

# Calcium and Vitamin D Intake and Risk of Incident Premenstrual Syndrome

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**Background:** Premenstrual syndrome (PMS) is one of the most common disorders of premenopausal women. Studies suggest that blood calcium and vitamin D levels are lower in women with PMS and that calcium supplementation may reduce symptom severity, but it is unknown whether these nutrients may prevent the initial development of PMS.

**Methods:** We conducted a case-control study nested within the prospective Nurses' Health Study II cohort. Participants were a subset of women aged 27 to 44 years and free from PMS at baseline in 1991, including 1057 women who developed PMS over 10 years of follow-up and 1968 women reporting no diagnosis of PMS and no or minimal menstrual symptoms. Intake of calcium and vitamin D was measured in 1991, 1995, and 1999 by a food frequency questionnaire.

**Results:** After adjustment for age, parity, smoking status, and other risk factors, women in the highest quin-

tile of total vitamin D intake (median, 706 IU/d) had a relative risk of 0.59 (95% confidence interval, 0.40-0.86) compared with those in the lowest quintile (median, 112 IU/d) ( $P=.01$  for trend). The intake of calcium from food sources was also inversely related to PMS; compared with women with a low intake (median, 529 mg/d), participants with the highest intake (median, 1283 mg/d) had a relative risk of 0.70 (95% confidence interval, 0.50-0.97) ( $P=.02$  for trend). The intake of skim or low-fat milk was also associated with a lower risk ( $P<.001$ ).

**Conclusions:** A high intake of calcium and vitamin D may reduce the risk of PMS. Large-scale clinical trials addressing this issue are warranted. Given that calcium and vitamin D may also reduce the risk of osteoporosis and some cancers, clinicians may consider recommending these nutrients even for younger women.

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IT IS ESTIMATED THAT AS MANY AS 85% to 90% of premenopausal women regularly experience affective and/or physical symptoms before the onset of menses.<sup>1</sup> While symptoms are mild in most women, 8% to 20% experience symptoms that meet the clinical definition of premenstrual syndrome (PMS),<sup>1-3</sup> a disorder characterized by moderate to severe symptoms that substantially interfere with normal life activities and interpersonal relationships.<sup>4,5</sup> Symptoms are limited to the luteal phase of the menstrual cycle, abate shortly after the onset of menses, and commonly include depression, irritability, fatigue, abdominal cramping, breast tenderness, and headaches.<sup>1</sup> Women in whom affective symptoms predominate may also meet the criteria for premenstrual dysphoric disorder,<sup>6</sup> a more severe form of PMS that is associated with significant impairment of normal functioning<sup>6,7</sup>; recent studies<sup>1,8</sup> estimate that 5% to 8% of premenopausal women meet the criteria for premenstrual dysphoric disorder. Women

presenting with symptoms are commonly prescribed oral contraceptives (OCs), gonadotropin-releasing hormone agonists, and serotonin reuptake inhibitors.<sup>9</sup> While these therapies may be effective at treating PMS in many women, they are also associated with substantial adverse effects and can be expensive.<sup>9-11</sup> Alternatives to hormone therapy, such as dietary supplementation, are being evaluated.

Several randomized trials<sup>12-14</sup> have shown that calcium supplementation significantly reduces premenstrual symptom occurrence and severity. Thys-Jacobs and colleagues<sup>12</sup> observed a 48% reduction in a total luteal symptom score ( $P<.001$ ) in 248 women supplemented with 1200 mg/d of elemental calcium as calcium carbonate for 3 months compared with 249 women given a placebo. Other trials have also observed significant reductions in premenstrual symptom occurrence with calcium supplementation of 1000 mg/d<sup>13</sup> and 1336 mg/d.<sup>14</sup> While data support the efficacy of calcium in the treatment of PMS, it is not

known whether high calcium intake in asymptomatic women can prevent PMS from developing. Furthermore, few studies have explored whether vitamin D, a steroid hormone that regulates calcium absorption and metabolism, may also be associated with the disorder. To evaluate these relationships, we conducted a case-control study nested within the prospective Nurses' Health Study II (NHS2) cohort.

## METHODS

The NHS2 is a cohort of 116 678 US female registered nurses who responded to a mailed questionnaire in 1989. The participants were 25 to 42 years old at the initial mailing and provided information on their medical history and health-related behaviors, such as use of OCs, menstrual and pregnancy history, and smoking status. Cohort members have completed questionnaires every 2 years thereafter to update information on various risk factors and to identify new diagnoses of disease. As of 2001, the rate of follow-up for each questionnaire cycle has been at least 89%.

