A prospective study of caffeine and coffee intake and premenstrual syndrome[1,2]

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ABSTRACT

Background: Clinically significant premenstrual syndrome (PMS) affects 15–20% of premenopausal women, substantially reducing quality of life. Women with PMS often are counseled to minimize caffeine intake, although only limited evidence supports this recommendation.

Objective: We evaluated the association between total caffeine, coffee, and tea intake and the development of PMS in a case-control study nested within the prospective Nurses' Health Study II.

Design: All participants were free from PMS at baseline (1991). PMS cases reported a new clinician-made diagnosis of PMS on biennial questionnaires between 1993 and 2005, and then confirmed symptom timing and moderate-to-severe impact and severity of symptoms with the use of a retrospective questionnaire (n = 1234). Controls did not report PMS and confirmed experiencing no symptoms or few mild symptoms with limited personal impact (n = 2426). Caffeine, coffee, and tea intake was measured by food-frequency questionnaires every 4 y, and data on smoking, body weight, and other factors were updated every 2–4 y. Logistic regression was used to evaluate the associations of total caffeine intake and frequency of coffee and tea consumption with PMS.

Results: After adjustment for age, smoking, and other factors, total caffeine intake was not associated with PMS. The OR comparing women with the highest (quintile median = 543 mg/d) to the lowest (quintile median = 18 mg/d) caffeine intake was 0.79 (95% CI: 0.61, 1.04; P-trend = 0.31). High caffeinated coffee intake also was not associated with risk of PMS or specific symptoms, including breast tenderness (OR for ≥4 cups/d compared with <1/mo: 0.73; 95% CI: 0.48, 1.12; P-trend = 0.44).

Conclusions: Our findings suggest that caffeine intake is not associated with PMS, and that current recommendations for women to reduce caffeine intake may not help prevent the development of PMS. *Am J Clin Nutr* 2016;104:499–507.

Keywords: premenstrual syndrome, women's health, caffeine, coffee, tea

INTRODUCTION

Clinically significant premenstrual syndrome (PMS)[7] affects 15–20% of premenopausal women, resulting in the disruption of normal life activities and interpersonal relationships (1). PMS is characterized by moderate to severe physical and affective symptoms during the luteal phase of the menstrual cycle (2). Symptoms often include irritability, mood swings, anxiety, depression, bloating, food cravings, breast tenderness, and difficulty concentrating. Previous research suggests that dietary factors may play an important role in the development of PMS (3, 4). Currently, the American Congress of Obstetrics and Gynecology, Association of Reproductive Health Professionals, and other groups recommend that women experiencing PMS avoid caffeine entirely, particularly women experiencing breast tenderness (5). These recommendations are based largely on the results of a series of 4 cross-sectional observational studies by Rossignol et al. (6–9), along with 3 additional similar studies (10–12), which observed a strong positive association of caffeine and caffeinated beverage intake with PMS. However, since then, 3 studies of prevalent PMS have reported no association (13–15). All previous studies potentially were subject to reverse causation, and did not control well for other important risk factors, such as smoking and adiposity (16, 17). To our knowledge, no large, long-term prospective studies have evaluated whether caffeine intake is associated with the development of PMS.

In this study, we evaluated the associations of total caffeine intake and frequency of coffee and tea consumption with incident PMS in a subset of participants of the Nurses' Health Study II (NHS2), taking into account a variety of potential confounders. Because current medical recommendations are targeted particularly at women experiencing breast tenderness, we also evaluated

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[2] Supplemental Figure 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[7] Abbreviations used: FFQ, food-frequency questionnaire; NHS2, Nurses' Health Study II; PMS, premenstrual syndrome.

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whether total caffeine intake and coffee consumption were associated with 3 specific symptoms of PMS: breast tenderness, fatigue, and irritability.

METHODS

The NHS2 is a prospective study of 116,678 female US registered nurses who were 25–42 y old in 1989 when they responded to a mailed baseline questionnaire, indicating their consent to participate in the study. We conducted our analyses within the PMS substudy, a nested case-control study established within the NHS2 in 2001 (18). Information regarding lifestyle behaviors and medical conditions, including dietary factors and PMS status, has been collected through biennial mailed questionnaires since inception of the cohort, and the follow-up rate for each cycle has been ≥89%. The study protocol was approved by the institutional review board at Brigham and Women's Hospital in Boston, Massachusetts.

Case and control ascertainment

Case and control ascertainment in the NHS2 PMS substudy has been described previously (**Supplemental Figure 1**) (3, 4, 18, 19). Briefly, we included women who did not indicate that they had PMS on the 1989 or 1991 questionnaires and were thus at risk for PMS during follow-up. Because diet was of particular interest in the PMS substudy, we further excluded women with implausible caloric intake based on food-frequency questionnaires (FFQs) (<500 or ≥3500 kcal/d). Each woman reporting a new clinician diagnosis of PMS on the study questionnaire between 1993 and 2005 was assigned a reference year, which was equal to her year of first diagnosis. Because women who did not report a PMS diagnosis did not have a diagnosis year, we assigned each such woman a randomly chosen reference year between 1993 and 2005 to ensure that cases and controls provided information about comparable time periods. In both groups, we then excluded women who had a diagnosis of cancer, endometriosis, usually irregular menstrual cycles, or infertility before their reference year to prevent inclusion of women with similar symptoms of PMS resulting from other conditions. Of eligible women, 4108 women reported PMS and were considered potential cases. Of all eligible women not reporting PMS (n = 28,389), we randomly selected 3248 women to serve as potential controls.

