Recreational Physical Activity and Premenstrual Syndrome in College-Aged Women

RECREATIONAL PHYSICAL ACTIVITY AND PREMENSTRUAL SYNDROME IN COLLEGE-AGED WOMEN

A Thesis Presented

by

AIMEE KROLL

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ABSTRACT

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It is estimated that up to 85% of premenopausal women experience at least one premenstrual symptom and 15-20% meet clinical criteria for premenstrual syndrome (PMS). PMS has a high morbidity level and reduces the quality of life for many women of reproductive age, with pharmaceutical treatments having limited efficacy and substantial side effects. Physical activity has been recommended as a method of reducing menstrual symptom severity. However, little evidence exists to support a clear relationship between physical activity and PMS. Using a cross-sectional design, we evaluated the relationship between physical activity and PMS and menstrual symptoms among 186 women aged 18-30 who participated in the University of Massachusetts Vitamin D Study. PMS and menstrual symptoms were assessed with a modified version of the Calendar of Premenstrual Experiences. A total of 44 women met established criteria for PMS, while 46 met criteria for controls. Physical activity was assessed using a validated questionnaire similar to the one used in the Nurses' Health Study II. Physical activity was calculated as metabolic equivalent task-hours (METs) per week. Diet and other lifestyle factors were assessed by questionnaire. After adjusting for age and

depression diagnosis, we found that each 10 MET-hour/week increase in physical activity was associated with a non-significant 3% increase in prevalence of PMS (95% CI: 0.94-1.14). After adjusting for BMI and percent body fat, results were similar (OR=1.02, 95% CI: 0.93-1.13). We found no evidence that physical activity was associated with the occurrence of specific menstrual symptoms among all 186 women. Results do not support a significant relationship between physical activity and prevalent PMS.

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CHAPTER I

INTRODUCTION

Premenstrual syndrome (PMS) is a condition occurring in the luteal phase of the menstrual cycle prior to the onset of a woman's menstrual period. It is estimated that up to 85% of women who menstruate experience at least one premenstrual symptom, occurring within the two weeks before menses and easing after menstruation begins.[1] PMS is estimated to occur in 8-20% of women and substantially reduces quality of life.[2-4] Over 300 PMS symptoms have been described,[5] ranging from emotional and behavioral symptoms such as depression, angry outbursts, irritability, crying spells, anxiety, confusion, social withdrawal, poor concentration, sleep disturbance, and thirst and appetite changes, to physical symptoms including breast tenderness, bloating and weight gain, headache, swelling of the hands or feet, and aches or pains.[1]

The causes of PMS are not clear. PMS is thought to be caused by an underlying neurobiological vulnerability to normal fluctuations in the circulating sex hormones estrogen and progesterone levels during the menstrual cycle.[6,7] The role of sex steroids in PMS is supported by observations that symptoms often improve with treatments resulting in ovulation suppression.[6] In addition, studies suggest that PMS is uncommon in anovulatory menstrual cycles, and that women with elevated levels of sex hormones have more severe symptoms.[5] Another hypothesis on the etiology of PMS proposes that emotional and physical symptoms may result from hormonal fluctuations during the menstrual cycle that alter brain neurotransmitter or neuropeptide function.[6,7] In particular, some studies have observed luteal phase abnormalities in serotonin function in

women with PMS and a more severe form of PMS, premenstrual dysphoric disorder (PMDD), compared to symptom free controls. Serotonin levels may be related to menstrual symptoms including depression, irritability, anger, and increased cravings for carbohydrates.[6] Dietary intake of chocolate, alcohol, sugary drinks, and vitamin B6 have also been examined for their potential role in PMS, but results are inconclusive.[7] Genetic predisposition to specific symptoms has been suggested by studies examining symptom occurrence in mother-daughter and twin relationships.[5]

The diagnostic definition for PMS established by the American College of Obstetricians and Gynecologists (ACOG), states that symptoms must be present in the 5 days before a woman's period for at least three menstrual cycles in a row and end within 4 days after her period starts.[1] Symptoms must interfere with normal life activities and may cause impairments in work performance, family and social activities, and sexual relationships.[8] In contrast, the World Health Organization definition does not include timing, but only states that one symptom be present regardless of severity.[8] Because there are no universally accepted diagnostic criteria, it is difficult to determine accurate prevalence rates and the impact of symptoms.

Recreational physical activity has been recommended as a method of reducing PMS occurrence and severity. ACOG recommends aerobic exercise, in particular to reduce fatigue and depression associated with PMS.[1] The U.S. Department of Health and Human Services recommends regular physical activity as a treatment for PMS[9] and some sources suggest that aerobic exercise is an effective alternative to pharmaceutical treatments in easing PMS.[10] Because the etiology of PMS is still unclear, identifying modifiable risk factors is important as PMS has such a high morbidity level and reduces

the quality of life for many women of reproductive age, and pharmaceutical treatments have limited efficacy and substantial side effects.[7]

There are several plausible biological mechanisms by which physical activity could reduce PMS symptoms. Aerobic physical activity may increase endorphin levels,[6,11] decrease levels of estrogen[12,13] and other steroid hormones,[6] improve transport of oxygen in muscles,[12] reduce cortisol levels,[12] and improve psychological well-being.[11,14] All of these mechanisms support an inverse association of physical activity on PMS symptoms.

Although physical activity has a multitude of health benefits, its association with reducing PMS occurrence and symptom severity is not well documented. Previous observational studies examining this relationship have had inconsistent findings, with some studies suggesting a protective effect,[11,14-20] one showing no association[21] and two studies finding an increased risk of PMS symptoms among exercising women.[22,23] One trial compared physical activity regimens for sedentary and active women;[20] however, to our knowledge, no randomized control trials have included a non-exercising control group.[6] Additionally, several of these studies had sample sizes of fewer than 100 total subjects.[15-17,19] To our knowledge, only one study[22] of physical activity and PMS adjusted for body mass index (BMI), a factor that likely also affects menstrual symptoms. One study examining obesity and PMS found that the prevalence of symptoms was significantly higher in obese women compared to underweight women (OR=2.9, 95% CI: 1.1-7.5).[24] Failure to control for BMI may thus lead to confounding due to the underlying relationship between physical activity and BMI.

Given that PMS etiology is still unclear and there is a need for knowledge of modifiable risk factors, it is important to determine if physical activity may reduce the risk of PMS. Therefore, we investigated the relationship between physical activity and PMS using data from the University of Massachusetts (UMass) Vitamin D Study, a cross-sectional study of 186 college-aged women.

CHAPTER II

PHYSIOLOGY OF PHYSICAL ACTIVITY AND PREMENSTRUAL SYNDROME

PMS occurs during the late luteal phase of the menstrual cycle. On average, one menstrual cycle lasts 25-36 days beginning with the first day of menstruation. This first phase of the cycle is known as the follicular phase and occurs on the first day of menses when estrogen and progesterone levels decrease at the end of the previous cycle. Following the follicular phase, the ovulatory phase of the cycle begins approximately on day 13 or 14 with a surge in luteinizing hormone that stimulates the release of an egg (ovulation). The luteal phase begins after ovulation, and usually lasts approximately 14 days, unless fertilization has occurred [25]. PMS occurs during the luteal phase of the cycle, most often with one week before menses.

