July 2016

Macronutrients and the risk of premenstrual syndrome

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MACRONUTRIENTS AND THE RISK OF PREMENSTRUAL SYNDROME

A Dissertation Presented

by

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Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

May 2016

School of Public Health and Health Sciences
Biostatistics and Epidemiology

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ACKNOWLEDGMENTS

I would like to express my deep appreciation and gratitude to my advisor and the chair of my dissertation committee, Dr. Elizabeth Bertone-Johnson, for her advice over the last three years and dedication to this research and my development as a researcher. I owe much of my success to her mentorship, patience, and encouragement during my doctoral studies.

I would also like to thank the members of my dissertation committee, Dr. Brian Whitcomb, Dr. Carol Bigelow, and Dr. Lisa Troy for their guidance and time to review drafts and provide constructive feedback. Additionally, thank you to all the faculty and staff who have contributed to my development as an epidemiologist during my time at the University of Massachusetts Amherst.

Finally, I would like to thank my family and friends for their support during this time. Their moral support and unwavering belief in me were invaluable to the completion of this dissertation.

ABSTRACT

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MAY 2016

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Premenstrual syndrome (PMS) affects 8-20% of reproductive-aged women, impacting work, family, and social interactions. Limitations in available PMS treatments, including side effects and limited medication efficacy, indicate the need for improved prevention. Modifiable risk factors for prevention of PMS include dietary factors. Several micronutrients have been identified as risk factors, but there has been little evaluation of macronutrients. Thus, the research aim was to examine prospectively whether macronutrient consumption was associated with PMS development among a subset of women enrolled in the Nurses' Health Study II cohort.

Chapter 1 evaluates the association of fat intake and PMS risk. Among 3,638 women, total fat intake was not associated with PMS risk, but stearic acid was associated with a 25% decrease risk of PMS. As this was the first study to observe this association, the finding needs to be replicated.

Chapter 2 assesses intake of carbohydrates and PMS risk. Overall, carbohydrate intake was not associated with PMS risk but maltose was

associated with a 45% increased risk of PMS. Again, this is the first study to find this and replication is needed.

Chapter 3 evaluates intake of protein and PMS risk. Protein intake was not associated with PMS risk. Additionally, substitution of macronutrients for each other did not suggest that any macronutrient was importantly associated with PMS risk.

In conclusion, macronutrient intake was not associated with risk of developing PMS after controlling for micronutrient intake and other potential confounders. Micronutrients may play a more important role in PMS development than macronutrient intake.

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CHAPTER 1

DIETARY FAT INTAKE AND THE RISK OF PREMENSTRUAL SYNDROME

Abstract

Approximately 8-20% of reproductive aged women experience premenstrual syndrome (PMS), a cyclical late luteal phase disorder of the menstrual cycle whereby the daily functioning of women is affected by emotional and physical symptoms. Women with PMS are encouraged to reduce fat intake as a way to reduce premenstrual symptoms, though research supporting this recommendation is limited, and its role in the development of PMS is unclear. The purpose of this study was to examine the association between intake of specific dietary fatty acids and the development of PMS among a subset of participants in the prospective Nurses' Health Study II cohort. We compared 1,257 women reporting clinical diagnosis of premenstrual syndrome, confirmed by premenstrual symptom questionnaire and 2,463 matched controls with no or minimal premenstrual symptoms. Intakes of total fat, fat subtypes, and individual fatty acids were assessed quadrennially via food frequency questionnaires. After adjustment for age, body mass index, smoking, calcium, and other factors, intakes of total fat, monounsaturated, polyunsaturated, and trans fat measured 2-4 years before the reference year were not associated with PMS. High saturated fat intake was associated with lower risk of PMS (relative risk [RR] quintile 5 [median = 28.1 g/day] versus quintile 1 [median = 15.1 g/day] = 0.75; 95% confidence interval [CI] = 0.58-0.97; p for trend = 0.04). This association was largely driven by stearic acid intake, with women in the highest quintile (median = 7.4 g/day) having a RR of 0.75 versus those with the lowest intake (median = 3.7 g/day) (95% CI = 0.57-0.98; p for trend = 0.03). Individual

polyunsaturated and monounsaturated fats, including omega-3 fatty acids, were not associated with risk. Overall, fat intake was not associated with higher risk of PMS. High intake of stearic acid may be associated with a lower risk of developing premenstrual syndrome. Additional prospective research is needed to confirm this finding.

Introduction

Premenstrual syndrome (PMS) is a cyclical late luteal phase disorder of the menstrual cycle whereby the daily functioning of women is affected by emotional and physical symptoms. It is estimated that approximately 8-20% of reproductive aged women meet clinical diagnostic criteria for PMS.[1,2] Several treatment options exist (e.g., oral contraceptives, gonadotropin-releasing hormone agonists, antidepressants); however, there may be side effects and efficacy is relatively low.[3] Thus, it is important to identify modifiable risk factors to prevent the initial development of premenstrual syndrome, particularly those that are easy to implement, such as dietary recommendations.

The American Congress of Obstetricians and Gynecologists (ACOG) recommends reducing fat intake to treat PMS.[4] However, evidence supporting these recommendations is limited, and it is unclear whether they apply to the prevention of PMS development.[5] A small number of retrospective studies have reported inconsistent relationships between premenstrual symptoms with consumption of fats.[6,7] Among retrospective studies, because of issues related to establishing temporality, it is unknown whether increased fat and fatty acid intake precedes the development of PMS. Additionally, little attention has been given to specific types of fat, with most studies evaluating either total fat[6,7] or evening primrose oil.[8] To our knowledge, no previous

study has prospectively evaluated whether total fat, fat subtypes, or individual fatty acid intake is associated with risk of developing PMS.

Therefore, we evaluated the relation between intake of specific dietary fatty acids 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 a large prospective cohort of 116,686 US female registered nurses, aged 25-42 years in 1989, that has assessed demographics, health-related behaviors, diet, and medical history biennially and diet quadrennially for over 25 years.[9] Response rates have been ≥89% for all questionnaire cycles. The original NHS2 study protocol was approved by the Intuitional Review Board at Brigham and Women's Hospital.

Classification of PMS cases and controls

The NHS2 PMS Sub-Study has been described previously.[9,10] Briefly, we identified all NHS2 members who had not reported diagnosis of PMS by a clinician in either 1989 or 1991 and thus were at risk of developing PMS. Premenopausal women reporting a new clinician-made diagnosis of PMS during the follow-up period in 1991-2005 (1993-2007 questionnaires) were selected as potential cases (n=4,108) with the diagnosis year used as their reference year. Potential controls were randomly selected from women that did not report a diagnosis of PMS from 1991-2005 (3,248) and were randomly assigned a reference year (1991-2005), and then were frequency matched to cases on age and reference years. Women who had reported a history of cancer (other than non-melanoma skin cancer), endometriosis, extremely irregular menstrual cycles,

infertility, hysterectomy, or menopause prior to their assigned reference year were excluded. 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.

All potential cases and controls were sent a modified version of the Calendar of Premenstrual Experiences (COPE) questionnaire[10,11] that assessed the occurrence of 26 physical and affective symptoms in the two-years prior to their specific reference year, the timing of symptoms, and the impact of symptoms on several domains of daily functioning.

There were 1,257 women that met clinical diagnostic guidelines for PMS. Specifically, the cases had: 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; 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 week after menses ended.[9]

Women that had no or minimal symptoms that did not impact daily function domains were controls (n=2,463). Specifically they had: 1) confirmed 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 all life activities and relationship domains.[9]

Participants who did not meet these definitions were excluded from further analysis, allowing for a comparison of women at the two extreme ends of the spectrum of premenstrual symptom experience in order to reduce the likelihood of misclassification of cases as controls and vice-versa.

Assessment of fat intake and other factors

In the NHS2, a 131-item semi-quantitative food frequency questionnaire (FFQ) was first given in 1991 and then every four years thereafter. We used food intake information reported on the FFQ to assess the intake of total fat, saturated fat, monounsaturated fat, polyunsaturated fat, trans fat, dairy fat, animal fat, vegetable fat, total omega-3, total omega-6, the ratio of omega-6 to omega-3, and specific fatty acids including stearic acid, oleic acid, arachidonic acid, linoleic acid, conjugated linoleic acid, linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). The FFQ included food high in fat such as red meat, chicken with skin, bacon, processed meats, fish, eggs, butter, margarine, whole milk, cheese, ice cream, French fries, potato chips, peanut butter, and nuts. Additionally, participants were asked about the types of fat used for frying and baking and whether fish oil or cod liver oil supplements are used. Participants indicated the frequency to which they consumed a specific portion size of each food item, with a 9-option range from "never or less than once per month" to "6 or more times per day." To calculate each participant's dietary fat intakes, the portion size of each food item was multiplied by the indicated frequency of consumption and summed across all foods and fat content. Dairy fat is a subset of animal fat (animal fat also includes dairy fats), which includes all fat from the foods in the "Dairy Foods" section on the FFQ except for margarine and non-dairy whitener and fat from the dairy products used as ingredients in other FFQ items. Nutrient intakes were adjusted for total energy using the residual method.[12]

The validity of similar FFQs have been evaluated previously in the Nurses' Health Study. The energy adjusted correlation between intakes reported by FFQ and

mean intake measured via two 1-week diet records was 0.51, 0.59, 0.41, and 0.51 for total fat, saturated fat, polyunsaturated fat, and monounsaturated fat, respectively.[12]

Adjusted intakes from food and supplement sources at baseline (1991) and the 2-4 year period prior to each woman's reference year were evaluated. Dietary information from 3,660 Sub-Study participants was available for analyses of intake at baseline in 1991 and for 3,638 women for analyses of intake 2-4 years before the reference year.

