Published in final edited form as:

J Phys Act Health. 2013 July ; 10(5): 727–733.

Objective Habitual Physical Activity and Estradiol Levels in Obese Latina Adolescents

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Abstract

Background—Lifetime physical activity (PA) is associated with decreased breast cancer (BC) risk; reports suggest that PA during adolescence contributes strongly to this relationship. PA lowers production of sex hormones, specifically estradiol, or decreases insulin resistance (IR), thereby lowering risk. Overweight Latina adolescents are insulin resistant and exhibit low levels of PA, potentially increasing their future BC risk.

Methods—37 obese Latina adolescents (15.7 ± 1.1 yrs) provided measures of PA using accelerometry; plasma follicular phase estradiol, sex-hormone binding globulin, total and free testosterone, dehydroepiandrosterone-sulfate (DHEAS); IR using HOMA-IR; body composition via DEXA. Partial correlations and stepwise linear regressions assessed cross-sectional relationships between sex hormones, IR and PA. Body composition, and age were included *a priori* as covariates.

Results—Estradiol was negatively associated with accelerometer counts per minute (CPM) ($r = -0.4$; $p = 0.02$), percent time spent in moderate PA (%MPA) ($r = -0.5$; $p = 0.006$), and percent time in moderate or vigorous PA (%MVPA) ($r = -0.5$; $p = 0.007$). DHEAS was positively associated with CPM ($r = 0.4$, $p = 0.009$), %MPA ($r = 0.3$, $p = 0.04$), and %MVPA ($r = 0.3$, $p = 0.04$). Other sex hormones and IR were not associated with PA measures.

Conclusion—This study is the first to show that higher habitual PA was inversely associated with estradiol in obese adolescents.

Keywords

Accelerometer; insulin resistance; sex hormones; breast cancer

Introduction

Physical activity has many known benefits, and is recognized as the strongest known modifiable risk factor for breast cancer. Lifetime physical activity (PA) is known to significantly decrease breast cancer risk^{1,2}; however recently, a large prospective study

showed that PA during adolescence contributed more strongly to this association than activity performed as an adult². Alarming, adolescence is a period of marked decline in PA amongst females³, especially in those of low socioeconomic status⁴. The 2007 Youth Health Risk Behavior Survey showed that the majority of female Latino adolescents are inactive, with only 21.9% meeting recommended levels of moderate or vigorous PA (MVPA)⁵; additionally, the NHANES report using objective measurement of PA showed that obese female Latino adolescents spent less than 20 minutes per day in MVPA, significantly less than their lean counterparts⁶.

While the exact mechanisms through which PA decreases breast cancer risk are unknown, several mechanisms have been proposed, including the decreased production or bioavailability of hormones, such as estradiol, or insulin, and improved insulin sensitivity^{7,8}. Our group has shown that Latino adolescents living in Los Angeles are extremely insulin resistant⁹, and that approximately one-third are pre-diabetic or have metabolic syndrome¹⁰; however, less is known about breast cancer risk factors within this population in association with physical activity. Breast cancer has been linked to declines in PA^{1,2}, increased levels of estrogens and androgens¹¹, and insulin resistance¹². Given that breast cancer is the leading cause of cancer death amongst Latino women¹³, it is important to examine the impact of a modifiable risk factor, such as PA, upon recognized biomarkers associated with breast cancer. Furthermore, little is known about the impact of low level habitual activity captured by accelerometers upon these biomarkers within this population.

Adolescence is a period characterized by marked increases in sex hormone levels and rapid proliferation of undifferentiated breast tissue², and is modeled as a period when breast tissue is the most sensitive to mutagenesis¹⁴. A number of cross-sectional studies have looked at PA in association with estradiol levels, but none was conducted during this critical time window of adolescence, nor was PA objectively measured in any study^{15–17}. Thus, the purpose of this study is to examine the relationship between objectively measured habitual PA, using accelerometers, circulating plasma sex hormone levels and insulin resistance in Latina adolescents. We hypothesize that higher levels of habitual activity will be related to lower sex hormones levels, specifically estradiol, and insulin resistance.