### IDENTIFICATION OF PMS CASES AND CONTROLS

Information on PMS was first collected on the baseline NHS2 questionnaire in 1989, when participants were asked if they had ever received a physician diagnosis of the disorder. 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- to 4-year period and, if so, to indicate the period during which the diagnosis had been made.

In January 2002, we conducted a substudy among NHS2 participants to identify women reporting the disorder whose menstrual symptom experience met established criteria for PMS and women who had not been diagnosed as having PMS and experienced few, if any, menstrual symptoms. To accomplish this, we identified all members of the cohort who had not reported a diagnosis in 1989 or 1991 and were, thus, considered to be at risk for incident PMS at the start of follow-up. Because we were interested in evaluating dietary factors, we excluded from this group participants who reported an implausibly low or high calorie intake ( $<500$  or  $\geq 3500$  cal/d) on the food frequency questionnaire completed in 1991 or 1995.

To make the timing of comparisons between cases and noncases as similar as possible, we assigned each woman a reference year. For women who first reported PMS on an NHS2 study questionnaire between 1993 and 2001 (ie, self-reported cases), the reference year was the year of diagnosis. Because women who did not develop PMS during the study period (ie, noncases) did not have a year of diagnosis, we assigned each a randomly chosen reference year between 1993 and 2001, corresponding to the possible years of case diagnosis. We then used these reference years to guide our assessment of eligibility for the PMS substudy, measure menstrual symptom experience, and assess vitamin D and calcium intake at similar time points for cases and noncases.

To reduce the likelihood of including women with menstrual symptoms attributed to causes other than PMS, we excluded women who had reported a diagnosis of cancer, endometriosis, usually irregular menstrual cycles, or infertility before their reference year. Furthermore, to ensure that cases and noncases were premenopausal and at risk of developing PMS, we restricted inclusion to women who had not reported menopause or a hysterectomy before their reference year. From among all remaining eligible women, we selected 6000 women to partici-

pate in the PMS substudy, including 3430 women who reported a diagnosis of PMS and 2570 who did not. For case selection, we gave preference to women with recent reference years; noncases were then frequency matched to cases by reference year.

We mailed participants a 2-page questionnaire based on the Calendar of Premenstrual Experiences designed by Mortola et al.<sup>15</sup> Women were asked to report whether they had experienced any of 26 different symptoms most months of the year for at least several days each month during the 2-year period before their specified reference year, and about 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%) of the women self-reporting and 2504 (97.4%) of the women not reporting PMS.

We used information provided on the supplemental questionnaire to identify from among those self-reporting PMS the women who met the definition of the disorder established by Mortola et al.<sup>15</sup> We defined cases as women with the following: (1) the occurrence of at least 1 physical and 1 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 of the onset of menses, and (5) symptoms absent in the week after menses. Overall, 1057 (35.6%) of the 2966 women met these criteria and were included as validated PMS cases in the subsequent analysis.

We then identified from among participants who had not reported a PMS diagnosis those women who experienced either no menstrual symptoms or only mild symptoms that had no substantial effect on life activities and relationships. A total of 1968 (78.6%) of the 2504 noncases met these criteria and were included in subsequent analyses as validated controls.

### ASSESSMENT OF CALCIUM AND VITAMIN D INTAKE AND OTHER FACTORS

Each participant's intake of calcium and vitamin D from foods and supplements was evaluated at several points during the 10-year study period. In 1991, 1995, and 1999, participants completed a 131-item semiquantitative food frequency questionnaire (SFFQ). Women were asked to record how often they consumed a single serving of each food listed during the previous year, with possible response options ranging from less than once per month to 6 or more times per day. Calcium and vitamin D-rich food items listed on the SFFQ included skim, low-fat, and whole milk, yogurt, hard cheese, cottage cheese, and spinach. To calculate each woman's intake of calcium from foods, we multiplied the portion size of a single serving of each food by its reported frequency of intake. We then multiplied the total amount consumed by the calcium content of the food, and summed the calcium contributions from all foods. This process was then repeated to calculate vitamin D intake from foods.