Information on other factors potentially associated with PMS and diet were collected on the biennial questionnaires and included: 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.[13] Lastly, other nutrients such as B-vitamins, iron, and calcium were assessed by FFQ and calculated using similar methods as fat intake.

Statistical analysis

Age-adjusted baseline characteristics of PMS cases and controls were compared using generalized linear modeling. We used unconditional logistic regression models to estimate relative risks (RR) of PMS for women across quintiles of fat intake and calculated 95% confidence intervals (CI) comparing the risk of PMS in each of the four highest quintiles compared to the lowest quintile adjusting for age. Multivariable logistic regression models additionally adjusted for reference year, age, age at menarche, current body mass index (BMI; weight [kg]/height [m^2]), physical activity, oral contraceptives, parity [pregnancies lasting ≥6 months], smoking [pack-years], previous use of antidepressants, significant childhood trauma, previous diagnosis of depression, total

intake of vitamins B_6, B_1, iron, and calcium. Primary analyses used intake at 2-4 years prior to diagnosis; additional models were run using the intake at baseline to assess the possibility of latent effects. Additional analyses also adjusted subtypes of fat for the effect of other subtypes (e.g., saturated fat was adjusted for monounsaturated, polyunsaturated, and trans fat) and each source of fat was adjusted for the other sources (e.g., dairy fat was also adjusted for vegetable and animal fat). The Mantel extension test for trend was used to examine the presence of linear trend across quintiles modeling the median of each quintile as a continuous variable.

We further assessed whether the relationship of dietary fat and PMS varied by age at reference year (<40 versus ≥40 years) and smoking (past/never versus current) via stratified analyses. The multiplicative interaction terms were evaluated using likelihood ratio test, where the interaction terms were calculated as the products of a binary stratification factor and indicators of the macronutrient quintile. We also restricted analyses to non-oral contraceptive users.

SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. Two-sided p-values <0.05 were considered statistically significant for all analyses.

Results

Baseline characteristics of PMS cases and controls are shown in Table 1. Cases were heavier at baseline and age 18, had a slightly earlier age at menarche, and had higher history of oral contraceptive use, smoking, significant childhood trauma, depression and antidepressant use. Additionally, cases on average consumed less vitamin D, calcium, and vitamins B_6 and B_{12} than controls.

Table 2 presents age-adjusted and multivariate-adjusted RR and 95% CI for types of fats consumed 2-4 years prior to the reference year and the risk of developing PMS. In analyses adjusted only for age, total fat, polyunsaturated fat, and monounsaturated fat were each positively associated with risk of developing PMS (p for trend <0.05 for all). However, after controlling for BMI, smoking, and additional covariates, these positive associations were attenuated and no longer significant. In multivariable adjusted models (Model 1), high saturated fats was inversely associated with risk of PMS (RR quintile 5 versus quintile 1 = 0.75; 95% CI = 0.58-0.97). When the models additionally adjusted for other fats (Model 2), saturated fat estimates were slightly stronger (RR quintile 5 versus quintile 1 = 0.63; 95% CI = 0.44-0.92). The estimates for other sub-types of fats were largely unchanged and interpretations did not change.

Table 3 shows results from models assessing risk of PMS related to sources of fats. Intakes of vegetable and dairy fats were unrelated to PMS risk, with estimates for all quintiles approximately equal to one. High animal fat intake was related to a non-significant lower risk of PMS in age-adjusted (p for trend = 0.53) and multivariable adjusted (Model 1) models (p for trend = 0.17). Additional adjustment for the other sources of fat (Model 2) did not affect the interpretations of the estimates.

Results for models of fatty acid intake and PMS risk are presented in Table 4. Stearic acid, a saturated fatty acid, was inversely associated with PMS risk. Women with the highest intake of stearic acid (quintile median = 7.4 g/day) had significant 25% lower risk of PMS than women with the lowest intake (quintile median = 3.7 g/day) (95% CI = 0.57-0.98; p for trend = 0.03). We did not find intake of other individual fatty acids to be associated with risk.

Results evaluating fat and fatty acid intake at baseline (data not shown), to assess latent effects, were largely similar to those evaluating fat intake at reference year, including results for stearic acid. High intake of stearic acid (quintile median = 7.6 g/day) had 20% lower risk, albeit non-significant, than those with the lowest intake (quintile median = 4.1 g/day; 95% CI = 0.62-1.05; p for trend = 0.12). However, there were a few exceptions. The omega-3s from marine sources, EPA and DHA, showed significant positive associations with PMS, with evidence of linear trend. In fully adjusted models, women with the highest EPA intake at baseline (quintile median = 0.12 g/day) had 1.32 times the risk of PMS as those with the lowest (quintile median = 0.01 g/day; 95% CI = 0.99-1.75; p for trend = 0.009). Women with high DHA intake (quintile median = 0.26 g/day) had 1.49 times the risk of PMS as those with the lowest intake (quintile median = 0.05 g/day; 95% CI = 1.14-1.94; p for trend = 0.004). These findings were counter to expectation and physiological explanations are unknown.

As BMI could potentially lie in the casual pathway of an association between fat intake and PMS risk and could mediate associations, multivariable analyses were repeated without adjusting for BMI in the model and estimates were unchanged. Analyses stratified by age and smoking status did not suggest effect modification by any of these factors and there were no significant interactions.

Discussion

We did not find intake of total fat associated with risk of developing PMS. High intake of saturated fat, specifically stearic acid, was significantly associated with lower risk. Other individual fatty acids, including omega-3 fatty acids, were not consistently associated with risk.

Few studies have comprehensively assessed how fat and fatty acid intake may be related to PMS. To date no studies of PMS have utilized prospectively assessed fat or fatty acid intake other than supplement trials. Prior research of the relation between fat intake and PMS has been limited to consideration of symptom presence and/or severity, rather than risk of developing PMS. Both Nagata et al. (2004) and Gold et al. (2007) assessed total fat intake with premenstrual symptoms using cross-sectional study designs.[6,7]

Nagata et al. examined whether total fat and fat subtypes were associated with the severity of premenstrual symptoms among 189 female Japanese students aged 19-34 years.[6] Total fat, saturated fat, and monounsaturated fat were associated with higher overall symptom severity in the premenstrual phase as well as for pain severity specifically.

In contrast, in the Study of Women's Health Across the Nation (SWAN), Gold et al. found total fat intake to be associated with lower cravings/bloating symptoms in older premenopausal women, but was unrelated to the other symptoms assessed, including back pain/cramps, breast pain, or headaches.[7]

The inconsistencies in the findings among these studies may be due to the cross-sectional study design. With the cross-sectional design assessing symptoms, temporality cannot be established and it becomes unclear whether the women are consuming foods with higher fat sources due to cravings in order to alleviate symptoms or whether higher intakes of fat are physiologically involved in the development of premenstrual symptoms. Secondly, the SWAN cohort is an older population (42-52 years) and thus may be capturing perimenopausal symptoms.

Saturated fat was inversely associated with the risk of developing PMS in our study and appeared to be largely driven by stearic acid. The inclusion of stearic acid in the model for saturated fat attenuated the results and the estimates for saturated fat became null (RR quintile 5 versus quintile 1 = 1.07; 95% CI = 0.63-1.82). Stearic acid associations with PMS risk were similar after adjustment for saturated fat; however, due to wider confidence intervals the associations were no longer significant (RR quintile 5 versus quintile 1 = 0.68; 95% CI = 0.40-1.18). Laboratory and clinical evidence suggests that stearic acid may be physiologically different from other saturated fats.[14-17] Stearic acid appears to have a neutral effect or may even lower cholesterol levels as opposed to increasing lipid levels,[14,15] and may potentially lower risk of breast cancer [16] and cardiovascular disease.[15] A common source of stearic acid is cocoa butter, which is a primary component of chocolate.[17] Many women report chocolate cravings premenstrually and may increase chocolate intake to improve symptoms.[18] In post hoc analyses, we evaluated whether chocolate intake may explain the association between stearic acid and PMS risk. When we adjusted for chocolate intake the relationship was slightly attenuated (RR quintile 5 versus quintile 1 = 0.80; 95% CI = 0.60-1.07). As no other studies have evaluated the relationship between stearic acid and PMS, additional studies specifically evaluating whether stearic acid intake may reduce PMS risk or be beneficial in treating premenstrual symptoms are warranted.

Several clinical trials have tested the efficacy of treating premenstrual symptoms with fatty acid supplements. Clinical trials looking at supplements of omega-3s, a mixture of polyunsaturated fatty acids (GLA, oleic, linoleic, other polyunsaturated fats, and vitamin E),[19] and krill oil (high in omega-3)[20] have suggested that these supplements

can alleviate premenstrual symptoms. Doses and durations of supplementation varied; Sohrabi used 2g of omega-3 for one full cycle and then during the late luteal phase for two cycles,[21] Filho used 1-2g of the polyunsaturated fatty acids for six months,[19] and Sampalis compared 2g of krill oil to 2g fish oil for one full cycle then during the late luteal phase for two more cycles.[20] These doses are comparable to our highest quintile of intake for omega-3. However, our study did not find an association with risk of PMS for polyunsaturated fat, oleic, linoleic, or omega-3 fatty acids. Additionally, there was very little supplement use of fish oil or cod liver oil in our study.

