Published in final edited form as:

Med Sci Sports Exerc. 2018 August ; 50(8): 1704–1709. doi:10.1249/MSS.0000000000001598.

Influence of Estradiol Status on Physical Activity in Premenopausal Women

Edward L. Melanson^{1,2,3}, Kate Lyden⁴, Ellie Gibbons², Kathleen M. Gavin^{2,3}, Pamela Wolfe², Margaret E Wierman^{1,5}, Robert S. Schwartz^{2,3}, and Wendy M. Kohrt^{2,3}

¹Division of Endocrinology, Metabolism, and Diabetes, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO

²Division of Geriatric Medicine, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO

³Eastern Colorado VA Geriatric Research, Education, and Clinical Center, Aurora, CO

⁴KAL Research & Consulting LLC, Denver, CO

⁵VA Eastern Colorado Health Care System, Aurora, CO

Abstract

Purpose—To determine the effects of 5 months of ovarian hormone suppression in premenopausal women on objectively measured physical activity (PA).

Methods—Participants (age = 35±8 yr; body mass index = 27±6 kg·m⁻²) received monthly intramuscular injections of gonadotropin releasing hormone agonist therapy (GnRH_{AG}) which suppresses pituitary gonadotropins and results in suppression of ovarian sex hormones. Women were randomized to receive concurrent transdermal E₂ (GnRH_{AG}+E₂; n=30) or placebo (GnRH_{AG}+PL, n=31). PA was assessed for 1 week before and during each month of the 5-month intervention using a hip-worn accelerometer (Actical, Mini Mitter Co., Inc., Bend, OR). Estimates of time spent in sedentary, light, and moderate-to-vigorous physical activity (MVPA) were derived using a previously published equation. Subsets of participants in each group were also randomized to a supervised progressive resistance exercise training program.

Results—Total MVPA tended towards being higher (p=0.08) in the GnRH_{AG}+E₂ group at month 4. There were no significant effects of intervention or time in sedentary or light PA. In the subset of women who did not participate in structured exercise training for which Actical data were obtained (N=16 in each group), total MVPA was higher at month 4 (p=0.01).

Conclusion—Physical activity levels appear to be maintained at a higher level in women undergoing pharmacological suppression of ovarian function with E₂ add back when compared with women treated with placebo. These data provide proof of concept data that E₂ contributes to

Corresponding Author: Edward L. Melanson, Ph.D. (Ed.melanson@ucdenver.edu), MS 8106, 12801 East 17th Ave, RC1 South RM 7103, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, Phone: (303) 724-0935 FAX: (303) 724-3920.

Conflict of Interest: The authors have no conflicts to declare. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and statement that results of the present study do not constitute endorsement by ACSM.

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the regulation of PA in humans. However, given the exploratory nature of this study, future confirmatory investigations will be necessary.

Keywords

Humans; estrogens; resistance exercise; gonadotropin releasing hormone; effects of sex steroids

INTRODUCTION

Pre-clinical studies have demonstrated that the loss of estradiol (E_2) or disruption of E_2 signaling causes excess fat gain in female rodents, particularly in abdominal regions.(1–4) In ovariectomized animals, this is prevented by E_2 treatment.(5) Similarly, suppression of gonadal function by gonadotropin releasing hormone agonist ($GnRH_{AG}$) therapy in humans causes excess fat gain (6–10) with abdominal fat accrual.(11) In both women(11) and men, (8) limited evidence indicates that such changes are specifically related to E_2 deficiency. One mechanism that may contribute to excess fat gain in response to E_2 suppression is a reduction in energy expenditure (EE). In animals, the gain in fat mass resulting from loss of E_2 or E_2 signaling has been associated with decreases in both resting (REE) and total energy expenditure (TEE).(12–16) In premenopausal women, we have previously shown that acute (6 days) and chronic (5 months) suppression of ovarian hormones caused decreases in REE(17, 18) and TEE,(18) and the decrease in REE was prevented by E_2 treatment.(18)

The decrease in TEE with loss of E_2 or disruption in E_2 signaling is due, in part, to a decline in spontaneous physical activity (SPA) and the associated energy expenditure (PAEE). Both ovariectomy (OVX)(3, 19) and the disruption of E_2 receptor signaling(4) in rodents cause a dramatic decline in spontaneous physical activity that is fully rescued by E_2 treatment.(20) However, the effects of E_2 on physical activity (PA) in humans have not been extensively explored. Evidence from the Study of Women's Health Across the Nation (SWAN) suggests that physical activity declines across the menopause.(21) In NHANES III, the prevalence of women reporting being physical inactive was lower in women who ever used HT (28.5%) when compared with those who had never used HT (40.0%).(22) We are aware of only one study that obtained objective measures of PA across the menopause transition; in that study, physical activity at the time of menopause decreased by approximately 50% compared to 3–4 years prior to menopause.(23) However, whether the decline in PA was related to the loss of E_2 , or instead biological aging or other factors associated with the menopausal transition, could not be determined.