We measured use of calcium supplements, vitamin D supplements, and multivitamins by the SFFQ in 1991, 1995, and 1999, and with standard biennial NHS2 questionnaires in 1993 (calcium) and 1997 (calcium and vitamin D). Participants were asked if they took supplemental vitamin D and/or calcium, including antacids containing calcium, like Tums and dolomite; calcium users were asked to specify the dose of elemental calcium ( $<400$ , 400-900, 901-1300, and  $\geq 1300$  mg/d). We asked women using multivitamins to specify the brand, formula, and dose. For each nutrient, we then summed the contributions from all supplements. Finally, we calculated each woman's total intake of calcium and vitamin D by summing nutrient intake from food and supplemental sources.

**Table 1. Age-Standardized Characteristics of Premenstrual Syndrome Cases and Controls at Baseline (1991)**

Characteristic*	Cases (n = 1057)†	Controls (n = 1968)†	P Value‡
Age, y§	34.4 (4.3)	35.0 (3.9)	<.001
BMI			
Present	24.6 (0.2)	23.7 (0.1)	<.001
At the age of 18 y	21.4 (0.1)	21.1 (0.07)	.03
No. of full-term pregnancies	1.7 (0.04)	1.7 (0.03)	.52
Age at first birth, y	25.9 (0.1)	26.1 (0.1)	.22
Age at menarche, y	12.4 (0.04)	12.5 (0.03)	.08
MET of physical activity per wk	22.9 (1.8)	23.3 (1.3)	.88
Smoking status¶			
Current	12.3	6.5	<.001
Past	26.5	18.2	<.001
History of tubal ligation¶	18.2	16.8	.34
OC use¶			
Ever	85.7	77.7	<.001
Current	10.7	9.9	.51
Duration of >4 y	42.0	36.6	.004
Ever used antidepressants¶	12.1	4.7	<.001
Total calcium intake, mg/d#	1027 (12.9)	1057 (9.4)	.06
Total vitamin D intake, IU/d#	390 (7.6)	401 (5.6)	.22

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); MET, metabolic equivalent task; OC, oral contraceptive.

\*All characteristics (except for age) were standardized to the age distribution of cases and controls in 1991.

†Data are given as mean (SE) unless otherwise indicated.

‡Calculated using the F statistic.

§Data are given as mean (SD).

||Described by Ainsworth et al.<sup>17</sup>

¶Data are given as percentage of each group.

#Adjusted for total calorie intake by the residual method.<sup>16</sup>

Intakes of all nutrients were adjusted for total calorie intake using the residual method.<sup>16</sup>

We collected information on other factors potentially associated with PMS or calcium and vitamin D intake throughout the study period. Information on age, smoking status, body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters), number of full-term pregnancies (ie, pregnancies that lasted >6 months), tubal ligation, and OC use was updated biennially. Physical activity level was assessed in 1991 and 1997, and used to calculate metabolic equivalent task hours per week.<sup>17</sup> We use the 3 SFFQs to measure intake of carbohydrates, vitamins B<sub>6</sub> and E, magnesium, manganese, and carotenoids. Finally, our supplemental menstrual symptom questionnaire inquired about antidepressant use.

## STATISTICAL ANALYSIS

We evaluated the association between calcium, vitamin D, and risk of PMS in several ways. First, we assessed the effect of total intake of calcium and vitamin D (ie, from foods and supplements combined) during the 2- to 4-year period immediately preceding each participant's reference year by dividing women into quintiles based on their nutrient intake on the SFFQ immediately preceding their reference year. Quintile cut points were based on the distribution of nutrient intake in the entire NHS2 cohort. We repeated this process to classify participants into quintiles based on intake of calcium and vitamin D from food sources only. We then considered the effect of calcium and vitamin D from supplements only by dividing women into categories based on their supplement use in the 2- to 4-year

period before the reference year, using information from SFFQs and main NHS2 questionnaires. Finally, to evaluate the effect of nutrient intake during earlier years, we divided women into quintiles and categories of total, dietary, and supplemental calcium and vitamin D intake based on their reported intake levels in 1991 only.

Besides calcium supplements and multivitamins, milk was the greatest source of calcium and vitamin D in our study population. We divided participants into categories based on their frequency of intake of a 240-mL serving of skim or low-fat, whole, and all types of milk combined before the reference year and in 1991 only.