There are several biological mechanisms by which physical activity may reduce the occurrence of PMS. These include an increase in endorphin levels,[6,11] a stabilization of hormone levels and their effect on the hypothalamic-pituitary axes,[6,12,13] improvements to oxygen in muscles,[12] and an overall improvement to psychological well-being.[11,14]

Endorphin levels in the body are the highest during the late follicular phase of the cycle and tend to decrease during the late luteal and menstrual phases.[6,12] Low endorphin levels may contribute to PMS by decreasing a general overall feeling of wellbeing and leading to depression and other low emotional states.[6] Physical activity has been shown to increase beta-endorphin levels, which improves mood and thus could reduce emotional symptoms.[6,11]

Physical activity may also improve PMS symptoms by impacting circulating hormone levels acting on the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is a part of the neuroendocrine system and is involved in regulating many body processes including digestion, the immune system, mood and emotions, sexuality, energy storage and expenditure, and stress reduction.[26,27] A study by Roca and colleagues (2003) found that women with PMS did not have a normal increase in HPA axis response following a treadmill stress test conducted during the luteal phase compared to control women, and that menstrual cycle related variation in HPA axis function was affected by both progesterone and estrogen levels.[28] These findings suggest that women with PMS have a decrease in HPA axis response during the symptomatic period, which could contribute to physical and emotional symptoms.[28]

Physical activity may also impact the HPA axis by reducing cortisol levels through a modification to psychological or behavioral reaction to stress. One study found that women with daily stress and suffering from PMS had higher levels of cortisol than control subjects,[29] while a second study found that women who experienced more stress on a day-to-day basis (and thus had higher cortisol levels) had more frequent and severe PMS.[30]

Other studies have found that physical activity may affect the hypothalamic-pituitary-gonadal (HPG) axis causing a decrease to estrogen and progesterone levels, resulting in fewer menstrual symptoms.[6] If physical activity decreases estrogen levels, this may also impact some of the major neurotransmitters that regulate mood and behavior, such as serotonin and Gamma Amino Butyric acid (GABA) that are affected by fluctuating estrogen levels during the luteal phase.[5]

Cramping, a common symptom of PMS, is caused by elevated tonic activity of the myometrium (uterine smooth muscle), which is stimulated by the sympathetic nervous system. If pain results from hypoxia of the uterine muscle, vasoconstriction caused by stress (due to the enhanced sympathetic activity that results from environmental stress) would cause more pain, while physical activity could possibly alleviate this symptom.[12]

Physical activity has also been shown to affect a women's psychological outlook by improving self-esteem and providing a distraction from other thoughts, which could provide relief from emotional symptoms associated with PMS.[11,14] Increased physical activity has been found to reduce tension, anger, depression, and low self-esteem, all of which are symptoms of PMS.[12] Physical activity may also improve the functioning of the immune system, increasing the body's resistance to stress.[14]

In summary, there is biological evidence in support of an association between physical activity and reduction of PMS symptoms through a variety of physiological mechanisms. These include increases to endorphin levels, helping to maintain the proper HPA axis response, decreases to sex steroids levels by impacting the HPG axis, reducing hypoxia of the uterine muscle, and improving emotional and psychological states of mind.

CHAPTER III

EPIDEMIOLOGY OF PHYSICAL ACTIVITY AND PREMENSTRUAL SYNDROME

There have been a number of epidemiological studies examining the relationship between physical activity and PMS. A majority of these studies have found a protective effect.[11,14-19] However, one study showed no association[21] and two studies found an increased risk of PMS symptoms among women who exercised regularly.[22,23] All of these studies were observational except for one nonrandomized intervention study comparing physical activity regimens for sedentary and active women.[20] No randomized control trials that have included a non-exercising control group have been published.[6] Additionally, some of these studies had sample sizes of fewer than 100 women.[15-17,19] Due to the cross-sectional design of most of these studies,[11,14,16-18,22,23] temporality bias makes it difficult to determine if exercising is etiologically related in the development of PMS, or if those with PMS exercised more or less than those without PMS.

Rasheed and colleagues (2003)[23] examined the relationship between several possible risk factors, including physical activity, and PMS among college-aged women in Saudi Arabia. They conducted a cross-sectional study with 488 women enrolled in nursing, medical laboratory technology and respiratory therapy educational programs who were between the ages of 17 and 27. They collected information on risk factors through a self-administered questionnaire that asked about level of physical activity (none, daily housework of at least 2 hours, three weekly sessions of walking or aerobic/rhythmic exercises for at least 20 minutes, or participation in sports). Women were also asked to report whether they had experienced any of 14 menstrual symptoms

during the last 6 months for 3 or more cycles within one week prior to the onset of menstruation. Scores were assigned based on whether the symptom was described as mild (score=1; daily activities not affected and no medication taken), moderate (score=2; daily activities not affected but medication was taken), or severe (score=3; daily activities were affected despite medication). Each woman was assigned a PMS symptom score from 0 (no symptoms) to 42 (maximum of 14 severe symptoms). The authors found that 96.6% of women in the study reported experiencing at least one menstrual symptom within the last 6 months. Findings from a univariate analysis show that physically active women were more likely to have high PMS symptom scores compared to sedentary women, with 45.3% of physically active women having high ranged scores (10-33) compared to 30.6% of sedentary women ($P<0.01$). It is unclear how the women were divided into physically active and sedentary groups, as there was no description of this categorization, and no further statistical analysis on the difference between the two groups was conducted. Due to the cross-sectional design, temporal bias is an issue for this study, as it is unclear whether women experienced PMS and started or stopped exercising to alleviate symptoms, or exercised regularly and never experienced PMS. The total score for PMS symptoms was also arbitrarily categorized into three levels (0, 1-9, ≥10) without any explanation for this process. Because information was collected by questionnaire, misclassification of outcome is a limitation of the study as the question on PMS asked about symptoms during the last 6 months, which can be difficult to remember at one point in time.

A longitudinal study, conducted by Choi *et al.*[14] examined the relationship between physical activity and changes in emotional and physical symptoms during the

menstrual phase to determine if symptoms worsened during the luteal premenstrual phase. The study included 143 women ages 15-48 from the United Kingdom who were categorized based on how often they said they exercised each week. Women were classified as competitive athletes (those training for competitive or public events), high exercisers (3 or more times per week), low exercisers (less than 3 times per week), or sedentary. Women were asked to complete a mood questionnaire every night for one month beginning on the first day of their menstrual cycle and ending on the first day of their following period, with the premenstrual phase being defined as the 5 days prior to menstruation. The questionnaire included 42 items describing moods and physical states. The authors found that during the premenstrual phase, high exercisers had the lowest mean score for negative affect characteristics including irritability and fatigue, and the lowest mean score for physical symptoms such as cramps and dizziness. Sedentary women, low exercisers, and competitive exercisers had higher mean scores than the high exercisers in all of these groups; however, there was no linear relationship between physical activity and improved PMS symptoms. One potential limitation of this is study is the reproducibility of symptom scores over time. Although symptoms were examined within the 5 days before menstruation, questionnaires were only administered for one month, and therefore it is difficult to determine whether these symptoms occurred for the women in every menstrual cycle or only during that month. Because the women knew that this study was being conducted to examine physical activity and the menstrual cycle, they may have been more aware of symptoms while filling out the questionnaire than during an unobserved cycle. This is likely not to differ by physical activity level.

