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Protein intake and the risk of premenstrual syndrome

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Abstract

Objective: To examine the relationship between protein intake and the risk of incident premenstrual syndrome (PMS).

Design: Nested case-control study. Food frequency questionnaires were completed every four years during follow-up. Our main analysis assessed protein intake 2–4 years before PMS diagnosis (for cases) or reference year (for controls). Baseline (1991) protein intake was also assessed.

Setting: Nurses' Health Study II (NHS2), a large prospective cohort study of registered female nurses in the United States.

Subjects: Participants were premenopausal women between the ages of 27 to 44 (mean: 34), without diagnosis of PMS at baseline, without a history of cancer, endometriosis, infertility, irregular menstrual cycles, or hysterectomy. Incident cases of PMS (n=1,234) were identified by self-reported diagnosis during 14 years of follow-up and validated by questionnaire. Controls (n=2,426) were women who did not report a diagnosis of PMS during follow-up and confirmed experiencing minimal premenstrual symptoms.

Results: In logistic regression models adjusting for smoking, body mass index, B vitamins, and other factors, total protein intake was not associated with PMS development. For example, the odds ratio for women with the highest intake of total protein 2–4 years before their reference year

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(median: 103.6 g/day) versus those in the lowest (median: 66.6 g/day) was 0.94 (95% confidence interval: 0.70–1.27). Additionally, intakes of specific protein sources and amino acids were not associated with PMS. Furthermore, results substituting carbohydrates and fats for protein were also null.

Conclusions: Overall, protein consumption was not associated with risk of developing premenstrual syndrome.

Keywords

Premenstrual syndrome; diet; protein; Nurses' Health Study II; epidemiology

INTRODUCTION

Up to 20% of reproductive aged women meet clinical diagnostic criteria for premenstrual syndrome (PMS),[1, 2] a cyclical disorder characterized by physical and emotional symptoms occurring during the late luteal phase of the menstrual cycle and abating within a few days following the onset of menses. While the etiology of PMS is still largely unknown, an interaction between hormonal, neural, genetic, psychosocial, and dietary factors likely contributes.[3]

We hypothesize that protein intake may be related to PMS through several potential physiological mechanisms, including actions of sex steroid hormones and neurotransmitters, and/or the renin-angiotensin-aldosterone system.[5] Protein intake may alter sex hormone levels, as 17-beta- estradiol and progesterone levels are found to decrease with increasing soy protein intake.[6] Higher animal protein intake has been associated with higher total and free estradiol levels and lower sex hormone binding globulin levels, potentially due to the increase in exogenous hormones.[7] Additionally, high protein intake and intake of specific amino acids may plausibly lower PMS risk, as tryptophan, glutamate, and other amino acids are precursors to neurotransmitters implicated in PMS etiology/[8, 9] Lastly, protein intake is reported to increase levels of renin, aldosterone, and vasopressin[10], vasoactive hormones of the renin-angiotensin-aldosterone system (RAAS), dysfunction of which has been suggested to contribute to PMS.[11, 12]

Women with PMS consumed higher intakes of protein in the premenstrual phase (luteal) compared to the postmenstrual phase (follicular), with no change in intake among controls, in one study examining energy intake over the menstrual cycle.[4] The small number of retrospective studies of the relation between premenstrual symptoms and consumption of protein have reported inconsistent findings[13-15] Additionally, due to the retrospective study designs, it is uncertain whether increased protein or amino acid intake precedes the development of PMS or whether intake is affected by symptom occurrence. To our knowledge, no previous study has prospectively evaluated whether protein intake is associated with risk of developing PMS.

Therefore, we evaluated the relationship between protein intake and the development of premenstrual syndrome in the Nurses' Health Study II (NHS2) PMS Sub-Study, a case-control study nested within the prospective NHS2.

METHODS

Study Population

The NHS2 is an ongoing prospective cohort study that has followed 116,430 US female nurses, aged 25–42 years in 1989, since the first mailed questionnaire. Information on health-related behaviors and medical history has been updated biennially and diet quadrennially for over 25 years.[16] Response rates have been at least 89% for all questionnaire cycles.

