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Adiposity and sex hormones across the menstrual cycle: the BioCycle Study

Edwina H. Yeung, PhD[1], **Cuilin Zhang, MD, PhD**[1], **Paul S. Albert, PhD**[1], **Sunni L. Mumford, PhD**[1], **Aijun Ye, PhD**[1], **Neil J. Perkins, PhD**[1], **Jean Wactawski-Wende, PhD**[2,3], and **Enrique F. Schisterman, PhD**[1]

[1]Epidemiology Branch, Division of Epidemiology, Statistics, and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland [2]Department of Biotechnical and Clinical Laboratory Sciences, University at Buffalo, Buffalo, New York [3]Department of Social and Preventive Medicine, University at Buffalo, Buffalo, New York

Abstract

Objective—To investigate the influence of adiposity on patterns of sex hormones across the menstrual cycle among regularly menstruating women.

Subjects—The BioCycle Study followed 239 healthy women for 1–2 menstrual cycles, with up to 8 visits per cycle timed using fertility monitors.

Methods—Serum estradiol (E2), progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex hormone binding globulin (SHBG) were measured at each visit. Adiposity was measured by anthropometry and by dual energy x-ray absorptiometry. Differences in hormonal patterns by adiposity measures were estimated using nonlinear mixed models, which allow for comparisons in overall mean levels, amplitude (i.e. lowest to highest level within each cycle), and shifts in timing of peaks while adjusting for age, race, energy intake, and physical activity.

Results—Compared to normal weight women (n=154), obese women (BMI≥30 kg/m^2, n=25) averaged lower levels of progesterone (−15%, P=0.003), LH (−17%, P=0.01), FSH (−23%, P=0.001) and higher free E2 (+22%, p=0.001) across the cycle. To lesser magnitudes, overweight women (BMI: 25–30, n=60) also exhibited differences in the same directions for mean levels of free E2, FSH, and LH. Obese women experienced greater changes in amplitude of LH (9%, p=0.002), and FSH (8%, p=0.004), but no differences were observed among overweight women. Higher central adiposity by top compared to bottom tertile of trunk-to-leg fat ratio by DXA was

Corresponding Author: Edwina Yeung, PhD, 6100 Executive Blvd, 7B03, Bethesda, MD 20892, Tel: 301-435-6921, Fax: 301-402-2084, yeungedw@mail.nih.gov.

CONFLICT OF INTEREST

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associated with lower total E2 (−14%, p=0.005) and FSH (−15%, p=0.001). Peaks in FSH and LH occurred later (~0.5 day) in the cycle among women with greater central adiposity.

Conclusion—Greater total and central adiposity were associated with changes in mean hormone levels. The greater amplitudes observed among obese women suggest compensatory mechanisms at work to maintain hormonal homeostasis. Central adiposity may be more important in influencing timing of hormonal peaks than total adiposity.

Keywords

adiposity; body mass index; body composition; sex hormones; menstrual cycle; progesterone; estradiol

INTRODUCTION

The high prevalence of obesity among women of reproductive age is a worldwide concern. In the United States, 55% to 65% of women between 20–39 years old are currently overweight or obese as defined by having a body mass index (BMI) above 25 kg/m^2.(1) The impact of obesity on reproductive health is not well understood.

Although body fat and positive energy balance is necessary for normal reproductive function, body fat at the extremes may be detrimental.(2) Obesity is associated with decreased levels of sex hormone binding globulin (SHBG) which in turn controls the bioavailability of estradiol and testosterone.(3) Adipose tissue is also directly involved with steroid production and metabolism.(4) Despite these biological links, previous studies investigating levels of estradiol (E2) by adiposity measures have been conflicting.(2;5–8) Decreased overall mean levels of luteinizing hormone (LH) during the follicular phase have also been associated with obesity.(6;7;9;10) However, cross-sectional measures do not capture the pattern of LH across different phases of the cycle, and in particular the mid-cycle LH surge. Similarly, follicle-stimulating hormone (FSH) has not been frequently explored longitudinally although there is evidence that levels may be decreased across the menstrual cycle among older obese women.(7)

Thus, few studies have examined whether patterns of sex hormones over the whole menstrual cycle differ by measures of body adiposity among healthy premenopausal women. Moreover, there is scarce evidence for how central adiposity may be differentially associated with sex hormone patterns. Previous studies were limited in their measurements or in reducing repeated measurements into summary measures in analysis. Thus, our objective was to investigate the association of sex hormone patterns as characterized by mean levels, amplitude (i.e. lowest to highest level) and timing of hormonal peaks over the menstrual cycle with measures of adiposity among regularly menstruating women.

PARTICIPANTS AND METHODS

Study population

The BioCycle Study recruited 259 healthy (2005–2007), premenopausal women between 18–44 years of age and followed them for 1 (n=9) or 2 (n=250) menstrual cycles for the

original purpose of studying the effects of sex hormones on measures of oxidative stress.(11;12) Women with self-reported cycle length of 21–35 days for each cycle during the past six months were included. Exclusions were made based on factors that would influence hormone levels such as oral contraceptive use in the past 3 months, breastfeeding in the past 6 months, certain medication use, ovulatory disorders, history of chronic diseases (e.g. heart disease, diabetes mellitus, etc), history of polycystic ovary syndrome (PCOS), or gastrointestinal disease. Women with self-reported body mass index (BMI) greater than 35 kg/m^2 were not screened.

The University at Buffalo Health Sciences Institutional Review Board (IRB) approved the study and served as the IRB designated by the National Institutes of Health for this study under a reliance agreement. All participants provided written informed consent.