In one of the first and most cited studies examining physical activity and PMS, Timonen and Procopé[18] recruited 748 women from the Helsinki University in Finland into a cross-sectional study. They collected data on physical activity and PMS with a 60-question survey. The authors compared women who were studying physical education (n=136) and those in other programs (n=612) with the assumption that those studying physical education exercised more frequently than those studying other fields. They found that the percentage of women experiencing premenstrual and menstrual low back pain, premenstrual and menstrual pelvic pain, premenstrual and menstrual headache, premenstrual nervousness, irritability, anxiety, depression and fatigue were all significantly higher ($P<0.05$) in women studying in other programs compared to those studying at the Institute of Physical Education. These findings, however, are based on the assumption that physical education students were more active, though this assumption was not validated. Other researchers in the field have criticized this study because 54% of the population was under 22, an age group where anovulation occurs quite frequently (9-70% of cycles); because only a single cycle was assessed, it was unclear whether menstrual symptoms were assessed during an ovulatory cycle when symptoms are more likely to occur.[13] Possible confounding by BMI is also an issue.

In summary, previous studies of physical activity and PMS have reported inconsistent results, with most finding physical activity inversely associated with menstrual symptom severity. However, limitations of several of the studies that found this protective effect include recall bias, using different definitions of PMS, and likely misclassification of physical activity levels. Other studies have had small sample sizes, and thus had limited power to assess this relationship. To our knowledge, only one study

in this review adjusted for BMI.[22] Our study will use validated physical activity and PMS assessments, and evaluate many covariates associated with PMS, including BMI.

CHAPTER IV

SUMMARY

Up to 85% of women who menstruate experience at least one menstrual symptom two weeks before menstruation begins.[1] The ACOG defines PMS as a disorder in which symptoms are present in the 5 days before a woman's period begins for at least three menstrual cycles in a row and that end within 4 days after her period starts, which substantially interfere with normal life activities.[1] Although many prominent organizations, including the U.S. Department of Health and Human Services,[9] recommend physical activity for easing PMS symptoms, there is little conclusive evidence of a benefit of physical activity. Results of observational studies are inconsistent and there are clear opportunities for bias and misclassification in studies examining these two factors. Because the etiology of PMS remains unclear and the effectiveness of pharmaceutical treatments is limited, knowledge of modifiable risk factors is important to help alleviate symptoms in women who suffer each cycle.

Physical activity may reduce PMS symptoms through a number of physiological mechanisms. These mechanisms include increasing endorphin levels, regulating hormone levels, increasing oxygen supply to the muscles, reducing cortisol levels, and promoting a less stressful and better outlook on life.

Several epidemiological studies suggest a protective effect of physical activity on PMS symptoms. Although these studies had several limitations including temporality bias and misclassifications, they provide some evidence that physical activity may minimize symptom occurrence.

Using a cross-sectional design, we examined the association between physical activity and prevalent PMS using data from the UMass Vitamin D Study. Recreational physical activity and prevalent PMS was assessed through validated questionnaires in a group of menstruating college-aged women. We controlled for BMI and several other possible confounding factors.

CHAPTER V

HYPOTHESES AND SPECIFIC AIMS

Using a cross-sectional design, we evaluated the relationship between recreational physical activity and prevalent PMS symptoms among college-aged women. The following aims were addressed:

Specific Aim 1: To assess the association between physical activity and risk of PMS.

Hypothesis 1: College-aged women who participate in recreational physical activity will be less likely to experience PMS than women who do not participate in recreational physical activity.

Specific Aim 2: To examine the effect BMI has on the relationship between physical activity and PMS and menstrual symptoms.

Hypothesis 2: Results adjusted for BMI will be stronger than those unadjusted for BMI.

Specific Aim 3: To examine if physical activity is associated with the occurrence of specific menstrual symptoms.

Hypothesis 3: Women who participate in more recreational physical activity will be less likely to experience moderate-severe symptoms compared to women who participate in less physical activity.

CHAPTER VI

METHODS

Study Design and Population

This study examined the relationship between physical activity and PMS/menstrual symptoms using data from the University of Massachusetts (UMass) Vitamin D Study, a cross-sectional study that was conducted at UMass in Amherst, Massachusetts between March 2006 and June 2008. The primary purpose of the UMass Vitamin D Study was to assess factors associated with vitamin D status in young women. A secondary aim of the study was to assess dietary, lifestyle, and biochemical factors associated with PMS.

Participants were women aged 18-30. Women were invited to participate in the study through fliers posted on the UMass campus. Women of all ethnicities were welcome to participate. Women were ineligible to participate if they: were pregnant or not currently menstruating; were experiencing untreated depression; reported high blood pressure or elevated cholesterol, kidney or liver disease, bone disease such as osteomalacia, digestive disorders, rheumatologic disease, multiple sclerosis, thyroid disease, hyperparathyroidism, cancer, type 1 or type 2 diabetes, or polycystic ovaries; or were currently using corticosteroids (such as prednisone, anabolic steroids, anticonvulsants, Tagmet, Cimetidine, or propranolol). Participants were asked to complete food-frequency and demographic questionnaires, provide a fasting venous blood sample (45 mL) drawn in the early morning during the late luteal phase of the menstrual cycle, and provide a urine sample via a clean catch. The following

measurements were also taken: fasting blood sugar via glucometer; hemoglobin via hemoglobinometer; blood pressure; waist circumference; height; weight; and a dual energy X-ray absorptiometry (DEXA) bone scan to determine body composition and bone mineral density. Study participation required 1.5 to 2 hours of time to complete the measurements, and participants were given $10 compensation as well as the results from the DEXA scan, blood glucose test, and a nutrient analysis of their diet. A total of 186 women participated in the study.

Exposure Assessment

Physical activity was assessed through a self-reported questionnaire. Participants were asked to report the average time they spent each week over the past month engaging in specific activities including walking, hiking, jogging, running, bicycling, aerobics or dancing, tennis or other racket sports, swimming, yoga or Pilates, and weight training. Response options ranged from zero minutes to 11+ hours per week. Questionnaire responses were used to calculate metabolic equivalent task (MET) hours per week, which considers the duration and intensity of physical activity. METs are a measure of energy expenditure equal to the ratio of metabolic rate at work to resting metabolic rate, and vary by intensity of a specific type of physical activity. One MET is defined as the energy expended while sitting quietly.[31] We examined physical activity in both continuous METs per week and in tertiles of METs per week.

Validity of Exposure Assessment

The questions on physical activity were based on a previous questionnaire used in the Nurses' Health Study II (NHSII) and have been previously validated in a population of 147 young women.[32] Test-retest correlation for the questionnaires administered 2-years apart were 0.59. Correlation between activity level reported in 7-day activity diaries and that reported on the questionnaire was 0.62. The types of physical activity included on the questionnaire were the most common types of physical activity reported by women in the University of Pennsylvania Alumni Health Study.[32]

Outcome Assessment

Information on menstrual symptoms was collected through self-reported questionnaire. Participants were asked to provide information on 26 different symptoms by responding to the following statement: "For each symptom listed below, please indicate whether you experience it most months of the year, for at least several days before your menstrual period begins." Participants were asked not to include symptoms that they experienced throughout their entire menstrual cycle, or symptoms that start only when their period starts. Participants were asked to indicate the usual severity of each symptom as mild, moderate, severe, or "not at all". Participants were also asked to indicate whether their overall severity of symptoms was "minimal" (no effect on normal activities); "mild" (noticeable, but not troublesome); "moderate" (interferes with normal activities); or "severe" (intolerable, prevents normal activities).

In addition, women were asked to report the number of days before their period when symptoms usually began, as well as the number of days the symptoms lasted after

their period began. Women were then asked to report whether they experienced relationship discord with family or a partner; relationship discord with friends or coworkers; poor work performance or attendance; social isolation; and suicidal thoughts, and to indicate the severity of each of these problems (mild, moderate, or severe). Finally, women were also asked to report whether they had ever been clinically diagnosed with PMS.