Methods

Participants

Forty-five overweight (95th BMI age- and gender- specific percentile) Latina adolescent females were recruited and provide cross-sectional data for this study. Participants had to meet the following selection criteria: female, Latino descent (all four grandparents being Latino), 14 to 18 years of age, BMI 95th percentile (CDC age- and gender- specific values determined by EpiInfo 2005 (CDC, Atlanta, GA)), no history of use of hormonal contraceptives or other hormonal medications, no previous or current pregnancy, no personal history of diabetes or other major illness. Two of the 45 girls were excluded from analysis due to inability to capture blood draw during follicular phase, and 6 were excluded due to insufficient accelerometer data (required minimum was 4 days with 8 hours of recording). Thus, a subset of 37 participants was included in the present analysis. This study was approved by the institutional review board of the University of Southern California, and informed written parental consent and child assent were obtained before participation.

Adiposity measures

Weight and height were measured to the nearest 0.1kg and 1cm, respectively, using a beam medical scale and wall-mounted stadiometer; Body mass index (BMI, kg/m²) and BMI percentiles for CDC age- and gender-specific values were determined using EpiInfo 2005

(CDC, Atlanta, GA). Total fat mass and total lean mass were measured by dual energy x-ray absorptiometry (DEXA) using a Hologic QDR 4500W (Hologic, Bedford, MA).

Menstrual measures

Menstrual cycles were monitored two months prior to study and all blood draws were performed during the follicular phase of the menstrual cycle (within the first 8 days, on average 5.7 days into the cycle). Trained medical staff collected length of previous period, age at menarche, and assessed Tanner staging.

Assays

After an overnight fast and at approximately 7:30 AM, blood was collected. Blood samples were centrifuged immediately for 10 min at 2500 RPM and 8–10°C to obtain plasma, and plasma aliquots were frozen at –70°C until assayed. Glucose was assayed in duplicate on a Yellow Springs Instrument 2700 Analyzer (Yellow Springs Instrument, Yellow Springs, OH) using the glucose oxidase method. Insulin was assayed in duplicate using a specific human insulin ELISA kit from Linco. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated [$\text{HOMA-IR} = \text{fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose } (\text{mmol/l}) / 22.5$]¹⁸. Estrone, estradiol, androstenedione and testosterone were quantified by validated radioimmunoassays after organic solvent extraction and Celite column partition chromatography. Chromatographic separation of the steroids was achieved using different concentrations of toluene in isooctane and ethyl acetate in isooctane. DHEAS and SHBG were quantified in a direct chemiluminescent immunoassay using the Immulite Analyzer (Siemens Medical Solutions Diagnostics, Malvern, PA). The SHBG concentration and an average albumin concentration were then utilized in a validated algorithm with total testosterone or total estradiol to calculate free testosterone and free estradiol, respectively¹⁹. The minimal detection limit for androstenedione, testosterone, estrone, estradiol, DHEAS and SHBG were 0.03 ng/ml, 1.5 ng/dL, 4 pg/ml, 2 pg/ml, 3 µg/dL and 1 nM, respectively (with intra-assay and inter-assay variation 4–7.5%, and 8–13% respectively).

Physical Activity Measurement

Physical activity was objectively measured using the biaxial Actigraph accelerometer (GT1M; Actigraph, LLC, Pensacola, FL). The Actigraph accelerometer is a reliable instrument, valid for measuring activity in children and adolescents²⁰. Participants were instructed to wear the Actigraph on their right hip for seven consecutive days, capturing weekend and weekday wear, except while participating in water-based activities or during nighttime sleep. Furthermore, accelerometer data collection occurred outside of participant menses to capture habitual activity levels. Epoch length was set to 15 seconds, and the data were reduced, with the epochs collapsed to 60 seconds, using an adapted version of the SAS code used for the 2003–2004 National Health and Nutrition Examination Survey (NHANES) available at http://riskfactor.cancer.gov/tools/nhanes_pam. The intensity thresholds for moderate (2,200 counts) and vigorous (5,999 counts) activity were set at the adult and older adolescent cut-points used in NHANES²¹ since the average weight of the adolescents in our study was 88 kg and all girls were in advanced pubertal stages. Additionally, a sedentary cut point of 100 counts was used²².