We were unable to use prospective symptom charting to assess incident PMS in our large, ongoing prospective cohort. However, we used strict criteria to classify PMS cases and controls, excluding women in the middle of the symptom spectrum and thus reducing the likelihood of misclassification of cases as controls and vice-versa. Women that experience severe symptoms each month and women that experience no symptoms or very minimal symptoms are likely to accurately recall symptom experience and unlikely to be misclassified between the two groups.[9] Additionally, in a previous validation study our method of classifying PMS cases was found to be comparable to methods additionally using report of prospective symptom charting as part of clinical diagnosis.[10]

Participants may either over-report or under-report their intake of foods containing fats or fatty acids either unintentionally or purposefully due to beliefs about what they should be eating. This misclassification would attenuate our findings, though it is less likely, as previous validation studies have found fat intakes from FFQ data to be reasonably well correlated with diet record ($r>0.41$).[12] Secondly, several previous studies

within the NHS2 suggest that FFQs are sensitive enough to detect associations between fats and outcomes such as endometriosis or cardiovascular disease at similar ranges of intake.[22,23] Additionally, the range of intake for total fat and subtypes of fat (i.e., saturated, monounsaturated, polyunsaturated, and trans fat) within our study was comparable to previous observational studies of PMS.[6,7]

Overall, we did not find intake of dietary fats to be associated with higher risk of PMS, though high intake of stearic acid was associated with a statistically significant lower risk of PMS. As this is the first study to suggest this association, additional prospective studies are needed to further evaluate whether stearic acid may reduce risk of developing PMS or improve existing symptoms.

Table 1.1. Age-standardized characteristics of premenstrual syndrome cases and controls at baseline (n=3,660): NHS2 PMS Sub-Study, 1991-2005.

	Cases (n=1234)	Controls (n=2426)	
Characteristics[1]	**Mean (SD)**	**Mean (SD)**	**p-value[3]**
Age, years	33.9 (4.2)	34.5 (3.9)	<0.0001
Body mass index (kg/m^2)			
At baseline (1991)	24.6 (5.2)	23.7 (4.7)	<0.0001
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)	0.05
Age at first birth, years[2]	25.9 (3.9)	26.1 (3.7)	0.10
Number of full-term pregnancies (≥6 months)	1.6 (1.2)	1.6 (1.2)	0.36
Physical activity, METS/week	22.9 (60.2)	23.6 (55.6)	0.74
Pack-years of cigarette smoking	8.3 (64.7)	4.8 (50.2)	0.09
Alcohol intake, g/day	3.1 (6.5)	3.1 (5.7)	0.99
Total calorie intake, kcal/day	1826 (537)	1813 (520)	0.62
Vitamin D intake food sources, IU/day[4]	255 (119)	266 (123)	0.01
Total vitamin B_6 intake, mg/day[4]	5.8 (15.6)	8.6 (26.3)	<0.0001
Total vitamin B_{12} intake, mg/day[4]	9.4 (8.5)	10.1 (14.2)	0.04
Total thiamin intake, mg/day[4]	3.2 (6.0)	3.6 (8.2)	0.09
Total riboflavin intake, mg/day[4]	3.6 (5.7)	4.1 (8.2)	0.07
Total iron intake, mg/day[4]	25.8 (24.8)	24.9 (23.3)	0.35
Total zinc intake, mg/day[4]	15.7 (10.28)	15.9 (10.7)	0.59
Total potassium intake, mg/day[4]	2925 (499)	2897 (501)	0.17
Total calcium intake, mg/day[4]	1030 (403)	1063 (421)	0.03
	%	**%**	**p-value[3]**
History of tubal ligation	15	16	0.66
Oral contraceptive use			
Ever	85	77	<0.0001
Current	12	11	0.33
Duration > 4 years	43	37	0.001
Smoking status			
Current	13	7	<0.0001
Past	27	17	<0.0001
Previously diagnosed with depression	15	7	<0.0001
Previously used antidepressant medication	12	5	<0.0001
History of childhood trauma	18	9	<0.0001

[1]All characteristics, except age, standardized to the age distribution of participants in 1991

[2]Limited to parous women

[3]Calculated using generalized linear model

[4]Energy adjusted values

Table 1.2. Age-adjusted and multivariable relative risks (RR)[1] and 95% confidence intervals (CI) for quintiles of dietary fat subtypes 2 to 4 years before diagnosis and risk of PMS (n=3,638): NHS2 PMS Sub-Study, 1991-2005.

	Quintile of fat intake					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**p-trend**
Total fat						
Median, g/day	46.4	55.6	62.3	68.2	76.8	
Case: Control Ratio	228:506	256:502	258:509	234:470	246:429	
RR (95% CI)						
Age-adjusted	Ref	1.13	1.13	1.11	1.29	0.05
Model 1	Ref	1.06 (0.84-1.34)	1.01 (0.80-1.28)	0.92 (0.72-1.18)	0.95 (0.73-1.23)	0.44
Saturated fat						
Median, g/day	15.1	18.9	21.6	24.3	28.1	
Case: Control Ratio	235:440	242:525	249:536	260:472	236:443	
RR (95% CI)						
Age-adjusted	Ref	0.85	0.86	1.01	0.98	0.65
Model 1	Ref	0.81 (0.63-1.02)	0.78 (0.61-0.99)	0.85 (0.66-1.09)	0.75 (0.58-0.97)	0.07
Model 2	Ref	0.74 (0.56-0.97)	0.68 (0.50-0.92)	0.73 (0.53-1.02)	0.63 (0.44-0.92)	0.04
Polyunsaturated fat						
Median, g/day	7.8	9.5	10.8	12.2	14.5	
Case: Control Ratio	247:540	245:474	229:484	251:490	250:428	
RR (95% CI)						
Age-adjusted	Ref	1.14	1.03	1.15	1.33	0.02
Model 1	Ref	1.13 (0.90-1.43)	0.99 (0.78-1.26)	1.11 (0.87-1.40)	1.14 (0.89-1.46)	0.36
Model 2	Ref	1.14 (0.89-1.45)	1.00 (0.78-1.29)	1.12 (0.86-1.44)	1.15 (0.88-1.52)	0.38
Monounsaturated fat						
Median, g/day	17.0	21.0	23.8	26.4	30.4	
Case: Control Ratio	233:502	251:523	261:505	236:462	241:424	
RR (95% CI)						
Age-adjusted	Ref	1.04	1.12	1.12	1.25	0.04
Model 1	Ref	0.98 (0.77-1.24)	1.00 (0.79-1.27)	0.93 (0.72-1.19)	0.97 (0.74-1.25)	0.70
Model 2	Ref	1.11 (0.84-1.47)	1.19 (0.86-1.64)	1.12 (0.77-1.62)	1.20 (0.79-1.81)	0.45

Table 1.2., Continued.

	Quintile of fat intake					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**p-trend**
Trans fat						
Case: Control Ratio	218:457	242:481	243:498	270:526	249:454	
RR (95% CI)						
Age-adjusted	Ref	1.04	1.01	1.06	1.14	0.25
Model 1	Ref	1.10 (0.86-1.41)	0.97 (0.76-1.25)	0.96 (0.75-1.23)	1.03 (0.79-1.34)	0.83
Model 2	Ref	1.17 (0.90-1.51)	1.05 (0.80-1.38)	1.04 (0.78-1.39)	1.11 (0.81-1.52)	0.80

[1]Model 1 adjusted for age (continuous), reference year (91-92, 93, 94-96, 97-98, 99-00, 01-02, 03-04), age at menarche (continuous), current body mass index (≤19.9, 20.0-22.4, 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 contraceptives (none, 1-23, 24-71, 72-119, ≥120 months), parity (nulliparous, 1-2, 3-4, ≥5 pregnancies >6 months), smoking (never, past 1-14, past 15-34, past 35+, current 1-14, current 15-34, current 35+ cig/day), previous use of antidepressants (never, ever), significant childhood trauma (5, 6-10, 11-15, 16-20, 21-25), previous diagnosis of depression (never, ever), and quintiles of total intake for vitamins B_6, B_1, iron, and calcium at 2 to 4 years before reference year

[2]Model 2 adjusted for factors included in Model 1 + mutually adjusted for other fat subtypes

Table 1.3. Age-adjusted and multivariable relative risks (RR)[1] and 95% confidence intervals (CI) for quintiles of dietary fat sources 2 to 4 years before reference year and risk of PMS (n=3,638): NHS2 PMS Sub-Study, 1991-2005.

	Quintile of fat intake					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**p-trend**
Animal fat						
Median, g/day	21.7	28.9	33.6	38.7	46.9	
Case: Control Ratio	243:466	228:504	260:524	259:488	232:434	
RR (95% CI)						
Age-adjusted	Ref	0.85	0.93	1.00	1.01	0.53
Model 1	Ref	0.77 (0.61-0.99)	0.81 (0.64-1.03)	0.85 (0.67-1.08)	0.78 (0.61-1.00)	0.14
Model 2	Ref	0.86 (0.67-1.10)	0.89 (0.69-1.14)	0.88 (0.68-1.13)	0.81 (0.61-1.07)	0.17
Dairy fat						
Median, g/day	5.9	9.5	12.0	15.1	20.5	
Case: Control Ratio	192:375	246:456	263:505	263:568	258:512	
RR (95% CI)						
Age-adjusted	Ref	1.04	0.98	0.87	0.95	0.33
Model 1	Ref	1.07 (0.83-1.38)	1.02 (0.79-1.33)	0.89 (0.69-1.15)	1.01 (0.77-1.32)	0.65
Model 2	Ref	1.10 (0.84-1.43)	1.16 (0.88-1.53)	1.03 (0.77-1.37)	1.07 (0.78-1.45)	0.82
Vegetable fat						
Median, g/day	18.2	23.3	27.4	31.2	37.9	
Case: Control Ratio	229:491	246:510	241:491	260:477	246:447	
RR (95% CI)						
Age-adjusted	Ref	1.05	1.05	1.20	1.23	0.03
Model 1	Ref	0.98 (0.77-1.24)	1.06 (0.83-1.34)	1.10 (0.86-1.40)	1.05 (0.82-1.35)	0.49
Model 2	Ref	1.13 (0.89-1.43)	1.01 (0.80-1.29)	1.04 (0.82-1.33)	0.98 (0.76-1.26)	0.60

[1]Model 1 adjusted for reference year, age, age at menarche, current body mass index, physical activity, oral contraceptives, parity, smoking, previous use of antidepressants, significant childhood trauma, previous diagnosis of depression, total intake of vitamins B_6, B_1, iron, and calcium at 2 to 4 years before reference year

[2]Model 2 adjusted for factors included in Model 1 + mutually adjusted for other fat subtypes

Table 1.4. Age-adjusted and multivariable relative risks (RR)[1] and 95% confidence intervals (CI) for quintiles of fatty acids 2 to 4 years before reference year and risk of PMS (n=3,638): NHS2 PMS Sub-Study, 1991-2005.

