JOURNAL OF WOMEN'S HEALTH
Volume 25, Number 9, 2016

DOI: 10.1089/jwh.2015.5529

The Association of Inflammation with Premenstrual Symptoms

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Abstract

Background: About 80% of women experience premenstrual symptoms (PMSx), and about 50% of women seek medical care for them, posing a large medical care burden. However, despite women's use of anti-inflammatory agents for relief from these symptoms, and the fact that anti-inflammatory agents provide relief from some PMSx, the relationship of inflammation to PMSx has not been well investigated.
Methods: We, therefore, undertook the present cross-sectional analyses using baseline data from the longitudinal Study of Women's Health Across the Nation (SWAN), a racially/ethnically diverse cohort of midlife women ($n = 2939$), to determine if a biomarker of inflammation, high-sensitivity C-reactive protein (hs-CRP), was associated with PMSx. We performed factor analyses with Varimax rotations to determine five groupings of eight symptoms to develop a parsimonious set of outcome variables. We conducted backward stepwise multiple logistic regression models for each grouping, eliminating non-significant ($p > 0.05$) covariates.
Results: Having an hs-CRP level >3 mg/L was significantly positively associated with premenstrual mood symptoms (adjusted odds ratio [aOR] = 1.27, 95% confidence interval [95% CI] 1.02–1.58), abdominal cramps/back pain (aOR = 1.40, 95% CI 1.09–1.80), appetite cravings/weight gain/bloating (aOR = 1.41, 95% CI 1.04–1.89), and breast pain (aOR = 1.26, 95% CI 1.02–1.55). Elevated hs-CRP level was not associated with premenstrual headaches or reporting three or more PMSx.
Conclusions: The significant relationships of specific groups of PMSx with elevated hs-CRP levels have potential clinical implications for treatment and possibly for prevention by advising women about the factors associated with inflammation and the potential for treatment with anti-inflammatory agents.

Introduction

Premenstrual symptoms (PMSx) include mood, physical, and cognitive symptoms that begin in the luteal phase of the menstrual cycle and end with, or shortly after, the onset of menstruation.[1] The frequency, type, severity, and combination of symptoms that comprise PMSx vary.[2] The most frequently reported symptoms are irritability, depression, fatigue, water retention, weight gain, breast tenderness, headaches, abdominal cramps, and mood swings.[3] About 80% of women may experience PMSx,[4] and about 50% of women seek medical care for them,[5–7] thus posing a large medical care burden.

The etiology of PMSx may be related to ovarian function, as suppression of ovarian hormone secretion markedly attenuates PMSx,[8] although differences in ovarian steroid hormones have not been consistently observed between symptomatic and asymptomatic women. Biologic, social, demographic, and behavioral factors have been inconsistently associated with PMSx.[2,9–12]

High-sensitivity C-reactive protein (hs-CRP) is an acute phase inflammatory marker that has been associated with cardiovascular disease risk[13] and is an outcome associated with menopausal vasomotor symptoms.[14] It has also been associated with some of the risk factors for PMSx, such as smoking, depressive symptoms, increasing age, and increased body mass index (BMI).[14] While some studies have investigated the associations of inflammation with PMSx, most of these have had relatively small samples of young (*e.g.*, ages 18–30 years) white women,[15,16] and have found suggestive, but not always significant differences in inflammation between women reporting and women not reporting emotional or physical PMSx.

Furthermore, anti-inflammatory agents have been found to provide relief from some PMSx.[17] It is thus possible that inflammation is the mechanism by which these factors increase the risk of PMSx. Therefore, establishing the role of inflammation in different types of PMSx in a large diverse sample of women would be informative in understanding the potential physiologic mechanisms involved in PMSx. We

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undertook these cross-sectional analyses of PMSx among a racially/ethnically diverse cohort of midlife women to determine if inflammation, as measured by hs-CRP, was associated with PMSx.

Methods

Study participants

This cross-sectional study used data on PMSx, health, reproductive, demographic, and lifestyle factors from the baseline questionnaires of the Study of Women's Health Across the Nation (SWAN), a longitudinal, multicenter, multiracial/-ethnic study of midlife women. SWAN is following a cohort of women ($N = 3302$ at baseline) from five racial/ethnic groups, at seven clinical sites located nationwide.[18] We recruited community-based cohorts of Caucasians and one non-Caucasian group at each site: African Americans in Pittsburgh, Boston, Detroit, and Chicago; Hispanics (Puerto Rican, Dominican, Cuban, Central and South American) in Newark, New Jersey; Japanese in Los Angeles; and Chinese in the Oakland, California area.

Participants were eligible for inclusion in the cohort if they were aged 42–52 years and pre- or early perimenopausal, had not undergone a hysterectomy or bilateral oophorectomy, were not pregnant, and were not using menopausal hormone therapy or oral contraceptives at baseline. In addition, participants were required to be able to speak English, Spanish, Cantonese, or Japanese, and to provide informed consent to participate and comply with the study protocol. All instruments and the study protocol were approved by the institutional review boards at all sites, and signed, written informed consent was obtained from all study participants.

From the total baseline sample of 3302 women, 57 were excluded for missing C-reactive protein (CRP) data; 129 additional women were excluded for missing data on PMSx; and an additional 2 women were excluded for missing information on whether the symptoms disappeared within 3 days of onset of their menstrual period.

Data collection

All SWAN participants completed a self-administered and interviewer-administered questionnaire at baseline.

Outcomes. These analyses included data from the baseline visit (administered during 1996–1997) at which participants indicated yes or no in response to the following question for each of eight symptoms: ''During the last year, have you had any of the following during at least half of your menstrual periods or in the week before them?'' The eight symptoms included the following: abdominal cramps/pain, breast pain/tenderness, weight gain/bloating, mood changes/suddenly sad, increase in appetite or cravings, anxious/jittery/nervous, back/joint/muscle pain, and severe headaches.