There is no clear consensus on the amount of time required for valid accelerometry measurement²³, so a modest level of 4 days with at least 8 valid hours of activity each was used for these analyses (n=37). Statistical analyses were repeated in a subsample (n = 32) of participants with 5 days of accelerometry data, and similar results were obtained. Accelerometer data are presented as the percentage time spent across activity levels, and total PA, or mean counts per minute (CPM). The percentage time across activity levels was calculated by summing the minutes within each activity threshold (sedentary PA (SPA),

light PA (LPA), moderate PA (MPA), vigorous PA (VPA), and combined moderate and vigorous PA (MVPA)), and then dividing that by the total minutes of wear per day. Mean CPM was calculated by dividing the total counts per day by the total minutes of wear per day.

Statistics

The data were assessed for normality and log-transformations were made if any variable significantly differed from a normal distribution (estradiol, testosterone, free-testosterone, SHBG, DHEAS, DEXA total fat, %VPA and HOMA-IR). An independent sample t-test was performed and there were no statistical differences in the baseline characteristics between the 6 participants excluded and the 37 participants with regular menstrual cycles who successfully collected valid accelerometer data. Primary analysis involved bivariate and partial correlations between PA measures and sex hormones, fasting insulin and IR. If the correlations were statistically significant, then a stepwise regression analysis was performed. For each stepwise regression, the dependent variables were the sex hormones of interest and the independent variables were the varying levels of PA. In all models, the following *a priori* covariates were included: age, total fat mass, total lean mass and HOMA-IR. Scatter plots were then produced to display these significant relationships. All analyses were performed using SPSS version 16.0, (SPSS, Chicago, IL), with $P < 0.05$ considered statistically significant.

Results

Table 1 shows the baseline characteristics of the participants with complete follicular phase blood collection and accelerometer data ($n=37$). Participants' ages ranged from 14 to 18 years, with a mean age of 15.7 ± 1.1 years and 89% in Tanner 5. All participants had previously experienced menarche at the mean age of 11.4 ± 1.3 years, on average 4.2 ± 1.9 years prior to study participation, and the average length of the previous menstrual phase was 5.3 ± 1.4 days. On average the accelerometer was worn for 6 days with a mean of 13 hours per day. Only 3.5 ± 2.3 percent of the day was spent in MVPA, and less than $.1 \pm .1$ percent of the day was spent in VPA.

Table 2 shows the partial correlations between PA and estradiol and DHEAS which were the only hormones assessed that were significantly related to PA before or after controlling for IR, age, total fat and total lean mass. IR, age, total fat and total lean were included *a priori* as covariates, and only age significantly associated with estradiol and only total body fat significantly associated with DHEAS; furthermore BMI %ile, total fat and lean mass did not significantly associate with measure of PA (results not shown). Estradiol was negatively associated with total PA ($r = -0.40$; $p=0.023$), %MPA ($r = -0.46$; $p=0.009$), and %MVPA ($r = -0.45$; $p=0.010$). Figure 1 displays the linear relationships between estradiol and total PA and %MPA. DHEAS was positively associated with total PA ($r=0.45$, $p=0.011$), %MPA ($r=0.37$, $p=0.038$), and %MVPA ($r=0.37$, $p=0.038$). Figure 2 displays the linear relationships between DHEAS and total PA and %MPA. Similar results were seen for PA expressed as minutes (data not shown). PA measures were not significantly related to HOMA-IR or any of the other sex hormones, before or after controlling for covariates. Additionally, markers of menstruation status, including age at menarche, years since menarche, and menses length, did not affect the association found between PA and estradiol and DHEAS.