We compared baseline characteristics of PMS cases and controls with *t* tests and Pearson  $\chi^2$  tests. We used odds ratios to estimate the relative risk (RR) of PMS for women across quintiles and categories of intake of calcium and vitamin D, and calculated 95% confidence intervals. For supplements, risk for each dosage was compared with that of nonusers. All statistical analyses were conducted with SAS statistical software (SAS Institute Inc, Cary, NC). We used multivariable logistic regression to adjust RRs for calcium and vitamin D for the effect of the other nutrient, and our analyses of nutrients from foods were controlled for the effects of supplements and vice versa. Multivariable analyses also adjusted for age, diagnosis year, number of full-term pregnancies, BMI, smoking status, tubal ligation, duration of OC use, antidepressant use, and intake of vitamin B<sub>6</sub> and potassium from foods and supplements. Several additional variables were not included in the final analysis because they were unrelated either to the development of PMS or to calcium and vitamin D intake, including age at first birth, physical activity, BMI at the age of 18 years, alcohol intake, and dietary intake of magnesium, manganese, vitamin E, linolenic acid, total carotenoids, and caffeine. The Mantel extension test for trend was used to evaluate linear trend across quintiles and categories by modeling the median value of each quintile or category as a continuous variable in the multivariable regression models.

We assessed whether the relationship between intake of calcium and vitamin D and risk of PMS differed in subgroups of participants by stratifying participants by age group (<35 vs  $\geq$ 35 years), BMI (<25.0 vs  $\geq$ 25.0), and smoking status (never or past smoker vs current smoker), and comparing RRs between levels of these factors. Interactions between variables and nutrient intakes were considered statistically significant if the Wald 2-sided *P* value for the interaction term in the multivariable model was <.05. Finally, we repeated our analyses in subgroups limited to women with no history of depression before their reference year and excluding women using OCs at the start of follow-up.

## RESULTS

Age-standardized characteristics of the 1057 validated PMS cases and the 1968 validated controls in 1991 are presented in **Table 1**. Cases had a significantly higher BMI than did controls, and were more likely to be current or past smokers. Ever use and long-term use of OCs was more common in PMS cases than controls, as was use of antidepressants. Cases and controls did not differ in terms of parity, age at first birth, age at menarche, tubal ligation, or physical activity. The calorie-adjusted mean total calcium intake was slightly lower in cases compared with controls, while the mean total vitamin D intake was not significantly different between the 2 groups.

Participants with the highest intake of total calcium before the reference year had an RR of 0.80 compared

**Table 2. Age-Adjusted and Multivariate Relative Risks of Premenstrual Syndrome by Intake of Calcium and Vitamin D From All Sources, Foods Only, and Supplements Only Before the Reference Year\***

Variable	Quintile†					P Value for Trend‡
	1	2	3	4	5	
<b>Total Calcium Intake</b>						
Median, mg/d	563	749	930	1180	1563	NA
Case-control ratio	188:330	216:404	206:374	235:455	210:401	NA
Relative risk						
Age adjusted	1.00	0.93	0.94	0.90	0.90	.38
Multivariate§	1.00	0.95	0.90	0.84	0.80	.13
95% Confidence interval	Referent	0.72-1.25	0.66-1.21	0.61-1.14	0.58-1.10	NA
<b>Calcium From Foods</b>						
Median, mg/d	529	684	812	997	1283	NA
Case-control ratio	177:321	214:367	221:400	234:390	209:486	NA
Relative risk						
Age adjusted	1.00	1.06	0.97	1.07	0.75	.01
Multivariate§	1.00	1.11	0.96	1.03	0.70	.02
95% Confidence interval	Referent	0.84-1.46	0.72-1.28	0.76-1.39	0.50-0.97	NA
<b>Total Vitamin D Intake</b>						
Median, IU/d	112	203	332	483	706	NA
Case-control ratio	200:353	198:403	203:391	257:410	197:407	NA
Relative risk						
Age adjusted	1.00	0.85	0.91	1.07	0.82	.50
Multivariate§	1.00	0.89	0.94	1.01	0.59	.01
95% Confidence interval	Referent	0.67-1.17	0.69-1.28	0.72-1.40	0.40-0.86	NA
<b>Vitamin D From Foods</b>						
Median, IU/d	91	162	214	315	383	NA
Case-control ratio	191:327	218:382	227:424	211:380	208:451	NA
Relative risk						
Age adjusted	1.00	0.97	0.89	0.93	0.77	.04
Multivariate§	1.00	1.05	0.91	0.88	0.69	.02
95% Confidence interval	Referent	0.80-1.39	0.68-1.21	0.65-1.20	0.50-0.96	NA
<b>Category of Intake</b>						
<b>Calcium From Supplements</b>						
Dose, mg/d	0	1-399	400-899	≥900	...	NA
Case-control ratio	661:1280	231:401	113:198	50:85	...	NA
Relative risk						
Age adjusted	1.00	1.07	1.10	1.16	...	.27
Multivariate§	1.00	1.03	1.13	1.13	...	.35
95% Confidence interval	Referent	0.81-1.30	0.85-1.50	0.75-1.71	...	NA
<b>Vitamin D From Supplements</b>						
Dose, IU/d	0	1-399	≥400	...	...	NA
Case-control ratio	567:1109	238:400	250:455	...	...	NA
Relative risk						
Age adjusted	1.00	1.14	1.03	...	...	.57
Multivariate§	1.00	1.24	0.91	...	...	.61
95% Confidence interval	Referent	0.96-1.59	0.67-1.23	...	...	NA

