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Original Contribution

Premenstrual Syndrome and Subsequent Risk of Hypertension in a Prospective Study

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The prevalence of hypertension is increasing among younger women, and new strategies are needed to identify high-risk women who should be targets for early intervention. Several mechanisms underlying hypertension might also contribute to premenstrual syndrome (PMS), but whether women with PMS have a higher risk of subsequently developing hypertension has not been assessed. We prospectively evaluated this possibility in a substudy of the Nurses' Health Study II. Participants were 1,257 women with clinically significant PMS (1991–2005) and 2,463 age-matched comparison women with few menstrual symptoms. Participants were followed for incident hypertension until 2011. Over 6–20 years, hypertension was reported by 342 women with PMS and 541 women without. After adjustment for age, smoking, body mass index, and other risk factors for hypertension, women with PMS had a hazard ratio for hypertension of 1.4 (95% confidence interval: 1.2, 1.6) compared with women without PMS. Risk was highest for hypertension that occurred before 40 years of age (hazard ratio = 3.3; 95% confidence interval: 1.7, 6.5; P for interaction = 0.0002). The risk associated with PMS was not modified by use of oral contraceptives or antidepressants but was attenuated among women with high intakes of thiamine and riboflavin ($P < 0.05$). These results suggest that PMS might be associated with future development of hypertension and that this risk may be modifiable.

cohort studies; diet; hypertension; premenstrual syndrome

Abbreviations: CI, confidence interval; DASH, Dietary Approaches to Stop Hypertension; HR, hazard ratio; NHS2, Nurses' Health Study 2; PMS, premenstrual syndrome.

Hypertension is among the strongest predictors of heart attack, stroke, heart failure, and kidney disease in women (1). Evidence suggests that the prevalence in young women is increasing (2), and despite the availability of effective treatments, less than half of hypertension in women younger than 40 years of age is treated (3, 4). New strategies are needed to identify high-risk women to target for increased screening and early intervention.

Clinically significant premenstrual syndrome (PMS) is experienced by 8%–15% of premenopausal women and substantially interferes with quality of life (5, 6). Emerging data suggest that several pathways underlying hypertension might also contribute to PMS. For example, renin-angiotensin-aldosterone system dysfunction contributes to hypertension by altering the regulation of sodium balance, blood volume, and arterial constriction (7). Renin-angiotensin-aldosterone system dysfunction also appears to be involved in symptoms of premenstrual edema, including abdominal bloating, swelling of extremities, and breast tenderness (8). Obesity increases the risk of hypertension by adversely impacting renin-angiotensin-aldosterone function and promoting chronic inflammation, as well as via other mechanisms (9, 10). Obesity has consistently been associated with PMS (11, 12), which might also have an inflammatory component (13). Furthermore, several dietary factors associated with hypertension, including intakes of calcium, potassium, vitamin D, and B vitamins (9, 10, 14), might also play a role in PMS development (15–17).

We evaluated whether women with clinically significant PMS had a higher risk of subsequently developing hypertension than did women with few menstrual symptoms in a substudy conducted within the prospective Nurses' Health Study II (NHS2). Our primary goal was to determine whether PMS occurrence predicted subsequent risk of hypertension. Our secondary goal was to assess whether specific medications and dietary interventions used to treat PMS could attenuate the higher risk of hypertension and thus be preferentially recommended to treat PMS in high-risk women.

METHODS

Study population

The NHS2 is a prospective study of 116,686 US female registered nurses who responded to a mailed questionnaire in 1989. Participants, who were 25–42 years of age at baseline, provided information on their medical histories and health-related behaviors, including smoking and oral contraceptive use, and completed questionnaires every 2 years thereafter to update information on risk factors and to report new diagnoses. The follow-up rates of total potential person-years of observation since baseline are more than 90%. The study protocol was approved by the institutional review boards at Brigham and Women's Hospital and the University of Massachusetts, Amherst.

The NHS2 PMS Substudy

Women included in the present analysis participated in the NHS2 PMS Substudy, which has been described in detail previously (15). Briefly, from among participants who had not reported PMS on their NHS2 questionnaire in 1989, we identified women who reported by questionnaire a clinician-made diagnosis of PMS between 1991 and 2005 ($n = 4,108$). As a comparison group, we randomly selected 3,248 women who did not report PMS (1989–2005) and assigned each a randomly chosen reference year comparable to the possible years of PMS diagnosis. To reduce the likelihood of including women with PMS-type symptoms caused by conditions other than PMS, we excluded from both groups women who reported cancer, endometriosis, highly irregular menstrual cycles, infertility, or hysterectomy before the reference year.

