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Original Contribution

Intake of Selected Minerals and Risk of Premenstrual Syndrome

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Iron, potassium, zinc, and other minerals might impact the development of premenstrual syndrome (PMS) through multiple mechanisms, but few studies have evaluated these relations. We conducted a case-control study nested within the prospective Nurses' Health Study II (1991–2001). Participants were free from PMS at baseline. After 10 years, 1,057 women were confirmed as PMS cases and 1,968 as controls. Mineral intake was assessed using food frequency questionnaires completed in 1991, 1995, and 1999. After adjustment for calcium intake and other factors, women in the highest quintile of nonheme iron intake had a relative risk of PMS of 0.64 (95% confidence interval (CI): 0.44, 0.92; *P* for trend = 0.04) compared with women in the lowest quintile. Women in the highest quintile of potassium intake had a relative risk of 1.46 (95% CI: 0.99, 2.15; *P* for trend = 0.04) compared with women in the lowest quintile. High intake of zinc from supplements was marginally associated with PMS (for intake of ≥25 mg/day vs. none, relative risk = 0.69, 95% CI: 0.46, 1.02; *P* for trend = 0.05). Intakes of sodium, magnesium, and manganese were unrelated to PMS risk. These findings suggest that dietary minerals may be useful in preventing PMS. Additional studies are needed to confirm these relations.

dietary iron; minerals; premenstrual syndrome

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; NHS2, Nurses' Health Study II; PMS, premenstrual syndrome.

Approximately 8% to 15% of women of reproductive age suffer from premenstrual syndrome (PMS), a disorder characterized by physical and emotional symptoms restricted to the luteal phase of the menstrual cycle that substantially impair life activities and social relationships (1). Common symptoms include breast tenderness, abdominal bloating, appetite changes, depression, and anxiety (2). Because symptoms are varied and are restricted to the luteal phase, the pathophysiology of PMS likely involves multiple systems affected by hormonal cyclicity (3).

Dietary intakes of certain micronutrients, including calcium, vitamin D (4), thiamin, and riboflavin (5), have been previously associated with the development of PMS, but the role of minerals has not been thoroughly explored. Iron, magnesium, zinc, copper, manganese, potassium, and sodium may be involved in the pathophysiology of PMS through a variety of mechanisms. Blood levels of potassium, magnesium, and zinc fluctuate across the menstrual cycle (6). Lower blood levels of zinc and magnesium have been observed in women with PMS compared with controls (7–9). Magnesium (10–12) and potassium (13) have been studied as treatments for premenstrual symptoms in a few small studies, with inconclusive results. To our knowledge, only one previous study has evaluated the effect of dietary manganese on PMS, and in that study, manganese was examined in combination with calcium (14).

It is unknown whether dietary intakes of iron, magnesium, zinc, copper, manganese, potassium, and sodium contribute to the initial development of PMS. We conducted a case-control study nested within the prospective Nurses' Health Study II (NHS2) to evaluate the association between mineral intake and the risk of PMS.

MATERIALS AND METHODS

The NHS2 is a prospective cohort study of 116,678 female US registered nurses who replied to a mailed questionnaire in 1989 when they were 25–42 years old. Information regarding various lifestyle factors and medical conditions has been collected biannually via mailed questionnaire, with a response rate of 89% or higher for each questionnaire cycle. The study protocol was approved by the Institutional Review Board at Brigham and Women's Hospital.

Identification of cases and controls

The establishment of the NHS2 PMS substudy has been described previously (4, 5, 15). Briefly, from among all women who had not reported PMS in 1989 or 1991, we identified 3,430 who reported a new clinician diagnosis of PMS on an NHS2 questionnaire between 1993 and 2001. We assigned each a "reference year" equal to their diagnosis year that we used to determine eligibility and assess menstrual symptom experience and diet. We then identified 2,570 women who did not report PMS between 1989 and 2001 as potential controls; because these women did not have a diagnosis date, we assigned each a randomly chosen year between 1993 and 2001 as her reference year. To prevent the inclusion of women with symptoms that could be attributed to other causes, we excluded women who had a diagnosis of cancer, endometriosis, usual irregular menstrual cycles, or infertility before their reference year. Because of our interest in diet, we also excluded women who reported an implausible total calorie intake on diet questionnaires (<500 or ≥3,500 cal/day).

In 2002, we mailed participants a questionnaire based on the Calendar of Premenstrual Experiences (16) to confirm PMS diagnoses in cases and verify that controls did not have PMS. Participants provided information on the presence or absence of 26 specific symptoms for at least several days each month in most months of the year in the specific 2 years before their individual reference year. We also measured age at start of symptoms, timing of symptom onset and cessation during an average cycle, overall severity of symptoms, and symptom influence on personal relationships, social functioning, and work-related activities. This questionnaire was completed by 86.5% of potential cases ($n = 2,966$) and 97.4% of potential controls ($n = 2,504$).