Study visits

Participants attended up to eight clinic visits per menstrual cycle. Visits were timed using fertility monitors (Clearblue™ Easy Fertility Monitor, Inverness Medical, Waltham, MA) for days corresponding to menstruation, mid and late follicular phase, LH/FSH surge, ovulation, and early, mid and late luteal phase.(13) Participants contacted the clinical center at the first sign of monthly bleeding and came in for the menstruation visit the following day. Fertility monitoring of first morning urine began on calendar day 6 of the cycle. Monitor indications of low, high, and peak fertility were based on monitor readings of urinary estrone-3-glucuronide and LH levels and were used to time mid-cycle and subsequent visits. Participants attended the clinic on the day the monitor indicated “peak fertility” and the two days that followed (i.e. corresponding to ovulation). If no indication of peak fertility was given by calendar day 14, a visit was scheduled the next day and monitoring continued for an additional 10 days. Dates of other visits were scheduled using an algorithm accounting for self-reported cycle length.(14) There was high compliance to the study protocol with 94% of women completing at least 7 clinic visits per cycle, with the main reason for fewer visits being shorter cycle length.(13)

Data collection

Anthropometry was measured by trained personnel using standard protocols.(15) Weight was measured on a balance scale to the nearest quarter pound and height by stadiometer to the nearest half centimeter. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Waist circumference (WC) was measured in duplicate with a tape measure applied horizontally midway between the iliac crest and lowest lateral portion of the rib cage. Hip girth was measured to the nearest 0.1 cm at the level of the symphysis pubis anteriorly and at the maximal protrusion of the gluteal muscles posteriorly. At the end of the study, 248 women participated in a dual energy x-ray absorptiometry (DXA) scan (Hologic Discovery Elite, software version 12.4.1, Waltham, MA) to measure fat and lean mass from which total percent body fat and percent trunkal fat were derived. Women missed the DXA scan primarily because it was the last visit of the second cycle and some women solely participated for one cycle (n=9).

Extensive demographic and lifestyle information was also collected. Information on age, race, education, smoking, and alcohol consumption were self-reported. Physical activity was assessed by using the International Physical Activity Questionnaire (IPAQ) which estimated vigorous and moderate intensity activities related to work, transportation, housework, and leisure time.(16) Metabolic equivalents minutes per week (METs) were derived from the responses. Women were grouped into low, moderate, and high levels of physical activity according to standard IPAQ categories.(16) Total energy intake was assessed by four 24-hour dietary recalls, conducted during specific times of the cycle including menses, the follicular phase, ovulation, and the mid luteal phase. The intakes were averaged across the cycle. Average total energy intake was derived using the Nutrition Data System for Research (NDSR) software version 2005 (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN).

Laboratory assays

Overnight 12-hour fasting blood was drawn in the morning (0700–0830 h). Samples were sent to Kaleida Laboratories in Buffalo, NY for analysis with all samples from each participant's cycle run together in one batch to control for inter-assay differences. Serum E2, progesterone, LH, FSH, SHBG, and insulin were measured using a competitive chemiluminescent enzymatic immunoassay (Immunlite 2000, Siemens Medical Solutions Diagnostics, Deerfield, IL). Inter-assay coefficients of variation of analytes for three level quality control materials were <10%, <14%, <4%, <4%, <10%, and <8% respectively. Very few samples (<1%) had levels below the limit of detection (LOD) and in those circumstances they were replaced with the LOD divided by the square-root of two. Albumin and fasting plasma glucose testing were performed on a LX 20 automated chemistry analyzer (Beckman Coulter, Inc. Miami, FL) with CV of 3%. Insulin resistance was calculated based on the homeostasis model (HOMA-IR) using the equation: fasting insulin (μU/ml) × fasting glucose (mmol/l) / 22.5, and beta-cell function (HOMA-beta) by the equation: 20 × fasting insulin (μU/ml)/fasting glucose (mmol/l) −3.5. (17)

Statistical analysis

Hormone levels were log-transformed for normality. Free E2 levels were calculated based on a mathematical model using measured total E2, SHBG, and albumin values available from all visits.(18) Demographic characteristics and baseline measures of insulin resistance and SHBG were compared by categories of BMI. Chi-square and ANOVA tests were used to test for differences, where appropriate.

Differences in hormonal patterns between groups of women categorized by anthropometric variables (e.g. normal weight (BMI<25), overweight (25–<30), and obese (≥30)) or as continuous variables (e.g. BMI in kg/m^2) were estimated using nonlinear mixed models that flexibly model menstrual cycle patterns.(19) To completely capture the hormonal pattern in this cohesive statistical model, we excluded anovulatory cycles and those missing cycle length information. We excluded 42 cycles (8%) previously identified as being anovulatory by peak progesterone levels <5ng/ml and no observed serum LH peak on the mid or late luteal phase visit.(20) In addition, 24 (5%) ovulatory cycles were excluded due to missing cycle length information; 5 from the first cycle and 19 from the second, predominantly due

to the inability to reach participants to obtain the date of onset of bleeding of the cycle after follow-up ended. The mean age (24; SD 8) and BMI (23; SD 3) of the cycles excluded for missing cycle length data (n=24) were similar to those with data. Altogether the analysis using these models included information for 443 cycles from 239 women.

Specifically, these models ($y_{ijk} = \Phi_{1ik} + \exp(\Phi_{2ik})\, f[(t_{ijk} / T_{ik} - a \log it(\Phi_{3ik}))] + \varepsilon_{ijk}$; with i = subject, j = time, k = cycle) allow for assessment of differences in three components of the hormone curves: 1) mean levels over the menstrual cycle (Φ_1), 2) amplitude of change in levels from the nadir to peak (Φ_2), and 3) shifts in timing of peaks (Φ_3). Random effects for women (and cycles within women) for the mean ($\Phi_{1ik} = X_{1i}\beta + b_{1i} + b_{1ik}$) and amplitude ($\Phi_{2ik} = X_{2i}\beta + b_{2i} + b_{2ik}$) were included to account for the correlation between repeated measurements. Due to the low intra-individual variability of SHBG over the menstrual cycle, amplitude and phase shift differences were not interpretable and therefore not reported.

These models did not require uniform visit days, but rather standardized time was derived by taking the calendar day of the clinic visit divided by the observed cycle length so that the start of the menstrual cycle is at time 0 and the end of the cycle is at time 1.0. For analyses of the mean and amplitude differences, we further centered on day of ovulation (defined as the day after detection of the LH peak by the fertility monitor) at a time of 0.5. For phase shift differences, we did not center on time so that the results could be interpreted as differences in timing of the whole hormonal pattern rather than with respect to ovulation.

The mean and amplitude differences were calculated (by exponentiating the coefficients Φ_1 and Φ_2) as percent differences in hormone levels compared to the reference group indicated. The percent difference is interpreted on the original scale for the mean and on the log scale for the amplitude. The coefficient for the phase shift (Φ_3) was transformed using the following formula: $\frac{e^{C_1+C_0}}{1+e^{C_1+C_0}} - \frac{e^{C_0}}{1+e^{C_0}}$, where C_1 represents the coefficient of the category of interest and and C_0 represents the coefficient of the reference category (or the intercept for continuous measures). This transformation results in a number from 0 to 1. Assuming an average normal menstrual cycle length of 28 days, the resulting number was multiplied by 28 to derive the number of days shifted.