	Quintile of fat intake					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**p-trend**
Stearic acid (18:0)						
Median, g/day	3.7	4.8	5.6	6.3	7.4	
Case: Control Ratio	240:427	231:550	279:527	225:482	247:430	
RR (95% CI)						
Age-adjusted	Ref	0.74	0.93	0.82	1.00	0.65
Model 1	Ref	0.76	0.84	0.70	0.75	0.03
95% CI[2]		0.60-0.96	0.66-1.06	0.54-0.90	0.57-0.98	
Oleic acid (18:1)						
Median, g/day	15.7	19.3	21.9	24.4	28.2	
Case: Control Ratio	235:504	243:519	268:509	239:448	237:436	
RR (95% CI)						
Age-adjusted	Ref	1.01	1.13	1.16	1.19	0.06
Model 1	Ref	0.94	1.00	0.98	0.91	0.64
95% CI[2]		0.74-1.19	0.79-1.26	0.77-1.27	0.70-1.18	
Linoleic acid (18:2)						
Median, g/day	6.6	8.1	9.3	10.6	12.8	
Case: Control Ratio	248:522	240:486	242:467	240:519	252:422	
RR (95% CI)						
Age-adjusted	Ref	1.04	1.09	0.99	1.31	0.04
Model 1	Ref	1.01	1.06	0.95	1.12	0.53
95% CI[2]		0.80-1.29	0.83-1.34	0.75-1.20	0.87-1.43	
Conjugated linoleic acid (c-9,c-12 18:2)						
Median, g/day	57.7	78.2	93.2	108.7	134.8	
Case: Control Ratio	237:430	211:488	261:526	265:502	248:470	
RR (95% CI)						
Age-adjusted	Ref	0.77	0.88	0.94	0.92	0.87
Model 1	Ref	0.75	0.79	0.87	0.80	0.39
95% CI[2]		0.58-0.96	0.62-1.01	0.68-1.11	0.62-1.03	
Linolenic acid (18:3)						
Median, g/day	0.72	0.86	0.97	1.09	1.33	
Case: Control Ratio	247:523	241:509	234:440	258:494	242:450	
RR (95% CI)						
Age-adjusted	Ref	1.02	1.14	1.15	1.18	0.08
Model 1	Ref	0.95	1.11	1.12	1.01	0.61
95% CI[2]		0.75-1.20	0.87-1.41	0.88-1.41	0.80-1.29	

Table 1.4., Continued.

	Quintile of fat intake					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**p-trend**
Arachidonic acid (20:4)						
Median, g/day	0.08	0.11	0.14	0.17	0.23	
Case: Control Ratio	239:506	276:555	245:516	226:479	236:360	
RR (95% CI)						
Age-adjusted	Ref	1.05	1.02	1.02	1.42	0.004
Model 1	Ref	0.98	0.95	0.89	1.11	0.59
95% CI[2]		0.78-1.24	0.75-1.21	0.70-1.14	0.86-1.43	
EPA (20:5)						
Median, g/day	0.01	0.02	0.04	0.07	0.12	
Case: Control Ratio	235:488	317:651	203:392	257:469	210:416	
RR (95% CI)						
Age-adjusted	Ref	1.04	1.09	1.17	1.10	0.31
Model 1	Ref	0.92	1.14	1.06	1.09	0.27
95% CI[2]		0.73-1.16	0.88-1.47	0.83-1.36	0.83-1.44	
DHA (22:6)						
Median, g/day	0.04	0.07	0.10	0.16	0.24	
Case: Control Ratio	257:547	259:510	262:523	225:413	219:423	
RR (95% CI)						
Age-adjusted	Ref	1.09	1.09	1.19	1.15	0.20
Model 1	Ref	1.16	1.19	1.21	1.20	0.24
95% CI[2]		0.92-1.46	0.95-1.51	0.94-1.55	0.92-1.57	
Omega-3 (18:3 + 20:5 + 22:5 + 22:6)						
Median, g/day	0.8	1.0	1.1	1.3	1.7	
Case: Control Ratio	269:575	243:454	254:512	237:475	219:400	
RR (95% CI)						
Age-adjusted	Ref	1.17	1.10	1.11	1.24	0.11
Model 1	Ref	1.24	1.13	1.11	1.19	0.35
95% CI[2]		0.98-1.56	0.90-1.43	0.88-1.40	0.93-1.52	
Omega-6 (cis-18:2 + 20:4)						
Median, g/day	6.9	8.3	9.5	10.8	13.2	
Case: Control Ratio	232:527	244:475	249:511	236:477	261:426	
RR (95% CI)						
Age-adjusted	Ref	1.19	1.12	1.15	1.46	0.002
Model 1	Ref	1.13	1.05	1.10	1.21	0.18
95% CI[2]		0.89-1.43	0.83-1.33	0.86-1.40	0.95-1.55	
Omega-6: Omega-3						
Median, g/day	6.2	7.5	8.3	9.3	11.2	
Case: Control Ratio	211:420	224:477	246:480	285:528	256:501	
RR (95% CI)						
Age-adjusted	Ref	0.93	1.01	1.03	0.99	0.81
Multivariate	Ref	0.84	0.94	0.92	0.86	0.44
95% CI[2]		0.65-1.08	0.73-1.21	0.72-1.19	0.66-1.12	

[1]Model 1 adjusted for reference year, age, age at menarche, current body mass index, physical activity, oral contraceptives, parity, smoking, previous use of antidepressants, significant childhood trauma, previous diagnosis of depression, total intake of vitamins B_6, B_1, iron, and calcium at 2 to 4 years before reference year

[2]95% CI is for multivariable model

CHAPTER 2

CARBOHYDRATE AND FIBER INTAKE AND THE RISK OF PREMENSTRUAL SYNDROME

Abstract

Premenstrual syndrome (PMS) is a cyclical late luteal phase disorder of the menstrual cycle whereby physical and emotional symptoms impact the daily functioning of reproductive aged women. Up to 20% of reproductive aged women are estimated to meet clinical diagnostic guidelines for PMS. Women with PMS are encouraged to reduce sugar intake and increase high-fiber food intake, particularly whole grains, to improve symptoms; however, research supporting these recommendations is limited, and its role in the development of PMS is unclear. The purpose of this study was to examine the relationship between carbohydrate and fiber intake and the risk of incident PMS among participants in the PMS Sub-Study of the prospective Nurses' Health Study II cohort. Incident cases of PMS (n=1,257) were identified by self-reported diagnosis of PMS during 14 years of follow-up and validated using a questionnaire based on the Calendar of Premenstrual Experience. Controls (n=2,463) were women who did not report a diagnosis of PMS during follow-up and confirmed experiencing no or minimal premenstrual symptoms. Carbohydrate and fiber intake was assessed four times during follow-up by food frequency questionnaire. Unconditional multivariable logistic regression was used to estimate relative risks (RR) and 95% confidence intervals (CI). Total carbohydrate intake 2-4 years prior to reference year was not associated with PMS development (RR comparing quintile 5 to quintile 1 = 0.99; 95% CI = 0.74-1.33). Additionally, intakes of specific types of carbohydrates or fibers were not associated with

PMS development, with the exception of maltose. After adjustment for body mass index, smoking, and other factors, women with the highest maltose intake (median = 3.0g/day) had an RR of 1.45 (95% CI = 1.11-1.89) compared to those with the lowest intake (median = 1.2g/day). Overall, carbohydrate and fiber consumption was not associated with risk of developing premenstrual syndrome. As this is among the first studies to suggest that maltose may be associated with PMS risk, this finding requires replication in further studies.

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.[24]

Because of the limited efficacy of pharmaceutical treatments for PMS, there is a need for identifying preventive and modifiable risk factors such as diet. Both the Association of Reproductive Health Professionals and the American Congress of Gynecology and Obstetrics suggest that women with PMS consume frequent small portions of complex carbohydrates, which are high in fiber, and reduce intake of sugar to improve symptom severity.[4,25] However, these recommendations are based on limited empirical evidence.[5] A small number of retrospective studies have reported inconsistent relationships between premenstrual symptoms with consumption of carbohydrates.[6,26,27] Among retrospective studies, temporality is a concern and thus it is unknown whether

increased carbohydrate and sugar intake or lower complex carbohydrates and fiber intake precedes the development of PMS. To our knowledge, no previous study has prospectively evaluated whether carbohydrate intake is associated with risk of developing PMS.

Therefore, we evaluated the relationship between carbohydrate intake and the development of premenstrual syndrome in the Nurses' Health Study 2 (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 116,686 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.[9] Response rates have been at least 89% for all questionnaire cycles. The Institutional Review Board at Brigham and Women's Hospital in Boston, MA approved the original NHS2 study protocol.

