Adiposity and the Development of Premenstrual Syndrome

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Abstract

Background: Moderate to severe premenstrual syndrome (PMS) affects 8%–20% of premenopausal women and causes substantial levels of impairment, but few modifiable risk factors for PMS have been identified. Adiposity may impact risk through the complex interaction of hormonal and neurochemical factors, but it is not known if adiposity increases a woman's risk of developing PMS. We have addressed these issues in a prospective study nested within the Nurses' Health Study 2.

Methods: Participants were a subset of women aged 27–44 and free from PMS at baseline, including 1057 women who developed PMS over 10 years of follow-up and 1968 controls. Body mass index (BMI), weight change and weight cycling were assessed biennially via questionnaire.

Results: We observed a strong linear relationship between BMI at baseline and risk of incident PMS, with each 1 kg/m² increase in BMI associated with a significant 3% increase in PMS risk (95% confidence interval [CI] 1.01–1.05). After adjustment for age, smoking, physical activity, and other factors, women with BMI ≥ 27.5 kg/m² at baseline had significantly higher risks of PMS than women with BMI < 20 kg/m² ($p_{\text{trend}} = 0.003$). A large weight change between age 18 and the year 1991 was significantly associated with PMS risk, whereas weight cycling during this period was not. BMI was positively associated with specific symptoms, including swelling of extremities, backache, and abdominal cramping (all $p < 0.001$).

Conclusions: Our findings suggest that maintaining a healthy body mass may be important for preventing the development of PMS. Additional studies are needed to assess whether losing weight would benefit overweight and obese women who currently experience PMS.

Introduction

MODERATE TO SEVERE PREMENSTRUAL SYNDROME (PMS) affects 8%–20% of reproductive-aged women.^{1–3} PMS is characterized by physical, emotional, behavioral, and cognitive symptoms occurring in the luteal phase of the menstrual cycle that cause substantial levels of impairment and interfere with interpersonal relationships and life activities.^{1,4} Because the efficacy of common pharmaceutical treatments remains relatively low (i.e., $< 60\%$),⁵ identifying ways to prevent the initial development of PMS is important. However, few population-based studies have identified modifiable factors that may be etiologically related to PMS.

Adiposity may plausibly be related to PMS through a variety of hormonal, neural, and behavioral mechanism, and

several studies have found women with PMS or menstrual symptoms more likely to be overweight and obese than women without PMS.^{3,6–10} To our knowledge, however, this relationship has not been assessed in prospective studies, and it is not known if adiposity contributes to the initial development of PMS. Furthermore, it is unclear whether a large weight gain within a short period of time or the repeated gaining and losing of weight, termed “weight cycling,” is associated with PMS risk independent of overall level of adiposity.

We assessed how adiposity, fat distribution, and weight change were associated with the development of PMS in a prospective study nested within the Nurses' Health Study 2 (NHS2). In addition, we examined whether adiposity may affect the development of specific menstrual symptoms.

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Materials and Methods

The NHS2 is a prospective epidemiological study of 116,678 registered nurses aged 25–42 from 11 U.S. states who responded to a mailed questionnaire in 1989. Participants provided information on their medical history and health-related behaviors, such as smoking and oral contraceptive (OC) use. Participants have completed questionnaires every 2 years to update information on health factors and identify new disease diagnoses. The response rate for each questionnaire cycle has been $\geq 89\%$. The study protocol was approved by the Institutional Review Board at Brigham and Women's Hospital.

The NHS2 Premenstrual Syndrome Substudy

Our procedure for identifying PMS cases and controls has been described previously.^{11,12} Briefly, in 1989, participants were asked if they had ever received a physician diagnosis of PMS. On subsequent questionnaires in 1993, 1995, 1997, and 2001, participants were asked if they had received a new diagnosis of PMS during the previous 2–4-year period and to indicate the timing of the diagnosis.