Abbreviation: NA, not applicable.

\*The reference year is equal to the year of diagnosis (for cases) or a randomly chosen year corresponding to the possible years of diagnosis (for controls). Numbers may not sum to 1057 cases and 1968 controls because of missing data on nutrient intake immediately before the reference year.

†Quintile 1 is the lowest level of intake, and quintile 5 is the highest level of intake.

‡Calculated using the median value of each quintile or category as a continuous variable in the multivariable regression model.

§Adjusted for level of other factors before the reference year, including age (<30, 30-34, 35-39, and ≥40 years), year of diagnosis (1993, 1994-1995, 1996-1997, 1998-1999, and 2000-2001), number of full-term pregnancies (0, 1-2, 3-4, or ≥5 lasting ≥6 months), body mass index (calculated as weight in kilograms divided by the square of height in meters) (<20.0, 20.0-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, and ≥30.0), smoking status (never smoker, past smoker of 1-24 cigarettes per day, past smoker of ≥25 cigarettes per day, current smoker of 1-24 cigarettes per day, and current smoker of ≥25 cigarettes per day), tubal ligation (no vs yes), duration of oral contraceptive use (never or 1-23, 24-71, 72-119, or ≥120 months), antidepressant use (never vs ever), and intake of vitamin B<sub>6</sub> (quintiles) and potassium (quintiles) from foods and supplements. Calcium and vitamin D intakes were adjusted for the effect of each other. Nutrients from foods and nutrients from supplements were adjusted for the effect of each other.

with those with the lowest intake (**Table 2**). Calcium from supplements was not associated with risk of PMS. In contrast, calcium from food sources was inversely associated with incident PMS. Women with the highest in-

take of calcium from foods had an RR of 0.70 compared with women with the lowest intake.

High total vitamin D intake before the reference year was also associated with a significantly lower risk of PMS.

**Table 3. Age-Adjusted and Multivariate Relative Risks of Premenstrual Syndrome by Dietary Intake of All Types of Milk, Skim or Low-Fat Milk, and Whole Milk Before the Reference Year\***

Variable	Skim, Low-Fat, and Whole Milk					P Value for Trend†
Frequency of intake, serving	≤1/wk	2-6/wk	1/d	2-3/d	≥4/d	NA
Case-control ratio	232:421	265:446	257:448	237:528	65:121	NA
Relative risk						
Age adjusted	1.00	1.06	1.03	0.79	0.90	.03
Multivariate‡	1.00	1.03	1.00	0.70	0.68	<.001
95% Confidence interval	Referent	0.81-1.31	0.78-1.27	0.55-0.90	0.47-1.00	NA
	Skim or Low-Fat Milk					
Frequency of intake, serving	≤1/wk	2-6/wk	1/d	2-3/d	≥4/d	NA
Case-control ratio	285:491	252:439	259:452	233:520	27:62	NA
Relative risk						
Age adjusted	1.00	0.98	0.98	0.75	0.68	.002
Multivariate‡	1.00	0.94	0.93	0.66	0.54	<.001
95% Confidence interval	Referent	0.74-1.18	0.74-1.18	0.52-0.83	0.32-0.91	NA
	Whole Milk					
Frequency of intake, serving	0	1/mo-1/wk	>1/wk	...	...	NA
Case-control ratio	880:1703	110:174	66:87	...	...	NA
Relative risk						
Age adjusted	1.00	1.18	1.41	...	...	.02
Multivariate‡	1.00	1.04	1.31	...	...	.16
95% Confidence interval	Referent	0.79-1.37	0.91-1.87	...	...	NA

Abbreviation: NA, not applicable.