Classification of PMS cases and controls

The NHS2 PMS Sub-Study, described previously[16, 17] includes a subset of premenopausal women who did not report that they had or ever had PMS on the 1989 or 1991 questionnaires. Over 14 years of follow-up (1993–2007 questionnaires), 4,108 participants reported new clinician-made diagnoses of PMS. For these women we assigned diagnosis year as their reference year. Women who had never reported a diagnosis of PMS by a clinician were randomly assigned a reference year between 1991 and 2005, of whom 3,248 were frequency matched to cases based on age and reference years. Among both groups, women with a history of cancer other than non-melanoma skin cancer, endometriosis, extremely irregular menstrual cycles, infertility, and hysterectomy prior to their reference year were excluded to limit the possibility that PMS-like symptoms were due to another condition. Additionally, because of our interest in diet, those with implausible caloric intakes (i.e., those below 500 calories and above 3,500 calories) were also excluded. Potential cases and controls were then mailed a modified version of the Calendar of Premenstrual Experiences (COPE) questionnaire[7, 18] assessing occurrence, timing, and impact on several domains of daily functioning of 26 premenstrual symptoms in the specified 2-year period before their individual reference year to confirm case and control status.[16] The response rates were 86% for potential cases and 79% for potential controls.

PMS cases included women that met case criteria for PMS defined by Mortola et al.[18] Specifically, case criteria included: 1) ≥1 physical and ≥1 affective menstrual symptoms; 2) overall symptom severity of “moderate” or “severe” OR “moderate” or “severe” effect of symptoms on at least one life activity or relationship domains; 3) symptoms begin ≤14 days prior to start of menses; 4) symptoms end ≤4 days after start of menses; and 5) symptoms not present in the week after menses ended.[16] Among self-reported cases that responded, 14% did not meet criteria 1, 52% for criteria 2, 6% for criteria 3, 12% for criteria 4, and 17% did not meet criteria 5 (percentages not mutually exclusive). Controls included women that had no or minimal symptoms that did not impact daily function domains. Control criteria included: 1) no PMS diagnosis; 2) either no menstrual symptoms OR an overall symptom severity of “minimal” or “mild”; and 3) either “no effect” or “mild” effect of symptoms on the life activities and relationship domains. Among those that had not reported a PMS diagnosis and responded, 6% did not meet criteria 1, 12% for criteria 2, and 11% for criteria 3. To minimize the likelihood for misclassification of the outcome, women who did not meet either case or control criteria (n=2,946) were excluded from further analysis. This resulted in 1,257 validated PMS cases and 2,463 validated controls that met criteria.

Assessment of protein intake and other factors

Intakes of protein containing foods were assessed via a semi-quantitative 131-item food frequency questionnaire (FFQ) beginning in 1991 and subsequently every four years thereafter. We assessed the intake of total protein, sources of protein (i.e., animal, vegetable, dairy), the ratio of animal to vegetable protein, and specific amino acids (i.e., tryptophan, tyrosine, glutamate). To calculate each woman's total intake of protein and amino acids, the portion size of a single serving of each food or supplement was multiplied by the reported intake frequency. The total amount of each food consumed was then multiplied by the protein or amino acid nutrient content of the food item, and contributions from all food items were summed. Protein intake was then adjusted for total energy intake using the residual method.[19]

The validity of similar FFQs for measuring total protein intake has been demonstrated previously.[19] In an analysis of 92 women, the energy-adjusted correlation between intakes reported by the FFQ and the mean of intake measured with two 1-week diet records was 0.42 for total protein intake.[19]

For each participant, we evaluated protein intake at both baseline (1991) and 2–4 years before her individual reference year (the most recent, but still prospective FFQ), to assess longer term and recent protein intake, respectively. For analyses, dietary information was available for 3,660 Sub-study participants at baseline (n cases=1,234, n controls=2,426) and 3,638 women 2–4 years prior to reference year (n cases=1,222, n controls=2,416).