For determining the associations between adiposity and sex hormone patterns, multiple measures of adiposity were used. Primarily, BMI categories (<25, 25–30, >30 kg/m^2) were used in analyses to determine the associations between general adiposity and sex hormone patterns. As a measure of central adiposity, total trunkal fat was divided by the average leg fat from both legs measured by DXA. Tertiles of trunk-to-leg fat ratio were modeled.

The models account for confounding through adjustment of covariates on all three parameters of interest (i.e. mean, amplitude, and phase shift). Confounders were determined *a priori* because of their known associations with adiposity and sex hormones according to previous research. The models adjusted for age (continuous), race (white, black, other), average energy intake per cycle (quartiles), and physical activity (IPAQ categories). A second model adjusting for insulin resistance by log HOMA-IR (continuous) was also

tested. Analyses for the nonlinear mixed models with harmonic terms were conducted in R v.2.9.2 (R Foundation for Statistical Computing, 2009).

We also used a generalized linear mixed model (GLIMMIX) in SAS to evaluate the risk of anovulation by BMI categories using data from all women (including ovulatory and anovulatory cycles) in this study. Comparison of baseline characteristics and analyses on anovulation were performed using SAS v9.2 (SAS Institute, Cary, NC).

RESULTS

Median cycle length was 28 days and did not differ significantly by BMI categories. Women who were overweight or obese tended to be older, white, married, and were slightly less educated but all differences were non-significant ($p>0.10$) (Table 1). Those who were leaner tended to be of other race (which comprised a group of mostly Asian women). Total body fat and other measures of adiposity, insulin and insulin resistance were positively associated with BMI as expected. HOMA-beta was increased among those with higher BMI to accommodate for increased insulin resistance. Baseline SHBG levels were reduced by 18 nmol/l among obese compared to normal weight women ($p<0.001$).

The patterns of sex hormones over the menstrual cycle for overweight and obese women differed from the patterns of normal weight women. Figure 1 shows these patterns, without adjustment for demographic or lifestyle factors, which follow the general shape expected for patterns of hormonal variability.(21) For the mean levels, significant trends in increased free E2 and decreased FSH and LH with increasing BMI were observed even after adjusting for age, race, energy intake, and physical activity. Overweight women experienced increased levels of free E2 (+15%) and decreased levels of FSH (−16%) and LH (−10%). (Table 2A) Obese women experienced yet greater differences in hormone levels (free E2 (+22%), progesterone (−15%), FSH (−23%), and LH (−17%)). Increases in the amplitude of hormone levels (i.e. the change from the lowest to the highest level over the cycle) were observed for obese women. For log-transformed LH, obese women had a 9% increase in amplitude. This increase resulted in a higher LH surge among obese women compared to normal weight women (Figure 1D). An increase in amplitude of log-transformed FSH (9%) was also observed. (Table 2B) Amplitudes were not significantly different among overweight women. Results adjusting for HOMA-IR were similar (data not shown). There were no significant differences in timing of sex hormone peaks by categories of BMI. (Table 2C)

Greater central adiposity, as expressed by increasing tertiles of trunk-to-leg fat ratio, was also associated with differences in sex hormone patterns. (Table 3) Women in the highest tertile of trunk-to-leg fat ratio had decreased mean levels of total E2 (−14%), and FSH (−15%) compared to those in the lowest tertile. Sex hormones FSH and LH peaked slightly later among women at the highest tertile of trunk-to-leg fat ratio compared with the lowest tertile. (Table 3C) For example, women had an LH surge on average nearly half a day ($p=0.03$) later.

We investigated associations with sex hormone patterns using other measures of adiposity that were available. BMI was correlated with percent body fat ($r=0.74$), trunkal fat ($r=0.87$),

WC (r=0.84) and hip circumference (r=0.86) but less so with trunk-to-leg fat ratio (r=0.55) and waist to hip ratio (r=0.30). Results regarding the association of sex hormone patterns and adiposity using continuous measures of anthropometry and body composition, reflected these correlations and findings for BMI were similar to percent body fat, WC, hip circumference, and percent trunkal fat, while the results for WHR were similar to those by trunk-to-leg fat ratio. (Supplementary Table A1)

Of the 42 anovulatory cycles, 3 were from women who were obese (7%) and 6 from women who were overweight (14%). Their mean age was 22(SD 5) years and percent body fat was 27(SD 5) percent, suggesting that they tended to be leaner and younger than women with ovulatory cycles. In secondary analyses using linear mixed models, risk of anovulation was not associated with being overweight (OR 0.62; 95%CI: 0.30–1.26) or obese (OR 0.65; 95% CI: 0.25–4.55; nor with central adiposity by trunk-to-leg fat ratio tertiles ($p>0.6$). In sensitivity analyses, results for BMI were similar when 8 women who were underweight ($BMI<19\ kg/m^2$) were excluded from analyses as well as when 5 women who had an early follicular LH to FSH ratio greater than 2 (as a proxy of undiagnosed PCOS) were excluded (data not shown).

DISCUSSION

In this study of 239 healthy, premenopausal women, greater total adiposity by BMI was associated with significantly higher free E2 and lower progesterone, LH and FSH over the menstrual cycle. However, despite having lower LH and FSH throughout the cycle, women with greater adiposity by BMI tended to have increased amplitudes of these gonadotropins, suggesting compensatory mechanisms at work to maintain hormonal homeostasis. Central adiposity by trunk-to-leg fat ratio was associated with decreased total E2, progesterone, and FSH, and may additionally affect the timing of ovulation; women at the highest tertile of trunk-to-leg fat ratio had later rises in FSH and LH.

The association between adiposity and E2 throughout the cycle has implications on reproductive health. Follicular phase E2 is related to oocyte quality, endometrial morphology and follicular diameter, and lower ovulatory E2 results in lower pregnancy and conception rates.(2) Most studies investigating levels of total E2 have found decreased mean levels of total E2 (2;6;8) or urinary estrone conjugate (E1c) (7) with one study finding no association.(5) In the present investigation, we found decreased total E2 to be associated with central adiposity by trunk-to-leg fat ratio but not with BMI after accounting for lifestyle factors including energy intake. The difference in association is not accounted for by the use of DXA for measurement of central adiposity because, similar to using BMI, no reduction in total E2 was found for percent body fat by DXA. On the other hand, BMI was associated with increased free E2, considered the biologically active form of the hormone due to reduced SHBG. That there would be increased free E2 with no change or even decreased total E2 suggests that SHBG is the driving force behind the concomitant increase in one and decrease in the other.