\*The reference year is equal to the year of diagnosis (for cases) or a randomly chosen year corresponding to the possible years of diagnosis (for controls). Numbers may not sum to 1057 cases and 1968 controls because of missing data on nutrient intake before the reference year.

†Calculated using the median value of each category as a continuous variable in the multivariate regression model.

‡Adjusted for age, year of diagnosis, number of full-term pregnancies, body mass index, smoking status, tubal ligation, duration of oral contraceptive use, antidepressant use, and intake of vitamin B<sub>6</sub> and potassium from foods and supplements. The fourth footnote to Table 2 provides the categories for these variables.

Compared with women in the lowest quintile, those with the highest vitamin D intake had an RR of 0.59. Supplemental vitamin D did not seem to be associated with risk, while women with a high intake of vitamin D from foods had a significantly lower risk. Results based on intakes of both nutrients in 1991 only were nearly identical and are not shown.

Frequent milk consumption was also associated with lower risk (**Table 3**). Participants consuming 4 servings or more per day of any type of milk had an RR of 0.68 compared with those reporting 1 serving or less per week. Whole milk intake was associated with a modest increase in risk, while women who frequently consumed skim or low-fat milk had a significantly lower risk of developing PMS; the RR for women consuming 4 servings or more per day of skim or low-fat milk compared with those reporting 1 serving or less per week was 0.54. The relationship between milk intake and risk of PMS did not vary by level of calcium or vitamin D supplementation (results not shown). Results based on milk intake in 1991 only were similar to those before the reference year, although slightly attenuated, and are not shown.

Results stratified by BMI at the reference year suggested a stronger association between calcium and risk of PMS in overweight women than in normal-weight women, although we did not observe a statistically significant interaction ( $P = .32$ ). In women with a BMI of less than 25.0, high calcium intake was not associated with a lower risk of PMS. In this group, the RRs for quintiles

2 through 5 vs quintile 1 were 0.87, 0.97, 0.92, and 0.99 (95% confidence interval, 0.66-1.50) ( $P = .85$  for trend), respectively. In contrast, in overweight women (BMI,  $\geq 25.0$ ), the RRs for quintiles 2 through 5 vs quintile 1 were 1.03, 0.85, 0.60, and 0.52 (95% confidence interval, 0.30-0.92) ( $P = .003$  for trend), respectively. We did not find evidence that the relationship between calcium and vitamin D intake and PMS varied by age or smoking status (results not shown). Results of analyses limited to women with no diagnosis of depression before the reference year and those not using OCs at baseline were similar to those of the main analysis (results not shown).

#### COMMENT

Findings from our nested case-control study suggest that a high dietary intake of vitamin D and calcium may lower the risk of incident PMS. We observed a significantly lower risk of developing PMS in women with high intakes of vitamin D and calcium from food sources, equivalent to about 4 servings per day of skim or low-fat milk, fortified orange juice, or low-fat dairy foods such as yogurt. These dietary intakes correspond to approximately 1200 mg of calcium and 400 IU of vitamin D from food sources. While previous studies have observed the benefits of calcium supplements for treating PMS, this is the first, to our knowledge, to suggest that calcium and vitamin D may help prevent the initial development of PMS.

Calcium and vitamin D may influence the development of PMS through their relationship to endogenous estrogens. Calcium, parathyroid hormone, and vitamin D levels have been observed to fluctuate across the menstrual cycle in response to changes in estradiol at ovulation and during the luteal phase in several,<sup>10,18-22</sup> but not all,<sup>23,24</sup> studies. In a study<sup>18</sup> of repeated blood samples drawn during a single menstrual cycle from 7 women with PMS and 5 menstrual symptom-free women, calcium levels were lower at ovulation than during the early follicular phase and had returned to their follicular levels by the end of the luteal phase. Cases with PMS also experienced a significant increase in parathyroid hormone levels at ovulation, followed by a decrease in the luteal phase. A similar increase was not observed in controls, who had lower parathyroid hormone levels at all phases of the menstrual cycle. 1,25-Dihydroxyvitamin D, the metabolically active form of the hormone, was also consistently higher in PMS cases than controls, while 25-hydroxyvitamin D levels were significantly lower at all phases. It is unclear why 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D may be differently related to PMS, although it has been suggested that the increase in estrogens occurring at ovulation may increase metabolism of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D.<sup>18,22</sup> Additional data provide support for a biological relationship between calcium, vitamin D, and PMS, including the observation of an increased risk of osteoporosis after menopause in women with PMS<sup>25</sup> and similarities between the symptoms of PMS and hypocalcemia, such as depression, anxiety, and fatigue.<sup>10,18</sup> Thys-Jacobs<sup>10</sup> suggests that women with luteal-phase symptoms consistent with PMS may be experiencing calcium dysregulation, vitamin D deficiency, and hyperparathyroidism. If PMS may be a consequence of deficiency in circulating levels of calcium and vitamin D, high dietary intakes of vitamin D and perhaps calcium may directly prevent the manifestation of PMS symptoms associated with deficiencies.