Participants were sent a questionnaire based on the Calendar of Premenstrual Experiences (18) that was used to assess the occurrence of 26 physical and affective symptoms, the timing of symptom onset and remission during the menstrual cycle, and the impact of symptoms on daily functioning. Completed questionnaires were received from 3,579 (87%) women who self-reported having experienced PMS and 3,087 (95%) comparison women. We used responses to identify women who met the criteria for moderate to severe PMS (18), including 1) the occurrence of at least 1 physical and 1 affective menstrual symptom; 2) overall symptom severity of moderate or severe or symptom impact on life activities and social relationships rated as moderate or severe; 3) symptoms beginning within 14 days before menses onset; 4) symptoms ending within 4 days of menses onset; and 5) symptoms absent in the week after menses ends. Overall, 1,257 (35%) of women who self-reported having experienced PMS met these criteria. This proportion is consistent with clinical studies of PMS using prospective symptom charting (19).

We used questionnaires about menstrual symptoms to limit our comparison group to women who confirmed that they experienced no menstrual symptoms or only mild symptoms with no personal impact. Ultimately, 2,463 (80%) comparison women met these additional criteria. To prevent misclassification between women with and without PMS, women who did not meet the criteria for either group were excluded from further analysis.

The accuracy of our approach to identifying PMS cases and controls was assessed previously among 135 substudy members (20). Menstrual symptom occurrence, timing, and severity in women who met our criteria for PMS were essentially identical to those of cases who reported that they completed clinician-supervised prospective symptom diaries, which are typically used in clinical practice to diagnose PMS. This high degree of similarity suggests that our method is comparable to prospective charting in its ability to classify PMS cases and controls in large epidemiologic studies.

Assessment of hypertension and blood pressure

On each NHS2 questionnaire, participants were asked whether they had received a clinician-made diagnosis of high blood pressure in the previous 2 years and, if so, when they had received the diagnosis. The validity of self-reported hypertension in a similar population (the Nurses' Health Study) was assessed in 2 ways (21). First, 51 participants who reported incident hypertension submitted their medical records for review; the diagnosis of hypertension was confirmed in 100% of cases, demonstrating the high sensitivity of self-report in this population of registered nurses. Secondly, 161 NHS members who had never reported incident hypertension by questionnaire had their blood pressure directly measured; none of these women (0%) had a measured blood pressure higher than 160/95 mm Hg, and only 8.6% had readings between 140/70 mm Hg and 160/95 mm Hg, thus confirming the high specificity of self-report.

In 1999, 2005, and 2009, participants were also asked to report their systolic and diastolic blood pressures if readings had been taken in the past 2 years. Response categories for systolic blood pressure were: <105, 105–114, 115–124, 125–134, 135–144, 145–154, 155–164, 165–174, and ≥175 mm Hg. Categories for diastolic blood pressure were <65, 65–74, 75–84, 85–89, 90–94, 95–104, and ≥105 mm Hg. To derive continuous variables for systolic and diastolic blood pressure, we assigned women the median value of their response category.

Assessment of covariates

Static factors measured at baseline in the NHS2 included race/ethnicity, age at menarche, height, and family history of hypertension. Time-varying factors measured every 2–4 years included weight (used to calculate body mass index; weight in kg/height in m^2), smoking status, physical activity level, alcohol consumption, menopausal status, hormone therapy use, receipt

of medical examinations, depression, and use of medications including oral contraceptives, antidepressants (including selective serotonin reuptake inhibitors and tricyclic antidepressants), and pain medications (including acetaminophen, ibuprofen, and aspirin). Additionally, we measured use of antidepressants on our menstrual symptom questionnaire. Dietary factors, including intakes of vitamin D, thiamine, riboflavin, vitamin B6, potassium, folate, sodium, calcium, and other nutrients and adherence to the Dietary Approaches to Stop Hypertension (DASH) diet (22), were assessed using a validated food frequency questionnaire every 2–4 years (23). Data on use of dietary supplements, including calcium, vitamin D, B vitamins, and iron, were also collected via food frequency questionnaire and the main NHS2 questionnaires. Level of stress was assessed in 2001 using the Cohen 4-item Perceived Stress Scale included on a supplementary questionnaire sent to 91,286 NHS2 members (24); completed responses were received from 3,295 (89%) of PMS Substudy members.