FSH was found to be decreased with measures of both total and central adiposity. Several hypotheses have been suggested for how this occurs including the indirect effects of E2 on

gonadotropin releasing hormone (GnRH) and also the direct effects of E2 binding to the pituitary.(21) We also found that the amplitude of FSH was associated with almost all measures of adiposity. The increased amplitude of FSH may have indicated attempts to increase levels to reach the threshold for ovarian function to be restored.(21)

Our observation that overall mean levels of LH through the menstrual cycle were decreased among obese women has been previously noted.(6;22) These changes in mean levels may have been driven by the negative feedback of increased levels of free E2.(21) On the other hand, E2 also plays a role in positive feedback to control the preovulatory LH surge through sensitizing the pituitary to gonadotropin-releasing hormone.(21) Our findings, particularly among obese women who exhibited low LH throughout the cycle but a larger LH surge than normal weight women (i.e. Figure 1D), demonstrate the effects of the increased free E2 in both modulating the increased negative feedback on overall levels and positive feedback on the LH surge (i.e. amplitude). Taken together with the findings from FSH, we hypothesize that the compensation for lower mean levels of the gonadotropins may lead to greater differences in the lowest to the highest levels (i.e. the amplitude) in the menstrual cycle among obese women.

That progesterone is decreased among obese women is most likely a consequence of the decreased mean levels of LH throughout the cycle inclusive of the luteal phase, and is consistent with previous studies.(23;24) Women who were obese (BMI≥30) had 20% lower progesterone levels compared to much thinner women (BMI<20) among a group of US nurses averaging 43 years in age.(8) Another study among older premenopausal (mean age 47 years) women also found lower (−35%) daily levels of progesterone (by urinary pregnanediol glucuronide) among obese compared to normal weight women.(25) However, urine measures are subjected to mis-measurement due to its affects on excretion of creatinine.(25) Thus, our 15% decrease with measured serum progesterone may be more reflective of actual circulating differences.

Our finding that central adiposity may delay the timing of hormonal peaks is of interest and agrees with previous findings that obese women tend to have longer follicular phases.(25) Nevertheless, it remains unclear as to whether these shifts have clinical significance due to the small difference in timing (i.e. by approximately half a day). From a research perspective, studies that measure hormone levels a certain number of calendar days after the start of menses may be more likely to miss the LH peak for centrally obese women and thus be biased towards lower LH.

Our study had several strengths including the study design which captured the variability of sex hormones using serum measures timed to specific phases of the menstrual cycle with the aid of fertility monitors. Previously, it has been shown that eight non-timed repeated measurements of E2 across the menstrual cycle are sufficient to capture at least 80% of the variability.(26) Here, we have improved upon this capture with the use of fertility monitors which are used to identify the LH surge. We were able to adjust for factors previously found to be associated with ovarian steroid hormone production including age, energy availability (through total energy intake by four 24 hour recalls per cycle) and physical activity.(2) In

addition, we were able to evaluate that insulin resistance by HOMA-IR did not affect our associations (data not shown).

Our study also has some limitations. We did not measure testosterone or conduct a clinical work-up for PCOS that have been found to be associated with obesity and irregular menstrual function. However, using LH to FSH ratio as a proxy for PCOS (which has a limited sensitivity of 66%(21)), excluding 5 women with increased levels did not affect our results in sensitivity analyses. Previously, it was found that hirsutism was associated with increased testosterone levels but obesity was not.(4) Thus, it is unlikely that these findings are driven by hyperandrogenism. We were unable to measure free E2 directly. However, we had repeated measures of E2, SHBG and albumin from which free E2 could be derived through a previously validated calculation.(18) We cannot determine the direction of causality for the differences by central compared to total adiposity as sex differences in body fat distribution has been attributed to differences in levels of estrogen.(27) For example, ovariectomized rats gain visceral fat and simultaneously lose subcutaneous fat, demonstrating that central adiposity may have resulted from differences in hormone levels rather than preceded them.(28) The data were also limited by the use of DXA scans rather than computer tomography or magnetic resonance imaging for measurement of visceral and subcutaneous adiposity. The statistical models used did not allow for imputation of missing values so the women with missing cycle length data had to be excluded. Future work on these methods may allow for imputation of these values. Our cohort may not be representative of all premenopausal women due to the inclusion/exclusion criteria; for example, women of extreme obesity (BMI>35) were not included and adiposity may have exaggerated effects on hormonal patterns among these women. Lastly, another potential limitation is that there were few overweight (n=60) and obese women (n=25) in the study which may have limited power to detect differences. However, the associations which were not statistically significant in our analysis usually had very small effect sizes, suggesting that the harmonic modeling approach is very powerful in detecting subtle differences in sex hormone patterns.