The goal of this study was to determine the effects of 5 months of ovarian hormone suppression in the absence or presence of E_2 add back on objectively measured PA. Because PA was an exploratory outcome in the parent trial, which evaluated changes in adiposity, REE, and TEE,(11, 18) the study was not powered to detect changes in PA. Therefore, these data represent a proof-of-concept investigation to evaluate whether ovarian hormone suppression is associated with a decrease in free-living PA, as occurs in rodents.

METHODS

Institutional Approval

This study was approved by the Colorado Multiple Institutional Review Board (COMIRB) and the Scientific Advisory and Review Committee at the University of Colorado Anschutz Medical Campus (CU-AMC). The study was registered on ClinicalTrials.gov (NCT00687739) on May 28, 2008.

Participants and screening procedures

Participants were healthy premenopausal women. Volunteers provided written informed consent to participate, with the knowledge that the risks of the study included menopause-like effects (e.g., weight gain, bone loss, menopausal symptoms). Volunteers underwent screening procedures, as previously described.(11, 18) Primary inclusion criteria were age (25 to 49 y) and normal menstrual cycle function (no missed cycles in previous year, cycle length 28 ± 5 d, confirmation of ovulatory status (ClearPlan Easy, Unipath Diagnostics, Waltham, MA)). Primary exclusion criteria were pregnancy or lactation; use of hormonal contraception, oral glucocorticoids, or diabetes medications; smoking; or body mass index (BMI) >39 kg/m².

Experimental design and study procedures

The parent trial was a randomized, double-blinded, placebo-controlled trial to determine the effects of E₂ deficiency on body composition and components of energy expenditure.(11, 18) All participants underwent suppression of ovarian sex hormones with gonadotropin releasing hormone agonist therapy (GnRH_{AG}, leuprolide acetate 3.75 mg, Lupron; TAP Pharmaceutical Products, Inc; Lake Forest, IL), delivered as monthly intramuscular injections. A single injection of leuprolide acetate produces an initial stimulation (for 1 to 3 wk) followed by a prolonged suppression of pituitary gonadotropins, and repeated monthly dosing suppresses ovarian hormone secretion.(24) Absence of pregnancy (urine test) was confirmed before each dosing. Participants were randomized to receive concurrent transdermal E₂ 0.075 mg/d (Bayer HealthCare Pharmaceuticals, Berkeley, CA) or placebo patches (GnRH_{AG}+E₂, n=35; GnRH_{AG}+PL, n=35). During these monthly visits, participants met with the research nurse practitioner. Participants were queried about changes in use of medications or health (e.g., doctor visits, hospitalizations), as well as any study-related problems/concerns over the past 4 weeks. Compliance to the transdermal patches was confirmed verbally each month during the monthly examination. The E₂ regimen was expected to maintain serum E₂ concentrations in the mid-to-late follicular phase range (100 to 150 pg/mL).

As previously described,(11, 18) some participants in each drug group in the parent study were also randomized to a supervised progressive resistance exercise training program (N=12 in each group) to attenuate the expected decrease in fat-free mass with GnRH_{AG} therapy. Not all those randomized to exercise were willing to participate in the exercise program and were therefore treated as non-exercisers for the analyses herein. The progressive resistance exercise intervention consisted of 4 d/wk for 18 weeks beginning in week 1 of sex hormone suppression.(11)

Physical activity

PA was assessed using a hip-worn accelerometer (Actical, Mini Mitter Co., Inc., Bend, OR). Sampling was performed at 32 Hz and data were stored in 1-minute epochs. The monitor measures accelerations in multiple planes, but is most sensitive to vertical movements of the torso when worn on the hip. The resulting raw output is activity counts, which represent both the summed quantity and magnitude of accelerations during each epoch. PA was assessed for 1 week before the intervention and for 1 week of each month of the 5-month intervention. Participants were instructed to wear the Actical at all times for 7 consecutive days, except when engaged in water activities (e.g., bathing, showering, or swimming) or sleeping. To be included in the final analysis, 4 days of valid data were required for each time point. A day was considered valid if there was at least 10 hours of wear time.