Information on other factors potentially associated with PMS and diet were collected on the biennial questionnaires, including age, smoking status, weight, pregnancy history, and oral contraceptive use. Height and menstrual cycle characteristics were assessed on the 1989 questionnaire. History of depression and antidepressant use were assessed on the menstrual cycle questionnaire. Childhood trauma was assessed in 2001 on a separate questionnaire.[20] Lastly, macronutrients and micronutrients including vitamin D, B vitamins, calcium, and other minerals were assessed by FFQ.

Statistical analysis

Age-adjusted means and standard deviations for continuous variables and frequencies for categorical variables were calculated using generalized linear modeling to compare distributions of demographic, behavioral, and lifestyle characteristics between cases and controls.

We used unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) of PMS for women across quintiles of protein and amino acid intake. Covariates were either selected as being important a priori or a 10% change in estimates. Multivariable logistic regression was conducted to assess the relationship between protein intake and PMS risk, controlling for age, reference year, age at menarche, body mass index [BMI; weight (kg)/height (m^2)], physical activity, ever use of oral contraceptives, parity (pregnancies lasting ≥6 months), smoking status and quantity (pack-years), ever use of antidepressants, significant childhood trauma, vitamin D from dietary sources and total intake of vitamins B_6, B_1, iron, and zinc.

Additionally, we mutually adjusted vegetable, animal, and dairy protein for one another, to control for potential confounding by variations in protein sources, where potential associations could be due to increases or decreases in the other protein sources. For example, vegetable protein was adjusted for intake of dairy and animal protein. Linear trend across quintiles was assessed using the Mantel extension test for trend, where the median value of each protein category was entered into the regression model as a continuous variable.

We further assessed whether a relation between protein and amino acid intake and PMS varied by age at reference year (<40 versus ≥40 years) and smoking status (past/never versus current) via stratified analyses, as etiology of PMS may vary between younger and older premenopausal women, and between smokers and non-smokers. The multiplicative interaction terms were evaluated using likelihood ratio tests, where the interaction terms were calculated as the products of a binary stratification factor and indicators of macronutrient quintile.

To assess the possibility that associations between higher protein intake and risk of PMS could be due to lower intake of fats or carbohydrates we conducted substitution analyses. For example, we compared associations when protein was substituted for fat by including terms in the model for the percent kcal from protein, the percent kcal from carbohydrates, the percent kcal from alcohol, and total kcal in the model, excluding percent kcal from fat. Additional substitution models were also conducted looking at substitutions for carbohydrates and fats.

Analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). Two-sided p-values <0.05 were considered statistically significant.

RESULTS

Characteristics of cases and controls 2–4 years prior to the reference year are shown in Table 1. Compared to controls, cases were younger and had a higher mean BMI both at 2–4 years prior to the reference year and at age 18. Cases were more likely to have used oral contraceptives, smoked, have been diagnosed with depression, used antidepressants, and had significant childhood trauma. Additionally, cases had lower intakes of vitamin D from food sources and higher intakes of B-vitamins at 2–4 years prior to the reference year.

Total protein intake 2–4 years prior to the reference year was not associated with development of PMS (Table 2). Overall, sources of protein were not associated with the development of PMS. While higher intakes of dairy protein were associated with lower risk of PMS in the age-adjusted model, the results were no longer significant after adjustments for vitamin D, B vitamins, and other covariates. Higher vegetable protein intake was non-significantly associated with increased risk of PMS in multivariable-adjusted models (p for trend = 0.08; OR quintile 5 versus quintile 2 = 1.26; 95% CI = 0.97–1.65). Results for vegetable, animal, and dairy protein intake were similar for mutually adjusted models. Lastly, intakes of tryptophan, tyrosine, and glutamate were not associated with the development of PMS (Table 3).