In conclusion, findings from the present study suggest that total and central adiposity may affect sex hormone patterns. Adiposity is associated with small but detectable differences in mean levels, amplitude, and timing of hormone peaks. Greater total and central adiposity were associated with different mean hormone levels but greater amplitude changes of the gonadotropins over the menstrual cycle suggesting possible compensatory mechanisms at work to maintain hormonal homeostasis. Further research on how androgens may affect these associations should also be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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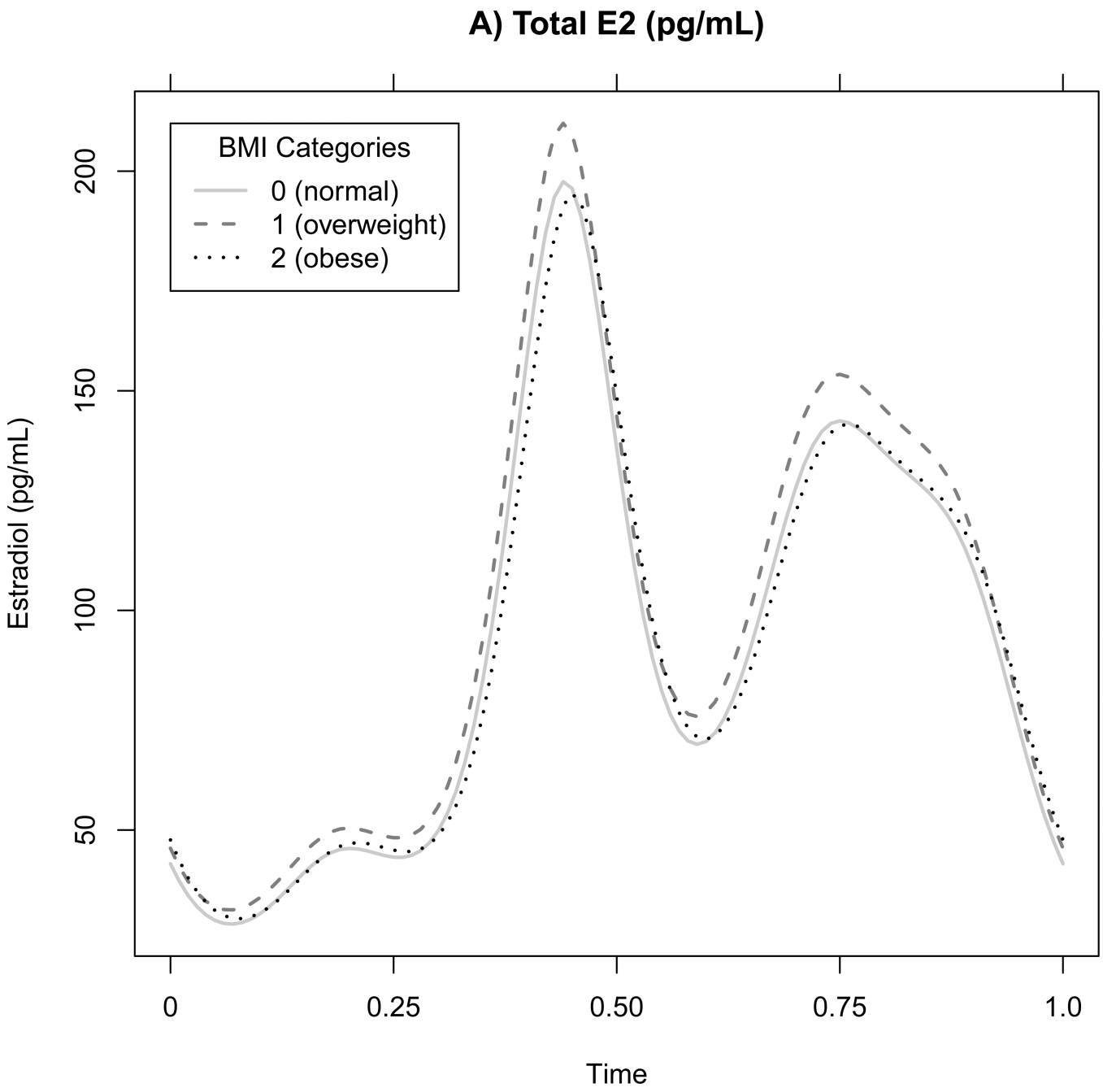