Our case definition was based on the criteria established by Mortola et al. (16). Participants were considered as cases if they reported: 1) the occurrence of at least 1 physical and 1 affective menstrual symptom; 2) having an overall symptom severity that was moderate or severe or having symptoms with a moderate or severe impact on life activities and social relationships; 3) symptoms that began within 14 days of the onset of menstruation; 4) symptoms that ended within 4 days of the onset of menses; and 5) symptoms that were absent in the week after menses ended. Ultimately, 1,057 (35.6%) potential cases met these criteria and were included in our analysis.

We considered women as confirmed controls if in addition to not reporting a diagnosis of PMS during the study period, they reported either no menstrual symptoms or only mild symptoms with no substantial effect on life activities and interpersonal relationships. A total of 1,968 (78.6%) potential controls met these criteria and were included in the analysis.

The validity of our approach was evaluated in 2007 among those participants whose diagnosis/reference year was 2001 ($n = 138$ cases and 377 controls) (15). Women who did not report prospective symptom charting as part of their diagnosis but who met the criteria of Mortola et al. were similar to those who also reported prospective charting with regard to symptom timing and severity.

Assessment of mineral intake and other factors

Participants completed a semiquantitative food frequency questionnaire (FFQ) as part of their main NHS2 questionnaires in 1991, 1995, and 1999 to estimate usual dietary intakes of 131 foods and supplements during the previous year. Participants were asked to indicate how frequently they consumed a specific portion size of each food item. Mineral-rich foods included on the FFQ were meats and spinach (rich in iron); nuts and fish (magnesium); and bananas, sweet potatoes, and other vegetables (potassium).

To calculate the intake of each mineral, we multiplied portion size by reported frequency of intake and then by mineral content for each food. Mineral content was then summed across all foods. We adjusted for total energy intake using the residual method (17).

Questions about intakes of multivitamins and multivitamin/mineral and iron, zinc, magnesium, and potassium supplements were included on each FFQ. Participants were asked to report whether they currently took multivitamins/minerals, the number of tablets per week, and the specific brand used. On all questionnaires, women were asked about use and dosage of individual zinc supplements. In 1991 and 1995, we additionally queried about doses of iron. We calculated the total intake of individual minerals by summing contributions from foods and supplements. We further estimated intakes of heme iron (derived from animal sources) and nonheme iron (derived from supplements and some plant foods), calculated as the difference between total iron and heme iron.

The validity of the FFQ has been evaluated previously (18–20). The energy-adjusted correlations between intakes reported by the FFQ and the mean of intake measured with two 1-week diet records were 0.66 for magnesium, 0.65 for zinc, and 0.50 for iron (20).

We collected information on other factors potentially associated with PMS and diet, such as age, smoking status, weight, pregnancy history, tubal ligation, and oral contraceptive use on biennial questionnaires throughout the study period. Height and menstrual cycle characteristics were assessed in 1989. Physical activity level was assessed in 1991 and 1997. History of depression and antidepressant use was assessed on the supplemental menstrual symptom questionnaire. Childhood trauma related to punitive parenting was assessed in 2001 using a separate questionnaire (21). Finally, information on dietary intakes of other nutrients,

Table 1. Age-standardized Characteristics of Cases and Controls at Baseline, Nurses' Health Study II Premenstrual Syndrome Substudy, 1991–2001

Characteristic[a]	Cases ($n = 1,057$)		Controls ($n = 1,968$)		*P* Value[b]
	Mean (SE)	%	Mean (SE)	%	
Age, years[c]	34.4 (4.3)		35.0 (3.9)		<0.001
Body mass indexd					
At baseline (1991)	24.6 (0.2)		23.7 (0.1)		<0.001
At 18 years of age	21.4 (0.1)		21.1 (0.07)		0.03
Age at menarche, years	12.4 (0.1)		12.5 (0.03)		0.08
Number of full-term pregnancies	1.7 (0.04)		1.7 (0.03)		0.52
Age at first birth, years[e]	25.9 (0.1)		26.1 (0.1)		0.22
Physical activity, MET-hours/week	23.0 (1.8)		23.3 (1.3)		0.88
Ever used oral contraceptives		85.7		77.7	<0.001
Smoking status					
Current smoker		12.3		6.5	<0.001
Past smoker		26.5		18.2	<0.001
Ever used antidepressant medications		12.1		4.7	<0.001
History of significant childhood trauma		14.8		7.9	<0.001

Abbreviations: MET, metabolic task equivalent; SE, standard error.
[a] All characteristics, except for age, were standardized to the age distribution of participants in 1991.
[b] Calculated using the *t* statistic.
[c] For age, standard deviation is presented instead of standard error.
[d] Weight (kg)/height $(m)^2$.
[e] Limited to parous women.

such as vitamin B6, calcium, and vitamin D, were assessed by FFQ.

Statistical analysis

Baseline characteristics of PMS cases and controls were compared using age-standardized generalized linear models. Using Spearman correlation coefficients, we evaluated the correlation between energy-adjusted intakes of individual minerals including calcium, which was associated with a lower risk of PMS in a previous study in this population (4).