To confirm PMS diagnoses in cases and verify the absence of PMS in controls, we mailed participants a questionnaire based on the Calendar of Premenstrual Experiences, which assessed the occurrence and timing during the menstrual cycle of 26 physical, behavioral, and affective symptoms, and the effect of symptoms on daily functioning (20). The questionnaire was completed by 87% of potential cases (n = 3579) and 95% of potential controls (n = 3087). Women responding to the PMS questionnaire did not differ substantially from nonrespondents in terms of age (34.4 y compared with 34.5 y), BMI (in kg/m^2; 24.0 compared with 24.8), ever-use of oral contraceptives (81.9% compared with 83.7%) and other baseline characteristics.

We used responses to the menstrual symptom questionnaire to further limit our cases to women who met established criteria for moderate-to-severe PMS (20). PMS cases met the following criteria: *1*) the occurrence of ≥1 physical and 1 affective menstrual symptoms; *2*) overall symptom severity was moderate or severe or symptoms had a moderate or severe impact on life activities and social relationships; *3*) symptoms began within 14 d of the onset of menstruation; *4*) symptoms ended within 4 d of the onset of menses; and *5*) symptoms were absent in the week after menses ended. A total of 1257 (35%) of potential cases met these criteria.

Controls were women who confirmed that they had not been diagnosed with PMS during the study period and who did not report any menstrual symptoms or reported only mild symptoms with no substantial effect on life activities and interpersonal relationships on the questionnaire. Of potential controls, 2463 (80%) met these criteria. Because we excluded women who did not meet either the case or control definitions, we were able to compare women on the extreme opposite ends of the spectrum of menstrual symptom experience, thereby reducing potential misclassification of cases as controls, and vice-versa (18, 19).

The validity of PMS case and control identification was assessed previously in 135 substudy members first reporting PMS in 2001 and 371 not reporting PMS (1989–2001) (19). Cases meeting the criteria for PMS in our study were very similar to cases also reporting clinician-supervised prospective charting in terms of symptom frequency (e.g., mean number of physical symptoms: 5.5 compared with 6.1, $P > 0.05$), timing of occurrence (e.g., mean number of days symptoms began before onset of menses: 5.7 compared with 6.1, $P > 0.05$) and severity (e.g., symptoms caused moderate-to-severe social isolation: 10% compared with 17%, $P > 0.05$). In analyses of 2 risk factors (age and calcium intake), ORs for PMS when both case definitions were used were nearly the same, which suggests that our method was comparable to prospective charting in terms of PMS classification in large epidemiologic studies (18).

Assessment of caffeine, coffee, and other dietary factors

Participants completed validated semiquantitative FFQs in 1991, 1995, 1999, and 2003, assessing their mean intake of 131 foods, beverages, and supplements over the preceding year (21–23). Each questionnaire asked participants to estimate, on average, how often they consumed specific food and beverage items, including caffeinated coffee, decaffeinated coffee, caffeinated tea, herbal tea, other caffeinated beverages, cream, and sugar. Participants reported their consumption by indicating 1 of 9 frequency categories for each food and beverage (i.e., never; 1–3 servings/mo; 1, 2–4, or 5–6 servings/wk; and 1, 2–3, 4–5, or ≥6 servings/d).

Total caffeine intake was estimated by summing the caffeine content of all foods and beverages included on the FFQ. The caffeine and nutrient content of foods and beverages was calculated primarily with the use of contemporaneous USDA food composition data (21). For each item, we multiplied the frequency of consumption of a single serving by the caffeine content per serving [e.g., 8 ounce (237 mL) cup of coffee = 137 mg; 8 ounce (237 mL) cup of tea = 47 mg; 12 ounce (354 mL) caffeine-containing carbonated beverages = 46 mg; and 1 ounce (30 g) chocolate = 7 mg]. Total intake of other nutrients included as covariates (i.e., alcohol, calcium, vitamin D, potassium, and vitamin B-6) in our analyses were derived similarly. We adjusted all nutrients for total energy intake with the use of the residual method (24). The validity of the FFQ was assessed by comparison

with four 1-wk diet records in a random subset (n = 173) of women in the Nurses' Health Study, a comparable population of female health professionals. High correlation coefficients were observed between the 2 methods of assessment for coffee, tea, and caffeinated soda (coffee: r = 0.80; tea: r = 0.93; and caffeinated soda: r = 0.85) (22).

Assessment of covariates

With the use of the biennial questionnaires, we assessed other factors potentially relevant to the caffeine–PMS relation, including age, age at menarche, BMI, smoking, parity, oral contraceptive use and duration, childhood trauma, physical activity, and other nutrients. Information on age, height, and age at menarche was collected at baseline. Updated information regarding other factors, including weight, parity, oral contraceptive use, smoking, and physical activity, were collected biennially. Baseline height and current weight from each questionnaire were used to calculate BMI. Physical activity was assessed in 1991, 1997, and 2001 by asking women how much time they spent each week participating in specific recreational activities, from which metabolic equivalent task–hours were calculated. The use of medications, including antidepressants, was first assessed in 1993 and was assessed each questionnaire year thereafter. A history of clinician-diagnosed depression was reported on main NHS2 questionnaires in 2003 and 2005, as well as on the menstrual symptom questionnaire. For covariates with missing data, we imputed values with the use of information provided on adjacent questionnaires. A small number of participants were missing covariate data across all questionnaire cycles (e.g., data on BMI and oral contraceptive use were missing for 0.0003% of participants, and those for smoking were missing for 0.003% participants). We assigned these women to a missing indicator category for these covariates. We conducted analyses with the use of both complete-case (n = 971 cases and 2199 controls) and missing indicator methods; estimates were similar between the 2 methods, and thus we have reported results from models by using the missing indicator method.