Responses to the menstrual symptom questionnaire were used to identify women meeting clinical criteria for PMS based on those developed by Mortola *et al.*[33] A woman was considered a case if she reported: 1) at least one physical and one affective menstrual symptom; 2) overall symptom severity of "moderate" or "severe", impact of symptoms on life activities and relationships of "moderate" or "severe", or one or more individual symptoms rated as "severe"; 3) symptoms beginning within 14 days of the start of menses; 4) symptoms ending within 4 days of the start of menses; and 5) symptoms are absent in the week after menses. The menstrual symptom questionnaire was also used to identify women with few or no menstrual symptoms to serve as controls. Controls were women who reported: 1) overall symptom severity of "none" or "mild" for all individual symptoms; 2) overall symptom severity of "none", "minimal" or "mild"; 3) impact of symptoms on life activities and relationships of "not a problem" or "mild" for all items; and 4) no previous clinical diagnosis of PMS.

Validity of Outcome Assessment

The questionnaire used for this study to assess PMS is based on the Calendar of Premenstrual Experiences designed by Mortola *et al.*[33] and similar to that used in the

NHSII.[34] A validation study on the questionnaire used in the NHSII showed that menstrual symptom timing, occurrence, and severity in PMS cases identified with those criteria were similar for women who reported that the "gold standard" of prospective symptom charting had been used in making their diagnosis.[34]

Covariate Assessment

Covariate information was collected through a self-reported questionnaire measuring factors including age, age at first menstruation, current oral contraceptive use, smoking status, marijuana use, hours of sleep per weeknight, history of reproductive tract infections, and history of depression or bipolar disorder. Results from the food frequency questionnaire were used to determine intake of vitamin D and calcium from food sources as well as daily alcohol consumption. Body composition was measured by study staff through use of a DEXA scan. Height and weight were measured directly and used to calculate BMI (weight [kg]\height $[m]^2$).

Data Analysis Plan

Specific Aim 1: To assess the association between physical activity and risk of PMS.

Univariate Analysis

We calculated the number and percent of subjects based on PMS status as well as by tertile of METs/week of physical activity. We also calculated the distribution of physical activity in METs/week based on PMS status.

Bivariate Analysis

We cross-tabulated covariates with outcome and exposure variables to evaluate potential confounders. We also cross-tabulated continuous covariates with PMS status in a separate analysis. Cross-tabulations were evaluated using a chi-square test to determine if the observed distribution fit the expected distribution when the cell size was sufficient, and with Fisher's Exact test if cell counts were small (<5).

Multivariate Analysis

The relationship between physical activity and PMS was modeled using multivariable logistic regression. Two analyses were conducted; the first examined physical activity categorized into tertiles of MET-hours/week, the second examined continuous physical activity in units of 10 MET-hours/week as the exposure. We calculated odds ratios (ORs) and 95% confidence intervals (95% CI).

Confounders were evaluated by examining the physical activity/PMS relationship by running the model with each covariate separately. Any covariate whose addition to the model changed the odds ratio by 10% or more was retained in the model as a confounder.

Specific Aim 2: To examine the effect BMI has on the relationship between physical activity and PMS and menstrual symptoms.

Multivariate Analysis

Confounding by BMI and percent body fat were examined by evaluating the physical activity/PMS relationship in regression models with and without these variables and comparing odds ratios between the models. Effect modification was assessed by stratifying our population by BMI (<22.5 vs. ≥ 22.5 kg/m^2) and then calculating stratum specific odds ratios for the relationship between continuous BMI and PMS. We then created a multiplicative interaction term (continuous physical activity*BMI strata) and included this term in the multivariable regression model along with terms for continuous physical activity and BMI. The Wald P-value for the interaction terms was used to assess whether interaction was significant ($P<0.05$).

Specific Aim 3: To examine if physical activity is associated with the occurrence of specific menstrual symptoms.

Multivariate Analysis

The relationship between physical activity and PMS symptoms was modeled using multivariable logistic regression. For this analysis, we evaluated continuous levels of physical activity, in 10 MET-hours/week. Symptoms were dichotomized into none/mild or moderate/severe, based on the previously identified criteria. We included those covariates identified as confounders in the main analysis.

The data analysis for this paper was performed using SAS software, Version 9.2 for Windows (SAS Institute Inc., Cary, NC, USA).

CHAPTER VII

SIGNIFICANCE

Previously published studies on physical activity and PMS have reported inconsistent results. Because physical activity is a potential modifiable risk factor for a condition that affects many women, additional research to evaluate this relationship is important. Results from this study could help inform future research and randomized trials that examine exercise and PMS. The results could also be used to help modify current guidelines recommending exercise as a treatment for PMS and menstrual symptoms.

CHAPTER VIII

HUMAN SUBJECT PROTECTION

The Vitamin D Study was approved by the Institutional Review Board at UMass Amherst in Amherst, Massachusetts. All participants were required to sign informed consent documents prior to their participation, the completion of questionnaires, or biologic sample collection. Participants were provided specific information about confidentiality and told that they are allowed to withdraw from the study at any time.

All participant personal information, including questionnaires, biologic samples, and clinical measurements are kept in a secure location in the UMass Vitamin D Study office at the School of Public Health UMass Amherst. All participant names and ID's are stored in locked filing cabinets separate from study data to maintain confidentiality. Questionnaires and all data are identified by ID numbers only. All computerized documents are password protected.

There are no known risks to the study participants, except for the possibility of discomfort associated with having blood pressure taken, blood drawn, urine collected, undergoing studies of genetic factors, or undergoing a DEXA scan. As mentioned earlier, the participant can withdraw at any time, also preventing any emotional distress that may occur. Accidental breach of confidentiality is highly unlikely to occur, as security procedures are maintained for every document involved in the study. There are no known benefits to the participants, except for receiving their $10 compensation as well as the results from the DEXA scan, blood glucose test, and a nutrient analysis of their diet. Data are used for medical statistical purposes only.

CHAPTER IX

PERMISSION TO ACCESS DATA

I, Aimee Kroll, have been granted permission to use the data from the UMass Vitamin D study by the co-Principal Investigator of the Vitamin D Study, Elizabeth Bertone-Johnson, for the purposes of this thesis.

Signed:

_____
Elizabeth R. Bertone-Johnson, ScD

_____
Aimee Kroll

CHAPTER X

RESULTS

Table 2 shows the distribution of PMS status by study participants for those that met either the case or control criteria. About half (49%) of the total 186 participants met either one of these definitions, with 44 meeting case criteria and 46 meeting control criteria. Table 3 shows the distribution of participants by physical activity tertile for all 186 study participants. The ranges of MET values in our population was relatively large, with women in the highest tertile reporting at least 65 MET-hours per week. Table 4 shows the distribution of PMS cases and controls by physical activity tertile.

Characteristics of PMS cases and controls are presented in Table 5. A total of 4% of controls reported that they had ever smoked, compared to 30% of cases (P=0.001). For marijuana smoking, 17% of controls reported ever smoking marijuana compared to 32% of cases (P=0.11). Vitamin D status also differed between cases and controls, with 64% of cases and 83% of controls reporting intake from food sources over 100 IU/day or more (P=0.04). Intake of calcium from food sources had a similar pattern, with 58% of controls in the highest intake group (>1200 mg/day) and only 21% of cases (P=0.06). Age, age at first menses, BMI, alcohol consumption, hours of sleep per weeknight, current oral contraceptive use, history of reproductive tract infections, diagnosis of depression or bipolar disorder, and percent body fat did not differ significantly between cases and controls. Cases and controls also had similar mean values for age, age at first menses, BMI, alcohol consumption, vitamin D intake, calcium intake, and percent body fat (Table 6).