Statistical analysis

All analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina). We first compared characteristics of women with and without PMS at their diagnosis or reference year, which served as baseline for our analysis. We then compared the risk of incident hypertension between women with and without PMS using Cox proportional hazard regression models to calculate hazard ratios and 95% confidence intervals, in addition to 2-sided *P* values. Accrual of follow-up began on the date of return of the questionnaire on which incident PMS was reported or the date of return of the questionnaire in the year selected as the reference year (1991–2005). Person-time accrued until the diagnosis of hypertension, death, loss to follow-up, or the end of follow-up in June, 2011, whichever came first. Only women who were diagnosed with hypertension after a PMS diagnosis or the reference year were included in these analyses so that we could assess the degree to which PMS predicted risk of subsequent hypertension; women with prevalent hypertension at baseline were excluded.

We built 2 sets of models for our main analysis. Model 1 was adjusted only for age and time period. Model 2 was adjusted for age, time period, and all covariates for which inclusion resulted in a 10% change in the hazard ratio for the association between PMS and hypertension or that were significantly associated with risk of hypertension. Values for time-varying factors, including age, body mass index, pack-years of

Table 1. Age-Adjusted Characteristics by Premenstrual Syndrome Status at Baseline,[a] Nurses' Health Study II Premenstrual Syndrome Substudy, 1991–2011

Demographic or Lifestyle Characteristic	Women With PMS (*n* = 1,257)		Women Without PMS (*n* = 2,463)		*P* Value
	Mean (SD)	%	Mean (SD)	%	
Age, years	40.4 (4.3)		41.4 (4.3)		<0.001
Body mass index[b]	26.1 (5.6)		25.1 (5.6)		<0.001
Body mass index at age 18 years[b]	21.4 (3.2)		21.1 (3.2)		0.02
Age at menarche, years	12.4 (1.4)		12.5 (1.4)		0.04
No. of full-term pregnancies	2.0 (1.2)		2.0 (1.2)		0.49
Age at first birth, years[c]	26.6 (4.2)		26.6 (4.2)		0.64
Physical activity level, METs/week	19.6 (23.8)		21.0 (23.8)		0.11
Alcohol intake, g/day	4.0 (7.0)		3.9 (7.0)		0.78
DASH diet score	23.8 (5.1)		24.0 (5.0)		0.21
White race		98.1		98.1	0.98
Mother had more than a high school education		33.8		37.8	0.02
Current smoker		10.2		6.0	<0.001
Former smoker		29.9		18.4	<0.001
Current antidepressant use		16.9		5.3	<0.001
Current oral contraceptive use		8.5		3.5	<0.001
Ever used oral contraceptives		87.8		78.9	<0.001
Physical examination in previous 2 years		91.8		88.8	0.005
Previous diagnosis of hypertension[d]		12.0		6.6	<0.001

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; METs, metabolic equivalents of task; SD, standard deviation.

[a] The baseline for the prospective analysis of incident hypertension was equal to the time of premenstrual syndrome diagnosis or the reference year.

[b] Body mass index is expressed as weight (kg)/height $(m)^2$.

[c] Among parous women.

[d] These women were excluded from prospective analyses of incident hypertension.

cigarette smoking, physical activity level, DASH diet score, alcohol consumption, and postmenopausal hormone use, were updated throughout follow-up. The static factors included in model 2 were family history of hypertension, race/ethnicity, and annual income.

In addition to our main analyses, we performed analyses in which we stratified our population by age and body mass index to determine whether a relationship of PMS with hypertension varied by these characteristics. We then assessed how specific menstrual symptoms were related to the risk of hypertension by comparing the hazard ratios for hypertension in women who experienced each of the 26 symptoms to those of women who did not experience each symptom. Furthermore, we compared adjusted geometric mean systolic and diastolic blood pressures in 1999, 2005, and 2009 of women with PMS to those of women without PMS using generalized linear models.