If a participant answered yes to any one of the symptoms, she was also asked the following question: ''Did this/these characteristic(s) usually (more than half of the time) disappear within 1–3 days after your period started?'' Answering ''yes'' to this question was used as the criterion for a symptom to be considered premenstrual in the present multivariate analyses. Those who answered ''no'' or ''don't know'' were excluded from multivariate analyses (an additional 175 who reported symptoms answered no or don't know to whether the symptoms disappeared within 3 days of onset of their menstrual periods; so, the total number excluded = 363 when using this more conservative definition of PMSx, but only 188 were excluded if the more expanded criteria were used of reporting the symptom, but saying no or don't know in response to whether the symptom disappeared within 3 days of onset of their menstrual periods).

Independent variable. hs-CRP assays were performed at baseline using an ultrasensitive rate immunonephelometry (hs-CRP on BN100; Dade-Behring, Marburg, Germany). The method is based on monitoring light scattering during agglutination of CRP to polystyrene particles coated with monoclonal antibodies to CRP. The sensitivity of the assay (lowest detectable concentration) was 0.03 mg/dL. The interassay coefficients of variation at CRP concentrations of 0.05 and 2.2 mg/dL were 10%–12% and 5%–7%, respectively. Although hsCRP level is a continuous variable, a cutoff for elevated hsCRP has been established for clinical use[19] and was used to categorize hsCRP into elevated (>3 mg/L) and nonelevated (≤3 mg/L) for analyses.

Covariates. Age at baseline was analyzed as a continuous variable. Annual household income was self-reported and evaluated using a three-level categorical variable based on tertiles of total income reported <$35,000, $35,000–$75,000, and >$75,000. A binary categorical variable was used for the proportion of women with a college education. Race/ethnicity was self-identified as Caucasian, African American, Hispanic, Chinese, or Japanese and included both US-born and foreign-born women.

Menopausal status at baseline was defined using a dichotomous variable: (1) premenopausal (menstrual period in the prior 3 months with no change in regularity of periods) or (2) early perimenopausal (menstrual period in the prior 3 months with change in regularity of periods) without use of hormone therapy. Parity was self-reported and analyzed as a categorical variable.

Weight and height were measured using a calibrated balance beam scale and stadiometer, respectively. BMI (weight in kilograms/[height in meters]^2) was computed and analyzed as a four-level categorical variable: low (<18.5), normal (18.5–24.9), overweight (25–29.9), or obese (≥30). Comorbidity consisted of reporting of 1 or more of 10 chronic health conditions (heart disease, arthritis, high blood pressure, diabetes, high cholesterol, stroke, anemia, migraines, angina, and osteoporosis) during the past year and was treated as a categorical variable. Use of anti-inflammatory medications was assessed by self-reported use in the prior month of such prescription and nonprescription medications as assessed by SWAN pharmacologists, independent of report of PMSx.

Active smoking status was assessed by standard questions.[20] Passive smoke exposure was assessed by the validated instrument of Coghlin *et al.*[21] Never smokers with no passive smoke exposure were used as the referent group. Physical activity was measured by a composite score based on the Kaiser Permanente Activity Score,[22] a modification of the Baecke scale[23] assessing three domains: sports, leisure, and household activities. Usual servings of alcoholic beverages per week were analyzed as none, ≤1, and >1 (one serving = 12 oz. beer, 5 oz. wine, or 1.5 oz hard liquor).

Social support was assessed by a summed scale of how often four types of needed emotional and instrumental supports were available, with responses ranging from 0 = none of the time to 4 = all of the time[24] and analyzed by quartiles of the total score in the SWAN baseline cohort. A measure of the symptom sensitivity trait was measured at follow-up visit 01 using a summed score (degree of awareness of loud noise, hot or cold, hunger, pain, and things happening in one's body, with responses ranging from 1 = not at all true to 5 = extremely true)[25] and analyzed dichotomously as at or above versus below 15, the median for the SWAN cohort. Depressive symptoms were assessed by the Center for Epidemiologic Studies Depression (CES-D)[26] scale (score ≥16 on a 20-item scale of the extent to which each item was experienced in the previous week).

Data analyses

This was a cross-sectional analysis, using only data from the baseline visit. Descriptive statistics were computed using bivariate analyses for each symptom grouping (as described below), each independent variable, and each covariate. Categorical variables were analyzed using chi-square tests or Fisher's exact test for comparison of proportions, and *t*-tests and analysis of variance (ANOVA) were used for comparisons involving continuous variables. Unadjusted odd ratios (ORs) were computed for each symptom group by each independent variable.

We conducted factor analyses with Varimax rotations to determine appropriate groupings of the eight symptoms so that a parsimonious set of outcome variables could be evaluated. To determine whether to retain a particular symptom in a symptom grouping, we used factor loadings of 0.40 or more. If items loaded on more than one factor, the item with the highest loading was retained. Factors were accepted with an eigen value of 1.0 or greater. As in our prior work,[12] the five resulting PMSx groupings were as follows: (1) anxiety/jittery/nervous and mood changes, (2) abdominal cramps and back/joint/muscle pain, (3) increased appetite/craving and weight gain/bloating, (4) breast pain/tenderness, and (5) headaches. Because women often reported more than one symptom, associations of the independent variables with the total number of these five symptom groupings (>3 vs. ≤3) were also estimated.

To assess potential confounding variables, we calculated unadjusted odds ratios (ORs) and 95% confidence intervals (95% CIs), one variable at a time. To adjust simultaneously for confounding variables, multiple logistic regression models were developed for each PMSx grouping. Covariates that were associated (at $p < 0.15$) in unadjusted analyses were entered into backward stepwise multiple logistic regression models for each PMSx grouping with elimination of variables found not to be significant ($p > 0.05$). The independent variable, elevated hsCRP (>3 mg/L vs. ≤3 mg/L), was forced into all multiple logistic regression models. AIC goodness of fit test criteria were used for multiple logistic regression models. Interactions with race-ethnicity and menopause status were evaluated to determine if any relationships observed differed by these variables.

Results

The unadjusted proportion of women who reported each PMSx, except breast pain or headaches, was significantly increased for women who had hs-CRP values >3 mg/L (Table 1). In addition, mean age was significantly lower among women who reported all PMSx except for those reporting premenstrual breast pain. All symptoms were reported by significantly more Hispanics and early perimenopausal women and by significantly less Chinese and Japanese than Caucasian or premenopausal women. Most symptoms (except changes in appetite/weight/bloating and breast pain) were reported by fewer women with more than a high school education, higher annual income, and lower symptom sensitivity scores compared to those with a high school education or less, lower annual income, and higher symptom sensitivity.