When examining the distribution of covariates by physical activity tertile (Table 7), fewer women in the highest tertile were ever smokers or had their first menses before the age of 12 than in the lower two tertiles, though these differences were not significant. For example, 8% of women in the highest tertile were ever smokers compared to 17% in tertile 2 and 13% in tertile 1 (P=0.31). Current oral contraceptive use significantly differed between tertiles, with 28% of women in the highest tertile currently using oral contraceptives compared to 51% in tertile 2 and 39% in tertile 1 (P=0.03). Women in the highest tertile of physical activity consumed greater amounts of calcium when compared to women in the lower two tertiles (>1200 mg/day: Tertile 3- 46%; Tertile 2- 24%; Tertile 1- 21%) (P=0.01). Distribution of age, BMI, alcohol consumption, hours of sleep per weeknight, marijuana use, history of reproductive tract infections, diagnosis of depression or bipolar disorder, vitamin D intake, and percent body fat were similar across all three tertiles.

In unadjusted analyses physical activity was not associated with PMS. Women in tertile 2 had a non-significant 59% increased risk of PMS compared to women in tertile 1 (95% CI: 0.59-4.33) and women in tertile 3 had a non-significant 53% increased risk of PMS compared to women in tertile 1 (95% CI: 0.53-4.34). Results were similar after controlling for age and history of depression or bipolar disorder; the OR for women in tertile 2 versus tertile 1 was 1.62 (95% CI: 0.58-4.51) while the odds ratio for tertile 3 versus tertile 1 was 1.67 (95% CI: 0.57-4.92). When examining the association between continuous level of physical activity (per 10 MET-hours/week) and PMS, the multivariable odds ratio was 1.03 (95% CI: 0.94-1.14), where every 10 MET-hour/week

increase in physical activity corresponds to a non-significant 3% increase in PMS (Table 8).

Secondly, we were interested in examining the effect of adjustment for BMI and percent body fat on multivariable odds ratios. We included BMI as a measure of body mass, and included percent body fat from the DEXA scan as a measure of lean body mass. Table 9 shows four multivariable models: 1) not including BMI or percent body fat; 2) including only BMI; 3) including only percent body fat; and 4) including both BMI and percent body fat. There was no significant change in the odds ratios for physical activity among the four models, indicating that neither BMI nor percent body fat confounded the relationship between physical activity and PMS. When examining the relation between each 10 MET-hour/week change in physical activity and PMS risk, odds ratios and 95% confidence intervals were also similar for all four multivariable models (Table 9).

We also examined if BMI modified the relationship between physical activity and PMS. We found no significant difference in the relationship between continuous level of physical activity and PMS between strata. The odds ratio for women in the lower BMI category (<22.5 kg/m^2) was 1.06 (95% CI: 0.90-1.26) while the odds ratio in the higher BMI category (≥ 22.5 kg/m^2) was 1.01 (95% CI: 0.89-1.15) (Table 10). The P-value for interaction was 0.68.

We then examined the association between each 10 MET-hour/week change in physical activity and the occurrence of 26 specific menstrual symptoms, with our outcome being moderate-severe severity versus none-mild severity for each symptom (Table 11). All models were adjusted for age and history of depression or bipolar

disorder. Every 10 MET-hour/week increase in physical activity was associated with a 13% lower risk of headache (OR=0.87, 95% CI: 0.74-1.01); a 5% increased risk of food cravings, changes in appetite, irritability and emotional hypersensitivity (OR=1.05, 95% CI: 0.99-1.11); and a 10% increase in risk of forgetfulness (OR=1.10, 95% CI: 1.00-1.21).

In additional analyses, we examined the association between meeting recommended physical activity guidelines and risk of PMS. Current guidelines recommend at least 30 minutes of moderate intensity physical activity on most days of the week, corresponding to 10 MET-hours/week (0.5 hr * 4 METs * 5 days = 10 MET-hrs/week).[35] We found no evidence in decrease of risk in women who met this recommended criteria compared to those who did not meet the recommended physical activity criteria, either in unadjusted models or after adjusting for age and diagnosis of depression or bipolar disorder (multivariable OR=1.11, 95% CI: 0.31-3.99).

CHAPTER XI

DISCUSSION

In this cross-sectional study of 186 premenopausal women, we found no association of physical activity with PMS or menstrual symptoms. Results from age and history of depression or bipolar disorder adjusted models were also null. Physical activity modestly but non-significantly increased risk of moderate to severe food cravings, changes in appetite, irritability, emotional hypersensitivity and forgetfulness and reduced the risk of headache.

Unlike prior studies,[11,14-18,20] we found no significant decrease in risk of PMS or menstrual symptoms in women who were more physically active compared to women who were not physically active or who were less physically active. We observed no substantial association even after adjusting for BMI and percent body fat, which gave us a representation of lean body mass for each participant. However, our sample size was small and confidence intervals were wide, possible explaining our lack of significant findings. Given our small sample size, our power for the study was relatively low, with 80% power to detect an odds ratio of 2.7. It is possible that with a larger sample size, we may have had more power to detect a modest association. The range of physical activity in our study population may have also affected our results. Because the physical activity range was so high, we did not have enough power to examine substantially low activity women compared to high activity women, another possible explanation for our null findings.

Two previous studies[22,23] found an increased risk of PMS for physically active versus inactive women. Deuster *et al*. found that 10% of highly active women experienced PMS compared to 4.7% of inactive women, and inactive women had a significant 60% reduction in PMS symptoms (95% CI: 0.2-0.7) after adjustment for race, age, age at menarche, smoking, BMI, alcoholic drinks, and nutritional habits among other factors.[22] Rasheed *et al*. showed that 45.3% of physically active women had high premenstrual symptom scores compared to 30.6% of sedentary women based on a self-reported questionnaire on symptom severity.[23] Both of these studies were similar to ours by cross-sectional design and questionnaires that determined physical activity status and PMS and menstrual symptom severity.

It is possible that our results were affected by bias. Nondifferential misclassification of exposure may arise if physical activity is measured inaccurately, independent of PMS assessment. Because physical activity was measured through a self-reported questionnaire, it is possible that women under or over reported their physical activity, did not report on specific activities, or participate more in occupational or lifestyle physical activity compared to recreational activity. Any nondifferential misclassification of exposure that occurred will bias the results toward the null, therefore making any association weaker. However, we used a questionnaire that has been previously validated through comparisons with physical activity diaries, making it unlikely that any nondifferential misclassification of exposure would bias our results substantially.[32]

Nondifferential misclassification of outcome could occur if PMS and menstrual symptoms were measured inaccurately. Because menstrual symptoms were measured

with a self-reported questionnaire, it is possible that some nondifferential misclassification of outcome could occur, independent of physical activity assessment. Women may under or over report symptoms or severity of symptoms, not report on specific symptoms, or may have been unclear about the definition of symptom severity. However, we asked women about their usual menstrual symptoms, making it easier to recall specific symptoms and their severity if they occur each month, opposed to questions asking about a specific time period. Any nondifferential misclassification of outcome that occurred would have biased our results closer to the null.