We evaluated whether an association of PMS with hypertension could be modified by medication use or dietary factors. We accomplished this using the following procedure. First, we evaluated each participant's use of medications commonly used to treat PMS (25), including oral contraceptives, antidepressants, and pain medications (ibuprofen, acetaminophen, and aspirin). For each 2-year interval, we classified women as users or nonusers of each medication based on their questionnaire report at the start of the interval. Hypertension cases were assigned to the exposure status reported at the start of each interval. For pain medications, we also classified women by frequency of use (1–4 days/week or ≥5 days/week). We then stratified our population by both PMS status and medication use, updating information on medication use every 2 years, and compared the hazard ratios for hypertension between groups. For these analyses, we further adjusted each category of medication use for the other medications evaluated (model 3).

Table 2. Hazard Ratios for Hypertension by Premenstrual Syndrome Status, Nurses' Health Study II Premenstrual Syndrome Substudy, 1991–2011

PMS Status Stratified by Age or Body Mass Index	No. of Hypertension Cases	Person-Years	Cases per 100,000 Person-Years	Model 1[a]		Model 2[b]	
				HR	95% CI	HR	95% CI
Overall							
Without PMS	541	42,298	1,279	1.0	Referent	1.0	Referent
With PMS	342	17,005	2,011	1.6	1.3, 1.8	1.4	1.2, 1.6
Stratified by age, years							
<40							
Without PMS	33	11,402	289	1.0	Referent	1.0	Referent
With PMS	28	3,086	907	3.4	1.8, 6.4	3.3	1.7, 6.5[c]
40–45							
Without PMS	86	9,312	924	1.0	Referent	1.0	Referent
With PMS	75	4,540	1,652	1.9	1.3, 2.7	1.7	1.2, 2.5
>45							
Without PMS	422	21,584	1,955	1.0	Referent	1.0	Referent
With PMS	239	9,379	2,548	1.4	1.2, 1.7	1.2	1.0, 1.4
Stratified by body mass index[d]							
<25							
Without PMS	172	25,420	677	1.0	Referent	1.0	Referent
With PMS	75	8,269	907	1.5	1.1, 2.1	1.5	1.1, 2.0
25–29.9							
Without PMS	181	11,010	1,644	1.0	Referent	1.0	Referent
With PMS	134	5,658	2,368	1.3	1.0, 1.8	1.5	1.1, 2.0
≥30							
Without PMS	188	5,868	3,204	1.0	Referent	1.0	Referent
With PMS	133	3,078	4,321	1.3	1.0, 1.8	1.3	0.9, 1.8

Abbreviations: CI, confidence interval; HR, hazard ratio; PMS, premenstrual syndrome.

[a] Adjusted for age (in months; continuous) and time period (person-months).

[b] Adjusted for the variables in model 1 and body mass index; continuous), physical activity level (metabolic equivalent of task-hours per week; continuous), cigarette smoking (cumulative pack-years; continuous), family history of hypertension (yes or no), postmenopausal hormone use (never, 1–71 months, or ≥72 months), Dietary Approaches to Stop Hypertension diet score (quintiles), race/ethnicity (white or other), annual household income (<$50,000, $50,000–$99,000, or ≥$100,000), and daily alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥15 g).

[c] *P* for interaction <0.001.

[d] Body mass index is expressed as weight (kg)/height $(m)^2$.

For analyses of dietary factors, we evaluated micronutrients that had previously been associated with PMS in our populations. These included calcium, vitamin D, thiamine, riboflavin, and iron, intakes of which were inversely related to PMS (15–17), and vitamin B6 and potassium, intakes of which were positively associated with risk (16, 17). For each 4-year interval (because diet was assessed every 4 years), we divided women into quintiles based on level of intake in the NHS2 population and then combined women in quintiles 1–3 (the lowest 60% of the distribution) into a "low intake" category and women in quintiles 4–5 (the top 40% of the distribution) into a "high intake" category. We additionally evaluated multivitamin use (categorized as none, 1–4 days/week, or ≥5 days per week) and level of adherence to the DASH diet, categorizing women as having "low adherence" if their DASH diet score was in quintiles 1–3 and "high adherence" for quintiles 4–5. We then stratified our population by both PMS status and dietary factors, updating information on diet every 4 years, and compared the hazard ratios for hypertension between groups. As with medication analyses, hypertension cases were assigned to the exposure status reported at the start of each interval. For these analyses, we adjusted for all nondietary covariates and for medication use (model 3). Finally, we conducted sensitivity analyses repeating our main analyses, first adjusting for and then stratifying by frequency of physical examination (yes vs. no in previous 2 years) and chronic stress score (tertiles).

