	16.5	<0.01
Model 2	-0.04	-4.0	0.40	-0.06	-5.4	0.22	-0.03	-2.8	0.54	0.06	6.0	0.18
MVPA (MET hr/wk)												
Model 1	-0.11	-10.5	0.03	0.03	3.4	0.44	-0.03	-2.5	0.57	0.16	17.3	<0.01
Model 2	-0.02	-1.8	0.71	0.03	2.6	0.57	-0.02	-2.2	0.62	0.07	7.5	0.09
LPA (MET hr/wk)												
Model 1	-0.11	-10.7	0.03	-0.01	-0.8	0.85	-0.01	-1.2	0.79	0.15	15.8	<0.01
Model 2	-0.07	-6.9	0.14	-0.01	-1.3	0.77	-0.01	-1.1	0.82	0.10	10.0	0.02
By Type												

	Estradiol (pg/ml) (n=393)			Testosterone (ng/dL) (n=492)			DHEAS (ug/dL) (n=435)			SHBG (nmol/L) (n=493)		
	β	%	p-value	β	%	p-value	β	%	p-value	β	%	p-value
Aerobic activity (MET hr/wk)												
Model 1	-0.14	-12.7	0.01	0.02	2.5	0.59	-0.01	-0.7	0.88	0.18	20.0	<0.01
Model 2	-0.05	-4.9	0.31	0.02	1.5	0.75	-0.01	-0.5	0.92	0.09	9.8	0.04
Weight Training (MET hr/wk)												
Model 1	-0.09	-8.6	0.08	-0.02	-2.3	0.60	-0.06	-5.9	0.19	0.12	13.3	0.01
Model 2	-0.05	-4.8	0.30	-0.03	-2.7	0.54	-0.06	-5.8	0.20	0.09	9.5	0.03

Model 1 = adjusted for age (continuous), race (white, non-white), age at menopause (premenopausal, <45, 45 to <50, 50 to 52, >52 yrs) oophorectomy status (yes, no), parity (0, 1-2, 3+), age at menarche (continuous), physical activity in other intensities/type; Model 2 = Model 1 + BMI (continuous); % = change in sex hormone levels per standard deviation change in PA