Statistical analysis

We compared baseline characteristics between PMS cases and controls with available information on caffeine intake (n = 1234 cases and 2426 controls) with the use of generalized linear models adjusted for age. We divided participants into quintiles of total caffeine intake (in milligrams) according to the distribution of the overall NHS2 population, as well as categories reflecting 100-mg/d increments of total caffeine intake ($<$100, 100–199, 200–299, 300–399, 400–499, 500–599, 600–699, and $\geq$700 mg/d). Coffee and tea consumption was categorized according to frequency of intake (cups per day), with "never or less than once per month" serving as the referent. We assessed total caffeine, coffee, and tea intake at both baseline (1991) and 2–4 y before each participant's reference year to determine whether associations varied by timing of exposure. Furthermore, we repeated analyses with the use of total caffeine intake and frequency of coffee consumption assessed 0–3 y after each participant's reference year. This mimicked a cross-sectional study, allowing us to compare our results with previous studies and assess whether associations may have been affected by reverse causation if women changed their caffeine intake in response to PMS diagnosis or treatment (9, 25). All statistical analyses were conducted with SAS version 9.4 software.

We used logistic regression to model the association of PMS with total caffeine intake and frequency of total coffee, caffeinated coffee, decaffeinated coffee, total tea, caffeinated tea, and herbal tea consumption. We calculated ORs and 95% CIs by comparing odds of PMS to the lowest quintile or category of intake for each exposure. In multivariable models, we controlled for factors whose inclusion altered the OR for total caffeine and PMS by $\geq$10% and those that were significantly associated with PMS. These included age, diagnosis year, parity, BMI, pack-years of smoking, duration of oral contraceptive use, physical activity, history of childhood trauma score, use of antidepressant medication, diagnosis of depression before PMS, and intake of alcohol, calcium, vitamin D, vitamin B-6, and potassium. We tested for interaction effects by age, BMI, and smoking on the basis of biologic plausibility. A Hosmer-Lemeshow goodness-of-fit test indicated a well-fit model (P = 0.60) (26).

We also hypothesized that total caffeine intake and frequency of coffee consumption may be differently related to the breast tenderness, fatigue, and irritability symptoms of PMS, based on current recommendations and results of previous studies. We thus evaluated whether total caffeine intake and frequency of caffeinated and decaffeinated coffee consumption were associated with these symptoms in multivariable models, comparing risk of breast tenderness, irritability, and fatigue in PMS cases and controls without these symptoms.

To assess whether the associations were robust to potential misclassification of depression as PMS, we conducted sensitivity analyses, restricted to women without a history of depression before diagnosis (n = 1026 cases and 2256 controls). Additionally, to assess the potential misclassification of PMS status from use of oral contraceptives to treat premenstrual symptoms, we repeated our main analyses in women who did not use oral contraceptives at baseline (n = 1097 cases and 2203 controls). Many women diagnosed with PMS experience symptoms for several years before being diagnosed with clinically significant PMS. Therefore, to ensure that total caffeine intake was assessed at an etiologically relevant time, we conducted a final sensitivity analysis in women who reported symptom onset after 1991 (n = 411 cases and 2426 controls).

RESULTS

Among the 1234 cases included in our analysis, the mean age of PMS diagnosis was 40 y. At baseline, cases were slightly younger, had a higher mean BMI, had a higher mean intake of vitamin B-6, and were less physically active than controls (**Table 1**). Cases were more likely to report ever having used oral contraceptives and antidepressant medications and to have a history of substantial childhood trauma than were controls. Cases also were more likely to report being current smokers than were controls.

In analyses adjusting only for age, higher caffeine intake was modestly associated with PMS (**Table 2**). For example, women in the highest quintile of caffeine intake (median = 543 mg/d) had a nonsignificant higher odds of PMS (OR: 1.20; 95% CI: 0.96, 1.51) compared with women in the lowest quintile (median = 18 mg/d). However, after adjusting for covariates including smoking,

TABLE 1
Age-standardized characteristics of PMS cases and controls at baseline (1991): Nurses' Health Study II PMS substudy, 1991–2005[1]

Characteristic	Cases (n = 1234)	Controls (n = 2426)
Age,[2] y	33.9 ± 4.2	34.5 ± 3.9
BMI, kg/m^2	24.6 ± 0.1	23.7 ± 0.1
Age at menarche, y	12.4 ± 0.04	12.5 ± 0.03
Full-term pregnancies, n	1.6 ± 0.03	1.7 ± 0.02
Physical activity, MET-h/wk	22.8 ± 1.6	23.4 ± 1.1
Potassium intake, mg/d	2921 ± 14.1	2897 ± 10.1
Vitamin B-6 intake, mg/d	8.7 ± 0.6	5.8 ± 0.4
Vitamin D intake, IU/d	398 ± 7.0	400 ± 5.0
Calcium intake, mg/d	1029 ± 11.8	1062 ± 8.4
Alcohol intake, g/d	3.1 ± 0.2	3.1 ± 0.1
Caucasian, %	96.8	97.2
Ever used oral contraceptives, %	85.5	77.2
Current smoker, %	12.6	7.1
Ever used antidepressant medications,[3] %	15.5	7
History of substantial childhood trauma, %	14.1	8

[1]Values are means ± SEs or percentages, unless otherwise indicated. All characteristics were calculated with the use of generalized linear models adjusted for the age of participants in 1991. MET-h, metabolic equivalent task hours; PMS, premenstrual syndrome.
[2]Values are means ± SDs.
[3]Use before PMS diagnosis (for cases).