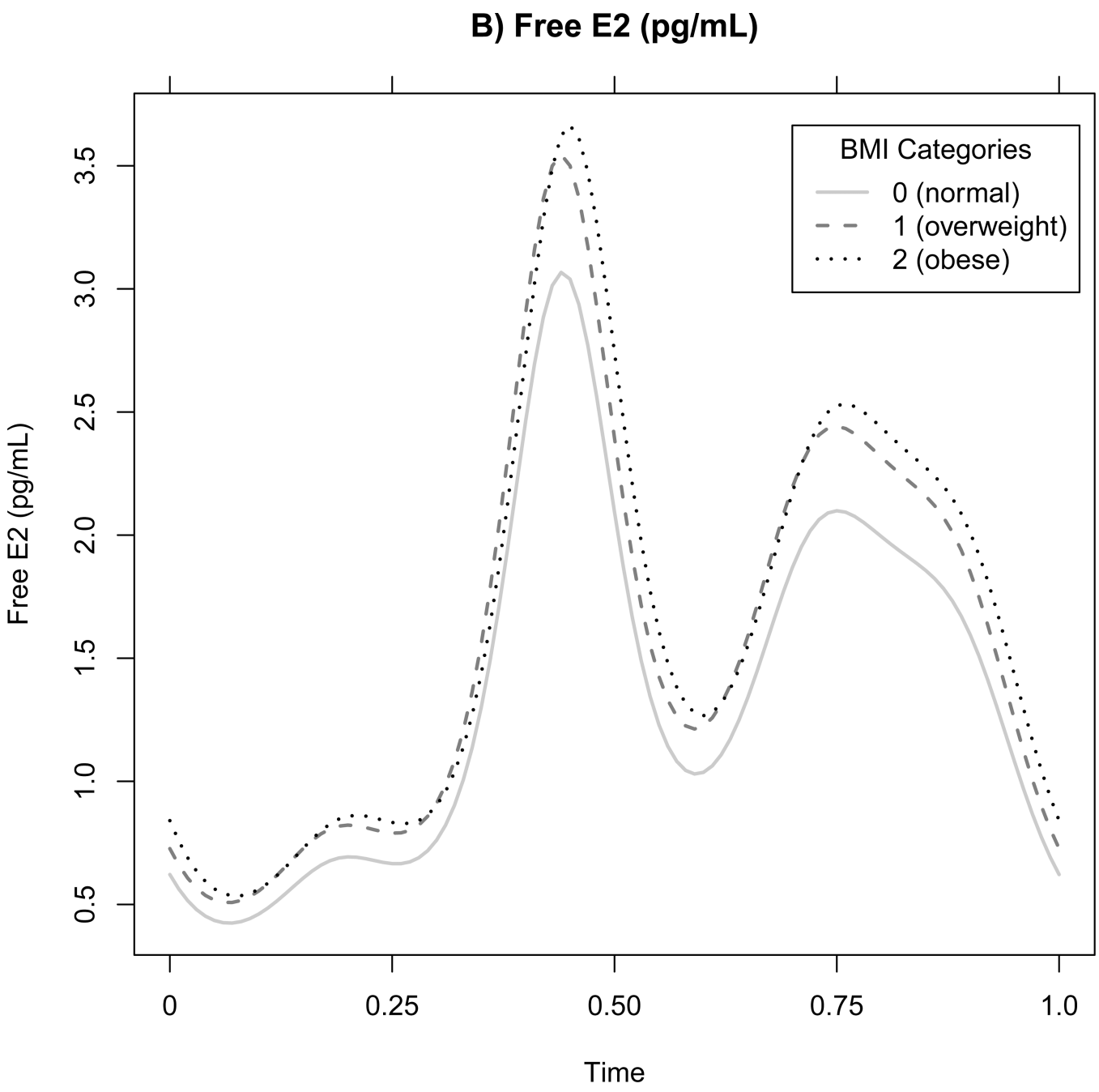

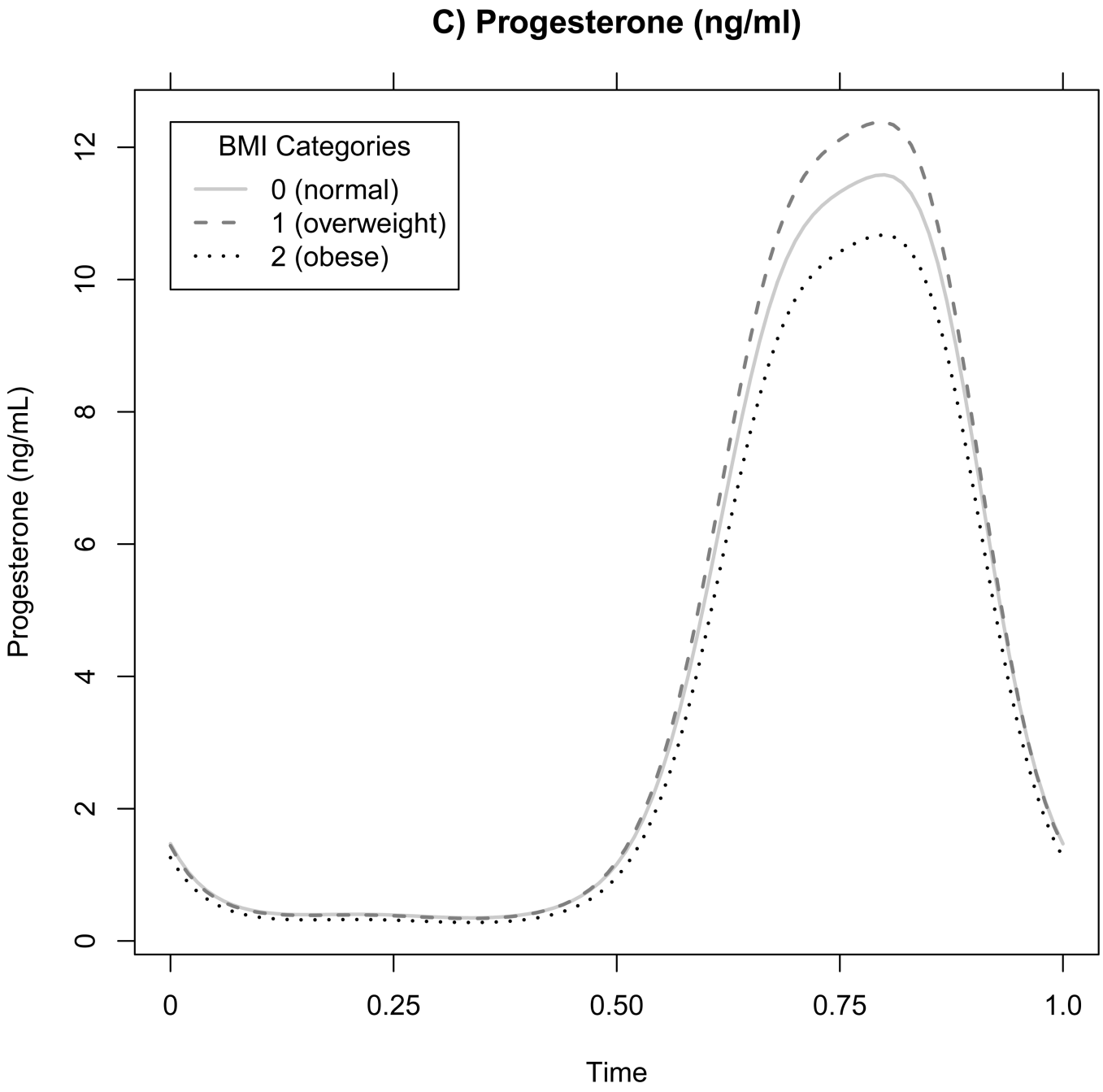

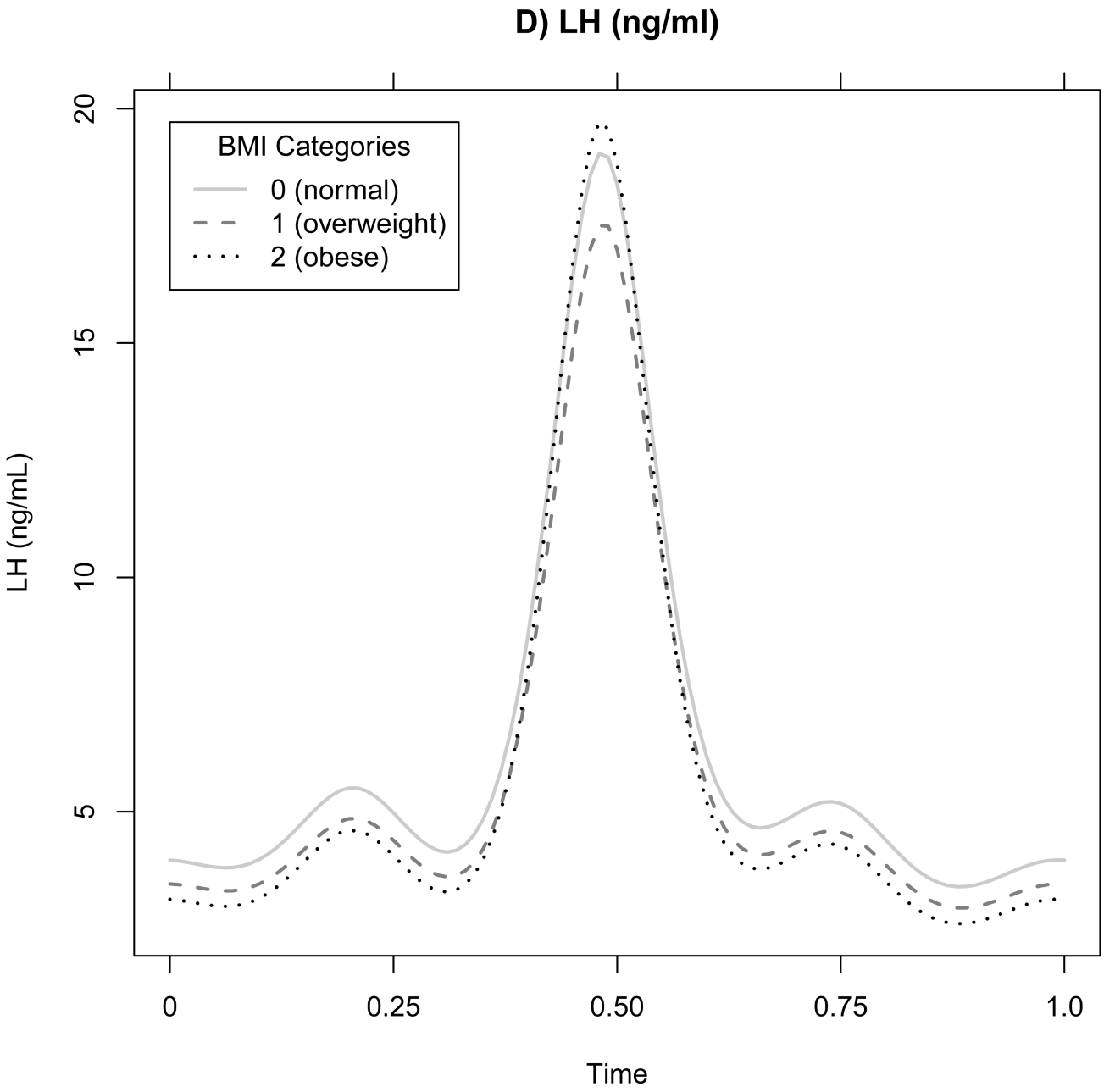

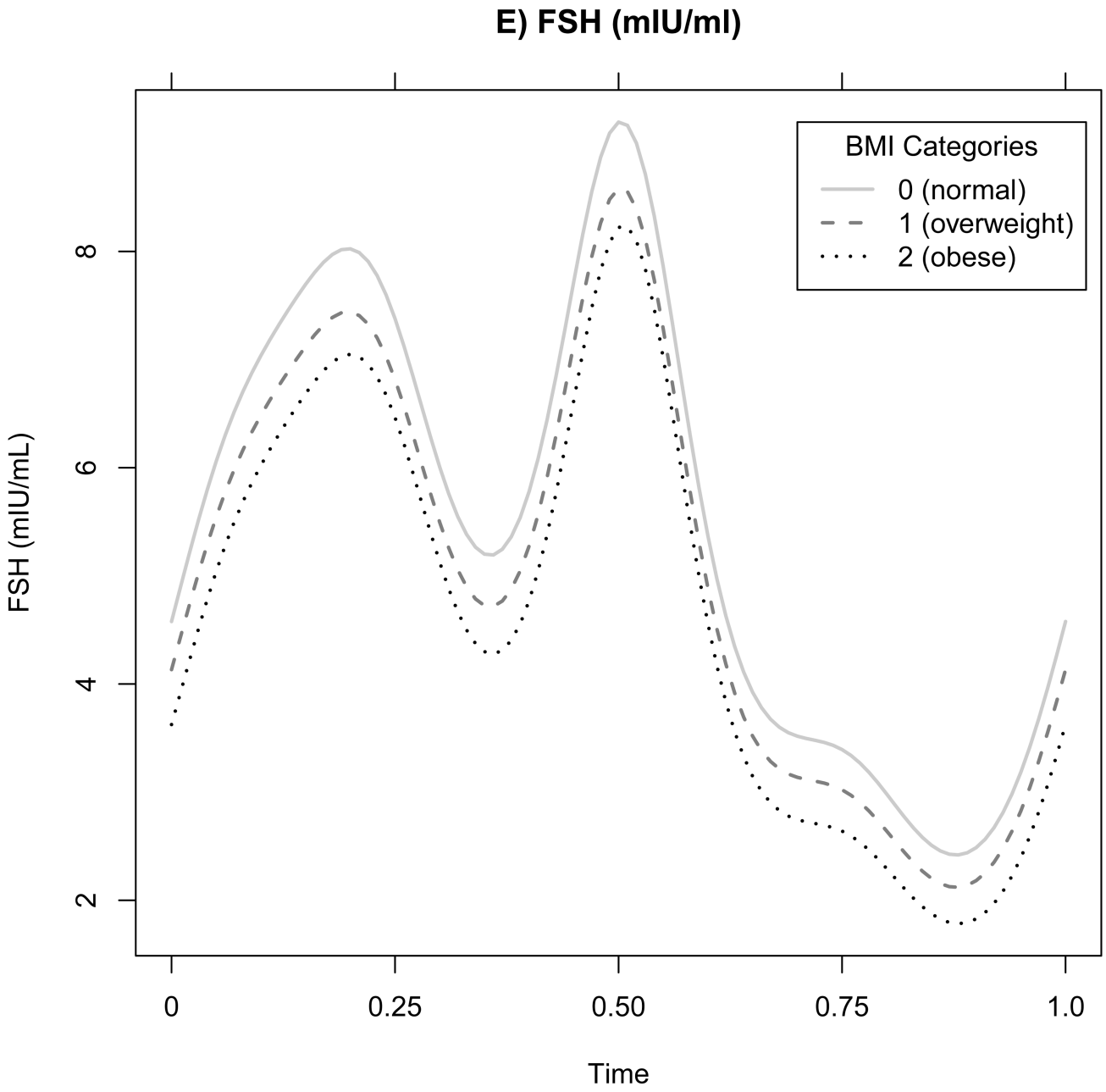

Figure 1.

Longitudinal patterns of total E2 (A), free E2 (B), progesterone (C), LH (D) and FSH (E) over the menstrual cycle by categories of BMI among 239 healthy, premenopausal women in the BioCycle Study. Unadjusted, geometric mean levels of the hormones are shown on the y-axis. The x-axis indicates time with 0 being the start of the menstrual cycle and 1.0 being the end. Cycles were centered on ovulation at time of 0.5. The solid line represents women with normal BMI (<25 kg/m^2), dashed line represents women who are overweight (25≥BMI>30 kg/m2), and dotted line represents women who are obese (BMI>30 kg/m^2).