Estimates of time spent in sedentary, light, and moderate-to-vigorous activity (MVPA) were derived using thresholds for number of accelerometer activity counts accumulated in a given epoch for the Actical in middle-aged adults.⁽²⁵⁾ To assess whether the levels of MVPA met the 2008 Guidelines for Physical Activity in Americans,⁽²⁶⁾ we examined the number of bouts lasting at least 10 minutes in duration with >80% of the bout categorized as MVPA (Guideline MVPA).⁽²⁶⁾ Guideline MVPA was calculated as both minutes per day (total minutes per day spent in MVPA bouts), and the number of bouts per day (the number of MPVA bouts per day). For participants in the non-exercise groups, we also determined the amount of time spent in spontaneous physical activity (SPA), defined as all minutes spent in light or MVPA performed in bouts lasting less than 10 min.

Sex Hormones

Blood samples for sex hormones were collected during baseline testing and during week 20 of the intervention. A single sample (~5 mL) was obtained in the morning (~8 AM), after an overnight fast (at least 10 hours), and at least 48 hours after the last bout of exercise. Baseline samples were obtained immediately prior to the first injection. Collection samples were stored at -80°C until analysis. Estrone (E₁), was determined by radioimmunoassay (Diagnostic Systems Lab, Webster, TX) with intra- and inter- assay CVs of 8.7% and 8.6%. E₂, P and total testosterone (T) were analyzed by chemiluminescence immunoassay with intra- and inter-day CVs of 4.3% and 8.2% for E₂, 4.4% and 7.9% for P, 3.6% and 5.7% for sex hormone-binding globulin, and 2.1% and 5.1% for T (Access 2 Immunoassay System Analyzer, Beckman Coulter, Fullerton, CA).

Statistical analysis

Baseline characteristics are presented as mean (SD) by group. Changes in these characteristics in response to the intervention are presented as mean (95% CI). The primary analysis evaluated differences in time spent in sedentary behavior and in light and MVPA between the GnRH_{AG}+PL and GnRH_{AG}+E₂ groups using a repeated measures maximum likelihood, cell means model regressing activity levels on group and time, controlling for baseline, using all available data. This approach is similar to a repeated measures ANCOVA, but has the advantage of not requiring case wise deletion of cases missing information at one or more time points. To minimize the number of statistical tests we estimated the overall group difference, the overall time effect, and the difference between groups at the month 4

time point. This time point was chosen because it was the last full month of the exercise intervention; participants in the exercise intervention stopped exercising 2 weeks prior to the follow-up assessments at month 5 to allow body weight and other metabolic outcomes to stabilize prior to the post-intervention assessments.

Because participation in the supervised exercise program could have influenced PA performed outside of the programmed exercise time, we also evaluated the effects of the intervention on the subset of women in each group who did not participate in the supervised exercise program. The maximum number of participants with valid PA data was 16 per group at visit 2; the minimum was 11 E2 and 14 PBO at visit 6. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). Data are reported as mean (SD) or mean (95% CI), unless otherwise specified.

RESULTS

Descriptive characteristics of participants in the GnRH_{AG}+E₂ (N=31) and GnRH_{AG}+PL (N=30) groups who had any PA data (61 of 70 participants in the parent trial) are in Table 1. At baseline, the groups were similar in age, weight, BMI, and body composition. As in the larger cohort, (11) FFM decreased over 5 months in the GnRH_{AG}+PL but not the GnRH_{AG}+E₂ group; no significant changes in weight, BMI, or FM were observed in either group over this time frame. (11) Changes in sex steroid hormones was similar to those observed in the larger cohort. E₂ decreased in GnRH_{AG}+PL (from 85.6 ± 41.2 to 21.8 ± 8.5 pg/mL; $p < 0.001$) and increased in GnRH_{AG}+E₂ (61.7 ± 46.5 to 99.2 ± 93.2 pg/mL; $p = 0.09$). Although we did not reach target, response to E₂ add back were highly variable. Nonetheless, the between group changes were significant. Progesterone and testosterone decreased in both groups (all $p < 0.03$), whereas SHBG decreased only in GnRH_{AG}+PL ($p < 0.01$).