Analyses evaluating protein and amino acid intake at baseline in 1991 were similar to results for reference year presented (results not shown). For example, the RR for total protein comparing the highest quintiles to the lowest quintile was 0.98 (95% CI = 0.72–1.34). As BMI may potentially lie within the causal path between protein intake and PMS, the analyses were repeated without BMI and estimates were unchanged. Analyses stratified by smoking status did not suggest effect measure modification and there were no significant interactions found. However, the association between protein and risk of PMS did differ by age at diagnosis (Table 4). For total protein, women younger than 40 at reference year had non-significant lower risk of PMS development with increasing protein intake. Additionally, interactions were significant for animal protein and vegetable protein sources (p for interactions < 0.01). Among women who were younger than 40 years at reference year, the OR for animal protein and vegetable protein with PMS comparing the highest quintiles of intake to the lowest quintiles were 0.58 (95% CI = 0.35–0.96) and 1.70 (95% CI = 1.10–2.62), respectively.

Table 5 presents the results of substitution models, where we assessed the effect of substituting equivalent calories from different macronutrients for others. This looks at the effect of the compensatory changes in other macronutrients while holding total calorie intake constant. In age- adjusted models, substitution of protein or fat, for carbohydrate calories appeared to increase risk of developing PMS. Substitution of protein for carbohydrate calories was associated with a 13% increase in PMS risk (95% CI = 1.01–1.26). However, after adjustment for micronutrient intake and other covariates, substitution of protein for carbohydrate calories was not associated with PMS (MV2 OR = 1.00; 95% CI = 0.85–1.17). Similarly, substitution of fat for carbohydrate calories was not associated after adjusting for micronutrients and other covariates (MV2 OR = 1.00; 95% CI = 0.92–1.07). Additional substitutions for fat or carbohydrates were not associated with PMS risk.

DISCUSSION

To our knowledge, this is one of the first studies to evaluate prospectively if protein and amino acid intake are associated with the development of PMS. Overall, we found little evidence that protein intake relates to PMS.

Results from previous studies of protein intake and premenstrual symptoms have been inconsistent. Nagata and colleagues (2004) evaluated the relationship of total protein intake and premenstrual symptoms among Japanese women aged 19–34 (n=189).[13] Total protein (mean protein intake = 76.9 g/day; SD = 35.3 g/day) was not correlated with change in total menstrual distress scores in the premenstrual phase. Barnard (2000) conducted a crossover study among 33 women comparing a low-fat vegetarian diet to normal diet with B-vitamin supplements and found that the low-fat vegetarian diet decreased the duration of premenstrual symptoms.[14] Intakes of protein and fat were significantly different between the normal diet (mean protein intake = 59.8 g/day; SD = 17.7 g/day) and low-fat vegetarian diet (mean protein intake = 43.5 g/day; SD = 11.5 g/day). However, it is unclear whether this is due to the vegetarian diet, lower protein intakes, B vitamin supplement, and/or the low fat diet. Lastly, Steinberg (1999) conducted a clinical trial assessing supplementation of tryptophan (6 g) in women with PMDD for 17 days, where supplementation with tryptophan

(n=37) was more effective than placebo (n=34) in reducing mood symptom severity among women with PMDD.[21] Our study found no association with tryptophan and risk of developing PMS; however, our mean intake of tryptophan was less than 1 gram (mean = 0.98 g/day; SD = 0.17 g/day).

Substitution of protein, for calories from either fat or carbohydrates was not associated with risk of developing PMS after adjusting for potential confounders. This is consistent with our previous findings that fat[22] and carbohydrates[23] were not associated with PMS risk. This further suggests that macronutrient intake is not associated with PMS risk after controlling for intake of micronutrients (e.g., calcium[16], B vitamins[24]) and other factors (e.g., smoking[25], BMI[26]) that are potentially correlated with macronutrient intake and have been significantly associated with PMS risk.