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Table 1

Baseline characteristics stratified by BMI categories among premenopausal women in the BioCycle Study

	All	BMI<25	BMI 25–<30	BMI≥30
Characteristic	**N=239**	**154**	**60**	**25**
Age (years)	27.8 (8)	26.7 (8)	30.3 (9)	28.8 (8)
Age at menarche (years)	12.4 (1)	12.6 (1)	12.1 (1)	12.1 (1)
Cycle length (days)*	28 (26–31)	29 (26–31)	28 (27–31)	28 (26–30)
Race (%)				
White	59.0	57.1	60.0	68.0
Black	20.1	18.2	25.0	20.0
Other Race	20.9	24.7	15.0	12.0
Education (%)				
High school or less	12.6	11.0	11.7	24.0
Some College	36.4	38.3	35.0	28.0
Bachelor/Associates	39.8	37.0	45.0	44.0
Graduate Program	11.3	13.6	8.3	4.0
Physical Activity (MET-minutes per week)				
Low	9.6	10.4	8.3	8.0
Moderate	36.4	37.7	30.0	44.0
High	54.0	52.0	61.7	48.0
Energy Intake (kcal/d)**	1612 (393)	1638 (395)	1550 (401)	1595 (328)
Weight (kg)	65.2 (11)	59.2 (7)	72.0 (7)	85.7 (7)
Height (cm)	164.3 (6)	164.7 (6)	163.5 (6)	163.3 (6)
BMI (kg/m^2)	24.2 (4)	21.8 (2)	26.9 (1)	32.1 (1)
Waist Circumference (cm)	74.9 (9)	70.5 (6)	79.9 (5)	90.5 (7)
Hip Circumference (cm)	99.7 (9)	95.2 (5)	104.5 (5)	116.2 (6)
WHR	0.8 (0.06)	0.7 (0.06)	0.8 (0.05)	0.8 (0.04)
Body Fat (%)†	29.6 (6)	26.7 (5)	33.1 (4)	39.0 (3)
Trunkal Fat (%)†	25.2 (7)	21.5 (6)	29.7 (4)	37.0 (3)
Trunk to leg fat ratio†	1.8 (0.05)	1.6 (0.05)	2.0 (0.05)	2.3 (0.06)

	All	BMI<25	BMI 25–<30	BMI≥30
Characteristic	**N=239**	**154**	**60**	**25**
Glucose (mmol/l)	4.85 (0.4)	4.8 (0.4)	4.9 (0.3)	5.0 (0.4)
Insulin (uU/mL)	6.99 (5)	6.2 (5)	7.6 (4)	10.2 (5)
HOMA-IR	1.53 (1)	1.4 (1)	1.7 (1)	2.3 (1)
HOMA-beta	25.0 (19)	22.0 (19)	27.8 (17)	37.3 (19)
SHBG (nmol/l)	46.7 (20)	50.4 (20)	43.4 (20)	32.0 (12)

Mean (SD) unless otherwise indicated. Baseline measures of HOMA-IR, HOMA-beta, and SHBG were according to the first visit during menses of the first cycle.

*Median cycle length (25^{th} – 75^{th} percentile)

**Average energy intake from four 24-hour recalls in first cycle

†Among women with DXA data (n=228)

Table 2

Relative overall mean (A), amplitude (B), and timing (C) of sex hormones among overweight and obese women compared to normal weight women in the BioCycle Study (n=443 ovulatory cycles)

	Total E2	Free-E2	Progesterone	FSH	LH
A) Mean, %[†]					
Overweight	5.30% (4.6)	**15.17% (4.1)****	3.35% (3.7)	**−15.60% (4.1)****	**−10.12% (5.0)***
Obese	1.39% (6.4)	**22.13% (5.6)****	**−15.00% (5.1)****	**−22.51% (5.7)****	**−16.91% (6.9)***
p- trend	*P=0.51*	***P<0.0001***	***P=0.04***	***P<0.0001***	***P=0.004***
B) Amplitude, %[†]					
Overweight	−1.33% (2.1)	−1.06% (2.1)	1.26% (4.3)	2.50% (2.0)	1.24% (2.2)
Obese	−1.83% (2.9)	−1.67% (2.9)	5.44% (6.1)	**7.92% (3.0)****	**9.23% (3.3)****
p- trend	*P=0.45*	*P=0.49*	*P=0.37*	***P=0.003***	***P=0.005***
C) Timing, day[‡]					
Overweight	0.22 (0.14)	0.24 (0.14)	−0.05 (0.07)	0.04 (0.12)	0.08 (0.16)
Obese	0.31 (0.19)	0.28 (0.19)	0.04 (0.10)	0.16 (0.15)	0.10 (0.19)

*p<0.05,

**p<0.01,

***p<0.001; All values (SE) adjusted for age, race, energy intake, and physical activity. Comparisons made to normal weight women (BMI<25 kg/m^2) as reference group. Overweight defined as BMI 25–<30 kg/m^2 and obese defined as BMI≥30 kg/m^2.

[†]Mean and amplitude differences are percent change for log-transformed hormone values.

[‡]All values of time were in number of days and modeled without centering on day of ovulation.

Table 3

Overall mean (A), amplitude (B), and timing (C) of sex hormones by tertiles of trunk-to-leg fat ratio in the BioCycle Study (n=443 ovulatory cycles)

Trunk-to-leg fat ratio tertiles	Total E2	Free E2	Progesterone	FSH	LH
A) Mean, %†					
Tertile 2	−1.39% (4.8)	6.90% (4.5)	−1.08% (3.9)	−7.99% (4.5)	−1.23% (5.4)
Tertile 3	**−13.51% (4.8)****	6.43% (4.5)	−6.15% (3.9)	**−14.70 (4.5)****	−4.56% (5.3)
p-trend	**P=0.003**	P=0.20	P=0.09	**P=0.001**	P= 0.38
B) Amplitude, %†					
Tertile 2	−1.92% (2.3)	−1.93% (2.2)	−5.68% (4.6)	2.47 (2.1)	−1.11% (2.5)
Tertile 3	−0.20% (2.3)	−0.13% (2.2)	−6.57% (4.6)	**5.58 (2.2)****	−0.53% (2.5)
p- trend	P= 0.94	P=0.91	P=0.18	**P=0.009**	P= 0.88
C) Timing, days‡					
Tertile 2	0.18 (0.15)	0.20 (0.15)	−0.04 (0.08)	0.09 (0.13)	0.13 (0.17)
Tertile 3	**0.49 (0.15)****	**0.47 (0.15)****	0.11 (0.08)	**0.50 (0.13)****	**0.39 (0.17)***

Tertile comparisons made against those in the first tertile of trunk-to-leg fat ratio. Tertiles 1, 2, and 3 had mean measures of trunk-to-leg fat ratio of 1.24, 1.68 and 2.36, respectively. All values are adjusted for age, race, energy intake, and physical activity.

*p<0.05,

**p<0.01;

†Mean and amplitude differences are percent change (SE) for log-transformed hormone values.

‡All values of time were in number of days (SE) and modeled without centering on day of ovulation.