Minutes spent in sedentary behavior and in different levels of PA for all women are shown in Table 2. Sedentary time decreased ($P = 0.02$), but MVPA ($P = 0.03$, Figure 1) and SPA ($P = 0.01$, Figure 2) increased in both groups during the intervention. At month 4, there were no differences between groups in sedentary time or SPA, but MVPA tended towards being higher in the GnRH_{AG}+E₂ group. There were no significant effects of intervention or time in light PA, guideline MVPA, or the number of guideline MVPA bouts.

Physical activity data for the twenty-eight women who did not participate in the supervised exercise program are presented in Table 3. Actical data were obtained on 16 non-exercising participants in each group. No significant time effects were observed in any of the PA outcomes. Total time in MVPA (Figure 3) tended towards being higher in GnRH_{AG}+E₂ ($P = 0.07$) compared to GnRH_{AG}+PL, but there were no group differences in any other measure. At month 4, MVPA ($P = 0.01$) and SPA ($P = 0.01$) were significantly higher in GnRH_{AG}+E₂.

DISCUSSION

Studies in animals (1, 2, 4, 16) and humans (6–11) provide clear evidence that loss of estrogen leads to weight gain and accumulation of central fat. (11) Although the mechanisms

contributing to these changes in body fat mass and distribution are not entirely understood, studies of rodents have demonstrated that E₂ signaling may play an important role in regulating SPA.(3, 16, 19, 20) However, isolating the effects of E₂ on PA in humans is very challenging. In this preliminary investigation, we demonstrated that although women in the GnRH_{AG}+PL and GnRH_{AG}+E₂ treatment arms had similar levels of PA at baseline and at 1 month, women in the GnRH_{AG}+E₂ group had higher levels MVPA during months 2–5 of treatment (Figures 1 and 2). This divergence coincides with the timeframe at which GnRH_{AG} treatment would be expected to be exerting maximal effects to suppress ovarian function. A single injection of leuprolide acetate produces an initial stimulation of GnRH (for up to 3 wk) followed by a prolonged suppression of anterior pituitary gonadotropins and gonadal sex steroids. Repeated monthly dosing maintains ovarian hormone suppression. We observed similar trends in MVPA when women who were not randomized to the supervised exercise program were analyzed separately. Because this study was not powered on PA outcomes, positive or negative findings should be interpreted cautiously. Nonetheless, these data provide the first proof-of-concept evidence that E₂ status may contribute to the regulation of physical activity in women as it does in rodents.

Although the mechanism is not completely understood, some studies suggest that E₂ influences PA via ER α -mediated alterations in dopaminergic activity and function.(27) Although some evidence exists that PA declines across the menopause,(21) and that PA is higher in women using HT,(22) convincing evidence in humans is lacking. These studies were limited by the use of self-report instruments to measure PA as well as the variety of HT regimens used by participants, which prevented the specific effects of E₂ to be determined. The best evidence to date supporting a role of sex steroids in regulating PA in humans comes from the study of Lovejoy et al.(23) Premenopausal women (N=103) who were approaching menopause were studied annually for 4 years. Menopausal status was confirmed by cessation of menstruation and follicle-stimulating hormone concentrations ≥ 30 mIU·ml⁻¹. Accelerometer counts dropped by ~50% over the 4 years before postmenopausal status was confirmed. However, it was still not possible to isolate the specific effects of E₂ on PA. In this study, we show that in women who are undergoing suppression of ovarian function replacing E₂ is associated with maintenance of higher levels of PA compared to women treated with placebo.

Although the PA outcomes in this study were designed to be exploratory, the randomized controlled study design, double blinding, robust pharmacological approach to control the sex steroid milieu, and the objective monitoring of physical activity are strengths that lend support to our conclusions. The conclusions should also be interpreted in light of several limitations. First, monitoring physical activity using a monitor worn on the hip is not well-suited for distinguishing sedentary behavior. Devices worn on the thigh are more sensitive to posture and perform better in classifying sedentary behavior.(28) However, these devices were not widely available when this study was conceived. Thus, it is possible there were differences between treatment arms in the allocation between sedentary behavior and light physical activities that were not detected. Second, GnRH_{AG} therapy does not completely reflect the changes that occur during the natural menopause transition. GnRH_{AG} results in a more abrupt suppression of sex hormones than menopause, and gonadotropins are suppressed rather than elevated. It should be noted that there was a wide range in response to