Most symptoms (except for breast pain or headaches) were reported by significantly more obese women, those with active or passive smoke exposure, and by women with elevated depressive symptom scores (for all symptoms) than normal weight women, women without active or passive smoke exposure, or women with lower depressive symptom scores. Parity, physical activity, hypertension, arthritis, and anemia were significantly positively and alcohol consumption was significantly negatively related to headaches. However, most of the differences were relatively small and likely significant because of the large sample size. Diabetes, cancer, high cholesterol, stroke, and thyroid disease were not significantly related to any symptoms, nor was heart disease except for a significant relationship to abdominal cramps and pain.

Unadjusted analyses

In unadjusted analyses, hs-CRP levels >3 mg/L were significantly associated with premenstrual mood symptoms, regardless of whether the conservative definition (symptom disappeared within 3 days of onset of menses) was used (OR = 1.46, 95% CI 1.22–1.75) or if the symptom did not disappear within 3 days of onset of menses (OR = 1.74, 95% CI 1.17–2.58) (Table 2). Similarly, in unadjusted analyses, hs-CRP levels >3 mg/L were significantly associated with premenstrual abdominal cramps/pain, regardless of whether the conservative definition was used (OR = 1.84, 95% CI 1.52–2.23) or if the symptom did not disappear within 3 days of onset of menses (OR = 2.36, 95% CI 1.61–3.46). Also, in unadjusted analyses, hs-CRP levels >3 mg/L were significantly positively associated with premenstrual appetite cravings/weight gain/bloating, regardless of whether the conservative definition (OR = 1.78, 95% CI 1.42–2.22) or less conservative definition (OR = 2.30, 95% CI 1.54–3.42) was used.

An elevated hs-CRP level was not associated with reporting premenstrual breast pain or headaches in unadjusted analyses. Other factors related to each symptom group were similar to those we found previously[12] (data not shown).

We also examined the unadjusted mean hs-CRP by number of symptom groups reported and found a trend of increasing means (from 3.11 ± 7.78 mg/L for none, 3.18 ± 9.12 mg/L for one, 3.06 ± 4.76 for two, 3.51 ± 5.31 mg/L for three, 4.25 ± 6.52 mg/L for four to 4.22 ± 5.38 mg/L for five symptoms) with increasing number of symptom groups, which was significant in ANOVA ($p = 0.026$), but the trend was not monotonic. However, because the distribution of hs-CRP was skewed to the right, we examined median hs-CRP by number of symptom groups reported and found that the median increased monotonically from 1.0 mg/L for none to 2.1 mg/L for five symptoms reported. Further, the unadjusted ORs for the association of elevated hs-CRP with number of symptoms

TABLE 1. DISTRIBUTIONS OF BASELINE CHARACTERISTICS BY SYMPTOM REPORTING

Independent variables and covariates	Mood				Cramps/back pain				Appetite/weight/bloat				Breast pain				Headaches				Total no. of symptoms			
	No		Yes		No		Yes		No		Yes		No		Yes		No		Yes		<3		>3	
	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD
Age,[a] (mean, SD)	46.8	2.8	46.2	2.6	46.7	2.8	46.2	2.64	47.0	2.7	46.2	2.6	46.4	2.7	46.3	2.7	46.4	2.7	46.2	2.6	46.6	2.8	46.1	2.6
hs-CRP[a] (mg/L)																								
≤3	522	26.9	1419	73.1	519	26.7	1422	73.3	338	17.4	1603	82.6	621	32.0	1320	68.0	1454	74.9	487	25.1	994	51.2	947	48.8
>3	196	19.6	802	80.4	164	16.4	834	83.6	104	10.4	894	89.6	313	31.4	685	68.6	715	71.6	283	28.4	418	41.9	580	58.1
Race/ethnicity[b]																								
African American	212	25.3	625	74.7	146	17.4	691	82.6	98	11.7	739	88.3	289	34.5	548	65.5	619	74.0	218	26.0	391	46.7	446	53.3
Caucasian	287	20.8	1091	79.2	310	22.5	1068	77.5	157	11.4	1221	88.6	407	29.5	971	70.5	1027	74.5	351	25.5	615	44.6	763	55.4
Chinese	82	37.8	135	62.2	98	45.2	119	54.8	88	40.6	129	59.4	91	41.9	126	58.1	176	81.1	41	18.9	158	72.8	59	27.2
Hispanic	43	16.8	213	83.2	34	13.3	222	86.7	33	12.9	223	87.1	49	19.1	207	80.9	149	58.2	107	41.8	80	31.2	176	68.8
Japanese	93	38.9	146	61.1	91	38.1	148	61.9	65	27.2	174	72.8	95	39.8	144	60.2	189	79.1	50	20.9	162	67.8	77	32.2
Education[c]																								
≤High School	374	22.6	1282	77.4	323	19.5	1333	80.5	259	15.6	1397	84.4	510	30.8	1146	69.2	1177	71.1	479	28.9	749	45.2	907	54.8
>High School	340	27.1	915	72.9	354	28.2	901	71.8	179	14.3	1076	85.7	415	33.1	840	66.9	970	77.3	285	22.7	648	51.6	607	48.4
Annual household income[d]																								
<$35,000	182	20.5	704	79.5	176	19.9	710	80.1	133	15.0	753	85.0	276	31.2	610	68.8	614	69.3	272	30.7	393	44.4	493	55.6
$35–75,000	299	25.3	882	74.7	272	23.0	909	77.0	181	15.3	1000	84.7	387	32.8	794	67.2	892	75.5	289	24.5	577	48.9	604	51.1
>$75,000	219	27.5	577	72.5	214	26.9	582	73.1	115	14.4	681	85.6	250	31.4	546	68.6	607	76.3	189	23.7	403	50.6	393	49.4
Menopausal status[e]																								
Premenopause	448	29.0	1099	71.0	407	26.3	1140	73.7	260	16.8	1287	83.2	530	34.3	1017	65.7	1196	77.3	351	22.7	822	53.1	725	46.9
Early perimenopause	256	19.4	1064	80.6	257	19.5	1063	80.5	168	12.7	1152	87.3	383	29.0	937	71.0	923	69.9	397	30.1	555	42.0	765	58.0
BMI (kg/m^2)[f]																								
<18.5	37	21.5	135	78.5	39	22.7	133	77.3	40	23.3	132	76.7	52	30.2	120	69.8	120	69.8	52	30.2	81	47.1	91	52.9
18.5–24.9	339	26.7	932	73.3	356	28.0	915	72.0	242	19.0	1029	81.0	395	31.1	876	68.9	956	75.2	315	24.8	648	51.0	623	49.0
25–29.9	189	24.9	569	75.1	170	22.4	588	77.6	96	12.7	662	87.3	234	30.9	524	69.1	563	74.3	195	25.7	357	47.1	401	52.9
>30	152	20.9	574	79.1	114	15.7	612	84.3	63	8.7	663	91.3	250	34.4	476	65.6	521	71.8	205	28.2	320	44.1	406	55.9
Parity[g]																								
None	141	28.0	363	72.0	111	22.0	393	78.0	65	12.9	439	87.1	154	30.6	350	69.4	391	77.6	113	22.4	244	48.4	260	51.6
1–3	490	24.2	1538	75.8	489	24.1	1539	75.9	322	15.9	1706	84.1	637	31.4	1391	68.6	1504	74.2	524	25.8	980	48.3	1048	51.7
4+	86	21.3	318	78.7	82	20.3	322	79.7	54	13.4	350	86.6	140	34.6	264	65.4	272	67.3	132	32.7	186	46.0	218	54.0
Smoke exposure[h]																								
Never smoker/no passive	395	26.9	1074	73.1	394	26.8	1075	73.2	270	18.4	1199	81.6	477	32.5	992	67.5	1106	75.3	363	24.7	758	51.6	711	48.4
Never smoker/ some passive	43	21.3	159	78.7	44	21.8	158	78.2	38	18.8	164	81.2	61	30.2	141	69.8	139	68.8	63	31.2	91	45.0	111	55.0
Former smoker/ no passive	139	22.0	494	78.0	139	22.0	494	78.0	69	10.9	564	89.1	190	30.0	443	70.0	470	74.2	163	25.8	281	44.4	352	55.6
Former smoker/ any passive	20	18.2	90	81.8	29	26.4	81	73.6	8	7.3	102	92.7	36	32.7	74	67.3	76	69.1	34	30.9	50	45.4	60	54.6