We analyzed mineral intakes from foods and supplements sources combined and separately because the bioavailability and impact of some micronutrients may vary according to the sources. For total intake and intake from food sources, participants were divided into quintiles based on their intakes of each mineral during the 2–4 year period before their individual reference year. For intakes from supplemental sources only, we classified women into 4 groups:

Table 2. Spearman Correlation Coefficients[a] for Energy-adjusted Total Intake of Selected Minerals, Nurses' Health Study II Premenstrual Syndrome Substudy, 1991–2001

	Heme Iron	Nonheme Iron	Magnesium	Manganese	Potassium	Sodium	Zinc	Copper
Heme iron	1.00							
Nonheme iron	−0.12	1.00						
Magnesium	−0.19	0.47	1.00					
Manganese	−0.22	0.47	0.65	1.00				
Potassium	−0.06*	0.18	0.72	0.37	1.00			
Sodium	−0.06*	0.12	0.10	0.12	0.06*	1.00		
Zinc	0.30	0.55	0.40	0.29	0.18	0.05*	1.00	
Copper	−0.03**	0.51	0.64	0.62	0.42	0.14	0.49	1.00
Calcium	−0.26	0.31	0.47	0.14	0.33	0.13	0.37	0.23

* $P < 0.01$; **Not significant.
[a] All other correlations were statistically significant at $P < 0.001$.

those who did not use supplements and approximate tertiles of supplement users. Additionally, we evaluated the association between mineral intake assessed at baseline (1991) and the risk of PMS.

Using logistic regression, we estimated relative risks and 95% confidence intervals comparing the risk of PMS in the highest quintiles or categories with that in the lowest (referent). Multivariable relative risks were adjusted for age, diagnosis year, number of full-term pregnancies (pregnancies lasting ≥6 months), body mass index (weight (kg)/height (m^2)), pack-years of smoking, tubal ligation, duration of oral contraceptive use, childhood trauma, antidepressant use, and intakes of alcohol, vitamin B6, calcium, and vitamin D. Analyses of intakes from foods were adjusted for intake of the same mineral from supplemental sources and vice versa. In additional analyses, we adjusted each mineral for the other minerals evaluated. To evaluate linear trends, we used a Mantel extension test, modeling the medians of each quintile or category as a continuous variable.

Additionally, we calculated molar ratios of intake of zinc versus copper and calcium versus magnesium because these minerals compete for binding sites in the intestine (22, 23). We divided total intakes of zinc, copper, calcium, and magnesium by their molecular weights (65.41, 63.55, 40.10, and 24.31, respectively) and then divided zinc by copper and calcium by magnesium. This protocol was then repeated to calculate ratios from food sources only.

We also conducted subanalyses restricted to women with no history of depression before diagnosis ($n = 882$ cases and 1,819 controls) and to those not using oral contraceptives at baseline ($n = 938$ cases and 1,779 controls). Finally, we stratified our population by age at diagnosis (<40 years or ≥40 years) to assess whether mineral intake may be differently associated with PMS diagnosed at younger ages than at older ages. We also assessed whether the mineral-PMS association was modified by body mass index (<25 or ≥25), alcohol (drinkers or nondrinkers), and smoking status (ever or never smokers). Likelihood ratio tests were conducted to test the significance of multiplicative interactions between these potential effect modifiers and all selected minerals.

RESULTS

Among the 1,057 women selected as cases, the mean age at diagnosis was 40 years. Age-standardized baseline characteristics of cases and controls are presented in Table 1. Compared with controls, cases were younger and had higher body mass indexes at baseline and at 18 years of age. Cases were more likely than were controls to be current or former smokers, to report the use of antidepressants and oral contraceptives, and to report a history of severe childhood trauma. We did not observe significant differences in other nondietary factors.

Total intakes of nonheme iron, magnesium, manganese, potassium, zinc, copper, and calcium were modestly to highly correlated (range of correlation coefficients, 0.14–0.72; all $P < 0.001$; Table 2). Magnesium was highly correlated with potassium and manganese ($r = 0.72$ and $r = 0.65$, respectively). In contrast, correlations of heme iron with other minerals, including nonheme iron, were low and in many cases inverse. Sodium intake was also not strongly correlated with other minerals.

In analyses of mineral intake 2–4 years before the reference years, we observed an inverse association between total intake of iron and PMS development (Table 3). After multivariable adjustment (model 1), we observed that participants in the highest quintile of total iron intake (median, 49.2 mg/day) had a 31% lower risk of PMS (relative risk = 0.69, 95% confidence interval (CI): 0.50, 0.95; P for trend = 0.03) than did those in the lowest quintile (median, 10.4 mg/day). This association appeared to be entirely driven by intake of nonheme iron; intake of heme iron was low and unrelated to PMS risk. Potassium intake was positively associated with the risk of PMS. Participants in the highest quintile of total potassium intake (median, 3,717 mg/day) had a multivariable-adjusted relative risk of 1.50 (95% CI: 1.11, 2.03; P for trend = 0.01) compared with women in the lowest quintile (median, 2,319 mg/day). There was no association between dietary intakes of magnesium, zinc, manganese, copper, and sodium and PMS risk.