RESULTS

Age-standardized baseline characteristics of 1,257 women with PMS and 2,463 women without PMS are presented in Table 1. Women with PMS were slightly younger and had slightly higher body mass indices ($P < 0.001$ for both), were more likely to have used oral contraceptives and antidepressants, and were more likely to be current or former

Table 3. Hazard Ratios for Hypertension Among Women Who Experienced Premenstrual Syndrome by Medication Use, Nurses' Health Study II Premenstrual Syndrome Substudy, 1991–2011

PMS Status and Medication Use	No. of Hypertension Cases	Person-Years	Cases per 100,000 Person-Years	Model 2[a]		Model 3[b]	
				HR	95% CI	HR	95% CI
Women without PMS[c]				1.0	Referent	1.0	Referent
Women with PMS							
Antidepressant use							
No	248	12,250	2,024	1.5	1.2, 1.8	1.4	1.2, 1.7
Yes	94	4,822	1,950	1.2	1.0, 1.6	1.2	0.9, 1.5
Oral contraceptive use							
No	329	15,992	2,057	1.4	1.2, 1.6	1.3	1.1, 1.6
Yes	13	1,079	1,204	1.4	0.8, 2.4	1.3	0.7, 2.4
Ibuprofen use, days/week							
None	156	7,419	2,103	1.4	1.1, 1.8	1.4	1.1, 1.8
1–4	147	8,051	1,826	1.5	1.2, 2.0	1.5	1.1, 1.9
≥5	38	1,562	2,432	1.5	1.0, 2.2	1.4	0.9, 2.1
Aspirin use, days/week							
None	264	12,652	2,087	1.4	1.2, 1.7	1.3	1.1, 1.6
1–4	69	3,837	1,798	1.3	0.8, 1.9	1.2	0.8, 1.8
≥5	9	582	1,547	0.8	0.4, 1.7	0.8	0.4, 1.5
Acetaminophen use, days/week							
None	203	10,456	1,942	1.2	1.0, 1.5	1.2	1.0, 1.5
1–4	122	5,992	2,036	1.6	1.3, 2.1	1.6	1.2, 2.0
≥5	17	604	2,813	1.7	1.0, 2.9	1.6	0.9, 2.8

Abbreviations: CI, confidence interval; HR, hazard ratio; PMS, premenstrual syndrome.

[a] Adjusted for age (in months; continuous), time period (person-months), body mass index (weight (kg)/height $(m)^2$; continuous), physical activity level (metabolic equivalent of task-hours per week; continuous), cigarette smoking (cumulative pack-years; continuous), family history of hypertension (yes or no), postmenopausal hormone use (never, 1–71 months, or ≥72 months), Dietary Approaches to Stop Hypertension diet score (quintiles), race/ethnicity (white or other), annual household income (<$50,000, $50,000–$99,000, or ≥$100,000), and daily alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥15 g).

[b] Adjusted for the variables in model 2 and current use of antidepressants (yes or no), oral contraceptives (yes or no), ibuprofen (none, 1–4, or ≥5 days/week), acetaminophen (none, 1–4, or ≥5 days/week), and aspirin (none, 1–4, or ≥5 days/week).

[c] The reference groups for each comparison were women without PMS who did not use the specific medication.

smokers ($P < 0.001$ for all). At baseline, 12.0% of women with PMS had already received a diagnosis of hypertension, compared with 6.6% of women in the comparison group ($P < 0.001$); these women were excluded from all prospective analyses. Women with PMS were more likely to have had a physical examination in the previous 2 years than were controls (91.8% vs. 88.8%; $P = 0.005$), although usage of medical services among our population was very high overall.

Hazard ratios for incident hypertension by PMS status are shown in Table 2. After adjustment for age, body mass index, physical activity level, and other factors (model 2), women with PMS had a hazard ratio for incident hypertension of 1.4 (95% confidence interval (CI): 1.2, 1.6) compared with women without PMS. In analyses stratified by age, the positive association of PMS with risk of hypertension was highest for women younger than 40 years of age (hazard ratio (HR) = 3.3, 95% CI: 1.7, 6.5; P for interaction < 0.001). The association of PMS with risk of hypertension did not vary significantly by body mass index.