BMI, and other factors (multivariable model 1), this association was completely attenuated; compared with women in the lowest quintile, women with the highest caffeine intake had an OR of 0.79 (95% CI: 0.61, 1.04). In analyses that used 100 mg/d cutoffs for total caffeine intake, even total caffeine intake ≥700 mg/d (the equivalent of >5 cups coffee/d) was not associated with PMS (OR: 0.77; 95% CI: 0.49, 1.19; P-trend = 0.35), although numbers were small for the highest 3 categories. Smoking was the strongest confounder of the caffeine–PMS relation in our multivariable analyses.

Similarly, in analyses adjusted only for age, higher total coffee consumption was associated with increased odds of PMS. Compared with nondrinkers, women consuming 1, 2–3, and ≥4 cups/d had ORs of 1.29, 1.40, and 1.27, respectively. However, after adjusting for confounders, the association of total coffee intake and incident PMS also was attenuated completely, even at the highest level of intake (OR comparing ≥4 cups/d with almost never: 0.83; 95% CI: 0.61, 1.14; P-trend = 0.43).

In multivariable analyses (multivariable model 2) that separately assessed caffeinated and decaffeinated coffee intake, intake of neither beverage was associated with the development of PMS. In a secondary analysis, we further adjusted intake of each beverage for cream and added sugar intake, pregnancy, employment status, rotating night-shift work, and use of aspirin and acetaminophen, but this did not change the results materially (data not shown). Caffeinated tea intake also was not associated with the development of PMS. After adjusting for intake of caffeinated coffee, decaffeinated coffee, and herbal tea, we found that women who drank ≥2 cups caffeinated tea/d compared with almost-never drinkers had an OR of 1.04 (95% CI: 0.82, 1.34; P-trend = 0.89).

To determine whether the relation of caffeine and coffee intake with PMS varied by timing of exposure measurement related to the timing of diagnosis, we compared results when total caffeine and frequency of coffee and tea consumption were assessed at 3 time periods: baseline (1991), 2–4 y before each woman's diagnosis or reference year, and at the time of PMS diagnosis (i.e., 0–3 y after diagnosis or reference year). Results for total caffeine and caffeinated and decaffeinated coffee consumption measured 2–4 y before the reference year and 0–3 y after the diagnosis year were very similar to baseline analyses (**Table 3**).

The multivariable OR for total caffeine intake and frequency of caffeinated and decaffeinated coffee consumption at baseline and specific symptoms of PMS are presented in **Table 4**. High total caffeine intake and frequent consumption of caffeinated coffee were not associated with increased odds of breast tenderness, irritability, or fatigue. For example, women who reported consuming ≥4 cups/d caffeinated coffee at baseline had an OR of 0.73 for PMS with breast tenderness compared with women reporting an intake of <1 cup/mo (95% CI: 0.48, 1.12). Decaffeinated coffee intake was not associated with breast tenderness or irritability, and was associated inconsistently with fatigue.

Interaction terms for caffeine intake on PMS by age, smoking, or BMI were not statistically significant (P = 0.27, P = 0.80, and P = 0.81, respectively). Results from subanalyses restricted to women who did not use oral contraceptives at baseline and women reporting no history of depression or antidepressant use were similar to results from main analyses (specific results not shown). In subanalyses restricted to women who did not have premenstrual symptoms at baseline, estimates for baseline total caffeine intake were also similar to results from main analyses.

DISCUSSION

In our prospective study, we found no compelling evidence that high intake of caffeine or coffee was associated with the development of PMS. Although we observed modest, nonsignificant increased odds in analyses when adjusting only for age, associations were attenuated completely after adjusting for smoking, BMI, and other PMS risk factors. Furthermore, we

TABLE 2
ORs (95% CIs) for intake of total caffeine and frequency of coffee and tea consumption at baseline on risk of PMS: Nurses' Health Study II PMS substudy, 1991–2005[1]