When we further adjusted analyses of each mineral for the other minerals evaluated (Table 3, model 2), the results were largely similar but slightly stronger for iron and slightly attenuated for potassium. Results from analyses of mineral intake measured at baseline (1991) were similar to those 2–4 years before the reference years (results not shown). For example, women in the highest quintile of potassium intake had a relative risk of 1.32 compared with those in the lowest quintiles (95% CI: 0.97, 1.79; P for trend = 0.03).

We observed that women with the highest zinc to copper ratio had a significantly lower risk of developing PMS (relative risk = 0.69, 95% CI: 0.50, 0.95; P for trend = 0.03; Table 3) compared with women with the lowest ratio, although this relation was attenuated and no longer significant after adjustment for intakes of other minerals. The ratio of calcium to magnesium was unrelated to the risk of PMS.

Results for mineral intakes from food sources only were similar to those for total intakes but in general were slightly attenuated (results not shown). For example, women in the highest quintile of intake of total iron from food sources (median, 19 mg/day) had a relative risk of 0.85 (95% CI: 0.64, 1.13; P for trend = 0.16) compared with women in the lowest quintile (median, 10 mg/day).

In the analyses of supplemental sources only, we observed nonsignificant inverse associations of both nonheme iron and zinc supplementation and PMS (Table 4). Women in the highest tertile of supplemental nonheme iron intake (median, 60.0 mg/day) had a relative risk of 0.80 (95% CI: 0.58, 1.10) compared with those who did not consume iron from supplements (among users, P for trend = 0.19). For zinc, women with the highest intakes from supplements (median, 25.0 mg/day) had a relative risk of 0.69 (95% CI: 0.46, 1.02) compared with women with no supplemental intake (among users, P for trend = 0.05). Supplemental intakes of magnesium, copper, potassium, and manganese were not associated with PMS risk.

Table 3. Total Intake of Selected Minerals 2–4 Years Before Reference Year and Risk of Premenstrual Syndrome, Nurses' Health Study II Premenstrual Syndrome Substudy, 1991–2001

Mineral and Quintile	Median, mg/day	No. of Cases	No. of Controls	Age-adjusted RR	Model 1[a]		Model 2[b]	
					RR	95% CI	RR	95% CI
Iron								
1 (Low)	10.4	192	346	1.00	1.00	Referent	1.00	Referent
2	12.4	202	396	0.93	0.88	0.66, 1.15	0.82	0.61, 1.09
3	14.8	229	396	1.04	0.91	0.69, 1.21	0.83	0.61, 1.13
4	21.7	220	409	0.97	0.78	0.58, 1.05	0.67	0.48, 0.94
5 (High)	49.2	212	417	0.89	0.69	0.50, 0.95	0.60	0.41, 0.86
P for trend				0.28		0.03		0.02
Heme iron								
1	0.6	183	400	1.00	1.00	Referent	1.00	Referent
2	0.9	220	391	1.22	1.08	0.82, 1.41	1.12	0.85, 1.48
3	1.0	205	418	1.09	0.90	0.69, 1.18	0.93	0.70, 1.24
4	1.3	244	435	1.24	0.97	0.74, 1.27	1.00	0.75, 1.35
5	1.6	203	320	1.39	1.07	0.80, 1.43	1.14	0.81, 1.61
P for trend				0.01		0.75		0.56
Nonheme iron								
1	9.4	218	385	1.00	1.00	Referent	1.00	Referent
2	11.4	205	399	0.91	0.90	0.69, 1.18	0.85	0.64, 1.13
3	14.1	220	384	1.00	0.95	0.72, 1.25	0.88	0.65, 1.20
4	21.4	206	397	0.91	0.81	0.60, 1.09	0.71	0.51, 1.00
5	49.2	206	399	0.88	0.71	0.52, 0.98	0.64	0.44, 0.92
P for trend				0.32		0.04		0.04
Magnesium								
1	237	191	370	1.00	1.00	Referent	1.00	Referent
2	280	223	418	1.04	1.09	0.83, 1.44	1.06	0.77, 1.46
3	311	216	435	0.98	1.13	0.84, 1.51	1.05	0.72, 1.52
4	350	213	397	1.07	1.08	0.80, 1.47	0.89	0.58, 1.37
5	415	212	344	1.23	1.30	0.93, 1.80	0.91	0.56, 1.50
P for trend				0.09		0.16		0.51
Manganese								
1	2.3	193	383	1.00	1.00	Referent	1.00	Referent
2	2.8	204	376	1.11	1.07	0.81, 1.41	1.07	0.80, 1.43
3	3.4	216	446	0.99	0.96	0.73, 1.25	0.96	0.70, 1.30
4	4.2	219	407	1.09	1.05	0.80, 1.38	1.06	0.76, 1.47
5	5.8	223	352	1.32	1.30	0.97, 1.73	1.30	0.90, 1.88
P for trend				0.03		0.06		0.13
Potassium								
1	2,319	203	391	1.00	1.00	Referent	1.00	Referent
2	2,684	221	430	0.98	1.07	0.82, 1.39	1.02	0.76, 1.36
3	2,952	212	437	0.96	1.07	0.81, 1.40	1.03	0.75, 1.42
4	3,248	209	393	1.06	1.14	0.86, 1.52	1.11	0.78, 1.58
5	3,717	210	313	1.37	1.50	1.11, 2.03	1.46	0.99, 2.15
P for trend				0.01		0.01		0.04