We evaluated how the occurrence of specific menstrual symptoms was associated with risk of hypertension (complete results not shown). In the multivariable analysis (model 2), hazard ratios for hypertension were highest for nausea (HR = 1.7, 95% CI: 1.0, 2.9), insomnia (HR = 1.6, 95% CI: 1.3, 2.1), backache (HR = 1.5, 95% CI: 1.2, 1.9), tendency to cry easily (HR = 1.5, 95% CI: 1.2, 1.8), swelling of extremities (HR = 1.5, 95% CI: 1.1, 1.9), and hot flashes (HR = 1.4, 95% CI: 1.0, 2.2).

After adjustment for age, body mass index, and other factors (model 2), geometric mean systolic and diastolic blood pressures self-reported at 3 time points were significantly higher in women with PMS than in women without. Mean systolic blood pressures in 1999, 2005, and 2009 were 119.2, 120.1, and 120.9 mm Hg, respectively, for women with PMS and 118.7, 119.9, and 120.2 mm Hg, respectively, for women without PMS (for between-group differences over time, $P = 0.02$). Mean diastolic blood pressures in 1999, 2005, and 2009 were 74.8, 75.3, and 75.2 mm Hg, respectively, for women with PMS and 74.5, 74.9, and 74.7 mm Hg, respectively, for women without PMS (for between-group differences over time, $P = 0.007$).

Table 3 shows hazard ratios for hypertension among women with PMS stratified by use of specific medications, each compared with women without PMS who did not use each specific medication. We did not find that the PMS-hypertension relation was modified by any of the medications evaluated (all $P > 0.05$). However, women with PMS who reported frequent aspirin use did not have a higher risk of hypertension (HR = 0.8, 95% CI: 0.4, 1.5).

We observed some evidence that the association of PMS with hypertension varied by micronutrient intake (Table 4). Although women with PMS who were in the lower 3 quintiles of thiamine intake had a hazard ratio for hypertension of 1.5 (95% CI: 1.2, 1.8) compared with women without PMS, PMS cases who reported higher thiamine intake had a hazard ratio of 1.1 (95% CI: 0.9, 1.4; $P = 0.03$). Results were nearly identical for riboflavin intake ($P = 0.03$), which was very highly correlated with thiamine intake ($r = 0.96$; $P < 0.001$), and were similar for folate ($P = 0.07$) and adherence to the DASH diet ($P = 0.31$). Finally, the hazard ratio for the association of PMS with hypertension risk did not change materially after either adjustment or stratification for frequency of physical examinations or level of perceived stress in 2001 (results not shown).

DISCUSSION

To our knowledge, this is the first prospective study in which PMS has been considered as a sentinel for future risk of hypertension. We found that women who met the criteria for moderate to severe PMS had a significant 40% higher risk of developing hypertension over the following 20 years compared with women who experienced few menstrual symptoms. The observed higher risk persisted after adjustment for established risk factors for hypertension, including body mass index, pack-years of cigarette smoking, physical activity level, alcohol consumption, postmenopausal hormone use, oral contraceptive use, and family history of hypertension. Results were strongest for hypertension that occurred before 40 years of age; in this age group, women with PMS had a 3-fold higher risk of developing hypertension compared with women without PMS.

There have been few previous studies in which the association of PMS with blood pressure and/or risk of hypertension has been directly evaluated. In 1 study, a significant rise in systolic and diastolic blood pressure during the luteal phase was observed in 273 Nigerian women classified as having PMS but not in 174 control women (26). Stamatelopoulos et al. (27) reported significant elevations in peripheral and central systolic blood pressure, pulse pressure, and mean arterial pressure during the luteal and menstrual phases in 21 PMS cases but no change in 15 controls. In addition, postmenopausal women who recalled having experienced 7 or more menstrual symptoms in their premenopausal years had a significantly higher prevalence of hypertension than did those who recalled fewer symptoms. Although mean systolic and diastolic pressures did not differ between 9 PMS cases and 9 controls in a third study, late luteal phase plasma volume, aldosterone activity, and renin activity were significantly higher in cases than in controls (28). Collectively, these studies provide support for the existence of underlying differences in vascular physiology in women with PMS compared with symptom-free women, which could plausibly predispose PMS cases to hypertension and cardiovascular disease later in life.