(continued)

TABLE 1. (CONTINUED)

Independent variables and covariates	Mood				Cramps/back pain				Appetite/weight/bloat				Breast pain				Headaches				Total no. of symptoms			
	No		Yes		No		Yes		No		Yes		No		Yes		No		Yes		<3		>3	
	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD
Current smoker	114	22.9	384	77.1	73	14.7	425	85.3	56	11.2	442	88.8	162	32.5	336	67.5	358	71.9	140	28.1	221	44.4	277	55.6
Alcohol servings/week[i]																								
None	373	25.8	1074	74.2	349	24.1	1098	75.9	237	16.4	1210	83.6	480	33.2	967	66.8	1043	72.1	404	27.9	703	48.6	744	51.4
1 or less	152	22.8	514	77.2	155	23.3	511	76.7	84	12.6	582	87.4	207	31.1	459	68.9	487	73.1	179	26.9	323	48.5	343	51.5
More than 1	191	23.4	626	76.6	177	21.7	640	78.3	120	14.7	697	85.3	244	29.9	573	70.1	631	77.2	186	22.8	382	46.8	435	53.2
Physical activity[j] (mean, SD)	9.5	2.0	9.4	2.2	9.6	2.1	9.4	2.2	9.3	2.0	9.5	2.2	9.4	2.1	9.5	2.2	9.5	2.1	9.3	2.3	9.5	2.0	9.4	2.3
Sx sensitivity score[k]																								
<15	329	30.7	744	69.3	311	29.0	762	71.0	203	18.9	870	81.1	368	34.3	705	65.7	821	76.5	252	23.5	599	55.8	474	44.2
≥15	301	20.8	1144	79.2	302	20.9	1143	79.1	195	13.5	1250	86.5	449	31.1	996	68.9	1054	72.9	391	27.1	650	45.0	795	55.0
CES-D score[l]																								
<16	656	29.2	1588	70.8	585	26.1	1659	73.9	378	16.8	1866	83.2	748	33.3	1496	66.7	1741	77.6	503	22.4	1199	53.4	1045	46.6
≥16	62	8.9	633	91.1	98	14.1	597	85.9	64	9.2	631	90.8	186	26.8	509	73.2	428	61.6	267	38.4	213	30.6	482	69.4
Social support score[m]																								
<11	124	17.8	574	82.2	153	21.9	545	78.1	108	15.5	590	84.5	243	34.8	455	65.2	479	68.6	219	31.4	302	43.3	396	56.7
11–12	137	21.4	503	78.6	137	21.4	503	78.6	82	12.8	558	87.2	191	29.8	449	70.2	487	76.1	153	23.9	298	46.6	342	53.4
13–14	163	24.9	491	75.1	160	24.5	494	75.5	97	14.8	557	85.2	208	31.8	446	68.2	482	73.7	172	26.3	325	49.7	329	50.3
15+	294	31.1	652	68.9	233	24.6	713	75.4	155	16.4	791	83.6	291	30.8	655	69.2	721	76.2	225	23.8	487	51.5	459	48.5
Anti-inflammatory medications[n]																								
No	493	26.4	1377	73.6	502	26.8	1368	73.2	329	17.6	1541	82.4	611	32.7	1259	67.3	1458	78.0	412	22.0	974	52.1	896	47.9
Yes	225	21.0	844	79.0	181	16.9	888	83.1	113	10.6	956	89.4	323	30.2	746	69.8	711	66.5	358	33.5	438	41.0	631	59.0
No. of comorbidities[o]																								
None	220	28.1	564	71.9	221	28.2	563	71.8	155	19.8	629	80.2	270	34.4	514	65.6	634	80.9	150	19.1	428	54.6	356	45.4
1	253	25.1	754	74.9	259	25.7	748	74.3	167	16.6	840	83.4	322	32.0	685	68.0	761	75.6	246	24.4	498	49.4	509	50.6
2	153	24.2	478	75.8	132	20.9	499	79.1	83	13.2	548	86.8	197	31.2	434	68.8	457	72.4	174	27.6	288	45.6	343	54.4
3+	92	17.8	425	82.2	71	13.7	446	86.3	37	7.2	480	92.8	145	28.0	372	72.0	317	61.3	200	38.7	198	38.3	319	61.7
Diabetes[p]																								
No	683	24.9	2057	75.1	633	23.1	2107	76.9	417	15.2	2323	84.8	865	31.6	1875	68.4	2020	73.7	720	26.3	1316	48.0	1424	52.0
Yes	26	17.6	122	82.4	36	24.3	112	75.7	19	12.8	129	87.2	56	37.8	92	62.2	113	76.4	35	23.6	72	48.6	76	51.4
High blood pressure[q]																								
No	571	24.4	1765	75.6	563	24.1	1773	75.9	369	15.8	1967	84.2	736	31.5	1600	68.5	1747	74.8	589	25.2	1128	48.3	1208	51.7
Yes	136	24.6	417	75.4	106	19.2	447	80.8	66	11.9	487	88.1	185	33.4	368	66.6	389	70.3	164	29.7	261	47.2	292	52.8
Osteoporosis[r]																								
No	703	24.7	2148	75.3	667	23.4	2184	76.6	433	15.2	2418	84.8	911	32.0	1940	68.0	2108	73.9	743	26.1	1377	48.3	1474	51.7
Yes	7	21.2	26	78.8	2	6.1	31	93.9	2	6.1	31	93.9	9	27.3	24	72.7	24	72.7	9	27.3	11	33.3	22	66.7
Arthritis[s]																								
No	631	26.2	1779	73.8	607	25.2	1803	74.8	389	16.1	2021	83.9	795	33.0	1615	67.0	1801	74.7	609	25.3	1208	50.1	1202	49.9
Yes	78	16.2	403	83.8	63	13.1	418	86.9	47	9.8	434	90.2	128	26.6	353	73.4	335	69.6	146	30.4	182	37.8	299	62.2
Fibroids[t]																								
No	578	25.1	1724	74.9	558	24.2	1744	75.8	367	15.9	1935	84.1	751	32.6	1551	67.4	1703	74.0	599	26.0	1128	49.0	1174	51.0
Yes	131	22.7	447	77.3	108	18.7	470	81.3	66	11.4	512	88.6	167	28.9	411	71.1	425	73.5	153	26.5	258	44.6	320	55.4
Cancer[u]																								
No	700	24.7	2133	75.3	659	23.3	2174	76.7	428	15.1	2405	84.9	902	31.8	1931	68.2	2097	74.0	736	26.0	1363	48.1	1470	51.9
Yes	10	17.5	47	82.5	11	19.3	46	80.7	8	14.0	49	86.0	19	33.3	38	66.7	38	66.7	19	33.3	26	45.6	31	54.4