In January 2002, we conducted a substudy among NHS2 participants to identify PMS cases and controls. First, we identified all cohort members who had not reported a diagnosis by 1991 and who, therefore, could possibly report a new diagnosis of PMS during our follow-up period (i.e., 1991–2001). To make sure that cases and controls provided information about eligibility, adiposity, and other factors during similar time periods, we assigned each woman a reference year. For women who reported a new diagnosis of PMS during the follow-up period, their reference year was equal to their year of diagnosis. Because control women did not develop PMS and thus did not have a year of diagnosis, we assigned each control a randomly chosen reference year between 1993 and 2001.

We used each woman's reference year to determine her eligibility for the substudy, to evaluate menstrual symptom experience, and to assess aspects of adiposity. To reduce the likelihood of including women with menstrual-type symptoms attributed to causes other than PMS, we excluded women who had reported a diagnosis of cancer, endometriosis, usually irregular menstrual cycles, infertility, hysterectomy, or menopause before their reference year. From among all remaining eligible women, we selected 6000 to participate in the PMS substudy, including 3430 women who reported a new diagnosis of PMS between 1993 and 2001 and 2570 who did not report PMS during this period. For case selection, we gave preference to women with the most recent reference years; noncases were then frequency-matched to cases by reference year.

We mailed all 6000 participants a two-page questionnaire based on the Calendar of Premenstrual Experiences designed by Mortola et al.¹³ Women were asked to report whether in the specific 2-year period before their reference year, they had experienced any of 26 different symptoms "most months of the year for at least several days each month before [their] menstrual period begins." We also asked about the age when symptoms first occurred, the timing of symptom onset and cessation during an average menstrual cycle, symptom severity, and the interference of symptoms with life activities and interpersonal relationships. Completed questionnaires were received from 2966 (86.5%) women self-reporting and 2504 (97.4%) women not reporting PMS.

We used information provided on the supplemental questionnaire to identify from among those self-reporting PMS the women who met our case definition, based on criteria established by Mortola et al.¹³ We defined cases as women who reported a new diagnosis of PMS during the follow-up period (1991–2001) and who also reported (1) the occurrence of at least one physical and one affective menstrual symptom, (2) overall menstrual symptom severity classified as moderate or severe or effect of symptoms on life activities and social relationships classified as moderate or severe, (3) symptoms beginning within 14 days of the onset of menses, (4) symptoms ending within 4 days after the onset of menses, and (5) symptoms absent in the week after menses ends. Overall, 1057 (35.6%) of the 2966 women self-reporting PMS met these criteria and were included as validated PMS cases in our analysis.

We then identified a comparison group from among participants who both did not report a diagnosis of PMS before or during the follow-up period (through 2001) and experienced either no menstrual symptoms or only mild symptoms that had no substantial effect on life activities and relationships. A total of 1968 of the 2504 noncases (78.6%) met these criteria and were included in subsequent analyses as validated controls. Women who did not meet criteria for either cases or controls were excluded from analysis.

The validity of our approach to identifying PMS cases and controls was assessed previously.¹⁴ Briefly, participants included 135 members of the NHS2 PMS substudy who first reported PMS by questionnaire in 2001 and 371 who never reported PMS (1989–2001). We found that the menstrual symptom occurrence, timing, and severity in women meeting criteria based on those established by Mortola et al.¹³ as assessed by our retrospective questionnaire were essentially identical to those in women who also reported clinician-supervised prospective symptom charting as part of their diagnosis. Validated cases experienced more affective and physical symptoms than unvalidated cases, and the symptoms were of greater overall severity and personal impact.

Assessment of adiposity, fat distribution, physical activity, and other factors

Current weight (lbs) was self-reported by participants on each biennial questionnaire. Weight at age 18 and height (inches) was measured in 1989. We calculated body mass index (BMI) as weight (kg)/height (m²). In 1993, we asked each participant to record the circumference of her waist at the navel and her hips at the widest part (including buttocks) to the nearest ¼ inch with a tape measure. We divided waist circumference by hip circumference to calculate waist/hip ratio. We assessed the effect of weight change on risk of PMS at various time periods. For example, we subtracted weight at age 18 from weight at the start of follow-up (1991). We then calculated weight change in the 2-year and 4-year periods before the reference year.