Stepwise linear regression analysis was performed, using estradiol or DHEAS as the dependent variable, controlling for IR, age, total fat and total lean mass to examine the additional variance explained by adding total PA or %MPA to the model. Total PA and %MPA explain an additional 12% and 16% of the variance of estradiol beyond the listed covariates ($p = 0.05$, and $p = 0.01$ respectively). Total PA and %MPA explain an additional

14% and 10% of the variance of DHEAS beyond the listed covariates ($p = 0.05$, and $p = 0.05$ respectively). While DHEAS and Estradiol were also significantly associated with %MVPA, only %MPA is presented since MVPA is a sum of MPA and VPA, and time spent in VPA was minute.

Discussion

As hypothesized, habitual PA was associated with lower estradiol levels; however habitual PA was not significantly associated with IR and was associated with higher DHEAS. PA, measured as counts per minute (CPM) and as time spent in moderate and vigorous PA, was inversely related to estradiol levels. A 33% higher activity level across participants, or approximately 100 CPM (which roughly translates into an increase of 250 kcals of energy expenditure per day²⁴), was associated with a 4.2 pg/ml decrease in estradiol. While lower estradiol was also associated with increased MVPA, the significant relationship with total PA supports the findings in epidemiological reports that generalized lifestyle activity, known as habitual activity, not just the high-level activity found in exercise, is potentially important for decreasing breast cancer risk. While decreased levels of estradiol are considered beneficial for breast cancer risk, estradiol levels that are too low can be detrimental for bone health. In our population, neither measure of physical activity nor estradiol was associated with bone mineral composition.

To our knowledge, this is the first study showing an inverse relationship between estradiol levels and objectively measured habitual PA in any pre-menopausal female population, much less a potentially high-risk adolescent population. Our data is consistent with previous studies in premenopausal women, showing higher subjectively reported habitual PA associated with lower estradiol^{15–17}; however across these studies, the earliest age of measurement was 24 years old, and all the PA was subjectively reported, which is less precise than the objective accelerometer measurement used in our study. The protective effect of activity during adolescence appears independent of activity levels in adulthood², furthering the importance of studying the physiological changes associated with PA during this critical time period. Capturing timed hormonal measurements in adolescents can be a difficult study design, especially with the increased menstrual irregularity seen in this population. Our study proves the feasibility of such measurement and opens towards future measurement of other more comprehensive biomarkers and hormone measurement, such as estrogen metabolites, oxidative stress, inflammation, associated with breast cancer risk.

Habitual activity levels were not associated with IR in this study. In other cross-sectional studies, elevated PA levels have been related to lower insulin resistance in youth^{25,26}. These studies found that IR, as measured by HOMA-IR, was inversely related to total PA²⁶ and MVPA^{25,26}, as measured with accelerometers. The null relationship between PA and IR in the current study, may in part, be explained by the overall low amount of PA exhibited by our participants. The average time spent in MVPA for the above youth studies was 140 ± 34 min/day²⁵ and 76 ± 40 min/day²⁶, while in our sample the average time spent in MVPA was markedly lower at 28 ± 18 min/day. Additionally, this study relied on the fasting HOMA-IR measure, and more precise measures of IR, such as the euglycemic clamp or a frequently sampled intravenous glucose tolerance test (FSIVGTT) may be required to elucidate the relationship at the low levels of PA seen in our population.

Higher levels of habitual PA were also significantly associated with higher DHEAS, however the relationship with DHEAS and breast cancer is not well understood in a pre-menopausal population. While a increasing levels of DHEAS have been associated with increasing risk of postmenopausal breast cancer¹¹, the association with premenopausal breast cancer has been mixed with some studies showing a decreased breast cancer risk with

high DHEAS levels^{27,28}, and others showing a null association^{29,30} or a positive association³¹. DHEAS peaks around 20 years of age and naturally decreases with age. One model of DHEAS activity suggests that in the context of the high estrogen levels seen among premenopausal women, DHEAS exhibits anti-estrogenic effects³². In our study, physical activity, which reduces risk of breast cancer, was statistically significant and positively associated with DHEAS, suggesting that higher levels of DHEAS during adolescence may be protective against breast cancer, however further work needs to be conducted to confirm this association.