Classification of PMS cases and controls

The NHS2 PMS Sub-Study described previously,[9,10] includes a subset of premenopausal women free of PMS prior to baseline in 1991. Over 14 years of follow-up (1993-2007 questionnaires), 4,108 participants reported new clinician-made diagnoses of PMS and the diagnosis year was used as the reference year. Women who had never reported a diagnosis of PMS were randomly assigned a reference year between 1991 and 2005, of which 3,248 were frequency matched to cases based on age and reference years. 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[10,11] assessing occurrence, timing, and impact on several domains of daily functioning of 26 premenstrual symptoms in the specified 2-year period before their reference year to confirm case and control status.[9]

PMS cases included 1,257 women that met clinical diagnostic guidelines for PMS. 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.[9] Controls included 2,463 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. To minimize the likelihood for misclassification of the outcome, women who did not meet either case or control criteria were excluded from further analysis.

Assessment of carbohydrate intake and other factors

Intakes of carbohydrate containing foods were assessed via a semi-quantitative 131-item food frequency questionnaire (FFQ) beginning in 1991 and subsequently every

four years after that. We assessed the intake of total carbohydrates, glycemic index and load, dietary insulin index, sugar (i.e., total, natural, added, sucrose, fructose, lactose, maltose, and glucose), fiber (i.e., total, vegetable, legume, cereal, and fruit), whole and refined grains, bran, germ, and starch. To calculate each woman's total intake of carbohydrates, glycemic index, glycemic load, dietary insulin index, sugars, fibers, grains, bran, germ, and starch, 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 nutrient content of the food item, and the nutrient contributions from all food items were summed. All nutrients were then adjusted for the total energy intake using the residual method.[12]

The validity of similar FFQs has been evaluated previously.[12,28] The energy-adjusted correlation between intakes reported by the FFQ and the mean of intake measured with two 1-week diet records was 0.59 for total carbohydrate intake.[12] The energy-adjusted correlations between intakes reported by the FFQ and the mean intake measured with three 4-day weighed food records were 0.55 for total carbohydrate, 0.53 for sugar, 0.40 for starch, 0.67 for fiber, 0.40 for glycemic index, and 0.38 for glycemic load.[28]

For each participant, we evaluated carbohydrate intake at both baseline (1991) and 2-4 years before the specific reference year was assessed. Dietary information was available for 3,660 Sub-Study participants at baseline and 3,638 women 2-4 years prior to reference year.

Information on other factors potentially associated with PMS and diet were collected, such as age, smoking status, weight, pregnancy history, tubal ligation, and oral

contraceptive use on the biennial questionnaires. 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.[13] Lastly, other nutrients such as vitamin D and calcium 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 obtain distributions of demographic, behavioral, and lifestyle characteristics between cases and controls.

We used unconditional logistic regression models to estimate relative risks (RR) of PMS for women across quintiles of carbohydrate intake and calculated 95% confidence intervals (CI) comparing the risk of PMS in each of the four highest quintiles compared to the lowest quintile adjusting for age. Multivariable logistic regression was conducted 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, alcohol intake, vitamin D from dietary sources and total intake of vitamins B_6, B_{12}, B_1, B_2, folate, iron, zinc, potassium, and calcium. Additionally we mutually adjusted carbohydrate subtypes for one another. Finally, trend was assessed using the Mantel extension test for trend, where the median value of each carbohydrate category was entered into the regression model as a continuous variable.

We further assessed whether the relationship between carbohydrates and PMS varied by age at reference year (<40 versus ≥40) and smoking (past/never versus current) via stratified analyses. 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.

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

Results

Baseline characteristics of cases and controls are shown in Table 1. Compared to controls, cases were younger and had a higher mean BMI both at baseline 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, calcium, and vitamins B_6 and B_{12} at baseline.

Total carbohydrate intake 2-4 years prior to the reference year was not associated with development of PMS (Table 2). For example, the RR for the highest quintile of intake (median = 273.0 g/day) compared to the lowest quintile of intake (median = 185.0 g/day) was 0.99 (95% CI = 0.74-1.33). Similarly, glycemic index and glycemic load were not associated with the development of PMS. While dietary insulin index was associated with lower risk of developing PMS in age-adjusted models, results adjusted for covariates were attenuated and no longer significant.

Total sugar, added sugars, natural sugars, sucrose, fructose, and glucose were not associated with the development of PMS (Table 3). High lactose intake was associated

with lower risk of PMS in age-adjusted analyses but after controlling for additional confounders such as BMI, smoking, and additional covariates, results were no longer significant. Maltose intake was linearly related to PMS risk (p for trend = 0.004). Women with the highest intake (median = 3.0 g/day) had a 45% higher risk of developing PMS compared to women with the lowest intake (median = 1.2 g/day) (95% CI = 1.11-1.89). The higher risk associated with maltose remained significant when adjusting for other types of sugar (RR quintile 5 versus quintile 1 = 1.44; 95% CI = 1.10-1.87, p for trend = 0.007).

Total fiber, vegetable fiber, cereal fiber, and fruit fiber were not associated with PMS development (Table 4). Fiber from legume sources appeared to have a u-shaped association with PMS development, with lower risk of developing PMS in the third and fourth quintiles of intake compared to the first quintile.

Intake of whole grains and refined grains were not associated with PMS development (Table 5). Additionally, intake of bran, germ, and starch were not linearly associated with PMS development.

Analyses evaluating carbohydrate intake at baseline in 1991 did not materially differ from the results shown. As BMI may potentially lie within the causal path between carbohydrates and PMS, the analyses were repeated without adjusting for BMI and estimates were unchanged. Analyses stratified by age and smoking status did not suggest effect modification of relative risks; statistical tests of interactions were all non-significant (all p for interaction >0.05).

Additional sensitivity analyses were performed to address the possibility of residual confounding, particularly in the model assessing maltose. These models

evaluated the effect of controlling for continuous alcohol intake rather than categorical, as well as, adjusting for beer. Neither of these steps affected the estimate from the primary analysis, suggesting that possible residual confounding by alcohol was of no consequence. Lastly, we performed analysis to assess the possibility that women modified dietary consumption of maltose, total sugar, or total carbohydrates in response to pre-diagnosis symptoms and, therefore, observed associations reflected reverse causality. To address this concern, we looked at the change from baseline in carbohydrate and sugar intake (intake at reference year – intake at baseline) in PMS cases and controls. Change in carbohydrate or sugar intake was not significantly different among cases and controls, providing no suggestion of reverse causation in our observations.

Discussion

To our knowledge, this is one of the first studies to evaluate how carbohydrates and fibers are associated with the development of PMS. Overall, we found little evidence that carbohydrate intake relates to PMS, though high intake of the sugar maltose was positively associated with risk.

Whereas we have considered diet as related to risk of PMS development, prior research of the relation between carbohydrate intake and PMS has been limited to consideration of presence and/or severity of symptoms. Among these previous studies, findings have been inconsistent. Nagata and colleagues (2004) evaluated the relationship of carbohydrates and premenstrual symptoms among 189 Japanese women aged 19-34 years.[6] After controlling for age, smoking status, and other factors, the authors found that total intake of carbohydrates was not significantly associated with the total Menstrual

Distress Questionnaire score ($r = -0.12$; $p > 0.05$) in the premenstrual phase. Johnson and colleagues assessed macronutrient intake in healthy, normally menstruating women (n=26) without complaints of menstrual distress, not necessarily PMS, and found that percentage of calories from carbohydrates was positively associated with negative affect ($r = 0.51$; $p < 0.01$) and behavior change ($r = 0.42$; $p < 0.05$).[26]

Cross and colleagues evaluated energy intakes during different phases of the menstrual cycle, including intake of carbohydrates, among women with PMS.[29] They found statistically significant increases in intake of total carbohydrates (44.6% versus 45.6% of kilocalories, $p = 0.05$) and simple sugars (18.9% versus 20.9%; $p < 0.001$) from the postmenstrual to the premenstrual phase among women with PMS but not among women without PMS. There was a non-significant decrease in intake of complex carbohydrates (25.6% versus 24.6% of kilocalories; $p = 0.07$). However, these differences are very small and may not be clinically relevant. Additionally, they did not evaluate whether these differences were significant in women with PMS compared to women without PMS.

While we found no association with either glycemic index or load and risk of PMS, Murakami and colleagues found an inverse association of glycemic index and premenstrual symptoms in Japanese dietetic students (n=640) aged 18-22 years (p for trend=0.016) but no association with glycemic load.[30] Similarly, they also found no association of fiber with premenstrual symptoms.

A potential reason why the previous studies found associations whereas we found no associations is study design; the previous studies were all retrospective, while our study was prospective. Women may be altering their diet in response to symptoms of

PMS as a method of managing them rather than carbohydrates or fiber leading to PMS development. It is important to note that the relationship between fat and symptom experience, like the previous studies, may have different associations than fat with development of PMS, which our study assessed. Secondly, the retrospective studies may be picking up carbohydrate cravings related to symptom experience rather than a physiological association when evaluated prospectively as the previous studies indicates that the eating behaviors differ by symptoms. Thus, they may be a consequence of the symptoms rather than the cause.

When looking at change in intake, the change in carbohydrate or sugar intake was not significantly different among cases and controls. This indicates that carbohydrate intake or sugar intake do not appear to change over time differently in PMS cases than controls. Women with PMS do not appear to increase their carbohydrate intake after diagnosis in response to symptoms to a greater extent than women without PMS.

To our knowledge, previous studies have not evaluated sugar intake with regard to development of PMS. Though two studies have assessed the association between intake of foods with high sugar contents in women with PMS or premenstrual symptom severity and found increases in both consumption premenstrually and increased symptom severity.[27,29]

There have been few studies of specific sugars with PMS risk and none that considered maltose. Maltose is a sugar found commonly in alcohols such as beer and foods such as yams and cereals. Within the entire NHS2 cohort, in 1991 the highest sources of variation for maltose were tomato sauce and candy bars containing chocolate. Previous studies have shown that women with PMS consume higher intakes of alcohol

compared to women without PMS,[7] including beer.[31] However, the positive association between maltose and PMS found in this study is unlikely to be driven by alcohol as we controlled for alcohol intake. Additionally, cases and controls had similar age-adjusted intakes of alcohol at baseline (3.1 g/day versus 3.1 g/day). Furthermore, Bertone-Johnson et al. (2009) found no association with alcohol intake and PMS development (RR = 1.19; 95% CI = 0.84-1.67) within the same PMS Sub-Study cohort. The mechanism for the association between maltose and premenstrual syndrome is unknown and it is unclear whether the association was due to chance; thus, additional prospective studies are needed to confirm.