Differences in our results compared to previous study findings could potentially be due to confounding by micronutrients. Nagata did not adjust for micronutrients such as vitamin D or B vitamins.[13] However, when we controlled for several micronutrients we still found no association.The reduction in premenstrual symptom severity for the crossover study by Barnard may have been due to additional differences other than fat intake and source of protein, including differences in micronutrient intakes.[14]

One potential reason why the previous studies found associations with tryptophan whereas we found no associations is study design. The previous studies were treatment trials for premenstrual symptoms, while our study assessed risk of developing PMS. Factors that are associated with treatment of existing PMS may not be similarly related to risk of developing PMS. Additionally, the supplementation dose in the treatment trials was substantially higher than the average dietary intake of tryptophan in our study; potential benefits of tryptophan are perhaps only achievable with higher intakes or supplementation than observable in our study. Furthermore, in studies of prevalent PMS observing associations with protein intake, it is unclear whether women may have altered their protein intake in response to symptoms of PMS as a method of managing them, or whether protein or amino acids intakes contribute to PMS development.

In stratified analyses, among younger women (<40 years old), higher intakes of protein from animal sources were inversely associated with PMS risk, whereas higher intakes of protein from vegetable sources was positively associated with PMS risk. These findings suggest that risk factors may differ for PMS diagnoses at younger versus older ages. However, as these findings were unexpected and the mechanism by which this could occur is unclear, future studies are needed.

Similar to other epidemiological studies that use FFQs to assess diet, protein intakes may be misclassified due to issues in the accuracy of food composition tables to assign a mean protein value for each food and women accurately reporting diet history. As exposure was assessed before the diagnosis of PMS, this misclassification is likely not different between women with PMS and women without PMS, and estimates would be biased towards the null. However, misclassification is minimized through the use of a validated FFQ, exclusion of those with implausible caloric intakes, adjustment for total energy, and ranked

comparisons of high intake versus low intakes using quintiles. Lastly, previous studies within the NHS2 cohort, using the same FFQ, have detected associations between meat and protein intake with other chronic illnesses.[27-29] Additionally, as the etiology of PMS is unknown, it is unclear which dietary exposure period would be most relevant to the development of PMS. While we assessed both longer term (baseline) and more recent protein intakes (2–4 years prior to diagnosis), we cannot exclude the possibility of associations with intakes even closer to diagnosis (<2–4 years prior) or further from diagnosis (e.g., childhood and adolescence). However, prior studies in this cohort have additionally detected associations with dietary intakes 2–4 years prior to PMS[16, 24, 30], indicating that it is a potentially relevant etiological period. Additionally, with the exposure being assessed prior to diagnosis of PMS, we exclude the potential for recall bias and reverse causation.

Due to the large prospective cohort study design, prospective charting was not feasible; however, misclassification of the outcome is minimized by comparing the two ends of symptom spectrum and excluding those in the middle who met criteria neither for cases nor for controls. Symptom recall is likely to be accurate for those who regularly experience severe symptoms that impair daily functioning and for those who regularly experience few, if any symptoms, and is unlikely to be misclassified between these two groups.[16] Secondly, participants had prospectively reported incident PMS diagnoses by a clinician, which were then confirmed by validated retrospective questionnaire. We previously observed that women meeting our criteria for PMS were comparable to those also reported prospective charting.[17]

In conclusion, we did not observe evidence that protein or amino acid intake was associated with PMS risk. Furthermore, macronutrient intake overall was not associated with PMS after adjusting for micronutrients. As this is the first study to examine protein intake and development of PMS, confirmation from additional prospective studies that there does not appear to be an important association is needed. Additionally, future studies should examine micronutrients as potential risk factors for PMS development.

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Table 1.

Age-standardized characteristics of premenstrual syndrome cases and controls at 2–4 years prior to reference year (n=3,638); NHS2 PMS Sub-Study, 1991–2005.