In 1993, we asked women to report how many times they had intentionally lost 5–9, 10–19, 20–49, and ≥ 50 lbs between the ages of 18 and 30 and in the previous 4 years, independent of illness and pregnancy. We defined mild to severe weight cycling as losing ≥ 10 pounds ≥ 3 times between the specified time periods, as described by Field et al.¹⁴

We collected information on other factors potentially associated with PMS and adiposity throughout the study period

in order to control for confounding. Information on age, number of pregnancies lasting longer than 6 months, age at first birth, tubal ligation, and OC use was updated biennially. Age at menarche and menstrual cycle characteristics were assessed in 1989. Total energy and macronutrient and micronutrient intake were measured by food frequency questionnaires (FFQ) in 1991, 1995, and 1999; nutrients were adjusted for total energy intake by the residual method.¹⁵ Our menstrual symptom questionnaire asked about diagnoses of depression, antidepressant use, and the timing of each. Childhood and adolescent trauma related to punitive parenting was assessed by supplemental questionnaire and used to create a childhood trauma score.¹⁶

Participation in physical activity was measured on questionnaires in 1991 and 1997. Women were asked how much time they spent each week participating in specific recreational activities, including walking or hiking outdoors, jogging, running, bicycling, calisthenics/aerobics, racket sports, lap swimming, and other aerobic activities, such as lawn-mowing. We used this information to calculate metabolic equivalent task (MET)-hours per week.¹⁷ These questions have been validated for use in this population and are described in detail elsewhere.¹⁸

Statistical analysis

All statistical analyses were conducted with SAS (SAS Institute, Inc., Cary, NC). We compared age-standardized baseline characteristics of PMS cases and controls with generalized linear models (PROC GLM) adjusting for age. We used odds ratios (OR) to estimate the relative risk (RR) of PMS for women across categories of adiposity and fat distribution and calculated 95% confidence intervals (CI). In multivariable analyses, we included factors in logistic regression models that were confounders of the adiposity-PMS relationship, as well as factors associated with adiposity or PMS or both in previous studies. These included age, diagnosis year, pack-years of

cigarette smoking, number of full-term pregnancies, tubal ligation, duration of OC use, antidepressant use, history of childhood trauma, and dietary intake of vitamin D and vitamin B₆ (see footnote to Table 2 for variable categories). All analyses were also adjusted for MET-hours of physical activity, although activity level did not vary significantly between cases and controls. Several additional variables were not included in the final analysis because they were unrelated to the development of PMS or BMI, including age at first birth, physical activity, BMI at age 18, and dietary intake of magnesium, manganese, potassium, vitamin E, linolenic acid, total carotenoids, and caffeine. The Mantel-extension test for trend was used to evaluate linear trend across categories by modeling the median value of each category as a continuous variable in the multivariable regression models. Analyses of waist circumference, waist/hip ratio, and weight cycling were limited to cases and controls with reference years after 1993, the year when these exposure variables were assessed. In addition, our analysis of BMI at age 18 excludes women with BMI <17 kg/m² to minimize the likelihood of including women with anorexia and associated physical and mental health conditions.

Finally, we assessed the relationship between BMI in 1991 evaluated continuously and risk of specific symptoms of PMS. For each symptom, we assessed whether BMI was associated with symptom risk, comparing cases reporting the symptom with controls not reporting the symptom; cases not experiencing a specific symptom and controls reporting the symptom were excluded from that analysis. Because of the large number of comparisons in this analysis, we considered *p* values <0.01 instead of *p* <0.05 to be statistically significant.