While the exact mechanism through which PA reduces breast cancer risk is not certain, evidence for changes in steroidal pathways has been the most clearly delineated. The overall level of estrogen is important because estradiol and its metabolites increase the mitotic activity of breast epithelial cells^{33,34}. PA at even moderate levels may work to decrease estrogen levels by increasing the frequency of anovulatory menstrual cycles or through increasing menstrual irregularity by increasing cycle length³⁵. A study of 168 high school girls found that even modest engagement in physical activity more than doubles the likelihood of anovulatory cycles or lengthened menstrual cycles (600 kcal and 750 kcal per week, respectively),³⁵ which is relevant to the range of activity seen in our population. Additionally, PA may suppress estrogen production through its impact on adipose tissue. Adipose tissue, specifically peripheral fat cells, represents a significant source of estrogen production with 20–30% of estrogen production derived from peripheral conversion, aromatization, of C-19 steroids (androstenedione and DHEA) in a non-pregnant, premenopausal woman³⁶. By reducing this peripheral conversion, one could significantly decrease overall estrogen levels and potentially lead to a “back-up” of the precursor androgens, reflected as increased serum levels. This “back-up” phenomenon has been demonstrated in a rat model exposed to aromatase inhibitors³⁷. In this model, aromatase inhibitors caused significant decreases in serum estrogen levels while simultaneously increasing serum androgen levels, including DHEAS. This is similar to the pattern seen in our study. Total body fat and lean tissue mass were controlled for in all analyses, so the mechanism may work independently of the overall size of fat or lean mass and rather alter the functioning of those tissues. It is also generally accepted that PA can improve insulin sensitivity³⁸, resulting in increased hepatic production of SHBG, therefore lowering the bioavailability of sex hormones⁷. Additionally, insulin can increase the hepatic production of insulin-like growth factor, which is hypothesized to have mitogenic effects^{7,39}. Although PA was not significantly related to insulin action in our analyses, this does not preclude the involvement of insulin pathways; potentially, the levels of PA in our study were too low or our measure of IR was too imprecise to capture an effect.

There are several limitations that should be noted. Our sample size was relatively small. This study was cross-sectional so that we cannot infer any causal relationships. We intend, in future analyses, to determine whether a prescribed exercise intervention affects estradiol levels. In addition, this study included only overweight, sedentary Latina adolescents, which may limit the generalizability of results to other adolescent populations. Furthermore, while the use of accelerometers to objectively measure PA is a strength of the study, the specific types of PA performed (such as walking, running, etc.) were not identified. Additionally, hormone values were generated from a single assay, which can be subject to variability, particularly estradiol, in pre-menopausal women; however we controlled for menstruation time and were able to detect significant associations. A single measurement of sex hormones is not ideal; however there is limited data in the literature on the association between habitual activity and sex hormones in adolescent populations, and this preliminary data is required to justify future comprehensive and more expensive hormone assessment.

In conclusion, PA showed a moderate association with decreased estradiol levels even in the context of very limited activity levels, which has interesting implications for future intervention trials. Intervention trials that focus on prescribed exercise programs, primarily aerobic activity, have had limited success in reducing estradiol or estrogen metabolite levels in pre-menopausal women⁴⁰. In this study, less than 30 minutes per day was spent in moderate or vigorous PA, with total PA across the day being a significant predictor of estradiol levels. Therefore, large randomized controlled intervention studies examining how changes in habitual physical activity, not just high-level exercise activity, impact sex hormones are warranted in order to elucidate the causal relationship of PA on estradiol and other sex hormones, and validate the preliminary findings presented in this study.