	Median, mg/d	Cases, *n*	Controls, *n*	Age-adjusted (OR 95% CI)	Multivariable 1[2] OR (95% CI)	Multivariable 2[3] OR (95% CI)
Total caffeine						
Q1	18	258	544	1	1	
Q2	82	252	586	0.90 (0.73, 1.11)	0.84 (0.67, 1.05)	
Q3	168	253	454	1.18 (0.95, 1.46)	1.07 (0.85, 1.35)	
Q4	354	264	464	1.24 (1.00, 1.53)	1.00 (0.79, 1.28)	
Q5	543	207	378	1.20 (0.96, 1.51)	0.79 (0.61, 1.04)	
P-trend				<0.01	0.31	
Total caffeine, mg/d						
<100	37	420	917	1	1	
100–199	147	293	590	1.09 (0.91, 1.31)	0.98 (0.80, 1.19)	
200–299	236	97	181	1.19 (0.90, 1.56)	0.99 (0.73, 1.34)	
300–399	361	203	335	1.38 (1.17, 1.70)	1.11 (0.87, 1.41)	
400–499	434	96	186	1.16 (0.89, 1.53)	0.83 (0.61, 1.14)	
500–599	542	32	66	1.10 (0.71, 1.70)	0.78 (0.48, 1.27)	
600–699	646	46	70	1.53 (1.03, 2.26)	1.02 (0.66, 1.57)	
≥700	825	47	81	1.36 (0.93, 1.98)	0.77 (0.49, 1.19)	
P-trend				<0.01	0.35	
Total coffee[4]						
<1 cup/mo		362	829	1	1	
1 cup/mo–1 cup/wk		103	194	1.21 (0.93, 1.59)	1.25 (0.94, 1.67)	
2–6 cups/wk		112	232	1.11 (0.86, 1.44)	1.10 (0.83, 1.45)	
1 cup/d		181	327	1.29 (1.04, 1.61)	1.23 (0.96, 1.57)	
2–3 cups/d		359	616	1.40 (1.17, 1.68)	1.18 (0.95, 1.47)	
≥4 cups/d		117	227	1.27 (0.98, 1.65)	0.83 (0.61, 1.14)	
P-trend				0.01	0.43	
Caffeinated coffee[4]						
<1 cup/mo		471	1011	1	1	1
1 cup/mo–1 cup/wk		105	192	1.17 (0.90, 1.52)	1.17 (0.88, 1.55)	1.14 (0.85, 1.52)
2–6 cups/wk		87	211	0.88 (0.67, 1.16)	0.85 (0.64, 1.15)	0.85 (0.62, 1.14)
1 cup/d		176	307	1.24 (1.00, 1.54)	1.18 (0.93, 1.50)	1.13 (0.88, 1.44)
2–3 cups/d		302	534	1.26 (1.05, 1.50)	1.03 (0.83, 1.28)	1.01 (0.81, 1.26)
≥4 cups/d		93	170	1.24 (0.94, 1.64)	0.80 (0.58, 1.11)	0.80 (0.57, 1.11)
P-trend				0.01	0.33	0.32
Decaffeinated coffee[4]						
<1 cup/mo		777	1551	1	1	1
1 cup/mo–1 cup/wk		193	393	1.01 (0.83, 1.22)	1.11 (0.90, 1.37)	1.08 (0.87, 1.35)
2–6 cups/wk		93	192	1.00 (0.77, 1.30)	0.95 (0.71, 1.26)	0.94 (0.70, 1.26)
1 cup/d		92	156	1.24 (0.94, 1.62)	1.33 (0.99, 1.79)	1.28 (0.94, 1.73)
≥2 cups/d		79	133	1.28 (0.96, 1.72)	1.14 (0.83, 1.57)	1.09 (0.79, 1.51)
P-trend				0.05	0.25	0.41
Total tea[5]						
<1 cup/mo		165	393	1	1	
1 cup/mo–1 cup/wk		158	440	0.90 (0.69, 1.16)	0.92 (0.69, 1.22)	
2–6 cups/wk		135	276	1.18 (0.90, 1.56)	1.20 (0.89, 1.62)	
1 cup/d		85	185	1.13 (0.82, 1.54)	1.19 (0.84, 1.69)	
≥2 cups/d		102	255	0.98 (0.73, 1.31)	0.97 (0.70, 1.34)	
P-trend				0.85	0.9	
Caffeinated tea[4]						
<1 cup/mo		400	819	1	1	1
1 cup/mo–1 cup/wk		308	576	1.10 (0.91, 1.32)	1.10 (0.90, 1.34)	1.09 (0.89, 1.33)
2–6 cups/wk		183	366	1.02 (0.82, 1.26)	1.08 (0.85, 1.36)	1.08 (0.85, 1.36)
1 cup/d		173	348	1.01 (0.81, 1.25)	0.95 (0.75, 1.20)	0.93 (0.73, 1.18)
≥2 cups/d		170	316	1.11 (0.89, 1.38)	1.06 (0.84, 1.36)	1.04 (0.82, 1.34)
P-trend				0.58	0.98	0.89

(Continued)

TABLE 2 (*Continued*)

	Median, mg/d	Cases, *n*	Controls, *n*	Age-adjusted (OR 95% CI)	Multivariable 1[2] OR (95% CI)	Multivariable 2[3] OR (95% CI)
Herbal tea[5]						
<1 cup/mo		370	956	1	1	
1 cup/mo–1 cup/wk		117	298	1.06 (0.83, 1.35)	1.20 (0.91, 1.57)	
2–6 cups/wk		87	131	1.76 (1.31, 2.38)	2.06 (1.48, 2.86)	
≥1 cups/d		71	164	1.13 (0.83, 1.53)	1.19 (0.85, 1.66)	
P-trend				0.09	0.06	

[1]PMS, premenstrual syndrome; Q, quintile.

[2]Multivariable logistic regression models adjusted for diagnosis year (1993, 1994–1995, 1996–1997, 1998–1999, or 2000–2001); age; pack-years of smoking (0, 1–5, 6–10, 11–15, 16–20, or ≥21); parity (0, 1–2, 3–4, or ≥5); duration of oral contraceptive use (never or 1–23, 24–71, 72–119, or ≥120 mo); history of childhood trauma score (5, 6–10, 11–15, or ≥16); depression before PMS, depression medication; BMI [in kg/m^2 (<20.0, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, or ≥30)]; physical activity (<3, 3 to <9, 9 to <18, 18 to <27, 27 to <42, or ≥42 metabolic equivalent task–hours/wk); and total intake of alcohol (0, >0 to <5, 5 to <10, 10 to <15, or ≥15 g/d), calcium, vitamin D, vitamin B-6, and potassium.