(*continued*)

Table 1. (Continued)

Independent variables and covariates	Mood				Cramps/back pain				Appetite/weight/bloat				Breast pain				Headaches				Total no. of symptoms			
	No		Yes		No		Yes		No		Yes		No		Yes		No		Yes		<3		>3	
	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD
Heart[v]																								
No	700	24.7	2135	75.3	666	23.5	2169	76.5	430	15.2	2405	84.8	906	32.0	1929	68.0	2096	73.9	739	26.1	1368	48.2	1467	51.8
Yes	10	19.2	42	80.8	4	7.7	48	92.3	6	11.5	46	88.5	15	28.8	37	71.2	38	73.1	14	26.9	21	40.4	31	59.6
Anemia[w]																								
No	486	25.3	1434	74.7	474	24.7	1446	75.3	336	17.5	1584	82.5	627	32.7	1293	67.3	1449	75.5	471	24.5	952	49.6	968	50.4
Yes	230	22.8	779	77.2	207	20.5	802	79.5	102	10.1	907	89.9	305	32.7	704	35.2	715	70.9	294	29.1	457	45.3	552	54.7
High cholesterol[u]																								
No	600	25.2	1783	74.8	563	23.6	1820	76.4	364	15.3	2019	84.7	760	31.9	1623	68.1	1777	74.6	606	25.4	1159	48.6	1224	51.4
Yes	116	21.3	429	78.7	118	21.6	427	78.4	78	14.3	467	85.7	170	31.2	375	68.8	384	70.5	161	29.5	248	45.5	297	54.5
Migraines[x]																								
No	628	25.4	1848	74.6	618	25.0	1858	75.0	399	16.1	2077	83.9	803	32.4	1673	67.6	1954	78.9	522	21.1	1258	50.8	1218	49.2
Yes	89	19.5	367	80.5	65	14.2	391	85.8	42	9.2	414	90.8	130	28.5	326	71.5	211	46.3	245	53.7	152	33.3	304	66.7
Stroke[u]																								
No	712	24.5	2194	75.5	676	23.3	2230	76.7	440	15.1	2466	84.9	926	31.9	1980	68.1	2148	73.9	758	26.1	1398	48.1	1508	51.9
Yes	6	18.8	26	81.2	7	21.9	25	78.1	2	6.2	30	93.8	8	25.0	24	75.0	20	62.5	12	37.5	14	43.8	18	56.3
Thyroid disease[y]																								
No	686	24.7	2090	75.3	647	23.3	2129	76.7	418	15.1	2358	84.9	888	32.0	1888	68.0	2053	74.0	723	26.0	1347	48.5	1429	51.5
Yes	31	19.5	128	80.5	36	22.6	123	77.4	22	13.8	137	86.2	46	28.9	113	71.1	112	70.4	47	29.6	63	39.6	96	60.4