Table continues

Table 3. Continued

Mineral and Quintile	Median, mg/day	No. of Cases	No. of Controls	Age-adjusted RR	Model 1[a]		Model 2[b]	
					RR	95% CI	RR	95% CI
Sodium								
1	1,684	201	402	1.00	1.00	Referent	1.00	Referent
2	1,932	192	412	0.93	0.90	0.69, 1.18	0.90	0.69, 1.18
3	2,116	213	392	1.10	0.99	0.75, 1.29	1.00	0.76, 1.31
4	2,308	226	375	1.23	1.14	0.88, 1.50	1.13	0.86, 1.49
5	2,586	223	383	1.18	1.05	0.81, 1.38	1.04	0.79, 1.38
P for trend				0.04		0.28		0.37
Zinc								
1	9.2	206	405	1.00	1.00	Referent	1.00	Referent
2	10.8	182	389	0.92	0.96	0.73, 1.26	0.94	0.71, 1.24
3	12.2	227	417	1.07	0.99	0.75, 1.29	0.97	0.74, 1.28
4	14.9	203	352	1.13	0.98	0.74, 1.31	1.03	0.76, 1.38
5	27.9	237	401	1.11	0.94	0.69, 1.29	0.96	0.65, 1.41
P for trend				0.24		0.75		0.92
Copper								
1	1.0	182	395	1.00	1.00	Referent	1.00	Referent
2	1.2	268	515	1.17	1.19	0.92, 1.54	1.18	0.89, 1.57
3	1.3	138	321	0.98	1.01	0.74, 1.37	0.98	0.69, 1.39
4	1.5	245	397	1.39	1.30	0.98, 1.72	1.20	0.85, 1.69
5	2.9	222	336	1.43	1.33	0.97, 1.81	1.39	0.93, 2.08
P for trend				0.004		0.12		0.13
Zinc to copper ratio[c]								
1	6.8	220	384	1.00	1.00	Referent	1.00	Referent
2	8.0	217	386	0.98	0.81	0.62, 1.06	0.85	0.63, 1.14
3	9.0	219	382	0.99	0.89	0.67, 1.17	0.97	0.70, 1.34
4	10.3	191	418	0.78	0.66	0.49, 0.88	0.72	0.49, 1.06
5	13.9	208	394	0.88	0.69	0.51, 0.95	0.82	0.51, 1.33
P for trend				0.15		0.03		0.59
Calcium to magnesium ratio[c]								
1	1.2	211	392	1.00	1.00	Referent	1.00	Referent
2	1.6	236	368	1.18	1.39	1.04, 1.85	1.47	1.08, 2.01
3	1.9	202	402	0.91	1.96	0.69, 1.34	1.09	0.74, 1.60
4	2.2	216	388	0.99	0.98	0.67, 1.41	1.16	0.73, 1.85
5	2.9	190	414	0.83	0.85	0.55, 1.30	1.10	0.61, 1.98
P for trend				0.03		0.18		0.81

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age (<30, 30–34, 35–39 or ≥40 years), year of diagnosis (1993, 1994–1995, 1996–1996, 1998–1999, or 2000–2001), number of full-term pregnancies (0, 1–2, 3–4, or ≥5 pregnancies lasting ≥6 months), body mass index (weight (kg)/height $(m)^2$) (<20.0, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, or ≥30.0), pack-years of smoking (quintiles), tubal ligation (no vs. yes), duration of oral contraceptive use (0, 1–23, 24–71, 72–119, or ≥120 months), antidepressant use (never vs. ever), history of childhood trauma score (5, 6–10, 11–15,or ≥16), and intakes of alcohol, vitamin B6, calcium, and vitamin D (quintiles). Heme iron was adjusted for nonheme iron and vice versa. Zinc to copper molar ratio was additionally adjusted for total zinc intake.

[b] Additionally adjusted for total intake of the other minerals in the table.

[c] Median values for ratios do not have units of measure.

Table 4. Intake of Selected Minerals From Supplemental Sources and Risk of Premenstrual Syndrome, Nurses' Health Study II Premenstrual Syndrome Substudy 1991–2001