the E₂ add back therapy. We targeted mid-to-late follicular phase concentrations (100–150 pg/mL), and mean E₂ concentrations in the GnRH_{AG}+E₂ group at month 5 was 99±93 pg/dL. However, mean E₂ concentrations at month 5 in the GnRH_{AG}+PL group was 21±9 pg/mL. Thus, although the mean E₂ concentrations were slightly below the targeted concentrations, the mean E₂ concentrations in the two groups at 5 months differed substantially. Finally, our study was limited to women, and whether E₂ would have similar effects on PA in men is not known. Such investigations are warranted given the findings that E₂ also contributes to body fat regulation in men.(8) In that study, suppressing gonadal function in men combined with aromatase inhibition to suppress estrogen synthesis caused an increase in visceral fat, whereas suppression of gonadal function without aromatase inhibition had no effect on visceral fat. The mechanisms contributing to this gain in fat in men with E₂ suppression have not been elucidated.

CONCLUSION

The results of this proof-of-concept study provide support for the hypothesis that physical activity levels are maintained at a higher level in women undergoing pharmacological suppression of ovarian function with E₂ add back when compared with women treated with placebo add-back. This provides the first preliminary evidence for the regulation of PA by E₂ in women. Given the exploratory nature of this study, confirmatory investigations will be necessary.

Acknowledgments

Supported by NIH grants P50 HD073063, R01 AG018198, P30 DK048520, UL1 TR001082, and K01 DK109053. Drs. Melanson, Kohrt, and Schwartz are also supported by resources from the Geriatric Research, Education, and Clinical Center at the Denver VA Medical Center. We are grateful to the nursing, bionutrition, core laboratory, information systems, and administrative staffs of the Clinical and Translational Research Center (CTRC) and Energy Balance Core of the Nutrition and Obesity Research Center for their support of the study. We also acknowledge the members of our research group who carried out the day-to-day activities for the project. Finally, we thank the women who volunteered to participate in the study for their time and efforts.

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Figure 1. Total moderate and vigorous physical activity (MVPA) in participants randomized to gonadotropin releasing hormone agonist therapy plus add-back of placebo (GnRH_{AG}+PL, N=31) or estradiol (GnRH_{AG}+E₂, N=30). * P<0.05 at month 4 timepoint. BL = baseline.

Figure 2.

Spontaneous physical activity (SPA) in participants randomized to gonadotropin releasing hormone agonist therapy plus add-back of placebo (GnRH_{AG}+PL, N=31) or estradiol (GnRH_{AG}+E₂, N=30). SPA tended towards being higher in GnRH_{AG}+E₂ (P=0.08), but there were no differences between groups at month 4 timepoint. BL = baseline.

Figure 3.

Total moderate and vigorous physical activity (MVPA) in non-exercising participants randomized to gonadotropin releasing hormone agonist therapy plus add-back of placebo (GnRH_{AG}+PL, N=16) or estradiol (GnRH_{AG}+E₂, N=16). * P<0.05 at month 4 timepoint. BL = baseline.

Table 1

Baseline characteristics (mean $\pm$ standard deviation; SD) of participants randomized to gonadotropin releasing hormone agonist therapy plus add-back of placebo (GnRH_{AG}+PL, N=31) or estradiol (GnRH_{AG}+E₂, N=30) and changes after 5 months of treatment (mean $\pm$ 95% confidence interval; 95% CI).

	GnRH _{AG} +E ₂		GnRH _{AG} +PL	
	Baseline Mean (SD)	Change Mean (95% CI)	Baseline Mean (SD)	Change Mean (95% CI)
Age (y)	36 (9)		35 (8)	
Body mass index (kg/m ²)	27.0 (5.6)	+0.1 (−0.3, +0.6)	27.4 (6.1)	−0.2 (−0.5, +0.2)
Weight (kg)	73.8 (17.2)	+0.2 (−1.2, +1.6)	74.2 (15.9)	−0.5 (−1.3, +0.4)
Fat mass (kg)	26.2 (11.3)	−0.3 (−1.3, +0.8)	27.3 (11.2)	+0.2 (−0.6, +0.9)
Fat-free mass (kg)	47.7 (6.7)	+0.5 (−0.1, +1.0)	47.0 (6.2)	−0.6 (−1.1, −0.2)
Estradiol (pg/mL)	61.7 (46.5)	+37.2 (−6.2, +80.5)	85.6 (41.2)	−63.8 (−95.0, −32.5)
Progesterone	0.84 (1.12)	−0.51 (−0.95, −0.07)	1.14 (1.50)	−0.83 (−1.41, −0.25)
Testosterone	36.4 (13.7)	−7.0 (−10.6, −3.3)	31.7 (16.8)	−4.5 (−7.6, −1.3)
SHBG	41.3 (15.9)	2.7 (−1.6, 7.0)	48.0 (24.0)	−8.2 (−13.2, −3.1)