Results

Baseline characteristics of cases and controls are presented in Table 1. Cases were significantly younger than controls and were more likely to be smokers and ever users of OC. Cases

TABLE 1. AGE-STANDARDIZED CHARACTERISTICS OF PREMENSTRUAL SYNDROME CASES AND CONTROLS AT BASELINE, NURSES' HEALTH STUDY 2 PMS SUBSTUDY, 1991–2001

Characteristic ^a	PMS cases (n = 1057)	Controls (n = 1968)	
	Mean (SE)	Mean (SE)	p value
Age	34.4 (4.3)	35.0 (3.9)	0.0002
Age at menarche	12.4 (0.04)	12.5 (0.03)	0.08
Number of full-term pregnancies	1.7 (0.04)	1.7 (0.03)	0.52
Total calorie intake (kcal/day)	1820 (16.0)	1803 (11.7)	0.38
Vitamin D intake (IU/day) ^b	390 (7.6)	401 (5.6)	0.22
Vitamin B ₆ intake (mg/day) ^b	9.1 (0.6)	5.9 (0.5)	<0.0001
Alcohol intake (g/day)	3.0 (0.19)	3.1 (0.14)	0.72
Pack-years of cigarette smoking	7.8 (1.7)	4.9 (1.2)	0.16
MET-hours/week of physical activity	22.9 (1.8)	23.3 (1.3)	0.88
	%	%	p value
Current smoking	12.3	6.5	<0.0001
Ever use of oral contraceptive	85.7	77.7	<0.0001
Current oral contraceptive use	10.7	9.9	0.51
Previous use of antidepressant medications	12.1	4.7	<0.0001
History of significant childhood trauma	18.4	8.5	<0.0001

^aAll characteristics except age standardized to the age distribution of cases and controls in 1991. Standard deviation (SD) presented for age instead of standard error (SE).

^bEnergy-adjusted using the residual method.¹⁵

and controls did not differ by other factors assessed, including MET-hours/week of physical activity and total calorie intake.

We observed a strong linear relationship between BMI at baseline and risk of incident PMS ($p_{\text{trend}} = 0.003$) (Table 2). Risk of PMS was significantly higher in women with BMI ≥ 27.5 compared with women with BMI < 20.0 kg/m². For example, the RR in women with BMI ≥ 35.0 kg/m² was 1.66 (95% CI 1.06-2.59). In analyses of continuous BMI level, each 1 kg/m² increase was associated with a significant 3% increase in PMS risk (RR 1.03, 95% CI 1.01-1.05). Results evaluating BMI measured 2 years before reference year were nearly identical (results not shown). BMI at age 18 was not associated with risk of PMS during the follow-up period.

Waist circumference was not linearly associated with risk of incident PMS ($p_{\text{trend}} = 0.15$) (Table 2). After additional adjustment for BMI evaluated as a continuous variable, women with waist circumference of ≥ 36 inches in 1993 had an RR of

1.16 (95% CI 0.76-1.79, $p_{\text{trend}} = 0.43$) compared with those with waist circumference of < 28 inches. We also did not observe a relationship between waist/hip ratio and risk of PMS; after additional adjustment for BMI, the RR comparing the highest vs. lowest quintile of waist/hip ratio was 0.85 (95% CI 0.53-1.36, $p_{\text{trend}} = 0.32$).

Compared with women who maintained a stable weight between age 18 and 1991, those reporting a gain of > 45 pounds (≥ 20 kg) had a significant 77% higher risk of developing PMS during the follow-up period (95% CI 1.26-2.49) (Table 3). Additional adjustment for BMI at reference year attenuated risk, but results remained significant (RR 1.59, 95% CI 1.04-2.42). Weight gain in neither the 2-year nor 4-year period before reference year was consistently associated with risk.