An association between PMS and hypertension could be explained alternatively by adverse effects of PMS medications on blood pressure. In several studies, investigators have observed that serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants increase blood pressure and the risk of hypertension (29–32) and found that use during pregnancy was associated with the risk of preeclampsia (33, 34). In contrast, use of selective serotonin reuptake inhibitors has generally not been associated with hypertensive disorders (30, 31, 34). In the present study, women with PMS who used antidepressants, the majority of which were selective serotonin reuptake inhibitors, did not have a higher risk of hypertension.

Table 4. Hazard Ratios for Hypertension Among Women Experiencing Premenstrual Syndrome by Adherence to the Dietary Approaches to Stop Hypertension Diet, Multivitamin Use, and Intake of Selected Micronutrients, Nurses' Health Study II Premenstrual Syndrome Substudy, 1991–2011

Category	No. of Hypertension Cases	Person-Years	Cases per 100,000 Person-Years	Model 2[a]		Model 3[b]	
				HR	95% CI	HR	95% CI
Women without PMS[c,d]				1.0	Referent	1.0	Referent
Women with PMS							
DASH diet adherence							
Low[d]	189	9,733	1,942	1.3	1.1, 1.6	1.3	1.0, 1.6
High	50	3,119	1,603	1.1	0.8, 1.5	1.1	0.8, 1.5
Multivitamin use, days/week							
None	141	6,683	2,110	1.6	1.2, 2.0	1.5	1.2, 1.9
1–4	73	4,058	1,799	1.6	1.2, 2.1	1.5	1.1, 2.0
≥5	102	5,388	1,893	1.3	1.0, 1.7	1.2	0.9, 1.6
Vitamin D intake							
Low	215	10,431	2,061	1.4	1.2, 1.7	1.4	1.1, 1.7
High	108	5,956	1,813	1.3	1.0, 1.7	1.2	1.0, 1.6
Calcium intake							
Low	207	10,396	1,991	1.4	1.1, 1.6	1.3	1.1, 1.6
High	116	5,990	1,936	1.3	1.0, 1.7	1.3	1.0, 1.6
Iron intake							
Low	198	9,620	2,058	1.4	1.1, 1.7	1.3	1.1, 1.6
High	125	6,767	1,847	1.3	1.3, 1.7	1.2	1.0, 1.6
Sodium intake							
Low	179	9,826	1,822	1.3	1.0, 1.6	1.2	1.0, 1.5
High	144	6,560	2,195	1.5	1.2, 1.9	1.5	1.2, 1.9
Potassium intake							
Low	206	10,501	1,962	1.2	1.0, 1.5	1.2	1.0, 1.4
High	117	5,886	1,988	1.2	1.0, 1.6	1.2	0.9, 1.5
Thiamine intake							
Low	217	9,949	2,187	1.5	1.2, 1.8	1.5	1.2, 1.8
High	106	6,438	1,647	1.2	0.9, 1.5	1.1	0.9, 1.4[e]

Table continues

We recently found that women with high dietary intakes of the B vitamins thiamine and riboflavin had significantly lower (25%–35%) risks of developing PMS (16). In a recent nutrient-wide association study, Tzoulaki et al. (14) reported that riboflavin, thiamine, and folacin from food sources were each inversely associated with blood pressure. High total folate intake has previously been associated with a lower risk of hypertension in the NHS2, even after adjustment for intakes of sodium, potassium, and vitamin D and for standard hypertension risk factors (35). Our results are consistent with these findings and suggest that improving B vitamin status in women with PMS might both reduce menstrual symptom severity and lower hypertension risk.

Our study has several potential limitations. Because our study is nested within a large prospective cohort study, we were unable to use prospective menstrual symptom diaries to classify PMS, as is the standard in clinical practice. However, our instrument has been endorsed by the American Congress of Obstetricians and Gynecologists (36, 37) and has been used previously in studies of PMS and blood pressure (26, 27). Importantly, we compared hypertension risks between women at extreme ends of the spectrum of menstrual symptoms; any misclassification between these groups should be minimal and would attenuate as opposed to exaggerate associations. Although hypertension was self-reported in the NHS2, self-report has been proven to have excellent sensitivity and specificity (21).