Our study was nested within a large, ongoing prospective cohort of 116,686 women and prospective charting of symptoms is infeasible in the context of large studies, as it is time intensive and cost prohibitive to collect diaries repeatedly from thousands of women. However, we used strict criteria to classify PMS cases and, as controls, women with minimal symptoms that had no impact on function.[9] Though some non-differential misclassification of the outcome is possible, its potential impact on findings is minimized by comparing the two ends of symptom spectrum and excluding those in the middle that met neither criteria. 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 PMS status is unlikely to be misclassified between these two groups.[9] Secondly, PMS was determined prospectively by report of clinician made diagnoses, which was then confirmed by retrospective questionnaire; this approach has been shown to be comparable reported prospective charting in a validation study.[10]

In conclusion, we did not observe evidence of an association of carbohydrate intake with PMS risk. Additionally, high sugar intake and low fiber intake were also not associated with PMS risk. Maltose may be associated with PMS development; however, since this is the first study to look at this relationship to our knowledge, further prospective studies are needed to confirm this association.

Table 2.1. Age-standardized characteristics of premenstrual syndrome cases and controls at baseline (n=3,660): NHS2 PMS Sub-Study, 1991-2005.

Characteristics[1]	Cases (n=1234) Mean (SD)	Controls (n=2426) Mean (SD)	p-value[3]
Age, years	33.9 (4.2)	34.5 (3.9)	<0.0001
Body mass index (kg/m^2)			
At baseline (1991)	24.6 (5.2)	23.7 (4.7)	<0.0001
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)	0.05
Age at first birth, years[2]	25.9 (3.9)	26.1 (3.7)	0.10
Number of full-term pregnancies (≥6 months)	1.6 (1.2)	1.6 (1.2)	0.36
Physical activity, METS/week	22.9 (60.2)	23.6 (55.6)	0.74
Pack-years of cigarette smoking	8.3 (64.7)	4.8 (50.2)	0.09
Alcohol intake, g/day	3.1 (6.5)	3.1 (5.7)	0.99
Total calorie intake, kcal/day	1826 (537)	1813 (520)	0.62
Vitamin D intake food sources, IU/day[4]	255 (119)	266 (123)	0.01
Total vitamin B_6 intake, mg/day[4]	8.6 (26.3)	5.8 (15.6)	<0.0001
Total vitamin B_{12} intake, mg/day[4]	10.1 (14.2)	9.4 (8.5)	0.04
Total thiamin intake, mg/day[4]	3.6 (8.2)	3.2 (6.0)	0.09
Total riboflavin intake, mg/day[4]	4.1 (8.2)	3.6 (5.7)	0.07
Total iron intake, mg/day[4]	24.9 (23.3)	25.8 (24.8)	0.35
Total zinc intake, mg/day[4]	15.9 (10.7)	15.7 (10.3)	0.59
Total potassium intake, mg/day[4]	2925 (499)	2897 (501)	0.17
Total calcium intake, mg/day[4]	1030 (403)	1063 (421)	0.03
	%	**%**	**p-value[3]**
History of tubal ligation	15	16	0.66
Oral contraceptive use			
Ever	85	77	<0.0001
Current	12	11	0.33
Duration > 4 years	43	37	0.001
Smoking status			
Current	13	7	<0.0001
Past	27	17	<0.0001
Previously diagnosed with depression	15	7	<0.0001
Previously used antidepressant	12	5	<0.0001
History of childhood trauma	18	9	<0.0001

[1]All characteristics, except age, standardized to the age distribution of participants in 1991

[2]Limited to parous women

[3]Calculated using generalized linear model

[4]Energy adjusted values

Table 2.2. Age-adjusted and multivariate relative risks (RR)[1] and 95% confidence intervals (CI) for dietary carbohydrate 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 carbohydrate						
Median, g/day	185.0	210.0	227.2	246.0	273.0	
Case: Control Ratio	239:412	243:506	244:503	259:502	237:493	
RR						
Age-adjusted	Ref	0.82	0.82	0.88	0.82	0.19
Multivariate	Ref	0.90	0.95	1.07	0.99	0.64
95% CI[2]		0.70-1.15	0.73-1.23	0.82-1.40	0.74-1.33	
Glycemic index (GI)						
Median	49.4	52.2	53.9	55.4	57.8	
Case: Control Ratio	239:448	231:488	254:454	248:523	250:473	
RR						
Age-adjusted	Ref	0.88	0.97	0.87	0.95	0.64
Multivariate	Ref	1.06	1.14	1.15	1.19	0.22
95% CI[2]		0.83-1.36	0.88-1.47	0.87-1.50	0.89-1.59	
Glycemic load (GL)						
Median	96.0	110.9	121.8	133.0	150.1	
Case: Control Ratio	234:413	233:490	267:512	250:498	238:503	
RR						
Age-adjusted	Ref	0.83	0.90	0.87	0.81	0.14
Multivariate	Ref	0.99	1.07	1.12	1.08	0.45
95% CI[2]		0.77-1.27	0.83-1.38	0.85-1.47	0.81-1.43	
Dietary insulin index (DII)						
Median	37.9	41.2	43.4	45.7	49.1	
Case: Control Ratio	218:385	259:439	226:483	256:556	263:553	
RR						
Age-adjusted	Ref	1.03	0.80	0.79	0.81	0.01
Multivariate	Ref	1.13	0.92	0.93	1.06	0.91
95% CI[2]		0.87-1.46	0.70-1.19	0.71-1.21	0.80-1.39	

[1]Adjusted for age (continuous), reference year (91-92, 93, 94-96, 97-98, 99-00, 01-02, 03-04), age at menarche (continuous), current body mass index (≤19.9, 20.0-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, ≥30 kg/m2), physical activity (<3, 3-8, 9-17, 18-26, 27-41, ≥42 METs), oral contraceptives (none, 1-23, 24-71, 72-119, ≥120 months), parity (nulliparous, 1-2, 3-4, ≥5 pregnancies >6 months), smoking (never, past 1-14, past 15-34, past 35+, current 1-14, current 15-34, current 35+ cig/day), previous use of antidepressants (never, ever), significant childhood trauma (5, 6-10, 11-15, 16-20, 21-25), alcohol intake (quintiles), vitamin D from dietary sources (quintiles) and quintiles of total intake for vitamins B_6, B_{12}, B_1, B_2, folate, iron, zinc, potassium, and calcium at 2-4 years prior to reference year.
[2]95% CI is for multivariable model.

Table 2.3. Age-adjusted and multivariate relative risks (RR)[1] and 95% confidence intervals (CI) for dietary sugar 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 sugar						
Median, g/day	69.1	87.3	102.6	119.1	147.9	
Case: Control Ratio	252:452	262:485	226:506	271:521	211:452	
RR						
Age-adjusted	Ref	0.96	0.79	0.92	0.81	0.08
Multivariate	Ref	1.04	0.89	1.04	0.83	0.22
95% CI[2]		0.82-1.33	0.69-1.15	0.81-1.34	0.63-1.10	
Added sugar						
Median, g/day	25.1	36.5	46.3	59.6	86.7	
Case: Control Ratio	242:438	262:511	260:572	233:484	225:411	
RR						
Age-adjusted	Ref	0.92	0.81	0.85	0.96	0.85
Multivariate	Ref	1.02	0.90	0.97	1.01	0.98
95% CI[2]		0.81-1.30	0.71-1.14	0.75-1.25	0.76-1.33	
Natural sugar						
Median, g/day	29.0	41.1	51.7	62.9	80.4	
Case: Control Ratio	225:399	256:483	264:492	248:546	229:496	
RR						
Age-adjusted	Ref	0.94	0.96	0.81	0.82	0.03
Multivariate	Ref	1.01	0.99	0.81	0.77	0.08
95% CI[2]		0.77-1.31	0.74-1.31	0.59-1.11	0.54-1.10	
Sucrose						
Median, g/day	24.1	33.0	39.8	48.2	62.5	
Case: Control Ratio	242:458	266:510	254:535	248:475	212:438	
RR						
Age-adjusted	Ref	0.97	0.89	0.97	0.90	0.41
Multivariate	Ref	1.04	0.92	1.05	0.91	0.54
95% CI[2]		0.82-1.32	0.73-1.18	0.82-1.35	0.70-1.19	
Fructose						
Median, g/day	11.8	16.6	20.7	25.5	34.8	
Case: Control Ratio	249:483	257:486	246:519	239:483	231:445	
RR						
Age-adjusted	Ref	1.02	0.91	0.95	1.00	0.85
Multivariate	Ref	1.13	0.92	1.01	0.95	0.50
95% CI[2]		0.89-1.44	0.72-1.17	0.79-1.30	0.73-1.24	

Table 2.3, Continued.