Reported having symptom during menstrual period or in week prior and that it disappeared in 3 days after start of menstruation.
[a]All significant differences at $p < 0.0001$ except breast pain not significant and headaches significant at $p = 0.048$.
[b]All significant differences at $p < 0.0001$.
[c]All significant differences at $p \leq 0.005$ except appetite cravings/weight gain/bloating and breast pain.
[d]All significant differences at $p \leq 0.03$ except appetite cravings/weight gain/bloating, breast pain, and >3 symptoms.
[e]All significant differences at $p < 0.0003$.
[f]Only significant differences for abdominal cramps/back pain and appetite cravings/weight gain/bloating at $p < 0.0001$ and >3 symptoms at $p = 0.025$.
[g]Only headaches significant at $p = 0.0018$.
[h]Only abdominal cramps/back pain and appetite cravings/weight gain/bloating significant differences at $p < 0.0001$, mood at $p = 0.027$ and >3 symptoms at $p = 0.0058$.
[i]Only significant difference for headaches at $p = 0.026$.
[j]Only significant differences for abdominal cramps/back pain and headaches at $p \leq 0.013$.
[k]Significant differences for mood, abdominal cramps/back pain, appetite cravings/weight gain/bloating, and >3 symptoms at $p \leq 0.0002$ and headaches at $p = 0.042$.
[l]All significant differences at $p \leq 0.0012$.
[m]Only significant difference for mood, headaches, and >3 symptoms s at $p \leq 0.0069$.
[n]All significant differences at $p \leq 0.0013$ except breast pain.
[o]All significant differences at $p \leq 0.0004$ except breast pain.
[p]Only significant difference for mood at $p = 0.043$.
[q]Only significant differences for abdominal cramps/back pain, appetite cravings/weight gain/bloating, and headaches at $p \leq 0.032$.
[r]Only significant difference for abdominal cramps/back pain at $p = 0.019$.
[s]All significant differences at $p \leq 0.0062$ except headaches at $p = 0.020$.
[t]Only significant differences for abdominal cramps/back pain at $p = 0.0046$ and appetite cravings/weight gain/bloating at $p \leq 0.0065$.
[u]All differences nonsignificant.
[v]Only significant difference for abdominal cramps/back pain at $p = 0.0075$.
[w]Significant differences for mood, abdominal cramps/back pain, appetite cravings/weight gain/bloating, headaches, and >3 symptoms at $p \leq 0.027$.
[x]All significant differences at $p \leq 0.0076$ except breast pain.
[y]Only significant difference for >3 symptoms at $p = 0.029$.
BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression; hs-CRP, high-sensitivity C-reactive protein; SD, standard deviation.

Table 2. Unadjusted Odds Ratios and 95% Confidence Intervals for Association of Elevated High-Sensitivity C-Reactive Protein with Each Premenstrual Symptom, SWAN Baseline

	Reported had symptom and that it disappeared within 3 days of onset of menses, n = *2978–3044*			*Reported had symptom, but not that it disappeared within 3 days of onset of menses,* n = *3114*		
Premenstrual symptom	*OR*	*95% CI*	p	*OR*	*95% CI*	p
Mood	1.46	1.22–1.75	<0.0001	1.74	1.17–2.58	0.0062
Abdominal cramps/back pain	1.84	1.52–2.23	<0.0001	2.36	1.61–3.46	<0.0001
Appetite cravings/weight gain/bloating	1.78	1.42–2.22	<0.0001	2.30	1.54–3.42	<0.0001
Breast pain	0.99	0.85–1.17	0.94	1.02	0.68–1.53	0.92
Headaches	1.16	0.98–1.38	0.084	1.11	0.68–1.83	0.68

95% CI, 95% confidence interval; OR, odds ratio; SWAN, Study of Women's Health Across the Nation.

reported also increased monotonically from 0.90 (95% CI 0.51–1.60) for one symptom to 2.21 (95% CI 1.35–3.62) for five symptoms reported; all 95% CIs for these ORs included 1.0 until four or more symptoms were reported.

Multivariable models

In backward stepwise multiple logistic regression models, removing variables not significant ($p > 0.05$), having an hs-CRP level >3 mg/L remained significantly positively associated with premenstrual mood symptoms (adjusted OR [aOR] = 1.27, 95% CI 1.02–1.58), using the conservative definition of the symptom disappearing within 3 days of onset of menses, after adjustment for age, race/ethnicity, blood draw within cycle days 2–5, menopausal status, CES-D ≥16, symptom sensitivity score ≥15, parity, social support, and comorbidities (Table 3). Having an hs-CRP level >3 mg/L also remained significantly positively associated with premenstrual abdominal cramps/back pain (aOR = 1.40, 95% CI 1.09–1.80) after adjustment for age, race/ethnicity, blood draw within cycle days 2–5, menopausal status, BMI category, CES-D ≥16, symptom sensitivity ≥15, use of anti-inflammatory medications in the past month, and education.

In addition, having an hs-CRP level >3 mg/L also remained significantly positively associated with reporting premenstrual appetite cravings/weight gain/bloating (aOR = 1.41, 95% CI 1.04–1.89) after adjustment for age, race/ethnicity, blood draw within cycle days 2–5, menopausal status, BMI category, physical activity score, CES-D ≥16, symptom sensitivity ≥15, use of anti-inflammatory medication, comorbidities, and physical activity. Having an hs-CRP level >3 mg/L also remained significantly positively associated with reporting premenstrual breast pain (aOR = 1.26, 95% CI 1.02–1.55) after adjustment for age, race/ethnicity, blood draw within cycle days 2–5, menopausal status, and BMI category.

Mood symptoms, abdominal cramps/back pain, appetite cravings/weight gain/bloating, and breast pain also remained significantly positively related to elevated hs-CRP, with similar magnitude of association, in adjusted models using the less conservative definition of not reporting disappearance of the symptom within 3 days of onset of menses. An elevated hs-CRP was not significantly related to premenstrual headache (aOR = 0.91, 95% CI 0.68–1.14) or to having three or more PMSx (aOR = 1.15, 95% CI 0.95–1.40) in multivariable models, regardless of definition used regarding disappearance of symptoms within 3 days of onset of the menstrual period and adjusted for age, race/ethnicity, blood draw within cycle days 2–5, menopausal status, CES-D ≥16, use of anti-inflammatory medications in the past month, and comorbidities.

We also computed adjusted ORs using the conservative definition for symptoms, but with a criterion of >5 mg/L for the elevation of hs-CRP, and found nearly identical results to those above for the lower cutoff except that the associations were somewhat stronger for abdominal cramps/back pain (aOR 1.56, 95% CI 1.15–2.10), weight gain/bloating (aOR 1.52, 95% CI 1.07–2.15), and reporting 3+ symptoms (aOR 1.50, 95% CI 1.18–1.89).