Women who met criteria for weight cycling between ages 18 and 30 had a 36% higher risk (95% CI 1.07-1.71) compared with women not reporting weight cycling; results were

TABLE 2. AGE AND MULTIVARIABLE RELATIVE RISKS OF PREMENSTRUAL SYNDROME BY DIFFERENT MEASURES OF ADIPOSITY, NURSES' HEALTH STUDY 2 PMS SUBSTUDY, 1991-2001

Aspect of adiposity	Cases ^a	Controls ^a	Age-adjusted RR	Multivariable ^b adjusted RR (95% CI)
Body mass index in 1991 (kg/m ²)				
<20.0	118	288	1.0	1.0 (referent)
20.0-22.4	316	654	1.22	1.14 (0.86-1.51)
22.5-24.9	241	457	1.33	1.28 (0.96-1.71)
25.0-27.4	132	214	1.58	1.28 (0.91-1.79)
27.5-29.9	87	122	1.82	1.48 (1.01-2.18)
30.0-34.9	78	109	1.85	1.58 (1.06-2.37)
≥ 35.0	59	81	1.95	1.66 (1.06-2.59)
				$p_{\text{trend}} = 0.003$
Body mass index at age 18 (kg/m ²)				
<20.0 ^c	334	695	1.0	1.0 (referent)
20.0-22.4	401	735	1.14	1.10 (0.90-1.34)
22.5-24.9	177	293	1.25	1.27 (0.99-1.64)
25.0-27.4	53	82	1.37	1.36 (0.90-2.05)
≥ 27.5	56	93	1.28	1.19 (0.80-1.78)
				$p_{\text{trend}} = 0.23$
Waist circumference in 1993 (inches) ^d				
<28	153	338	1.0	1.0 (referent)
28.0-30.0	113	223	1.13	1.10 (0.79-1.52)
30.0-32.0	81	201	0.90	0.83 (0.58-1.18)
32.0-36.0	95	192	1.11	1.02 (0.73-1.43)
≥ 36.0	85	129	1.47	1.40 (0.97-2.02)
				$p_{\text{trend}} = 0.15$
Waist/hip ratio in 1993 ^d				
<0.725	123	228	1.0	1.0 (referent)
0.725-0.775	126	287	0.82	0.76 (0.54-1.06)
0.775-0.825	136	278	0.89	0.86 (0.62-1.19)
0.825-0.875	66	136	0.90	0.92 (0.62-1.37)
≥ 0.875	52	83	1.13	0.95 (0.61-1.51)
				$p_{\text{trend}} = 0.96$

^aCase and controls numbers may not sum to 1057 cases and 1968 controls because of missing data.

^bMultivariable relative risks (RR) are adjusted for the following factors assessed at reference year: age (< 30 , 30-34, 35-39, ≥ 40 years), diagnosis year (1993, 1994-1995, 1996-1997, 1998-1999, 2000-2001), parity (0, 1-2, 3-4 or ≥ 5 pregnancies lasting ≥ 6 months), oral contraceptive use and duration (never, 1-23, 24-71, 72-119, ≥ 120 months), pack-years of cigarette smoking (6 categories), history of tubal ligation (no, yes), antidepressant use (never, ever), history of childhood trauma (four categories), physical activity (< 3 , 3-9, 9-18, 18-27, 27-42, ≥ 42 METs/week), and dietary intake of vitamin B₆ and vitamin D (each in quintiles).

^cExcludes women with BMI < 17 kg/m² at age 18.

^dAnalysis limited to cases and controls who provided information on waist and hip circumference, and those with reference years after 1993.

CI, confidence interval; RR, relative risk.

TABLE 3. AGE AND MULTIVARIABLE RELATIVE RISKS OF PREMENSTRUAL SYNDROME BY WEIGHT CHANGE AND WEIGHT CYCLING, NURSES' HEALTH STUDY 2 PMS SUBSTUDY, 1991–2001