Selection bias, in the form of non-comparable selection, may have occurred if women who experience PMS and are physically active were more motivated to participate in the study than other women, or if women who do not experience PMS symptoms and are not physically active were less motivated to participate. If women who have severe PMS and participate in high amounts of physical activity were more likely to join the study because they wanted to know what causes their symptoms, our results would be overestimated if exercise truly reduces PMS. However, because the study was conducted primarily to look at vitamin D status, women agreeing to participate in the study were unlikely to make a connection between questions asking about PMS and physical activity habits.

Information bias may occur in the form of recall bias if women who experience PMS and menstrual symptoms are more motivated to accurately report their physical activity habits compared to women who do not experience PMS. This is unlikely in our study, because as noted earlier the study's primary objective was to assess vitamin D status. It is unlikely that a participant could know that an association between physical

activity and PMS would be examined as the questions on the questionnaire were in separate unrelated sections. However, because physical activity is often recommended to help alleviate PMS, a woman may nonetheless make this connection. Because the questions on PMS come before the questions on physical activity in our study questionnaire, a woman who answered the questions on PMS and felt like it was an important issue based on her responses may be more likely to recall her physical activity differently compared to a woman who did not notice a trend with her questions on the PMS section. In this situation, a woman may underreport her physical activity if she believes she does not participate in enough physical activity to help ease menstrual symptoms and PMS. If this type of information bias did occur in our study, our results would be underestimated because she would be considered unexposed and experiencing PMS.

In a cross-sectional study, it is often difficult to determine whether the exposure preceded the outcome or vice versa. In our study, we are unable to know if women experiencing PMS started exercising to help alleviate symptoms, if women who have been exercising regularly do not experience PMS symptoms because of the physical activity, or if women who experience PMS do not participate in physical activity because their symptoms are so severe they do not feel well enough to exercise. Temporality bias in our study will bias our results depending on the scenario. If exercise is protective then we assume that cases exercise less than controls. If a case starts exercising more to treat her symptoms, she thus increases her exposure level and makes the overall level in cases more similar to controls, therefore biasing our results toward the null. In another example, if a case who has been exercising stops exercising because her symptoms are

severe, she thus decreases her exercise level and makes the overall level of activity in the cases even lower and more different from controls, therefore biasing our results away from null, making exercise look more protective.

Survival bias in a cross-sectional study can occur if people who are exposed are more likely to die due to the outcome. Because there is no risk of mortality from physical activity or PMS, this type of bias is not a concern in our study.

It is possible that there was some residual confounding that affected our results in either direction depending on the type of confounding variable. An example of a confounder that we did not collect data on is stress. Stress has been shown to be associated with a greater risk of PMS.[22] Confounding by stress could exist in two separate scenarios. If stress caused a woman to participate in more physical activity as a means of alleviating stress, and stress was the true cause of PMS, less PMS would be attributed to her physical activity, not the reduction of her stress, therefore biasing an inverse association to the null. Likewise, if a woman who experienced stress exercised less because she felt like she had too many other things to do, her PMS would bias an inverse association away from the null. Although stress may play a role in our findings, we believe that women who are under a great deal of stress probably would not take the time to participate in this study, therefore making this situation unlikely to affect our results substantially.

Another potential limitation of our study is using multiple comparisons to examine the relationship between physical activity and specific menstrual symptoms. We did not adjust for multiple comparisons in our analysis. However, doing so would not have had much affect on our results as they were null.

The results of our study could be applicable to premenopausal women, as the biological mechanisms that relate physical activity to PMS likely do not vary by race or ethnic origin.

In conclusion, we found no association with physical activity and the occurrence of PMS and menstrual symptoms. It is possible that our cross-sectional design led to several biases and that the temporal relationship between physical activity and PMS could not be examined in a cross-sectional study. The relationship between physical activity and PMS remains unclear. Further research in the form of prospective studies and randomized trials, to minimize biases associated with cross-sectional studies, should be conducted in this area before concluding that physical activity and PMS are associated.

TABLES

Table 1: Classification of Study Variables

Name	Description	Type	Variable Group
bloat	PMS symptom: Abdominal bloating • 1 = Not at all • 2 = Mild • 3 = Moderate • 4 = Severe	Categorical	Outcome
tender	PMS symptom: Breast tenderness • Categories as for variable "bloat," above	Categorical	Outcome
dizzy	PMS symptom: Dizziness • Categories as for variable "bloat," above	Categorical	Outcome
head	PMS symptom: Headache • Categories as for variable "bloat," above	Categorical	Outcome
hot	PMS symptom: Hot flashes • Categories as for variable "bloat," above	Categorical	Outcome
naus	PMS symptom: Nausea • Categories as for variable "bloat," above	Categorical	Outcome
swell	PMS symptom: Swelling in extremities • Categories as for variable "bloat," above	Categorical	Outcome
acne	PMS symptom: Acne • Categories as for variable "bloat," above	Categorical	Outcome
const	PMS symptom: Diarrhea/constipation • Categories as for variable "bloat," above	Categorical	Outcome
crave	PMS symptom: Food cravings • Categories as for variable "bloat," above	Categorical	Outcome
palp	PMS symptom: Palpitations • Categories as for variable "bloat," above	Categorical	Outcome
anx	PMS symptom: Anxiety/nervousness • Categories as for variable "bloat," above	Categorical	Outcome
appet	PMS symptom: Increased/decreased appetite • Categories as for variable "bloat," above	Categorical	Outcome
irrit	PMS symptom: Irritability • Categories as for variable "bloat," above	Categorical	Outcome
hyper	PMS symptom: Emotional hypersensitivity • Categories as for variable "bloat," above	Categorical	Outcome
fatig	PMS symptom: Fatigue • Categories as for variable "bloat," above	Categorical	Outcome

mood	PMS symptom: Mood swings • Categories as for variable "bloat," above	Categorical	Outcome
cry	PMS symptom: Tendency to cry easily • Categories as for variable "bloat," above	Categorical	Outcome
insom	PMS symptom: Insomnia • Categories as for variable "bloat," above	Categorical	Outcome
angry	PMS symptom: Angry outbursts • Categories as for variable "bloat," above	Categorical	Outcome
alone	PMS symptom: Desire to be alone • Categories as for variable "bloat," above	Categorical	Outcome
depres	PMS symptom: Depression • Categories as for variable "bloat," above	Categorical	Outcome
confus	PMS symptom: Confusion • Categories as for variable "bloat," above	Categorical	Outcome
forget	PMS symptom: Forgetfulness • Categories as for variable "bloat," above	Categorical	Outcome
cramp	PMS symptom: Abdominal cramping • Categories as for variable "bloat," above	Categorical	Outcome
back	PMS symptom: Lower back pain • Categories as for variable "bloat," above	Categorical	Outcome
pms	PMS symptom: Lower back pain • 1 = Case • 0 = Control	Categorical	Outcome
pa_tot	Recreational activity: MET hours/week	Continuous	Exposure
patert	Recreational physical activity: Tertiles	Categorical	Exposure
METS10	Recreational activity: 10 MET hours/week	Continuous	Exposure
age_m	Age menstrual periods began • 1 = ≤ 9 years old • 2 = 10 years old • 3 = 11 years old • 4 = 12 years old • 5 = 13 years old • 6 = 14 years old • 7 = 15 years old • 8 = 16 years old • 9 = ≥ 17 years old	Categorical	Covariate
curr_oc	Currently using OCs • 1 = Yes • 0 = No • 99 = blank	Categorical	Covariate
cur_smk	Currently smoke • 1 = Yes • 0 = No	Categorical	Covariate