Characteristics*	Cases (n=1222) Mean (SD)	Controls (n=2416) Mean (SD)	p-value‡
Age, years	37.2 (4.3)	38.6 (4.4)	<0.001
Body mass index (kg/m^2)			
At 2–4 years prior to reference year	25.3 (5.6)	24.6 (5.2)	<0.001
At age 18	21.4 (3.3)	21.1 (3.1)	0.02
Age at menarche, years	12.4 (1.4)	12.5 (1.4)	0.04
Age at first birth, years†	26.4 (4.2)	26.5 (3.9)	0.74
Number of full-term pregnancies (≥6 months)	1.9 (1.2)	1.9 (1.2)	0.40
Physical activity, METS/week	28.5 (95.8)	24.6 (65.3)	0.06
Pack-years of cigarette smoking	8.6 (65.2)	5.0 (50.4)	0.07
Alcohol intake, g/day	3.3 (6.0)	3.7 (6.8)	0.31
Total calorie intake, kcal/day	1815 (537)	1826 (518)	0.50
Vitamin D intake food sources, IU/day§	237 (113)	242 (125)	0.02
Total vitamin B_6 intake, mg/day§	9.9 (28.7)	6.8 (19.1)	<0.001
Total vitamin B_{12} intake, mg/day§	11.2 (18.9)	10.9 (19.9)	0.19
Total thiamin intake, mg/day§	4.4 (10.6)	3.9 (9.5)	0.04
Total riboflavin intake, mg/day§	4.9 (10.6)	4.3 (9.2)	0.02
Total iron intake, mg/day§	23.9 (23.4)	24.0 (22.5)	0.45
Total zinc intake, mg/day§	16.3 (10.5)	16.3 (12.1)	0.87
Total potassium intake, mg/day§	2996 (542)	2991(548)	0.22
Total calcium intake, mg/day§	1054 (449)	1084 (447)	0.26
	%	**%**	**p-value‡**
History of tubal ligation Oral contraceptive use	20	21	0.89
Oral contraceptive use			
Ever	86	79	<0.001
Current	8	6	0.47
Duration > 4 years Smoking status	61	57	0.004
Smoking status			
Current	12	6	<0.001
Past	28	18	<0.001
Previously diagnosed with depression	18	8	<0.001
Previously used antidepressant medication	15	7	<0.001
History of childhood trauma	17	9	<0.001

MET, metabolic equivalent of task

[*] All characteristics, except age, standardized to the age distribution of participants at 2–4 years prior to the reference year

[†] Limited to parous women

[‡] Calculated using generalized linear model

[§] Energy adjusted values

Table 2.

Age-adjusted and multivariate odds ratios (OR) and 95% confidence intervals (CI) for dietary protein intakes 2–4 years prior to reference year and risk of premenstrual syndrome (n=3,638); NHS2 PMS Sub-Study, 1991–2005.

	Q1	Q2	Q3	Q4	Q5	P_{trend}
Total protein						
Range, g/day	<73.4	73.4–80.6	80.7–87.2	87.3–95.0	>95.0	
Case: Control Ratio	236:419	233:556	269:542	272:516	212:383	
OR						
Age-adjusted	Ref	0.73	0.88	0.93	0.98	0.49
Model 1 *	Ref	0.73	0.91	0.90	0.94	0.83
95% CI †		0.57–0.94	0.70–1.18	0.68–1.19	0.70–1.27	
Animal Protein						
Range, g/day	<48.6	48.6–56.9	57.0–64.0	64.1–72.8	>72.8	
Case: Control Ratio	236:455	245:521	284:549	250:472	207:419	
OR						
Age-adjusted	Ref	0.90	0.99	1.02	0.94	0.99
Model 1 *	Ref	0.86	0.96	0.94	0.82	0.33
95% CI †		0.67–1.11	0.75–1.24	0.71–1.24	0.61–1.11	
vegetable Protein						
Range, g/day	<19.4	19.4–21.8	21.9–24.3	24.4–27.5	>27.5	
Case: Control Ratio	226:415	244:488	243:492	237:512	272:509	
OR						
Age-adjusted	Ref	0.94	0.92	0.87	1.01	0.95
Model 1 *	Ref	1.01	1.03	0.99	1.26	0.08
95% CI †		0.79–1.29	0.80–1.32	0.76–1.28	0.97–1.65	
Dairy Protein						
Range, g/day	<11.3	11.3–15.3	15.4–19.7	19.8–26.3	>26.3	
Case: Control Ratio	201:379	249:429	251:495	257:516	264:597	
OR						
Age-adjusted	Ref	1.08	0.93	0.90	0.81	0.01
Model 1 *	Ref	1.18	1.10	0.98	0.91	0.25
95% CI †		0.91–1.54	0.83–1.45	0.73–1.31	0.65–1.26	
Animal: Vegetable						
Range, g/day	<1.9	1.9–2.4	2.5–2.9	3.0–3.6	>3.6	
Case: Control Ratio	239:525	265:481	257:519	255:472	206:419	
OR						
Age-adjusted	Ref	1.21	1.08	1.18	1.06	0.72
Model 1 *	Ref	1.09	0.97	1.03	0.86	0.25
95% CI †		0.86–1.38	0.76–1.23	0.79–1.33	0.65–1.14	