[3]Multivariable model l plus intake of caffeinated coffee, decaffeinated coffee, and caffeinated tea mutually adjusted for each other.

[4]Control count does not sum to 2426 because of missing data.

[5]Herbal tea was not assessed until 1995; baseline for total and herbal tea is 1995.

found no evidence to suggest that total caffeine intake or coffee consumption were associated with increased odds of specific symptoms of PMS, such as breast tenderness, irritability, and fatigue, even in women reporting an intake of ≥4 cups caffeinated coffee/d. We also found that associations were fairly consistent across the 3 time points assessed.

The results of our study are consistent with 3 previous studies, including 2 cross-sectional studies that used retrospective reports of PMS and caffeine consumption (13–15). The third was prospective, which addressed methodologic problems of temporality in previous cross-sectional studies, but suffered from small sample size (n = 34 cases and 49 controls) and was largely unable to control for important confounders of the caffeine–PMS relation.

Our study results conflict with those of a series of 4 epidemiologic studies of caffeine and prevalent PMS by Rossignol et al. (6–9), which largely have provided the supporting evidence for the current medical recommendations. We posit that this inconsistency is due, at least in part, to the potential for residual confounding in the previous studies. For example, in one study, Rossignol et al. (6) reported a 7-fold increased prevalence of PMS in women who consumed 8–10 cups caffeine-containing beverages/d. In our age-adjusted models, we observed that high total caffeine intake and frequent coffee consumption were associated with increased odds of PMS; however, after adjustment for confounders, intake of caffeine and coffee was not associated with PMS, even at very high levels. The strongest confounder of the caffeine–PMS relation was smoking, which was correlated positively with caffeine intake; at baseline, caffeine intake was 264 mg/d higher in heavy smokers than in nonsmokers ($P < 0.001$). Lack of control for important confounders such as smoking may explain the strong positive association of caffeine and caffeinated beverage intake and PMS observed in previous studies.

In addition, it is possible that previous cross-sectional studies that reported a strong positive association were affected by reverse causation from the influence of PMS symptoms on the intake of coffee and other caffeine-containing foods and beverages (9). Women experiencing severe premenstrual symptoms plausibly could alter their caffeine consumption—either increasing intake to treat symptoms such as fatigue or decreasing intake in the hope of reducing symptoms. In our study, results were relatively consistent for intake measured at each time point, suggesting that the caffeine–PMS relation was relatively stable over time and that women with PMS did not clearly increase or decrease their coffee intake substantially after diagnosis.

Multiple mechanisms supporting an adverse impact of caffeine and coffee intake on PMS have been proposed. Caffeine antagonizes the action of the inhibitory neurotransmitter adenosine, resulting in the stimulant effects associated with caffeinated foods and beverages, as well as vasoconstriction (25, 27–30). Studies have found that higher caffeine intake is associated modestly with lower luteal phase concentrations of estradiol and higher concentrations of progesterone (31, 32). However, data do not suggest that any effects of caffeine on sex hormone concentrations are sufficient to interfere with ovulatory function (31, 33–35). Systematic reviews have concluded that caffeine and coffee intake is not associated with an increased risk of adverse reproductive outcomes, consistent with our findings (36, 37). Moreover, ample evidence indicates that moderate daily coffee intake is associated with lower risks of type 2 diabetes, heart disease, and all-cause mortality (38).

Our study has several limitations. Current recommendations for diagnosing PMS in clinical practice involve completion of daily symptom diaries. These methods were not feasible in our large prospective cohort. Alternatively, we used prospective reports of clinical diagnosis, followed by a validated retrospective premenstrual symptom questionnaire to identify PMS cases and controls (19, 20). Although we were unable to confirm prospectively the initial timing of symptom onset, women reported the age at which symptoms began. This allowed us to assess the caffeine–PMS relation in women without symptoms at baseline, which was consistent with our main analysis. It is notable that the previous studies reporting positive associations between caffeine or coffee and PMS also used retrospective symptom questionnaires; differences in measurement instruments and outcome misclassification thus are unlikely to explain differences in study findings. Furthermore, previous studies of diet and PMS in our population have observed significant associations

TABLE 3
Multivariable 1 ORs (95% CIs) for intake of total caffeine and frequency of coffee and tea consumption at baseline, 2–4 y before diagnosis, and 0–3 y after diagnosis and risk of PMS: Nurses' Health Study II PMS substudy, 1991–2005[1]