smk_mar	Do you smoke marijuana • 1 = Yes • 0 = No	Categorical	Covariate
alco	Alcohol consumption in grams per day	Continuous	Covariate
ill	Ever had any of the following clinician-diagnosed illnesses (mark all that apply) • 1 = Lactose intolerance • 2 = Depression (unipolar depression) • 3 = Bipolar disorder (manic depressive illness) • 4 = Endometriosis • 5 = Uterine fibroids • 6 = None of the above	Categorical	Covariate
wd_slp	On an average weekday, how many hours do you sleep per night? • 1 = ≤3 hours • 2 = 4-5 hours • 3 = 6-7 hours • 4 = 8-9 hours • 5 = ≥10 hours	Categorical	Covariate
rti	In the past 6 months, have you been treated by a healthcare provider/ treated yourself for any of the following reproductive tract infections (mark all that apply) • 1 = Bacterial vaginosis (BV) • 2 = Yeast • 3 = Chlamydia • 4 = Gonorrhea • 5 = Trichomoniasis • 6 = Syphilis • 7 = Genital warts • 8 = Genital herpes • 9 = Not sure • 10 = None of the above • 99 = missing	Categorical	Covariate
vitd_wo	Vitamin D intake per day (IU) from food sources	Continuous	Covariate
calc_wo	Calcium intake per day (mg) from food sources	Continuous	Covariate
Bodyfat	% Body fat from DEXA	Continuous	Covariate
Bmi	BMI Calculated	Continuous	Covariate
Agequart	Age quartiles: • 1 = 18-18.99 • 2 = 19-20.99 • 3 = 21-22.99 • 4 = ≥23	Categorical	Covariate
Men_age	Age at first menstruation: • 1 = ≤12 • 2 = >12	Categorical	Covariate
bmicat_a	BMI categories: • 1 = 16.5-24.9 • 2 = ≥25	Categorical	Covariate

Alcocat	Alcohol consumption: • 1 = 0 • 2 = 0.88-3.07 • 3 = 3.08-7.92 • 4 = 7.93-69.78	Categorical	Covariate
Wd_slp	Weekday sleep (hours): • 1 = 4-7 • 2 = ≥8	Categorical	Covariate
rticat	History of reproductive tract infection: • 1 = Yes • 0 = No • 2 = Missing	Categorical	Covariate
Illcat	Diagnosis of depression or bipolar disorder: • 1 = Yes • 0 = No	Categorical	Covariate
Vitdcat	Vitamin D intake: • 1 = <100 • 2 = ≥100	Categorical	Covariate
Calccat	Calcium intake: • 1 = 0-599 • 2 = 600-1200 • 3 = >1200	Categorical	Covariate
Bodyfatq	Body fat quartiles: • 1 = 14.5-26.1 • 2 = 26.2-31.6 • 3 = 31.7-37.3 • 4 = 37.4-50.1	Categorical	Covariate

Table 2: Distribution of PMS Status among Study Participants (n=186)

	N	%
PMS Case	44	24
PMS Control	46	25
Total	90	49

Table 3: Distribution of Physical Activity Status among Study Participants (n=186)

	N	%	Median	Range
Physical activity tertile 1	62	33	16.1	0-23.9
Physical activity tertile 2	63	34	42.8	24.1-65.1
Physical activity tertile 3	61	33	100.3	65.4-374.2

*Median and range in MET-hours/week

Table 4: Distribution of Physical Activity Status among PMS Cases and Controls (n=90)

	Physical Activity Tertile 1 N (% of tertile)	Physical Activity Tertile 2 N (% of tertile)	Physical Activity Tertile 3 N (% tertile)
PMS Case	12 (19)	18 (28)	14 (23)
PMS Control	17 (27)	16 (25)	13 (21)
Total	29 (46)	34 (53)	27 (44)

Table 5: Distribution of Categorical Covariates According to PMS Status, among Cases and Controls (n=90)*

	PMS Case (n=44)	PMS Control (n=46)	P-value**
	N (%)	N (%)	
Age			
18	6 (14)	9 (20)	
19-20	16 (36)	19 (41)	0.74
21-22	13 (30)	10 (22)	
23-30	9 (20)	8 (17)	
Age at first menses			
≤12	25 (57)	20 (43)	0.21
>12	19 (43)	26 (57)	
BMI (kg/m^2)			
16.5-24.9	35 (80)	37 (80)	0.92
≥25	9 (20)	9 (20)	
Current alcohol intake (grams/day)			
0	5 (11)	11 (24)	
0.88-3.07	12 (27)	15 (32)	0.29
3.08-7.92	15 (34)	10 (22)	
7.93-69.78	12 (27)	10 (22)	
Hours of sleep per weeknight			
4-7	35 (80)	31 (67)	0.19
≥8	9 (20)	15 (33)	
Current oral contraceptive use			
Yes	19 (44)	17 (37)	0.55
No	25 (56)	29 (63)	
Ever Smoker			
Yes	13 (30)	2 (4)	0.001
No	31 (70)	44 (96)	
Marijuana use (any)			
Yes	14 (32)	8 (17)	0.11
No	30 (68)	38 (83)	
History of reproductive tract infections in the past 6 months			
Yes	2 (5)	2 (4)	0.38
No	35 (79)	39 (85)	
Previous diagnosis of depression or bipolar disorder			
Yes	8 (18)	4 (9)	0.19
No	36 (82)	42 (91)	
Vitamin D intake from food sources only (IU/day)			
<100	16 (36)	8 (17)	0.04
≥100	28 (64)	38 (83)	
Calcium intake from food sources only (mg/day)			
0-599	15 (34)	6 (13)	
600-1200	20 (45)	27 (59)	0.06
>1200	9 (21)	13 (58)	
Percent body fat measured with DEXA scan			
14.5-26.1	10 (23)	14 (30)	
26.2-31.6	13 (30)	12 (26)	0.37
31.7-37.3	13 (30)	8 (18)	
37.4-50.1	7 (17)	12 (26)	

*Numbers may not add up to 44 cases and 46 controls due to missing data
**P-values from χ^2 test and Fisher's exact test (when cell sizes were <5)

Table 6: Distribution of Continuous Covariates According to PMS Status, among Cases and Controls (n=90)

	Cases (n=44) Mean (SD)	Controls (n=46) Mean (SD)	P-value (Student's t-test)
Age (year)	21.9 (3.4)	21.5 (3.5)	0.56
Age at first menses (year)	12.4 (1.4)	12.7 (1.2)	0.34
BMI (kg/m^2)	22.8 (2.9)	22.2 (3.2)	0.40
Current alcohol intake (grams/day)	6.8 (6.8)	5.1 (7.8)	0.27
Vitamin D intake from food sources only (IU/day)	188.4 (166.9)	209.6 (145.7)	0.52
Calcium intake from food sources only (mg/day)	880.2 (377.4)	954.8 (383.2)	0.36
Percent body fat	30.4 (7.3)	31.0 (8.4)	0.76

Table 7: Distribution of Covariates According to Physical Activity Status in all Participants (n=186)*