	Q1	Q2	Q3	Q4	Q5	p-trend
Lactose						
Median, g/day	4.0	9.5	14.8	21.8	35.0	
Case: Control Ratio	219:413	231:430	267:505	262:472	243:596	
RR						
Age-adjusted	Ref	0.99	0.98	1.02	0.74	0.005
Multivariate	Ref	1.04	1.13	1.08	0.75	0.11
95% CI[2]		0.79-1.37	0.83-1.54	0.76-1.54	0.49-1.14	
Maltose						
Median, g/day	1.2	1.6	1.9	2.3	3.0	
Case: Control Ratio	196:444	253:518	243:497	276:525	254:432	
RR						
Age-adjusted	Ref	1.09	1.09	1.18	1.31	0.01
Multivariate	Ref	1.17	1.20	1.33	1.45	0.004
95% CI[2]		0.91-1.50	0.93-1.54	1.03-1.71	1.11-1.89	
Glucose						
Median, g/day	12.0	16.2	19.5	23.8	32.2	
Case: Control Ratio	251:501	255:489	258:506	245:474	213:446	
RR						
Age-adjusted	Ref	1.03	1.01	1.02	0.94	0.55
Multivariate	Ref	1.14	1.06	1.08	0.91	0.31
95% CI[2]		0.90-1.45	0.83-1.35	0.84-1.38	0.69-1.18	

[1]Adjusted for age, reference year, age at menarche, body mass index, physical activity, oral contraceptive use, parity, smoking status, ever use of antidepressants, significant childhood trauma, alcohol intake, vitamin D from dietary sources and total intake of vitamins B_6, B_{12}, B_1, B_2, folate, iron, zinc, potassium, and calcium at 2-4 years prior to reference year.
[2]95% CI is for multivariable model.

Table 2.4. Age-adjusted and multivariate relative risks (RR)[1] and 95% confidence intervals (CI) for dietary fiber 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 fiber						
Median, g/day	12.6	15.5	17.9	20.8	25.5	
Case: Control Ratio	233:454	238:478	247:518	253:499	251:467	
RR						
Age-adjusted	Ref	1.00	0.95	1.02	1.10	0.36
Multivariate	Ref	1.04	0.98	1.08	1.11	0.48
95% CI2		0.81-1.35	0.75-1.29	0.81-1.45	0.80-1.53	
Vegetable fiber						
Median, g/day	3.2	4.6	6.0	7.5	10.5	
Case: Control Ratio	244:480	239:515	257:518	241:475	241:428	
RR						
Age-adjusted	Ref	0.93	1.02	1.05	1.16	0.08
Multivariate	Ref	0.92	1.04	1.00	1.03	0.70
95% CI[2]		0.73-1.18	0.81-1.33	0.77-1.31	0.77-1.37	
Legume fiber						
Median, g/day	0.1	0.4	0.8	1.1	2.2	
Case: Control Ratio	245:437	233:487	225:502	247:530	272:460	
RR						
Age-adjusted	Ref	0.86	0.81	0.85	1.10	0.11
Multivariate	Ref	0.82	0.80	0.78	1.02	0.36
95% CI[2]		0.65-1.05	0.61-1.00	0.61-0.99	0.80-1.31	
Cereal fiber						
Median, g/day	3.1	4.3	5.4	6.7	9.4	
Case: Control Ratio	213:368	221:441	249:483	263:581	276:543	
RR						
Age-adjusted	Ref	0.86	0.89	0.78	0.87	0.28
Multivariate	Ref	0.93	1.09	0.99	1.15	0.21
95% CI[2]		0.72-1.21	0.84-1.42	0.76-1.30	0.87-1.52	
Fruit fiber						
Median, g/day	1.1	2.0	2.9	4.1	6.3	
Case: Control Ratio	245:486	230:425	245:561	265:477	237:467	
RR						
Age-adjusted	Ref	1.08	0.87	1.12	1.03	0.63
Multivariate	Ref	1.18	0.94	1.14	0.94	0.54
95% CI[2]		0.92-1.51	0.73-1.20	0.88-1.48	0.71-1.25	

[1]Adjusted for age, reference year, age at menarche, body mass index, physical activity, oral contraceptive use, parity, smoking status, ever use of antidepressants, significant childhood trauma, alcohol intake, vitamin D from dietary sources and total intake of vitamins B_6, B_{12}, B_1, B_2, folate, iron, zinc, potassium, and calcium at 2-4 years prior to reference year.
[2]95% CI is for multivariable model.

Table 2.5. Age-adjusted and multivariate relative risks (RR)[1] and 95% confidence intervals (CI) for dietary grain 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
Whole grains						
Median, g/day	5.8	11.9	18.4	26.7	43.5	
Case: Control Ratio	210:419	227:437	264:499	259:530	262:531	
RR						
Age-adjusted	Ref	1.04	1.07	0.98	0.99	0.67
Multivariate	Ref	1.04	1.08	1.05	1.10	0.55
95% CI[2]		0.80-1.34	0.83-1.39	0.81-1.37	0.84-1.44	
Refined grains						
Median, g/day	39.2	52.0	61.8	73.6	93.2	
Case: Control Ratio	212:376	241:466	245:479	263:535	261:560	
RR						
Age-adjusted	Ref	0.90	0.90	0.87	0.81	0.08
Multivariate	Ref	1.00	1.05	1.10	1.12	0.30
95% CI[2]		0.77-1.28	0.82-1.36	0.85-1.43	0.86-1.47	
Bran						
Median, g/day	0.9	2.3	4.2	6.6	12.6	
Case: Control Ratio	204:387	246:480	251:501	267:554	254:494	
RR						
Age-adjusted	Ref	0.98	0.96	0.92	0.98	0.85
Multivariate	Ref	0.92	0.92	1.01	1.09	0.23
95% CI[2]		0.71-1.18	0.71-1.20	0.78-1.32	0.82-1.44	
Germ						
Median, g/day	0.3	0.5	0.8	1.2	2.2	
Case: Control Ratio	227:408	248:516	235:469	250:495	262:528	
RR						
Age-adjusted	Ref	0.86	0.90	0.90	0.89	0.65
Multivariate	Ref	0.77	0.91	0.91	0.87	0.88
95% CI[2]		0.60-0.98	0.71-1.18	0.70-1.17	0.67-1.13	
Starch						
Median, g/day	57.7	70.2	80.2	91.3	109.1	
Case: Control Ratio	219:393	237:453	253:485	239:541	274:544	
RR						
Age-adjusted	Ref	0.93	0.94	0.79	0.90	0.20
Multivariate	Ref	0.94	1.06	0.93	1.17	0.25
95% CI[2]		0.73-1.21	0.82-1.37	0.71-1.21	0.89-1.53	

[1]Adjusted for age, reference year, age at menarche, body mass index, physical activity, oral contraceptive use, parity, smoking status, ever use of antidepressants, significant childhood trauma, alcohol intake, vitamin D from dietary sources and total intake of vitamins B_6, B_{12}, B_1, B_2, folate, iron, zinc, potassium, and calcium at 2-4 years prior to reference year.
[2]95% CI is for multivariable model.

CHAPTER 3

PROTEIN INTAKE AND THE RISK OF PREMENSTRUAL SYNDROME

Abstract

Premenstrual syndrome (PMS) is a cyclical late luteal phase disorder of the menstrual cycle whereby symptoms affect daily functioning. Up to 20% of reproductive aged women are estimated to meet clinical diagnostic guidelines for PMS. Protein intake may be a modifiable risk factor for PMS, as many amino acids found in dietary protein are precursors of neurotransmitters, of which alterations in normal levels may lead to PMS. We examined the relationship between protein intake and the risk of incident PMS among participants in the PMS Sub-Study of the prospective Nurses' Health Study II cohort. Incident cases of PMS (n=1,257) were identified by self-reported diagnosis during 14 years of follow-up and validated using questionnaire. Controls (n=2,463) were women who did not report a diagnosis of PMS during follow-up and confirmed experiencing minimal premenstrual symptoms. Protein intake was assessed 4 times during follow-up by food frequency questionnaire. Unconditional multivariable logistic regression was used to estimate relative risks (RR) and 95% confidence intervals (CI). After adjustments for smoking, body mass index, B vitamins, and other factors, neither total protein intake at baseline nor 2-4 years prior to reference year were associated with PMS development. Additionally, intakes of specific sources of protein and amino acids were not associated with PMS. Overall, protein consumption was not associated with risk of developing premenstrual syndrome.

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.[24]

Because of the limited efficacy of pharmaceutical treatments for PMS, there is a need for identifying preventive or modifiable risk factors such as diet. 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. A small number of retrospective studies of relationships between premenstrual symptoms consumption of protein have reported inconsistent findings.[6,32,33] Among studies that have reported an association, issues related to establishing temporal ordering of dietary factors and PMS have resulted in uncertainty whether increased protein intake 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 2 (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 116,686 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.[9] Response rates have been at least 89% for all questionnaire cycles. The Institutional Review Board at Brigham and Women's Hospital in Boston, MA approved the original NHS2 study protocol.

Classification of PMS cases and controls

The NHS2 PMS Sub-Study, described previously,[9,10] includes a subset of premenopausal women free of PMS prior to baseline in 1991. 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 were randomly assigned a reference year between 1991 and 2005, of which 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[10,11] 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.[9]

PMS cases included 1,257 women that met clinical diagnostic guidelines for PMS. 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.[9] Controls included 2,463 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. To minimize the likelihood for misclassification of cases as controls the outcome, women who did not meet either case or control criteria were excluded from further analysis.

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: 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 the total energy intake using the residual method.[12]

The validity of similar FFQs for measuring total protein intake has been demonstrated previously.[12] 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.[12]

For each participant, we evaluated protein intake at both baseline (1991) and 2-4 years before her individual reference year. Dietary information was available for 3,660 Sub-study participants at baseline and 3,638 women 2-4 years prior to reference year.

Information on other factors potentially associated with PMS and diet were collected on the biennial questionnaires, including age, smoking status, weight, pregnancy history, tubal ligation, 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.[13] 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 relative risks (RR) and 95% confidence intervals (CI) of PMS for women across quintiles of protein and amino acid intake. 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 protein sources subtypes 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. 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

Baseline characteristics of cases and controls are shown in Table 1. Compared to controls, cases were younger and had a higher mean BMI both at baseline 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, calcium, and vitamins B_6 and B_{12} at baseline.