	At baseline		2–4 y before diagnosis		0–3 y after diagnosis	
	Median	OR (95% CI)	Median	OR (95% CI)	Median	OR (95% CI)
Total caffeine						
Q1	18	1	14	1	14	1
Q2	82	0.84 (0.67, 1.05)	80	0.77 (0.61, 0.98)	76	0.80 (0.63, 1.01)
Q3	168	1.07 (0.85, 1.35)	166	1.02 (0.80, 1.29)	159	0.85 (0.67, 1.07)
Q4	354	1.00 (0.79, 1.28)	350	1.06 (0.84, 1.34)	327	0.89 (0.71, 1.13)
Q5	543	0.79 (0.61, 1.04)	523	0.72 (0.55, 0.94)	483	0.82 (0.65, 1.05)
P-trend		0.31		0.33		0.60
Total coffee						
<1 cup/mo		1		1		1
1 cup/mo–1 cup/wk		1.25 (0.94, 1.67)		1.23 (0.90, 1.67)		1.33 (0.96, 1.84)
2–6 cups/wk		1.10 (0.83, 1.45)		1.38 (1.03, 1.83)		1.21 (0.89, 1.64)
1 cup/d		1.23 (0.96, 1.57)		1.28 (1.00, 1.65)		1.23 (0.96, 1.59)
2–3 cups/d		1.18 (0.95, 1.47)		1.18 (0.96, 1.46)		1.14 (0.92, 1.41)
≥4 cups/d		0.83 (0.61, 1.14)		0.76 (0.56, 1.05)		0.94 (0.69, 1.28)
P-trend		0.43		0.22		0.71
Caffeinated coffee						
<1 cup/mo		1		1		1
1 cup/mo–1 cup/wk		1.17 (0.88, 1.55)		1.40 (1.04, 1.88)		0.91 (0.67, 1.25)
2–6 cups/wk		0.85 (0.64, 1.15)		0.98 (0.72, 1.32)		0.98 (0.72, 1.32)
1 cup/d		1.18 (0.93, 1.50)		1.23 (0.97, 1.58)		1.00 (0.79, 1.28)
2–3 cups/d		1.03 (0.83, 1.28)		1.14 (0.92, 1.40)		0.98 (0.79, 1.20)
≥4 cups/d		0.80 (0.58, 1.11)		0.72 (0.52, 1.01)		0.84 (0.62, 1.15)
P-trend		0.33		0.25		0.48
Decaffeinated coffee						
<1 cup/mo		1		1		1
1 cup/mo–1 cup/wk		1.11 (0.90, 1.37)		1.01 (0.81, 1.25)		1.12 (0.91, 1.39)
2–6 cups/wk		0.95 (0.71, 1.26)		1.17 (0.89, 1.54)		1.39 (1.05, 1.85)
1 cup/d		1.33 (0.99, 1.79)		1.00 (0.74, 1.35)		1.00 (0.73, 1.37)
≥2 cups/d		1.14 (0.83, 1.57)		1.10 (0.79, 1.51)		1.08 (0.77, 1.50)
P-trend		0.25		0.58		0.62
Total tea[2]						
<1 cup/mo		1		1		1
1 cup/mo–1 cup/wk		0.92 (0.69, 1.22)		0.92 (0.70, 1.22)		1.00 (0.81, 1.24)
2–6 cups/wk		1.20 (0.89, 1.62)		1.06 (0.78, 1.44)		1.16 (0.92, 1.47)
1 cup/d		1.19 (0.84, 1.69)		1.14 (0.80, 1.63)		1.10 (0.85, 1.42)
≥2 cups/d		0.97 (0.70, 1.34)		1.09 (0.79, 1.50)		1.24 (0.98, 1.56)
P-trend		0.90		0.37		0.06
Caffeinated tea						
<1 cup/mo		1		1		1
1 cup/mo–1 cup/wk		1.10 (0.90, 1.34)		1.09 (0.90, 1.33)		0.89 (0.74, 1.08)
2–6 cups/wk		1.08 (0.85, 1.36)		0.92 (0.73, 1.16)		1.06 (0.84, 1.34)
1 cup/d		0.95 (0.75, 1.20)		0.98 (0.76, 1.26)		0.85 (0.64, 1.13)
≥2 cups/d		1.06 (0.84, 1.36)		1.12 (0.87, 1.44)		1.06 (0.82, 1.38)
P-trend		0.98		0.59		0.64
Herbal tea[2]						
<1 cup/mo		1		1		1
1 cup/mo–1 cup/wk		1.20 (0.91, 1.57)		1.03 (0.79, 1.34)		1.11 (0.91, 1.35)
2–6 cups/wk		2.06 (1.48, 2.86)		1.34 (0.96, 1.86)		1.25 (0.98, 1.59)
≥1 cups/d		1.19 (0.85, 1.66)		1.30 (0.94, 1.80)		1.23 (0.98, 1.55)
P-trend		0.06		0.06		0.05

[1]Multivariable logistic regression models adjusted for diagnosis year (1993, 1994–1995, 1996–1997, 1998–1999, or 2000–2001); age; pack-years of smoking (0, 1–5, 6–10, 11–15, 16–20, or ≥21); parity (0, 1–2, 3–4, or ≥5); duration of oral contraceptive use (never or 1–23, 24–71, 72–119, or ≥120 mo); history of childhood trauma score (5, 6–10, 11–15, or ≥16); depression before PMS, depression medication; BMI [in kg/m^2 (<20.0, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, or ≥30)]; physical activity (<3, 3 to <9, 9 to <18, 18 to <27, 27 to <42, or ≥42 metabolic equivalent task–hours/wk); and total intake of alcohol (0, >0 to <5, 5 to <10, 10 to <15, or ≥15 g/d), calcium, vitamin D, vitamin B-6, and potassium. PMS, premenstrual syndrome; Q, quintile.

[2]Herbal tea not assessed until 1995; baseline for total and herbal tea is 1995.