	Tertile 1 (n=62)	**Tertile 2 (n=63)**	**Tertile 3 (n=61)**	**P-value****
	Median=16.1 (MET-hrs/wk)	**Median=42.8 (MET-hrs/wk)**	**Median=100.3 (MET-hrs/wk)**	
	N (%)	**N** (%)	**N** (%)	
Age				
18	11 (18)	9 (14)	8 (13)	
19-20	28 (45)	27 (43)	28 (46)	0.54
21-22	9 (15)	13 (21)	17 (28)	
23-30	14 (22)	14 (22)	8 (13)	
Age at first menses				
≤12	36 (58)	35 (56)	26 (43)	0.18
>12	26 (42)	28 (44)	35 (57)	
BMI (kg/m^2)				
16.5-24.9	45 (74)	51 (81)	43 (70)	0.39
≥25	16 (26)	12 (19)	18 (30)	
Current alcohol intake (grams/day)				
0	10 (16)	16 (25)	13 (21)	
0.88-3.07	25 (40)	14 (22)	14 (23)	0.25
3.08-7.92	11 (18)	17 (27)	18 (30)	
7.93-69.78	16 (26)	16 (25)	16 (26)	
Hours of sleep per weeknight				
4-7	46 (74)	38 (60)	46 (77)	0.10
≥8	16 (26)	25 (40)	14 (23)	
Current oral contraceptive use				
Yes	24 (39)	32 (51)	17 (28)	0.03
No	38 (61)	31 (49)	44 (72)	
Ever Smoker				
Yes	8 (13)	11 (17)	5 (8)	0.31
No	54 (87)	52 (83)	56 (92)	
Marijuana use (any)				
Yes	16 (26)	16 (25)	14 (23)	0.92
No	46 (74)	47 (75)	47 (77)	
History of reproductive tract infections in the past 6 months				
Yes	4 (8)	4 (8)	2 (4)	0.77
No	49 (92)	49 (92)	48 (96)	
Previous diagnosis of depression or bipolar disorder				
Yes	10 (16)	8 (13)	5 (8)	0.41
No	52 (84)	55 (87)	56 (92)	
Vitamin D intake from food sources only (IU/day)				0.58
<100	17 (27)	14 (22)	12 (20)	
≥100	45 (73)	49 (78)	49 (80)	
Calcium intake from food sources only (mg/day)				0.01
0-599	9 (14)	14 (22)	7 (11)	
600-1200	40 (65)	34 (54)	26 (43)	
>1200	13 (21)	15 (24)	28 (46)	
Percent body fat measured with DEXA scan				
14.5-26.1	12 (21)	16 (26)	14 (24)	
26.2-31.6	11(19)	14 (23)	21 (36)	0.24
31.7-37.3	15 (26)	17 (28)	13 (22)	
37.4-50.1	20 (34)	14 (23)	10 (17)	

*Numbers may not add up to their respective tertile size due to missing data
**P-values from χ^2 test and Fisher's exact test (when cell sizes were <5)

Table 8: Odds Ratios and 95% Confidence Intervals for the Association of Physical Activity and PMS, among Cases and Controls (n=90)

			Unadjusted		Multivariable*	
	Cases (N)	**Controls (N)**	**OR**	**95% CI**	**OR**	**95% CI**
Physical activity (Median)						
Tertile 1 (16.1)	12	17	**1.00**	**Referent**	**1.00**	**Referent**
Tertile 2 (42.8)	18	16	1.59	0.59-4.33	1.62	0.58-4.51
Tertile 3 (100.3)	14	13	1.53	0.53-4.34	1.67	0.57-4.92

			Unadjusted		Multivariable*	
	Cases (N)	**Controls (N)**	**OR**	**95% CI**	**OR**	**95% CI**
Physical Activity (per 10 MET-hours/week)	44	46	1.03	0.94-1.13	1.03	0.94-1.14

*Adjusted for age and history of depression/bipolar disorder

Table 9: Multivariable* Odds Ratios and 95% Confidence Intervals for the Association of Physical Activity and PMS, with and without BMI and Percent Body Fat Included, among Cases and Controls (n=90)

	Multivariable: Not including BMI or % body fat		**Multivariable: with BMI**		**Multivariable: with % body fat**		**Multivariable: with BMI and % body fat**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Physical activity								
Tertile 1	**1.00**	**Referent**	**1.00**	**Referent**	**1.00**	**Referent**	**1.00**	**Referent**
Tertile 2	1.62	0.58-4.51	1.67	0.59-4.68	1.73	0.60-4.95	1.71	0.59-4.94
Tertile 3	1.67	0.57-4.92	1.62	0.55-4.82	1.82	0.60-5.47	1.56	0.50-4.87

	Multivariable: Not including BMI or % body fat		**Multivariable: with BMI**		**Multivariable: with % body fat**		**Multivariable: with BMI and % body fat**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Continuous physical activity (per 10 MET-hours/week)	1.03	0.94-1.14	1.03	0.94-1.14	1.04	0.94-1.14	1.02	0.93-1.13

*Adjusted for age and history of depression/bipolar disorder

Table 10: Multivariable* Odds Ratios and 95% Confidence Intervals for the Association of Physical Activity and PMS, by Category of BMI**, among Cases and Controls (n=90)

	Lower BMI <22.5 kg/m^2		**Higher BMI ≥22.5 kg/m^2**	
	OR	**95% CI**	**OR**	**95% CI**
Continuous physical activity (per 10 MET-hours/week)	1.06	0.90-1.26	1.01	0.89-1.15

*Adjusted for age and history of depression/bipolar disorder
**P-value for interaction = 0.68

Table 11: Multivariable* Odds Ratios and 95% Confidence Intervals of the Association Between Levels of Physical Activity** and Occurrence of Specific Menstrual Symptoms***, among All Participants (n=186)

Symptom	β	OR (95% CI)	P-value
Forgetfulness	0.10	1.10 (1.00-1.21)	0.04
Food cravings	0.05	1.05 (0.99-1.11)	0.09
Increased/decreased appetite	0.04	1.05 (0.99-1.11)	0.12
Irritability	0.05	1.05 (0.99-1.11)	0.08
Emotional hypersensitivity	0.05	1.05 (0.99-1.11)	0.07
Dizziness	0.04	1.04 (0.92-1.17)	0.56
Palpitations	0.04	1.04 (0.91-1.20)	0.55
Mood swings	0.03	1.03 (0.98-1.09)	0.28
Tendency to cry easily	0.03	1.03 (0.98-1.09)	0.28
Swelling in extremities	0.03	1.03 (0.91-1.18)	0.63
Breast tenderness	0.02	1.02 (0.97-1.08)	0.46
Abdominal bloating	0.02	1.02 (0.96-1.08)	0.52
Acne	0.01	1.02 (0.96-1.08)	0.63
Depression	0.02	1.02 (0.93-1.12)	0.65
Confusion	0.02	1.02 (0.89-1.17)	0.82
Back pain	0.007	1.01 (0.94-1.07)	0.84
Desire to be alone	0.006	1.01 (0.92-1.10)	0.90
Insomnia	0.009	1.01 (0.90-1.13)	0.87
Diarrhea/constipation	-0.003	1.00 (0.92-1.08)	0.95
Anxiety/nervousness	0.00006	1.00 (0.91-1.10)	0.99
Fatigue	-0.00998	0.99 (0.92-1.06)	0.78
Abdominal cramping	-0.03	0.97 (0.91-1.03)	0.31
Hot flashes	-0.07	0.93 (0.63-1.39)	0.73
Angry outbursts	-0.11	0.89 (0.78-1.03)	0.12
Nausea	-0.13	0.88 (0.69-1.11)	0.27
Headache	-0.14	0.87 (0.74-1.01)	0.07

*Adjusted for age and history of depression/bipolar disorder

**OR per 10 MET-hour/week increase in physical activity

***For each symptom, analysis compares moderate-severe vs. none-mild severity level

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