Table 2

(All subjects). Time (minutes/day) recorded in sedentary, light, and moderate and vigorous (MVPA) physical activity, guideline MVPA (total minutes spent in MVPA during bouts 10 minutes), and number of guideline bouts, and spontaneous physical activity (SPA, total minutes spent in light or MVPA performed in bouts lasting less than 10 min). Values are mean (standard deviation).

	Month of Intervention					
	Baseline	1	2	3	4	5
GnRH_{AG}+PL						
Number of observations	22	24	21	23	23	20
Sedentary	746 (32)	673 (40)	674 (35)	635 (33)	654 (31)	700 (35)
Light	141 (9)	171 (15)	158 (17)	177 (27)	138 (11)	141 (13)
MVPA	96 (7)	118 (11)	110 (11)	109 (9)	103 (9)	103 (7)
Guideline MVPA	32 (5)	40 (7)	35 (7)	34 (6)	31 (5)	35 (6)
Guideline bouts	1.6 (0.9)	2.4 (2.0)	2.1 (1.8)	2.0 (1.3)	1.7 (1.0)	1.8 (0.8)
SPA	69 (18)	70 (26)	75 (20)	84 (26)	77 (25)	67 (18)
GnRH_{AG}+E₂						
Number of observations	23	27	24	26	22	18
Sedentary	664 (29)	651 (31)	638 (35)	624 (38)	612 (33)	634 (29)
Light	171 (31)	165 (20)	149 (8)	152 (9)	159 (14)	127 (11)
MVPA	110 (8)	115 (8)	125 (8)	132 (8)	127 (10) *	118 (10)
Guideline MVPA	41 (6)	45 (5)	50 (6)	48 (6)	49 (7)	51 (7)
Guideline bouts	2.3 (1.4)	2.6 (1.6)	2.9 (1.6)	2.8 (1.6)	2.9 (1.8)	2.7 (1.6)
SPA	64 (18)	77 (25)	75 (26)	74 (20)	73 (31)	67 (16)

* P<0.05 vs. GnRH_{AG}+PL at month 4 time point.

Table 3

(Non-exercisers). Time (minutes/day) recorded in sedentary, light, and moderate and vigorous (MVPA) physical activity, guideline MVPA (total minutes spent in MVPA during bouts 10 minutes), number guideline bouts, and spontaneous physical activity (SPA, total minutes spent in light or MVPA performed in bouts lasting less than 10 min). Values are mean (standard deviation).

	Month of Intervention					
	Baseline	1	2	3	4	5
GnRH _{AG} +PL						
Number of observations	14	16	12	14	15	14
Sedentary	724 (34)	688 (48)	673 (45)	650 (39)	649 (39)	702 (43)
Light	146 (12)	172 (20)	158 (21)	156 (13)	144 (16)	145 (17)
MVPA	96 (10)	107 (14)	92 (9)	106 (12)	99 (12)	106 (9)
Guideline MVPA	33 (6)	34 (10)	20 (3)	28 (8)	30 (7)	36 (8)
Guideline bouts	1.7 (1.0)	3.2 (1.5)	3.3 (2.2)	2.6 (1.3)	1.9 (1.2)	1.5 (0.8)
SPA	64 (21)	73 (25)	72 (27)	78 (21)	69 (31)	69 (16)
GnRH _{AG} +E ₂						
Number of observations	14	16	14	15	14	11
Sedentary	642 (25)	653 (42)	640 (44)	633 (52)	608 (46)	656 (43)
Light	189 (50)	169 (34)	147 (13)	146 (13)	149 (12)	114 (13)
MVPA	118 (12)	117 (13)	130 (12)	132 (12)	129 (14) *	118 (14)
Guideline MVPA	49 (8)	48 (8)	53 (8)	52 (9)	53 (9) *	55 (9)
Guideline bouts	1.6 (0.8)	2.1 (2.2)	1.3 (0.7)	1.6 (1.2)	1.5 (0.9)	1.9 (0.8)
SPA	69 (21)	69 (29)	77 (25)	81 (24)	76 (31)	63 (20)

* P<0.05 vs. GnRH_{AG}+PL at month 4 time point.