Mineral and Tertile	Range, mg/day	Supplement Median[a]	Total Median[b]	No. of Cases	No. of Controls	Age-adjusted		Multivariable[c]	
						RR	95% CI	RR	95% CI
Nonheme iron									
Nonusers			13.1	705	1,350	1.00	Referent	1.00	Referent
1 (low)	0.4–15.4	10.0	22.0	122	202	1.15	0.90, 1.46	1.07	0.80, 1.43
2	15.5–30.0	18.0	34.1	115	207	1.04	0.82, 1.34	1.04	0.76, 1.42
3	30.1–240	60.0	74.5	115	209	0.99	0.77, 1.26	0.80	0.58, 1.10
P for trend[d]							0.36		0.19
Magnesium									
Nonusers			298	806	1,594	1.00	Referent	1.00	Referent
1 (low)	1–57	14	331	93	116	1.56	1.17, 2.08	1.64	1.17, 2.29
2	58–100	57	364	58	93	1.22	0.87, 1.71	1.02	0.69, 1.51
3	101–480	100	421	100	165	1.15	0.89, 1.50	1.30	0.93, 1.81
P for trend[d]							0.12		0.67
Manganese									
Nonusers			3.3	870	1,672	1.00	Referent	1.00	Referent
1 (low)	0.1–1.4	0.7	4.1	68	100	1.32	0.96, 1.81	1.30	0.90, 1.87
2	1.5–2.5	2.5	5.7	78	116	1.25	0.93, 1.69	1.41	0.98, 2.01
3	2.6–16.7	5.0	8.1	41	80	0.98	0.66, 1.44	0.90	0.57, 1.42
P for trend[d]							0.19		0.36
Zinc									
Nonusers			11.3	755	1,477	1.00	Referent	1.00	Referent
1 (low)	0.1–8.6	4.3	16.8	106	153	1.34	1.03, 1.74	1.34	1.00, 1.84
2	8.7–15.0	15	26.1	126	190	1.24	0.97, 1.58	1.25	0.91, 1.72
3	15.1–150	25	37.7	70	148	0.88	0.65, 1.19	0.69	0.46, 1.02
P for trend[d]							0.03		0.05
Copper									
Nonusers			1.2	827	1,594	1.00	Referent	1.00	Referent
1 (low)	0.03–1.10	0.3	1.7	79	110	1.37	1.01, 1.85	1.39	0.99, 1.97
2	1.2–1.9	1.2	2.9	43	73	1.09	0.74, 1.61	1.01	0.64, 1.58
3	2.0–6.0	2.0	3.2	108	191	1.03	0.80, 1.33	0.97	0.70, 1.35
P for trend[d]							0.15		0.50

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Median intake (mg/day) of nutrient from supplemental sources only among category members.

[b] Median intake (mg/day) of nutrient from food and supplemental sources combined among category members.

[c] Adjusted for age (<30, 30–34, 35–39, or ≥40 years), year of diagnosis (1993, 1994–1995, 1996–1996, 1998–1999, or 2000–2001), number of full-term pregnancies (0, 1–2, 3–4, or ≥5 pregnancies lasting ≥6 months), body mass index (weight (kg)/height $(m)^2$) (<20.0, 20.0–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, or ≥30.0), pack-years of smoking (quintiles), tubal ligation (no vs. yes), duration or oral contraceptive use (0, 1–23, 24–71, 72–119 or ≥120 months), antidepressant use (never vs. ever), history of childhood trauma score (5, 6–10, 11–15, or ≥16), and intakes of alcohol, vitamin B6, calcium, and vitamin D (quintiles). Intake of each mineral from supplements is adjusted for intake of the respective mineral from food sources only.

[d] Test for trend among users of supplements only.

Results from analyses in which we excluded women who used antidepressants before diagnosis and those using oral contraceptives at baseline were similar to results from the main analysis (results not shown). We did not observe evidence that the relation between mineral intake and PMS varied significantly by age at PMS diagnosis (<40 years vs. ≥40 years) or by body mass index, alcohol intake, or smoking status.

DISCUSSION

In the present prospective study, we found that a high intake of nonheme iron was associated with a lower risk of PMS. Additionally, we observed some evidence that high zinc intake, potentially in relation to copper intake, was associated with a lower risk of PMS, whereas potassium

intake was related to a higher risk. In general, results for mineral intakes from supplemental sources were consistent with those for total mineral intake.

Iron is a cofactor for the enzyme tryptophan hydroxylase, which catalyzes the conversion of tryptophan into 5-hydroxytryptophan, a precursor of serotonin (24). Many brain areas are rich in iron, particularly cells receiving input from the gamma-aminobutyric acid system, suggesting a functional association (24). To our knowledge, the relation of iron intake to PMS has not been studied before, but in some studies (25, 26), investigators have found low iron levels to be associated with a higher risk of postpartum depression, a disorder also associated with increased sensitivity to changes in ovarian hormone levels.

We observed a lower risk of PMS specifically related to intake of nonheme iron, which is found primarily in plant foods and supplements. The level of intake above which we observed an association (>20 mg/day) is higher than the current recommended dietary allowance for women 20–40 years of age (18 mg/day) (27). Although 1 serving of iron-fortified cereal provides this level of intake (100% of the recommended dietary allowance), it may otherwise be difficult to achieve this level from food sources alone. Additional studies of iron and PMS are needed to confirm this finding and determine whether the benefits of iron supplementation outweigh the potential harmful effects.

Potassium intake was positively associated with PMS risk in our study, even at levels below the current adequate intake of 4,700 mg/day (28). Potassium from the diet may act as an agonist of aldosterone (29), a mineralocorticoid shown to fluctuate across the menstrual cycle (30–32). A high aldosterone level has been proposed as a contributor to PMS symptoms (3), especially water retention symptoms, such as bloating. Medications acting on aldosterone, such as the diuretic spironolactone and the progestin drospirenone, have been shown to reduce PMS symptoms (33, 34). In post-hoc analyses, we evaluated whether potassium intake was more strongly associated with menstrual symptoms related to fluid balance than with other symptoms. Although potassium intake was in fact positively associated with abdominal bloating and swelling of the extremities, intake was also associated with other symptoms, like depression and irritability (results not shown). As few other studies (13, 35) have evaluated the role of potassium in PMS, further investigation of both total potassium intake and specific food sources of potassium is warranted.