The finding that frequent milk intake is protective against PMS is consistent with our results for calcium and vitamin D. Each serving of fortified milk contains approximately 300 mg of calcium and 100 IU of vitamin D; 4 servings per day would provide women with approximately the amount of calcium and vitamin D from food sources at which we saw a significantly lower risk of PMS. It is unclear why frequent consumption of skim or low-fat milk and whole milk may be differently related to PMS. It is likely that women who frequently drink whole milk have diets higher in saturated fat than women who drink skim milk, and saturated fat intake may be positively associated with the incidence of PMS. In a recent study in Japan,<sup>26</sup> women with a high dietary fat intake reported more severe menstrual symptoms than those with a lower intake. Future studies of incident PMS should evaluate the specific role of dietary fats.

Premenstrual syndrome involves a large variety of symptoms, many of which are experienced by most menstruating women and may be caused by disorders other than PMS.<sup>1,5</sup> Accurately differentiating between PMS cases and noncases may, therefore, be difficult. Our initial identification of cases among NHS2 participants was made

by self-report on mailed questionnaires, and was followed by a supplemental questionnaire measuring frequency, timing, and severity of menstrual symptoms. Because of the size of our cohort and the prospective nature of our study, we were unable to use prospective symptom charting to identify PMS cases, as is becoming the standard in clinical practice. Although many of our participants were required to recall their symptom history over several years, we tried to minimize the likelihood of symptom misreport in several ways. We preferentially included women first reporting PMS in the later years of follow-up to minimize the time over which symptoms were recalled. We also used established criteria to define PMS cases and controls to identify and compare women at the 2 extreme ends of the spectrum of menstrual symptom experience. Symptom recall is likely to be accurate for women who regularly experienced severe symptoms that interfered with life activities, and for those who experienced few, if any, menstrual symptoms. Consequently, misclassification of women at these 2 extremes should be limited.

An additional limitation of this study is that a relatively small proportion of our participants reported using supplemental calcium. As a result, we were unable to evaluate the effect of high doses of supplemental calcium on the risk of developing PMS. Randomized trials<sup>12-14</sup> of calcium supplementation for the treatment of PMS have reported greater benefit at calcium doses of 1200 to 1600 mg/d than at lower levels. It is possible that we were unable to observe a beneficial effect of calcium supplements because the intake levels in our population were too low. The use of calcium and vitamin D supplements to prevent incident PMS should be addressed in future prospective studies and large-scale clinical trials. In addition, because dietary intake and exposure to sunlight contribute to circulating levels of vitamin D, and because women differ in their ability to absorb calcium, the relation of plasma calcium and vitamin D metabolite levels to the incidence of PMS should also be evaluated.

Our study has several important strengths. It is among the first to collect information on dietary factors that may be associated with future development of PMS from women free from the diagnosis at baseline; this prospective assessment greatly reduced the likelihood of recall bias. We measured intake of calcium and vitamin D with an SFFQ that has been extensively validated in a similar population.<sup>16,27</sup> In addition, we were able to evaluate and control for confounding by several other factors, because information on parity, smoking, dietary intake of other nutrients, BMI, and other factors was collected prospectively on NHS2 questionnaires.

Our findings, together with those from several small randomized trials that found calcium supplements to be effective in treating PMS, suggest that a high intake of calcium and vitamin D may reduce the risk of PMS. Clinical trials of this issue are warranted. In the interim, given that calcium and vitamin D may also reduce the risk of osteoporosis and some cancers, clinicians may consider recommending these nutrients even for younger women.

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