Weight change parameter	Cases	Controls	Age-adjusted RR	Multivariable ^a adjusted RR (95% CI)
Weight change from age 18 to 1991				
Loss of ≥ 5 lbs	115	223	1.21	1.10 (0.79-1.55)
Loss or gain of < 5 lbs	129	297	1.0	1.0 (referent)
Gain of 5–14 lbs	253	503	1.17	1.22 (0.92-1.62)
Gain of 15–24 lbs	200	414	1.15	1.07 (0.80-1.44)
Gain of 25–44 lbs	185	301	1.48	1.33 (0.98-1.80)
Gain of ≥ 45 lbs	147	173	2.12	1.77 (1.26-2.49)
Weight change in 4 years before reference year				
Loss of ≥ 5 lbs	140	224	1.22	1.07 (0.82-1.41)
Loss or gain of < 5 lbs	353	705	1.0	1.0 (referent)
Gain of 5–14 lbs	305	642	0.94	0.82 (0.67-1.01)
Gain of 15–24 lbs	135	198	1.35	1.13 (0.85-1.49)
Gain of ≥ 25 lbs	80	127	1.27	0.97 (0.69-1.36)
Weight change in 2 years before reference year				
Loss of ≥ 5 lbs	173	252	1.41	1.20 (0.94-1.55)
Loss or gain of < 5 lbs	412	871	1.0	1.0 (referent)
Gain of 5–14 lbs	277	587	1.00	0.95 (0.77-1.16)
Gain of 15–24 lbs	93	117	1.66	1.44 (1.03-2.00)
Gain of ≥ 25 lbs	51	59	1.80	1.44 (0.94-2.22)
Weight cycling between ages 18 and 30 ^{b,c}				
No	734	1408	1.0	1.0 (referent)
Yes	191	222	1.66	1.36 (1.07-1.71)
Weight cycling between 1989 and 1993 ^b				
No	895	1607	1.00	1.0 (referent)
Yes	73	72	1.88	1.42 (0.98-2.05)

^aMultivariable relative risks (RR) are adjusted for the following factors assessed at reference year: age, diagnosis year, parity, oral contraceptive use and duration, pack-years of cigarette smoking, history of tubal ligation, antidepressant use, history of childhood trauma, physical activity, and dietary intake of vitamin B₆ and vitamin D. See footnote^b to Table 2 for variable definitions. Numbers of cases and controls may not sum to totals because of missing data.

^bWeight cycling was defined as having lost and regained ≥ 10 lbs at least three times during stated time period.¹⁴ Analysis limited to cases and controls with reference years after 1993.

^cAnalysis also limited to cases and controls age ≥ 30 by 1993.

attenuated after further adjustment for BMI and weight change between ages 18 and 30 (RR 1.22, 95% CI 0.94-1.57). Results for weight cycling between 1989 and 1993 were similar, with cyclers having a 42% higher risk of PMS than non-cyclers. After further adjustment for BMI and weight change between 1989 and 1993, the RR for weight cycling was 1.24 (95% CI 0.84-1.83).

BMI evaluated continuously was significantly and positively associated with risk of a variety of physical symptoms (Table 4). BMI was most strongly associated with swelling of the extremities, with each 1 kg/m² increase in BMI associated with a significant 11% increase in risk. In addition, each 1 kg/m² increase was associated with significant 5%–6% higher risks of backache, abdominal cramping, diarrhea or constipation, and food cravings. Risk of several emotional symptoms was also positively associated with BMI; each 1 kg/m² increase was associated with significant 3%–4% higher risks of crying easily, mood swings, and irritability.

Discussion

In our population of older premenopausal women, we observed a strong positive relationship between BMI and the development of PMS. Women who were obese at baseline had significantly higher risks of developing PMS over 10 years of

follow-up compared with lean women. BMI was also positively associated with risk of specific physical and emotional symptoms, including swelling of the extremities, backache, abdominal cramping, diarrhea/constipation, mood swings, and food cravings.

A limited number of previous studies have evaluated the relationship between adiposity and premenstrual symptoms and PMS, and to our knowledge, none of these studies have been prospective.^{3,6–10} Masho et al.⁷ found PMS prevalence to be 2.8-fold higher in obese women than underweight women (POR = 2.8, 95%CI 1.1-2.7) in a population-based study. In the Study of Women's Health Across the Nation (SWAN),⁸ the prevalence of food cravings and bloating was significantly higher in overweight and obese women than in normal weight women and lower in underweight women. However, BMI was unrelated to other symptom groups, including anxiety and mood changes, cramps and back pain, breast pain, and headaches.