In addition, in multivariable models for each symptom, we tested interaction of elevated hs-CRP with race/ethnicity and separately with menopausal status and found none of the interaction terms to be statistically significant. This indicated that the relationship of elevated hs-CRP to each symptom did not vary by menopausal status or across racial/ethnic groups, although the sample sizes in some racial/ethnic subgroups were probably too small to provide adequate statistical power to detect some meaningful differences as statistically significant. We also computed adjusted ORs for number of symptoms in relationship to hs-CRP >3 mg/L and found a trend of increasing adjusted ORs with increasing number of symptoms reported (from 0.66, 95% CI 0.64–1.30 for one symptom to 1.21, 95% CI 0.67–2.18 for five symptoms) (data not shown), although the 95% CIs were overlapping and none excluded 1.0.

Furthermore, because of the documented relationship of inflammation and depressive symptoms,[27,28] we reran all analyses for Table 3 excluding women with CES-D ≥16, and the adjusted ORs remained at a similar magnitude, although some 95% CIs included 1.0 due to the reduced sample size (data not shown). We also reran analyses, adjusting for currently taking ''medications for a nervous condition such as tranquilizers, sedatives, sleeping pills, or antidepression medication,'' which resulted in little change in adjusted ORs (data not shown). Interactions of each symptom group with the use of such medications were all nonsignificant.

Discussion

In our cross-sectional study, elevated hs-CRP (>3 mg/L), an acute phase biomarker of inflammation, was significantly related to a 26%–41% increased odds of reporting of premenstrual mood symptoms, abdominal cramps/back pain,

Table 3. Odds Ratios and 95% Confidence Intervals from Multiple Logistic Regression Models for Association of hs-CRP >3 mg/L with Each Premenstrual Symptom, Adjusted for Covariates, SWAN Baseline, $N = 2939$

	Mood *OR (95% CI)*	*Cramps/pain* *OR (95% CI)*	*Appetite/weight/bloat* *OR (95% CI)*	*Breast pain* *OR (95% CI)*	*Headaches* *OR (95% CI)*	*3 or more Sx* *OR (95% CI)*
hs-CRP >3 mg/L	1.27[a] (1.02–1.58)	1.40[a] (1.09–1.80)	1.41[a] (1.04–1.89)	1.26[a] (1.02–1.55)	0.91 (0.73–1.12)	1.15 (0.95–1.40)
Age per year	0.90[a] (0.87–0.93)	0.91[a] (0.88–0.95)	0.87[a] (0.83–0.90)	0.96[a] (0.93–1.00)	0.96[a] (0.92–0.99)	0.91[a] (0.88–0.94)
Race/ethnicity (ref: Caucasian)						
African American	0.60[a] (0.47–0.77)	1.29 (0.99–1.68)	0.71[a] (0.52–0.97)	0.85 (0.69–1.05)	0.93 (0.73–1.18)	0.78[a] (0.63–0.96)
Chinese	0.55[a] (0.39–0.77)	0.42[a] (0.30–0.59)	0.27[a] (0.19–0.38)	0.60[a] (0.44–0.81)	0.98 (0.66–1.47)	0.38[a] (0.27–0.54)
Hispanic	0.96 (0.63–1.48)	1.52 (0.96–2.40)	1.01 (0.62–1.65)	1.52[a] (1.05–2.20)	2.39[a] (1.69–3.38)	1.46[a] (1.02–2.09)
Japanese	0.51[a] (0.37–0.71)	0.67[a] (0.49–0.93)	0.51[a] (0.35–0.73)	0.68[a] (0.50–0.92)	1.08 (0.75–1.57)	0.50[a] (0.36–0.69)
Early peri- versus premenopause	1.68[a] (1.37–2.04)	1.45[a] (1.19–1.78)	1.40[a] (1.11–1.77)	1.37[a] (1.16–1.63)	1.44[a] (1.18–1.75)	1.50[a] (1.29–1.83)
Blood not drawn within cycle days 2–5	0.75[a] (0.60–0.96)	0.79 (0.62–1.01)	0.99 (0.74–1.31)	0.84 (0.68–1.04)	0.71 (0.55–0.91)	0.76 (0.61–0.95)
BMI, kg/m^2 (ref: 18.5–24.9)	—				—	—
<18.5		0.56[a] (0.36–0.87)	0.44[a] (0.28–0.70)	0.60[a] (0.40–0.89)		
25–29.9		0.99 (0.77–1.27)	1.41[a] (1.04–1.90)	0.88 (0.70–1.09)		
30+		1.16 (0.85–1.58)	1.33 (0.92–1.93)	0.64[a] (0.49–0.82)		
CES-D score ≥16 versus <16	2.65[a] (1.96–3.60)	1.47[a] (1.12–1.92)	1.51[a] (1.10–2.08)	—	1.69[a] (1.35–2.12)	1.93[a] (1.55–2.42)
Symptom sensitivity score ≥15 versus <15	1.61[a] (1.32–1.95)	1.32[a] (1.08–1.60)	1.33[a] (1.06–1.66)	—	—	1.38[a] (1.16–1.65)
Use of anti-inflammatory medications in past month	—	1.57[a] (1.26–1.94)	1.29[a] (1.00–1.67)	—	1.55[a] (1.27–1.89)	1.32[a] (1.10–1.58)
Parity (ref: 0)		—	—	—	—	—
1–3	1.35[a] (1.05–1.74)					
4+	1.51[a] (1.04–2.18)					
College education or more (ref: less than college)	—	0.77[a] (0.63–0.95)	—	—	—	
Social support (ref: <11)		—	—	—	—	—
11–12	1.04 (0.76–1.43)					
13–14	0.78 (0.58–1.06)					
15+	0.60[a] (0.45–0.80)					
No. of comorbidities (ref: none)		—		—		
1	1.21 (0.95–1.54)		1.05 (0.80–1.38)		1.38[a] (1.05–1.80)	1.21 (0.96–1.51)
2	1.23 (0.93–1.61)		1.38[a] (0.99–1.92)		1.44[a] (1.07–1.94)	1.28[a] (0.99–1.64)
≥3	1.57 (1.14–2.16)		2.01[a] (1.34–3.03)		2.65[a] (1.94–3.60)	1.73[a] (1.30–2.30)
Physical activity score	—	—	1.09[a] (1.03–1.15)	—	—	—

Using definition that reported premenstrual symptom disappeared within 3 days of onset of menses.
[a]Remained significantly associated using the less conservative definition of symptom not disappearing within 3 days of onset of menses.

appetite cravings/weight gain/bloating, and breast pain, but not headache, after adjusting for confounding variables. The results also revealed that the relationship of other risk factors to the different symptoms was not uniform across PMSx, suggesting different mechanisms for the occurrence of the different symptom groups. However, several factors (younger age, being in the early perimenopause, having an elevated depressive symptom score, and increased symptom sensitivity score) were associated with most symptoms with similar magnitudes of association.