Zinc is highly concentrated in the brain and might be involved in neuronal function (36). Although zinc transport between plasma and the brain is controlled by the blood-brain barrier, chronic zinc deficiency might reduce zinc concentrations in the hippocampus, induce abnormal glucocorticoid secretion, and elicit neuropsychological symptoms such as isolation and depression (36–38). In the present study, we observed an inverse association between high zinc intake from supplements (median, 25 mg/day) and PMS risk. Additionally, we observed 24%–29% lower risks of PMS among women in the top 2 quintiles of zinc to copper ratios (quintile medians, 10.3 and 13.9), though this association was not significant after adjustment for intakes of other minerals. In the United States, average zinc to copper molar ratios range from 5 to 14 (39), and a target ratio of less than 15 has been recommended because of the risk of decreasing copper absorption at higher intake levels (40). Although zinc to copper ratios among our population were within this range, absolute intakes of both nutrients were high compared with current recommended dietary allowances for women aged 20–40 years (zinc = 8 mg/day; copper = 0.9 mg/day) (27). The associations of zinc and copper intakes with PMS should be further studied.

Because of the large size of our population and the prospective design of our study, we were unable to use daily symptom records to identify women with PMS, as is recommended in clinical practice (1). Instead, we used prospective reports of clinical PMS diagnosis combined with a retrospective menstrual symptom questionnaire and established criteria to identify PMS cases and symptom-free controls. We thus compared women at the 2 extremes of the spectrum of menstrual symptom experience and thereby decreased the likelihood of misclassification between cases and controls. The validity of our assessment method has been assessed before (15) and has been found to be sensitive enough to identify risk factors for PMS (4, 5, 41–43). Additionally, because the women in our population were first diagnosed with PMS after 25 years of age, our findings may not be generalizable to women who develop PMS in adolescence or early adulthood. Future studies to confirm these relations among younger women are needed.

The present study suggests that high intakes of nonheme iron and perhaps zinc may be associated with a lower risk of PMS, whereas a high potassium intake may be associated with a higher risk. As this is among the first studies to evaluate mineral intake and the development of PMS, additional studies are warranted to confirm these findings and to determine whether mineral supplementation may hold promise for the prevention of PMS.