PMS is likely caused by a complex interaction of hormonal and neurochemical factors,⁵ and adiposity may increase risk through several mechanisms. Some studies have reported inverse associations between BMI and follicular phase estradiol levels in older premenopausal women,^{19–21} although others have not observed a relationship with follicular or luteal phase levels.^{22–24} In a recent study in our cohort, adult

TABLE 4. RISK OF SPECIFIC MENSTRUAL SYMPTOMS FOR EACH 1 kg/m² INCREASE IN BODY MASS INDEX AT BASELINE, NURSES' HEALTH STUDY 2 PMS SUBSTUDY, 1991–2001

Menstrual symptom	Cases ^a	Controls ^b	Multivariable RR (95% CI) ^c	p
Swelling of extremities	228	1762	1.11 (1.08-1.14)	<0.0001
Backache	405	1568	1.06 (1.03-1.08)	<0.0001
Abdominal cramping	339	1605	1.05 (1.03-1.08)	<0.0001
Diarrhea/constipation	395	1572	1.05 (1.03-1.08)	<0.0001
Food cravings	743	1213	1.05 (1.03-1.07)	<0.0001
Palpitations	81	1891	1.05 (1.00-1.09)	0.06
Tendency to cry easily	550	1561	1.04 (1.02-1.07)	0.001
Acne	363	1514	1.04 (1.02-1.07)	0.002
Mood swings	704	1603	1.04 (1.02-1.06)	<0.0001
Appetite changes	602	1379	1.04 (1.02-1.06)	0.0007
Dizziness	41	1904	1.03 (0.97-1.10)	0.30
Desire for aloneness	380	1805	1.03 (1.01-1.06)	0.02
Fatigue	557	1558	1.03 (1.01-1.05)	0.01
Irritability	884	1169	1.03 (1.01-1.05)	0.007
Breast tenderness	761	821	1.03 (1.01-1.05)	0.02
Anger	618	1700	1.03 (1.00-1.05)	0.02
Headache	483	1567	1.02 (1.00-1.05)	0.06
Depression	446	1797	1.02 (1.00-1.05)	0.07
Hypersensitivity	371	1736	1.02 (1.00-1.05)	0.09
Insomnia	210	1802	1.02 (0.98-1.05)	0.35
Abdominal bloating	660	1186	1.02 (0.99-1.04)	0.18
Forgetfulness	205	1865	1.01 (0.98-1.05)	0.52
Hot flashes	82	1875	1.01 (0.96-1.06)	0.75
Nausea	58	1900	1.00 (0.95-1.06)	0.99
Anxiety	336	1836	1.00 (0.97-1.02)	0.74
Confusion	103	1906	0.97 (0.92-1.02)	0.26

^aNumber of PMS cases reporting specific symptom.

^bNumber of controls not reporting specific symptom.

^cBeta coefficients are adjusted for the following factors assessed at reference year: age, diagnosis year, parity, oral contraceptive use and duration, pack-years of cigarette smoking, history of tubal ligation, antidepressant use, history of childhood trauma, physical activity, and dietary intake of vitamin B₆ and vitamin D. See footnote^b to Table 2 for variable definitions.

BMI was inversely associated with follicular and luteal phase total estradiol and luteal phase progesterone but unrelated to free estradiol levels²¹; compared with women with BMI <20, women with BMI ≥30 kg/m² had 39% lower follicular estradiol, 20% lower luteal estradiol, and 20% lower progesterone levels. Cyclic estrogen and progesterone fluctuations clearly contribute to the onset of PMS, as treatments suppressing ovulation are effective at preventing PMS symptoms.⁵ Whereas some evidence suggests that early luteal phase progesterone and perhaps estradiol levels may be higher in women with PMS compared with controls, women with PMS may also be more sensitive to cyclic hormone fluctuations, leading to more severe symptom experience.