TABLE 4
Multivariable 1 ORs and 95% CIs for intake of total caffeine and frequency of coffee consumption at baseline and specific premenstrual symptoms: Nurses' Health Study II PMS substudy, 1991–2005[1]

	Breast tenderness		Irritability		Fatigue	
	Cases, *n*	OR (95% CI)	Cases, *n*	OR (95% CI)	Cases, *n*	OR (95% CI)
Total caffeine						
Q1	183	1	161	1	122	1
Q2	190	0.95 (0.71, 1.28)	161	0.88 (0.63, 1.23)	129	0.97 (0.68, 1.39)
Q3	172	1.01 (0.74, 1.38)	148	1.06 (0.74, 1.50)	117	1.01 (0.68, 1.50)
Q4	195	1.08 (0.78, 1.49)	167	1.04 (0.73, 1.50)	126	1.22 (0.82, 1.81)
Q5	165	0.83 (0.58, 1.19)	125	0.79 (0.53, 1.19)	92	0.91 (0.58, 1.44)
P-trend		0.58		0.30		0.80
Caffeinated coffee						
<1 cup/mo	347	1	301	1	233	1
1 cup/mo–1 cup/wk	77	1.13 (0.78, 1.64)	66	1.17 (0.84, 1.62)	51	1.22 (0.85, 1.74)
2–6 cups/wk	61	0.76 (0.52, 1.12)	50	0.88 (0.62, 1.24)	40	0.82 (0.56, 1.20)
1 cup/d	119	1.12 (0.81, 1.55)	99	1.15 (0.87, 1.52)	81	1.22 (0.90, 1.67)
2–3 cups/d	220	1.02 (0.77, 1.36)	190	1.04 (0.81, 1.33)	143	1.15 (0.87, 1.51)
≥4 cups/d	69	0.73 (0.48, 1.12)	56	0.74 (0.50, 1.10)	38	0.90 (0.59, 1.39)
P-trend		0.44		0.37		0.96
Decaffeinated coffee						
<1 cup/mo	564	1	485	1	387	1
1 cup/mo–1 cup/wk	140	1.18 (0.90, 1.56)	120	1.08 (0.84, 1.39)	82	1.05 (0.80, 1.39)
2–6 cups/wk	65	0.99 (0.67, 1.45)	53	0.88 (0.63, 1.24)	37	0.74 (0.50, 1.10)
1 cup/d	67	1.33 (0.90, 1.98)	57	1.34 (0.95, 1.91)	49	1.62 (1.12, 2.33)
≥2 cups/d	57	1.21 (0.78, 1.87)	47	1.10 (0.75, 1.63)	31	0.88 (0.57, 1.37)
P-trend		0.29		0.39		0.88

[1]Multivariable logistic regression models adjusted for diagnosis year (1993, 1994–1995, 1996–1997, 1998–1999, or 2000–2001); age; pack-years of smoking (0, 1–5, 6–10, 11–15, 16–20, or ≥21); parity (0, 1–2, 3–4, or ≥5); duration of oral contraceptive use (never or 1–23, 24–71, 72–119, or ≥120 mo); history of childhood trauma score (5, 6–10, 11–15, or ≥16); depression before PMS, depression medication; BMI [in kg/m^2 (<20.0, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, or ≥30)]; physical activity (<3, 3 to <9, 9 to <18, 18 to <27, 27 to <42, or ≥42 metabolic equivalent task–hours/wk); and total intake of alcohol (0, >0 to <5, 5 to <10, 10 to <15, or ≥15 g/d), calcium, vitamin D, vitamin B-6, and potassium. PMS, premenstrual syndrome; Q, quintile.

(3, 4, 18, 19), which suggests that our assessment would be sensitive enough to detect an association between caffeine and PMS if one truly exists.

The caffeine content of individual foods and beverages can vary considerably and may contribute to some nondifferential misclassification of caffeine intake. However, misclassification between very high and very low consumption of caffeine, or between coffee drinkers and nondrinkers, is less likely; the consistency of our null findings for individual beverages, as well as caffeine, suggests that misclassification is an unlikely explanation for our results. Furthermore, caffeine intake assessed via FFQ has been sensitive enough to detect associations with other outcomes in the NHS2 cohort (39–41). In addition, we did not assess directly the use of caffeine-containing pain medications (i.e., Excedrin and Anacin) or include these in the calculation of total caffeine intake, potentially resulting in residual confounding or misclassification. However, when we controlled in addition for the use of acetaminophen and aspirin, estimates did not change materially.

Because NHS2 participants were ≥25 y old at baseline, we were unable to evaluate the association of caffeine intake and PMS in younger women, which may be different physiologically from that in older reproductive-age women. However, no association between caffeine intake and PMS was observed in a previous cross-sectional study of young adult women, suggesting that the association is etiologically similar across age groups (14). NHS2 participants are predominantly non-Hispanic white and college-educated, which limited our ability to evaluate these associations in women from different racial, ethnic, and socioeconomic backgrounds. Although we do not anticipate that the physiologic relation of caffeine and PMS would differ across demographic groups, additional prospective studies in more diverse populations are warranted.

The prospective design of our study and 14-y follow-up allowed us to assess whether caffeine and coffee intake could impact the initial development of PMS; to our knowledge, no other studies have addressed this question. It is important to note that we did not evaluate directly whether reducing caffeine or coffee intake could reduce the severity of prevalent PMS. We hypothesize from our null findings that reducing caffeine intake would not be effective at alleviating PMS symptoms. However, to answer this conclusively, randomized controlled trials restricting caffeine intake in women experiencing PMS are needed.

In summary, we did not find that high caffeine intake or frequent consumption of coffee or tea were associated with the development of PMS or specific premenstrual symptoms, including breast tenderness. Our results, in conjunction with those of other studies, suggest that current recommendations to reduce or eliminate caffeine to prevent PMS may be unnecessary.

The authors' responsibilities were as follows—JEM and SEH: contributed to the concept and design of the study and collected data; ACP-S: performed the statistical analysis; ACP-S and ERB-J: wrote the first draft of the manuscript and contributed to the interpretation of results; ERB-J: had primary responsibility for the final content; and all authors: designed the research, helped edit the manuscript, and read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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