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REFERENCES

1. Halbreich U. The diagnosis of premenstrual syndromes and premenstrual dysphoric disorder: clinical procedures and research perspectives. *Gynecol Endocrinol*. 2004;19(6): 320–334.
2. Mortola JF. Issues in the diagnosis and research of premenstrual syndrome. *Clin Obstet Gynecol*. 1992; 35(3):587–598.
3. Halbreich U. The etiology, biology, and evolving pathology of premenstrual syndromes. *Psychoneuroendocrinology*. 2003;28(suppl 3):55–99.
4. Bertone-Johnson ER, Hankinson SE, Bendich A, et al. Calcium and vitamin D intake and risk of incident premenstrual syndrome. *Arch Intern Med*. 2005;165(11): 1246–1252.
5. Chocano Bedoya P, Manson J, Hankinson S, et al. Dietary B vitamin intake and incident premenstrual syndrome. *Am J Clin Nutr*. 2011;93(5):1080–1086.
6. Das K, Chowdhury AR. Metallic ion concentration during menstrual cycle in normally menstruating women. *Indian J Med Sci*. 1997;51(2):52–54.
7. Posaci C, Erten O, Uren A, et al. Plasma copper, zinc and magnesium levels in patients with premenstrual tension syndrome. *Acta Obstet Gynecol Scand*. 1994;73(6):452–455.
8. Chuong CJ, Dawson EB. Zinc and copper levels in premenstrual syndrome. *Fertil Steril*. 1994;62(2):313–320.
9. Rosenstein DL, Elin RJ, Hosseini JM, et al. Magnesium measures across the menstrual cycle in premenstrual syndrome. *Biol Psychiatry*. 1994;35(8):557–561.
10. Quaranta S, Buscaglia MA, Meroni MG, et al. Pilot study of the efficacy and safety of a modified-release magnesium 250 mg tablet (Sincromag) for the treatment of premenstrual syndrome. *Clin Drug Investig*. 2007;27(1):51–58.
11. Khine K, Rosenstein D, Elin R, et al. Magnesium (mg) retention and mood effects after intravenous mg infusion in premenstrual dysphoric disorder. *Biol Psychiatry*. 2006; 59(4):327–333.
12. Walker A, De Souza MC, Marakis G, et al. Unexpected benefit of sorbitol placebo in Mg intervention study of premenstrual symptoms: implications for choice of placebo in RCTs. *Med Hypotheses*. 2002;58(3):213–220.
13. Reeves BD, Garvin JE, McElin TW. Premenstrual tension: symptoms and weight changes related to potassium therapy. *Am J Obstet Gynecol*. 1971;109(7):1036–1041.
14. Penland JG, Johnson PE. Dietary calcium and manganese effects on menstrual cycle symptoms. *Am J Obstet Gynecol*. 1993;168(5):1417–1423.
15. Bertone-Johnson ER, Hankinson SE, Johnson SR, et al. A simple method of assessing premenstrual syndrome in large prospective studies. *J Reprod Med*. 2007;52(9):779–786.
16. Mortola JF, Girton L, Beck L, et al. Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: the calendar of premenstrual experiences. *Obstet Gynecol*. 1990;76(2):302–307.
17. Willett WC. *Nutritional Epidemiology*. 2nd ed. New York, NY: Oxford University Press; 1998.
18. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122(1):51–65.
19. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol*. 1989;18(4):858–867.
20. Rimm EB, Giovannucci EL, Stampfer MJ, et al. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol*. 1992;135(10): 1114–1126.
21. Jun H, Rich-Edwards J, Boynton-Jarrett R, et al. Child abuse and smoking among young women: the importance of severity, accumulation, and timing. *J Adolesc Health*. 2008;43(1):55–63.
22. Solomons NK. Dietary sources of zinc and factors affecting its bioavailability. *Food Nutr Bull*. 2001;22(2):138–154.
23. Levine J, Stein D, Rapoport A, et al. High serum and cerebrospinal fluid Ca/Mg ratio in recently hospitalized acutely depressed patients. *Neuropsychobiology*. 1999; 39(2):63–70.
24. Yehuda S, Mostofsky D, eds. *Iron Deficiency and Overload: From Basic Biology to Clinical Medicine.* Totowa, NJ: Humana Press; 2010.
25. Albacar G, Sans T, Martn-Santos R, et al. An association between plasma ferritin concentrations measured 48 h after delivery and postpartum depression. *J Affect Disord*. 2010;131(1–3):136–142.
26. Beard J, Hendricks M, Perez E, et al. Maternal iron deficiency anemia affects postpartum emotions and cognition. *J Nutr*. 2005;135(2):267–272.
27. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: The National Academies Press; 2001.
28. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate*. Washington, DC: The National Academies Press; 2005.
29. Guyton AC, Hall JE. *Textbook of Medical Physiology*. 11th ed. Philadelphia, PA: Elsevier Saunders; 2006.
30. Chidambaram M, Duncan J, Lai V, et al. Variation in the renin angiotensin system throughout the normal menstrual cycle. *J Am Soc Nephrol*. 2002;13(2):446–452.
31. Fommei E, Ghione S, Ripoli A, et al. The ovarian cycle as a factor of variability in the laboratory screening for primary aldosteronism in women. *J Hum Hypertens*. 2009;23(2): 130–135.
32. Szmuilowicz E, Adler G, Williams J, et al. Relationship between aldosterone and progesterone in the human menstrual cycle. *J Clin Endocrinol Metab*. 2006;91(10):3981–3987.
33. Wang M, Hammarback S, Lindhe BA, et al. Treatment of premenstrual syndrome by spironolactone: a double-blind,

placebo-controlled study. *Acta Obstet Gynecol Scand*. 1995;74(10):803–808.
34. Hellberg D, Claesson B, Nilsson S. Premenstrual tension: a placebo-controlled efficacy study with spironolactone and medroxyprogesterone acetate. *Int J Gynaecol Obstet*. 1991; 34(3):243–248.
35. Torres S, Nowson C, Worsley A. Dietary electrolytes are related to mood. *Br J Nutr*. 2008;100(5):1038–1045.
36. Sowa-Kućma M, Legutko B, Szewczyk B, et al. Antidepressant-like activity of zinc: further behavioral and molecular evidence. *J Neural Transm*. 2008;115(12): 1621–1628.
37. Levenson C. Zinc: the new antidepressant? *Nutr Rev*. 2006; 64(1):39–42.
38. Takeda A, Tamano H. Insight into zinc signaling from dietary zinc deficiency. *Brain Res Rev*. 2009;62(1):33–44.
39. Sandstead HH. Requirements and toxicity of essential trace elements, illustrated by zinc and copper. *Am J Clin Nutr*. 1995;61(3 suppl):621S–624S.
40. Brown KH, Wuehler SE, Peerson JM. The importance of zinc in human nutrition and estimation of the global prevalence of zinc deficiency. *Food Nutr Bull*. 2001;22(2):113–125.
41. Bertone-Johnson ER, Hankinson SE, Johnson SR, et al. Cigarette smoking and the development of premenstrual syndrome. *Am J Epidemiol*. 2008;168(8):938–945.
42. Bertone-Johnson ER, Hankinson SE, Johnson SR, et al. Timing of alcohol use and the incidence of premenstrual syndrome and probable premenstrual dysphoric disorder. *J Womens Health*. 2009;18(12):1945–1953.
43. Bertone-Johnson ER, Hankinson SE, Willett WC, et al. Adiposity and the development of premenstrual syndrome. *J Womens Health*. 2010;19(11):1955–1962.