In addition, because of the age of our participants at baseline (e.g., ≥27 years in 1991), we were not able to assess how PMS in younger women is associated with the risk of hypertension. Our findings might thus be generalizable only to women who develop PMS in their middle or older reproductive years, who might differ etiologically from women who develop PMS at earlier ages. In order to assess PMS as a predictor of future hypertension, women with existing hypertension at the time of PMS occurrence were excluded from

Table 4. Continued

Category	No. of Hypertension Cases	Person-Years	Cases per 100,000 Person-Years	Model 2[a]		Model 3[b]	
				HR	95% CI	HR	95% CI
Riboflavin intake							
Low	217	9,921	2,187	1.5	1.2, 1.8	1.5	1.2, 1.8
High	106	6,466	1,639	1.2	0.9, 1.5	1.1	0.9, 1.4[e]
Vitamin B6 intake							
Low	208	9,918	2,097	1.5	1.2, 1.8	1.4	1.2, 1.7
High	115	6,468	1,778	1.3	1.0, 1.6	1.2	1.0, 1.5
Folate intake							
Low	213	10,001	2,130	1.4	1.2, 1.7	1.4	1.1, 1.7
High	110	6,386	1,723	1.1	0.9, 1.4	1.1	0.8, 1.4

Abbreviations: CI, confidence interval; DASH, Dietary Approaches to Stop Hypertension; HR, hazard ratio; PMS, premenstrual syndrome.

[a] Adjusted for age (in months; continuous), time period (person-months), body mass index (weight (kg)/height $(m)^2$; continuous), physical activity level (metabolic equivalent of task-hours per week; continuous), cigarette smoking (cumulative pack-years; continuous), family history of hypertension (yes or no), postmenopausal hormone use (never, 1–71 months, or ≥72 months), Dietary Approaches to Stop Hypertension diet score (quintiles), race/ethnicity (white or other), annual household income (<$50,000, $50,000–$99,000, or ≥$100,000), and daily alcohol consumption (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥15 g).

[b] Adjusted for the variables in model 2 and current use of antidepressants (yes or no), oral contraceptives (yes or no), ibuprofen (none, 1–4, or ≥5 days/week), acetaminophen (none, 1–4, or ≥5 days/week), and aspirin (none, 1–4, or ≥5 days/week).

[c] The reference groups for each comparison were women without PMS who had low levels of adherence to the DASH diet or low micronutrient intakes.

[d] For each energy-adjusted dietary factor, low intake or adherence indicates quintiles 1–3 and high intake or adherence indicates quintiles 4–5. Absolute cutpoints for each dietary factor varied slightly between questionnaire years as the distribution of intake in the Nurses' Health Study II population changed. In 1999 (approximately the midpoint of follow-up), cutpoints for high adherence or intake were as follows: DASH Diet score, ≥25; vitamin D, ≥404 IU/day; calcium, ≥1,260 mg/day; iron, ≥19.4 mg/day; sodium, ≥2,288 mg/day; potassium, ≥3,237 mg/day; thiamine, ≥2.65 mg/day; riboflavin, ≥3.17 mg/day; vitamin B6, ≥3.48 mg/day; and folate, ≥643.7 μg/day.

[e] $P < 0.05$ for comparison of women with PMS who had a low intake of the dietary factor versus women with PMS who had a high intake of the dietary factor.

analyses. It is possible for women who have diagnosed hypertension to develop PMS subsequently; however, because of the minimal overlap in the ages at diagnosis of these 2 outcomes, this is expected to impact a very small proportion of observations, and methodologic studies have suggested that biases of this nature related to selection/exclusions tend to have very minimal effects (38, 39). Additional studies in which the relationships of menstrual symptom experience with blood pressure changes and incident hypertension in young adult women are evaluated are needed to determine whether these relationships are present earlier in life. Despite the large sample size available for these analyses, the possible role of chance cannot be eliminated. Finally, our population is quite homogeneous with respect to race/ethnicity and socioeconomic status. Future studies to confirm our findings among more ethnically diverse populations will be important.

In summary, in this prospective study conducted over 20 years, we observed that women who met the criteria for moderate to severe PMS had significantly higher rates of subsequently developing hypertension, especially before the age of 40 years. This observation warrants confirmation in other prospective studies.

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