Alternatively, obesity may alter neurotransmitter function through its effect on estrogen and progesterone. In some studies, PMS and premenstrual dysphoric disorder (PMDD) cases have demonstrated abnormalities of the serotonin, gamma-aminobutyric acid (GABA), and other systems compared with symptom-free controls.⁵ Estrogen enhances serotonin action by increasing synthesis, transport, reuptake and receptor expression, and postsynaptic responsiveness. Thus, it is plausible that lower estradiol levels associated with adiposity may lead to impaired serotonin function and contribute to the occurrence of PMS. This hypothesis is supported by clinical studies finding selective serotonin reuptake inhibitors (SSRIs) to be effective at treating premenstrual mood symptoms, food cravings, appetite changes, and abdominal bloating.²⁵ In our

study, BMI was positively associated with many of these symptoms. Furthermore, the major progesterone metabolite, allopregnanolone, binds to GABA-A receptors and increases receptor sensitivity.⁵ Epperson et al.²⁶ found follicular phase cortical GABA levels to be significantly lower in PMDD cases than in controls and to change in the opposite direction during the luteal phase. Thus, lower progesterone levels associated with obesity may impair GABA function and further contribute to the development of mood symptoms in PMS.

Increased adiposity may contribute to water-retention symptoms in PMS through dysregulation of the renin-angiotensin-aldosterone system (RAAS), leading to increased sodium and fluid retention.²⁷ Estrogen stimulates the RAAS and increases fluid retention, whereas late luteal phase progesterone appears to counteract these effects.^{5,28} Finally, adiposity may be related to PMS by affecting vitamin D status. Obese individuals are at greater risk for vitamin D deficiency, as the main circulating vitamin D metabolite, 25-hydroxyvitamin D, is sequestered in adipose tissue. Vitamin D also plays a role in RAAS regulation.²⁹ A previous study in our population found dietary intake of vitamin D to be inversely related to PMS incidence, although we were unable to assess the contribution of endogenously produced vitamin D.¹¹ Additional studies evaluating the potential interplay of adiposity, sex steroid hormones, and neurotransmitters in PMS development are needed.

Our study has several limitations. As our participants were aged 27–44 at baseline, we were not able to prospectively

evaluate the effect of adiposity and PMS at younger ages. Our results suggested that BMI at age 18 was not associated with PMS developing later in life (i.e., after age 27). Although adiposity at young ages may in fact not be associated with risk of PMS, it is also possible that women who were overweight or obese at age 18 developed PMS during adolescence or young adulthood. These women would have been ineligible for our study, as we excluded women who had already been diagnosed with PMS by the beginning of follow-up in 1991. Prospective studies of adolescent and young adult women are needed to further assess this relationship.

After adjusting for BMI, we did not find measures of central adiposity (e.g., waist circumference, waist/hip ratio) or weight cycling to be independently related to the development of PMS. These aspects of adiposity may indeed be unrelated to PMS, but we were only able to assess them in a subset of our study population; thus, our power for these analyses was relatively low. In addition, because we assessed only the presence of specific menstrual symptoms and not the severity of each, we could not identify which symptoms were most problematic to participants. Future large studies assessing multiple aspects of adiposity and severity of specific menstrual symptoms will be important to improving understanding of PMS etiology. Finally, as our study population was predominantly white, our findings may not be generalizable to women of other racial and ethnic groups, although it is unlikely that the physiological relationship between adiposity and PMS differs substantially between populations.

Strengths of our study include our prospective assessments of adiposity and aspects of weight change during the follow-up period. In addition, we collected information on a wide variety of additional factors potentially related to PMS occurrence and adiposity, including physical activity, smoking, and diet, and have taken these into consideration in our analysis. Finally, we used established criteria to define PMS cases¹³ and controls in order to identify women at the two extreme ends of the spectrum of menstrual symptom experience, which limited the likelihood of misclassification and maximized our ability to identify risk factors for moderate to severe PMS.

Conclusions

Our findings suggest that maintaining a healthy body weight may be important for preventing the development of PMS. Additional studies are needed to assess whether losing weight would benefit overweight and obese women who currently experience PMS and to further evaluate potential underlying mechanisms of these relationships.

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Disclosure Statement

No competing financial interests exist.

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