Acknowledgments

Funding Sources:

This work was supported by the following: NIDDK K01 (1K01DK078858), NCI K05 (5K05CA136967), the M01 RR 00043 from NCI/NIH, and USC Graduate Provost fellowship. We would like to thank all the Childhood Obesity Research Core (CORC) research team, particularly the study trainer Matt Mejia, as well as the nursing staff at the CTU. In addition, we are grateful for our study participants and their families for their involvement. The results of the present study do not constitute endorsement by JPAH.

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Figure 1.

a. Relationship between %MPA and Estradiol (pg/ml), adjusted for age, total fat (kg), total lean (kg), and HOMA-IR; $P = .009$. **b.** Relationship between Total PA and Estradiol (pg/ml), adjusted for age, total fat (kg), total lean (kg), and HOMA-IR; $P = .023$.

Figure 2.

a. Relationship between %MPA and DHEAS ($\mu\text{g/dL}$) adjusted for age, total fat (kg), total lean (kg), and HOMA-IR; $P = .038$. **b.** Relationship between Total PA and DHEAS ($\mu\text{g/dL}$) adjusted for age, total fat (kg), total lean (kg), and HOMA-IR; $P = .011$.

Table 1 Descriptive characteristics of the study sample (n=37)^a

	Mean (SD)
Age	15.7 (1.1)
Age at menarche	11.4(1.3)
Tanner (4/5) ^b	(4/33)
Body Composition:	
Weight (kg)	87.9 (15.8)
BMI %	97.6 (2.0)
BMI (kg/m ²)	34.8 (5.6)
BMI z-score	2.1 (0.3)
Waist (cm)	108.6 (10.1)
Hip (cm)	117.8 (10.1)
Total fat mass (kg)	36.2 (9.0)
Total percent body fat (%)	41.9 (4.7)
Total lean mass (kg) ^c	47.2 (7.5)
Biomarkers:	
Estradiol (pg/ml)	41.9 (13.6)
Estrone (pg/ml)	49.0 (16.0)
SHBG (nmol/L)	16.5 (7.8)
DHEAS (µg/dL)	170.7 (94.7)
Total Testosterone (ng/dL)	33.1 (14.6)
Free Testosterone (pg/mL)	9.7 (4.2)
Adrostenedione (ng/mL)	1.3 (0.5)
HOMA-IR	3.7 (1.9)
Fasting Insulin (µU/mL)	16.6 (8.5)
Physical Activity:	
Mean Hours of Wear per Day	12.9 (1.6)
Mean Days of Wear	5.8 (1.7)
Mean Count Per Minute	302.7 (97.7)
Percent Time SPA	63.2 (7.2)
Percent Time LPA	33.2 (6.9)
Percent Time MPA	3.5 (2.3)
Percent Time VPA	0.1 (0.09)
Percent Time MVPA	3.6 (2.3)

^aData presented as Mean (SD). SHBG= sex hormone binding globulin, DHEAS= dehydroepiandrosterone sulfate, SPA= sedentary physical activity, LPA= light physical activity, MPA= moderate physical activity, VPA= vigorous physical activity, MVPA= moderate + vigorous physical activity, HOMA-IR= homeostasis model assesment

^bData presented as frequency

^cTotal lean mass does not include bone mineral content.

Table 2 Physical Activity and Hormone Partial Correlations (n=37)^a

	Estradiol		DHEAS	
	r-value	p-value	r-value	p-value
% SPA	r= 0.108	p=0.558	r=-0.338	p=0.059
% LPA	r= 0.041	p=0.824	r= 0.234	p=0.197
% MPA	r=-0.455	p=0.009 **	r= 0.369	p=0.038 *
% MVPA	r=-0.450	p=0.010 **	r= 0.368	p=0.038 *
% VPA	r=-0.005	p=0.980	r= 0.092	p=0.617
CPM	r=-0.400	p=0.023 *	r= 0.445	p=0.011 *

^aPartial Correlations adjusted for age, total fat (kg), total lean (kg), and HOMA-IR. DHEAS= dehydroepiandrosterone sulfate

**
p 0.01

*
p 0.05