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 = 0.07; RR quintile 5 versus quintile 2 = 1.27; 95% CI = 0.97-1.66). 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 0.97 (95% CI = 0.71-1.32). 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. For total protein, women that were 40 or above at reference year had higher risk of PMS development with increasing protein intake, whereas women below 40 at reference year had lower risk of PMS development with increasing protein intake (p for interaction = 0.009). Additionally, interactions were significant for animal protein and vegetable protein sources (p for interactions < 0.01). For animal protein, for those 40 or above at reference year, PMS risk was higher for increasing animal protein intake and for those 40 and above during reference year, PMS risk was inverse with increasing animal protein intake. Whereas, the opposite was found for vegetable protein.

Table 4 presents the results of substation models, where we assessed the effect of substituting different macronutrients for others. This looks at the effect of the changes in other macronutrients instead of looking at absolute values only. In age-adjusted models, substitution protein or fats 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 in multivariable models ($RR_{continuous}$ = 1.01; 95% CI = 0.83-1.22). Similarly, substitution of fat for carbohydrate calories was not associated after adjusting for micronutrients and other covariates ($RR_{continuous}$ = 1.02; 95% CI = 0.87-1.18). 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 how 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).[6] Total protein (mean protein intake = 76.9 g/day; SD = 35.3 g/day) was found to be 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.[32] 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. 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 fat or carbohydrates was not associated with risk of developing PMS after adjusting for potential confounders. This is consistent with our previous findings (cite fat and carb paper) that fat and carbohydrates were not associated with PMS risk. This further suggests that macronutrient intake is not associated with PMS risk after controlling for confounding by micronutrients and other covariates.

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.[6] 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.[32]

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 PMS. Factors that are associated with treatment of existing PMS may not be similarly related to risk of developing PMS. Additionally, the dose in the treatment trials was substantially higher than the average intake of tryptophan in our study. If potential benefits of tryptophan are dependent upon higher intakes, we may not have observed associations because of the lower levels in our study. Women may be altering their diet in response to symptoms of

PMS as a method of managing them rather than protein or amino acids leading to PMS development.

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 that 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.[9] Secondly, participants had prospectively reported incident PMS diagnoses by a clinician which were then confirmed by validated retrospective questionnaire. Thus, those meeting Mortola criteria for PMS were comparable to those that met the Mortola criteria and additionally reported prospective charting.[10]

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.

Table 3.1. Age-standardized characteristics of premenstrual syndrome cases and controls at baseline (n=3,660); NHS2 PMS Sub-Study, 1991-2005.

Characteristics[1]	Cases (n=1234) Mean (SD)	Controls (n=2426) Mean (SD)	p-value[3]
Age, years	33.9 (4.2)	34.5 (3.9)	<0.0001
Body mass index (kg/m^2)			
At baseline (1991)	24.6 (5.2)	23.7 (4.7)	<0.0001
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)	0.05
Age at first birth, years[2]	25.9 (3.9)	26.1 (3.7)	0.10
Number of full-term pregnancies (≥6 months)	1.6 (1.2)	1.6 (1.2)	0.36
Physical activity, METS/week	22.9 (60.2)	23.6 (55.6)	0.74
Pack-years of cigarette smoking	8.3 (64.7)	4.8 (50.2)	0.09
Alcohol intake, g/day	3.1 (6.5)	3.1 (5.7)	0.99
Total calorie intake, kcal/day	1826 (537)	1813 (520)	0.62
Vitamin D intake food sources, IU/day[4]	255.4 (119.1)	266.8 (122.7)	0.01
Total vitamin B_6 intake, mg/day[4]	8.6 (26.3)	5.8 (15.6)	<0.0001
Total vitamin B_{12} intake, mg/day[4]	10.1 (14.2)	9.4 (8.5)	0.04
Total thiamin intake, mg/day[4]	3.6 (8.2)	3.2 (6.0)	0.09
Total riboflavin intake, mg/day[4]	4.1 (8.2)	3.6 (5.7)	0.07
Total iron intake, mg/day[4]	24.9 (23.3)	25.8 (24.8)	0.35
Total zinc intake, mg/day[4]	15.9 (10.7)	15.7 (10.3)	0.59
Total potassium intake, mg/day[4]	2925 (499)	2897 (501)	0.17
Total calcium intake, mg/day[4]	1030 (403)	1063 (421)	0.03
	%	**%**	**p-value[3]**
History of tubal ligation	15	16	0.66
Oral contraceptive use			
Ever	85	77	<0.0001
Current	12	11	0.33
Duration > 4 years	43	37	0.001
Smoking status			
Current	13	7	<0.0001
Past	27	17	<0.0001
Previously diagnosed with depression	15	7	<0.0001
Previously used antidepressant	12	5	<0.0001
History of childhood trauma	18	9	<0.0001

[1]All characteristics, except age, standardized to the age distribution of participants in 1991

[2]Limited to parous women

[3]Calculated using generalized linear modeling

[4]Energy-adjusted values

Table 3.2. Age-adjusted and multivariate relative risks (RR)[1] 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						
Median, g/day	66.6	77.3	84.8	92.1	103.6	
Case: Control Ratio	236:419	233:556	269:541	272:515	212:383	
RR						
Age-adjusted	Ref	0.73	0.88	0.93	0.98	0.49
Model 1	Ref	0.73	0.89	0.89	0.93	0.90
95% CI[2]		0.56-0.93	0.68-1.15	0.68-1.17	0.68-1.25	
Animal Protein						
Median, g/day	41.9	53.9	61.7	69.6	81.6	
Case: Control Ratio	236:455	245:521	284:549	250:471	207:418	
RR						
Age-adjusted	Ref	0.90	0.99	1.02	0.95	0.99
Model 1	Ref	0.86	0.95	0.93	0.81	0.29
95% CI[2]		0.67-1.10	0.74-1.23	0.70-1.22	0.60-1.09	
Vegetable Protein						
Median, g/day	17.2	20.3	22.7	25.3	30.0	
Case: Control Ratio	226:414	244:488	243:491	237:512	272:509	
RR						
Age-adjusted	Ref	0.94	0.92	0.87	1.01	0.95
Model 1	Ref	1.00	1.02	0.98	1.27	0.07
95% CI[2]		0.78-1.28	0.80-1.32	0.76-1.28	0.97-1.66	
Dairy Protein						
Median, g/day	7.9	12.5	16.2	21.3	29.9	
Case: Control Ratio	201:379	249:429	251:495	257:516	264:596	
RR						
Age-adjusted	Ref	1.07	0.93	0.90	0.80	0.01
Model 1	Ref	1.19	1.09	0.98	0.91	0.26
95% CI[2]		0.91-1.54	0.82-1.43	0.73-1.31	0.66-1.27	
Animal: Vegetable						
Median, g/day	1.6	2.3	2.8	3.4	4.3	
Case: Control Ratio	239:525	265:481	257:519	255:472	206:419	
RR						
Age-adjusted	Ref	1.26	1.08	1.19	1.04	0.72
Model 1	Ref	1.08	0.95	1.01	0.85	0.21
95% CI[2]		0.85-1.37	0.75-1.21	0.78-1.31	0.64-1.13	

[1]Adjusted for age (continuous), reference year (91-92, 93, 94-96, 97-98, 99-00, 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+ cig/day), ever use of antidepressants (never, ever), childhood trauma score (5, 6-10, 11-15, 16-20, 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.
[2]95% CI is for multivariable model.

Table 3.3. Age-adjusted and multivariate relative risks (RR)[1] 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						
Median, g/day	0.8	0.9	1.0	1.1	1.2	
Case: Control Ratio	229:417	232:523	284:580	270:486	207:410	
RR						
Age-adjusted	Ref	0.78	0.89	1.00	0.89	0.84
Model 1	Ref	0.82	0.98	1.05	0.89	0.98
95% CI[2]		0.64-1.05	0.75-1.26	0.80-1.39	0.66-1.21	
Tyrosine						
Median, g/day	2.3	2.7	3.0	3.3	3.7	
Case: Control Ratio	226:407	244:552	272:529	259:491	221:437	
RR						
Age-adjusted	Ref	0.80	0.91	0.95	0.87	0.92
Model 1	Ref	0.81	1.00	0.91	0.89	0.71
95% CI[2]		0.63-1.05	0.76-1.30	0.68-1.21	0.65-1.21	
Glutamate						
Median, g/day	12.8	14.6	15.8	17.0	18.8	
Case: Control Ratio	217:379	237:544	265:525	276:526	227:442	
RR						
Age-adjusted	Ref	0.76	0.89	0.91	0.87	0.86
Model 1	Ref	0.83	0.97	0.99	1.00	0.62
95% CI[2]		0.64-1.07	0.75-1.27	0.75-1.31	0.74-1.34	

[1]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.
[2]95% CI is for multivariable model.

Table 3.4. Age-adjusted and multivariate relative risks (RR) and 95% confidence intervals (CI) for macronutrient (% 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[1]	MV2[2]
Protein for fat	1.10 (0.97-1.25)	1.04 (0.91-1.19)	0.99 (0.85-1.16)
Protein for carbohydrate	1.13 (1.01-1.26)	1.12 (0.95-1.31)	1.01 (0.83-1.22)
Fat for carbohydrate	1.06 (1.00-1.13)	1.06 (0.94-1.20)	1.02 (0.87-1.18)
Fat for protein	1.05 (0.95-1.17)	0.98 (0.92-1.05)	1.00 (0.92-1.07)
Carbohydrate for fat	0.97 (0.92-1.02)	1.07 (0.97-1.17)	1.02 (0.90-1.15)
Carbohydrate for protein	0.99 (0.91-1.07)	1.05 (0.99-1.12)	1.01 (0.94-1.09)

[1]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.

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

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