The significant relationships of these PMSx with elevated hs-CRP levels have potential clinical implications for the treatment of these symptoms and possibly for prevention by advising women about the factors (*e.g.*, smoking, overweight, and obesity) that are associated with inflammation, as well as suggesting avenues for future mechanistic and epidemiologic research.

To date, little literature has focused on the relationship of inflammation to PMSx, despite the fact that some women use anti-inflammatory medications to treat these frequently occurring symptoms. The observation of significant relationships of inflammation with some PMSx suggests that inflammation may be involved in the occurrence of these symptoms, although this requires future investigation using longitudinal data to establish the temporal sequence.

Our results are consistent with those of some prior studies that have found suggestive, but not always significant differences in inflammation between women reporting and women not reporting emotional or physical PMSx. However, most of these studies have included relatively small samples and have studied young (*e.g.*, ages 18–30 years) white women.[15,16] The present results are a unique contribution in that these frequently occurring PMSx were examined in a large sample of midlife (not young) women from a diverse sample that included five racial/ethnic groups.

Strengths and limitations

This study had several significant strengths. First, the sample comprised a large, racially/ethnically diverse, community-based sample of midlife women. Thus, we had good statistical power to detect meaningful associations, and the results are likely to have fairly good generalizability. Second, the assessment of hs-CRP used a high-quality laboratory measure, risk factors were assessed using standardized validated instruments, and both types of assessments were made independently of symptom reporting, thus reducing bias and misclassification. Third, we simultaneously statistically controlled for a number of potential risk factors so that we could assess the independent effects of elevated hs-CRP and each risk factor while controlling for the effects of others, thus minimizing the likelihood of residual confounding.

However, the study also had some limitations. First, multiple statistical comparisons were made; so, some of the observed associations may have occurred by chance or represent markers for other uncontrolled factors; thus, caution must be used for interpreting marginally significant results as well as for significant results for modestly strong associations. Second, the study was cross-sectional; thus, the temporal relationships to symptom reporting could not be adequately assessed, and some associations may have resulted from some factors being used for self-medication or be a consequence of symptoms rather than being causally related (*e.g.*, anti-inflammatory medications, physical activity, and depressive symptoms). A longitudinal study is needed to resolve the temporal sequence of the associations observed here.

Third, all of the factors examined were recalled by participants and thus may lack accuracy of recall, although recall was unlikely to differ by hs-CRP status. Fourth, we did not have information on the presence of infection in participants at the time of blood draw, which could have influenced the results, although was unlikely to differ by symptom reporting. Fifth, due to time limitations for administration of the study instruments, we were not able to include an exhaustive list of symptoms so that some, such as irritability, were not included. Furthermore, the outcomes were not rare so that the ORs may have overestimated risk. Also, our sample sizes in some racial/ethnic groups may have been too small to detect interaction with elevated hs-CRP as statistically significant. Finally, we examined premenstrual symptoms; so, our findings may not apply to premenstrual syndrome.

Conclusions

Premenstrual mood symptoms, abdominal cramps/back pain, appetite cravings/weight gain/bloating, and breast pain, but not headache, appear to be significantly and positively related to elevated hs-CRP levels, a biomarker of inflammation, although with modestly strong associations, even after adjustment for multiple confounding variables. The results also suggest that the factors associated with each premenstrual symptom are complex, suggesting potentially different mechanisms for the etiologies of some symptoms. These results suggest that inflammation may play a mechanistic role in most PMSx, although further longitudinal study of these relationships is needed. However, recommending to women to avoid behaviors that are associated with inflammation may be helpful for prevention, and anti-inflammatory agents may be useful for treatment of these symptoms.

Acknowledgments

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the NIH Office of Research on Women's Health (ORWH) (Grant Nos. U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG 012546, U01AG012553, U01AG012554, and U01AG 012495). The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH, or the NIH. *Clinical centers:* University of Michigan, Ann Arbor–Siobán Harlow, PI 2011–present, MaryFran Sowers, PI 1994–2011; Massachusetts General Hospital, Boston, MA–Joel Finkelstein, PI 1999–present; Robert Neer, PI 1994–1999; Rush University, Rush University Medical Center, Chicago, IL–Howard Kravitz, PI 2009–present; Lynda Powell, PI 1994–2009; University of California, Davis/Kaiser–Ellen Gold, PI; University of California, Los Angeles–Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY–Carol Derby, PI 2011–present, Rachel Wildman, PI 2010–2011; Nanette Santoro, PI 2004–2010; University of Medicine and Dentistry–New Jersey Medical School, Newark–Gerson

Weiss, PI 1994–2004; and the University of Pittsburgh, Pittsburgh, PA–Karen Matthews, PI. *NIH program office:* National Institute on Aging, Bethesda, MD–Winifred Rossi 2012–present; Sherry Sherman 1994–2012; and Marcia Ory 1994–2001; National Institute of Nursing Research, Bethesda, MD–Program Officers. *Central laboratory:* University of Michigan, Ann Arbor–Daniel McConnell (Central Ligand Assay Satellite Services). *Coordinating center:* University of Pittsburgh, Pittsburgh, PA–Maria Mori Brooks, PI 2012–present; Kim Sutton-Tyrrell, PI 2001–2012; and New England Research Institutes, Watertown, MA–Sonja McKinlay, PI 1995–2001. *Steering Committee:* Susan Johnson, Current Chair and Chris Gallagher, Former Chair. We thank the study staff at each site and all the women who participated in SWAN.

Author Disclosure Statement

No competing financial interests exist.

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