Ref, reference category

*Adjusted for age (continuous), reference year (1991–92, 93, 94–96, 97–98, 1999–2000, 01–02, 03–04), age at menarche (continuous), body mass index (≤19.9, 20.0–22.9, 22.5–24.9, 25.0–27.4, 27.5–29.9, ≥30 kg/m^2), physical activity (<3, 3–8, 9–17, 18–26, 27–41, ≥42 METs), oral contraceptive use (none, 1–23, 24–71, 72–119, ≥120 months), parity (nulliparous, 1–2, 3–4, ≥5 pregnancies >6 months), smoking status (never, past 1–14, past 15–34, past 35+, current 1–14, current 15–34, current 35+ cigarettes/day), ever use of antidepressants (never, ever), childhood trauma score (5, 6–10, 11–15, 1620, 21–25), vitamin D from dietary sources (quintiles) and quintiles of total intake for vitamins B_6,B_1, iron, and zinc at 2–4 years before reference year.

†95% CI is for multivariable model.

Table 3.

Age-adjusted and multivariate odds ratios (OR) and 95% confidence intervals (CI) for amino acid intakes (g/day) 2–4 years prior to diagnosis and risk of premenstrual syndrome (n=3638); NHS2 PMS Sub-Study, 1991–2005.

	Q1	Q2	Q3	Q4	Q5	P_{trend}
Tryptophan						
Range, g/day	<0.8	0.8–0.9	0.9–1.0	1.0–1.1	>1.1	
Case: Control Ratio	229:417	232:523	284:580	270:486	207:410	
OR						
Age-adjusted	Ref	0.80	0.89	1.01	0.92	0.85
Model 1 *	Ref	0.83	1.00	1.07	0.91	0.94
95% CI †		0.65–1.07	0.77–1.30	0.81–1.41	0.67–1.24	
Tyrosine						
Range, g/day	<2.6	2.6–2.8	2.9–3.1	3.2–3.4	>3.4	
Case: Control Ratio	226:407	244:552	272:529	259:491	221:437	
OR						
Age-adjusted	Ref	0.79	0.92	0.95	0.91	0.92
Model 1 *	Ref	0.82	1.02	0.92	0.90	0.76
95% CI †		0.64–1.06	0.78–1.33	0.69–1.23	0.66–1.23	
Glutamate						
Range, g/day	<14.0	14.0–15.2	15.3–16.4	16.5–17.6	>17.6	
Case: Control Ratio	217:379	237:544	265:525	276:526	227:442	
OR						
Age-adjusted	Ref	0.75	0.88	0.90	0.89	0.86
Model 1 *	Ref	0.84	0.98	1.00	1.01	0.58
95% CI †		0.65–1.08	0.76–1.28	0.76–1.32	0.75–1.36	

Ref, reference category

*Adjusted for age, reference year, age at menarche, body mass index, physical activity, oral contraceptive use, parity, smoking status, ever use of antidepressants, childhood trauma, vitamin D from dietary sources and total intake of vitamins B_6, B_1, iron, and zinc at 2–4 years before reference year.

†95% CI is for multivariable model.

Table 4.

Multivariate odds ratios (OR) and 95% confidence intervals (CI) for dietary protein intakes 2–4 years prior to reference year and risk of premenstrual syndrome (n=3,638) stratified by age at diagnosis/ reference year; NHS2 PMS Sub-Study, 1991–2005.

	Quintile of protein intake, g/day					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**P for interaction**
Total protein						
<40 years old	1.00 (Ref)	0.71 (0.48 – 1.07)	0.65 (0.42 – 1.02)	0.68 (0.43 – 1.06)	0.80 (0.48 – 1.31)	<0.0001
≥ 40 year old	1.00 (Ref)	0.66 (0.47 – 0.92)	1.05 (0.75 – 1.47)	1.01 (0.70 – 1.45)	1.02 (0.68 – 1.51)	
Animal protein						
<40 years old	1.00 (Ref)	0.74 (0.49 – 1.12)	0.73 (0.48 – 1.12)	0.63 (0.40 – 1.00)	0.58 (0.35 – 0.96)	<0.0001
≥ 40 year old	1.00 (Ref)	0.87 (0.63 – 1.20)	1.06 (0.76 – 1.48)	1.11 (0.77 – 1.58)	0.95 (0.64 – 1.40)	
Vegetable protein						
<40 years old	1.00 (Ref)	0.84 (0.56 – 1.26)	1.38 (0.92 – 2.06)	1.55 (1.01 – 2.38)	1.70 (1.10 – 2.62)	<0.0001
≥ 40 year old	1.00 (Ref)	1.04 (0.75 – 1.45)	0.81 (0.57 – 1.14)	0.72 (0.50 – 1.03)	1.06 (0.74 – 1.52)	
Dairy protein						
<40 years old	1.00 (Ref)	1.16 (0.74 – 1.82)	1.10 (0.68 – 1.79)	1.00 (0.61 – 1.65)	0.74 (0.42 – 1.30)	0.0001
≥ 40 year old	1.00 (Ref)	1.12 (0.80 – 1.57)	1.02 (0.72 – 1.45)	0.91 (0.63 – 1.33)	0.95 (0.62 – 1.46)	

Ref, reference category

*Models are adjusted for age, reference year, age at menarche, body mass index, physical activity, oral contraceptive use, parity, smoking status, ever use of antidepressants, childhood trauma, vitamin D from dietary sources and total intake of vitamins B6, B1, iron, and zinc at 2–4 years before reference year.

Table 5.

Age-adjusted and multivariate odds ratios (OR) and 95% confidence intervals (CI) for macronutrient (5% kcal) substitution models 2–4 years prior to diagnosis and risk of premenstrual syndrome (n=3,638); NHS2 PMS Sub-Study, 1991–2005.

Substitution	Age Adjusted	MV1*	MV2†
Protein for fat	1.10 (0.97–1.25)	1.12 (0.95–1.32)	1.01 (0.84–1.23)
Protein for carbohydrate	1.13 (1.01–1.26)	1.04 (0.91–1.19)	1.00 (0.85–1.17)
Fat for carbohydrate	1.06 (1.00–1.13)	0.98 (0.92–1.05)	1.00 (0.92–1.07)
Fat for protein	1.05 (0.95–1.17)	1.06 (0.94–1.20)	1.01 (0.87–1.18)
Carbohydrate for fat	0.97 (0.92–1.02)	1.05 (0.99–1.12)	1.01 (0.94–1.09)
Carbohydrate for protein	0.99 (0.91–1.07)	1.06 (0.97–1.17)	1.02 (0.90–1.15)

MV, multivariable adjusted

*MV1= age, reference year, age at menarche, body mass index, physical activity, oral contraceptive use, parity, smoking status, ever use of antidepressants, childhood trauma, vitamin D from dietary sources and total intake of vitamins B6, B1, and iron.

†MV2= MV1 + history of depression, and total intake of calcium, vitamins B_{12} and B_2, folate, zinc, and potassium.