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Monthly variation of hot flashes, night sweats and trouble sleeping: Effect of season and proximity to the Final Menstrual Period (FMP) in the SWAN Menstrual Calendar substudy.

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Abstract

Objective: Although reproductive function is influenced by season, few studies have evaluated seasonal effects on menopausal symptoms. We assessed the impact of season and proximity to the final menstrual period (FMP) on frequency of symptom reporting.

Methods: 955 participants in the Study of Women's Health Across the Nation recorded whether or not they had experienced menopausal symptoms on a monthly menstrual calendar over a 10-year period. We modeled the log-odds of presence of a given symptom each month using a logistic mixed effects model, assuming a 3rd-order polynomial before the FMP and a different 3rd-order polynomial after the FMP. We assumed sine and cosine functions for month of the year.

Results: 5–10 years prior to the FMP, ~20% of women reported hot flashes and night sweats while ~40% reported trouble sleeping. Prevalence rose ~4 years before the FMP with a sharp jump in hot flash (~60%) and night sweats (~40%) prevalence coincident with the FMP. Peaks in hot flashes and trouble sleeping were observed in July with troughs in January. The peak and trough in night sweats occurred about one month earlier. Odds of hot flashes, night sweats and trouble sleeping were 66%, 50% and 24% greater, respectively, at the seasonal peak versus the seasonal minimum.

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Conclusion: Menopausal symptoms exhibit seasonal variation associated with the summer and winter equinoxes. Seasonal increases in night sweats precede increases in hot flashes. Prospectively recorded monthly symptom data demonstrate that hot flashes and night sweats increase notably coincident with the FMP.

Keywords

menopause; seasonality; hot flashes; sleep problems

INTRODUCTION

Several aspects of reproductive function vary by season including probability of birth, conception and early pregnancy loss, onset of menarche and menopause, menstrual cycle length, follicular phase length and sex steroid hormone levels in humans (1–8). The impact of light and dark cycles mediated through melatonin is one mechanism through which season influences reproduction but seasonal effects are likely influenced by multiple social and environmental mechanisms including food availability and activity (1, 9, 10).

A hallmark of menopause is the onset of vasomotor symptoms including hot flashes and night sweats, with up to 80% of women reporting at least some such symptoms (11, 12). However, few studies have considered the impact of season on menopausal symptom reporting, or accounted for seasonal variation when evaluating symptom prevalence or their timing in relation to the final menstrual period (FMP), a major determinant of these symptoms. Sievert and colleagues reported cross-country differences in the reporting of hot flashes, with more hot flashes reported in regions with colder mean temperatures and greater temperature variation, consistent with living at latitudes with greater variability in daylight hours. (13). Hunter and colleagues reported cross-country differences in hot flash reporting in Latin America and Spain, with higher temperatures and lower altitudes associated with increased prevalence (14). However, neither temperature nor temperature variation were associated with hot flashes or night sweats in two single country studies (15, 16). A national survey in the United States reported that some, but not all, women reported more symptoms in the summer (17). All of these studies were cross-sectional (13, 17) or included at most two time-points (14–16). Investigating this question in a longitudinal context is critical, as it enables investigation of symptom fluctuations over time and seasons within individual woman, thereby reducing potential confounding associated with assessing different individuals across seasons.

More studies have examined seasonal variability in sleep and sleep problems, but findings are inconsistent. For example, two Norwegian studies in adults reported increased difficulty initiating sleep in December compared to June (18, 19), a Finnish study reported worse sleep quality in the summer (20), while a third Norwegian study reported no monthly variation in reported insomnia (21). One cross-sectional US study found that pre-menopausal women reported more trouble sleeping in the November-January quarter than in the May-July quarter (22). We identified no studies focused on sleep complaints and seasonality in relation to menopause.

The multi-racial/ethnic Study of Women's Health Across the Nation (SWAN) Menstrual Calendar sub-study prospectively ascertained information on menopausal symptoms monthly over a 10-year period, providing a unique opportunity to evaluate the role of season in symptom reporting. The monthly calendar data also make it possible to more precisely model the trajectory of change in symptoms in relation to the FMP.

METHODS

As described elsewhere (23), the Study of Women's Health Across the Nation (SWAN) is a cohort study that has followed a multiethnic sample of 3302 midlife women as they transitioned from pre- to post-menopause. In brief, in 1996 seven clinical sites recruited a sample of white women and women from one specified minority group (African Americans in Pittsburgh, Boston, southeastern Michigan, and Chicago; Japanese in Los Angeles; Chinese in Oakland; and Hispanic women in Newark). Eligibility for enrollment into the cohort included being 42–52 years of age, having an intact uterus and at least one ovary, having had a menstrual period and no use of reproductive hormones in the previous 3 months, and self-identification in the targeted racial/ethnic groups of the clinical site. Women were followed approximately annually, with each visit including an interviewer-administered and self-administered questionnaire that ascertained information on menstrual characteristics, socio-demographic characteristics, lifestyle, and medical history as well as physical assessments and a blood draw. In addition, women kept a menstrual calendar that ascertained information on menstrual bleeding daily and on symptoms and hormone use (HT) monthly. The Menstrual Calendar sub-study was continued through 2006. Institutional Review Boards at each study site approved the protocol, and women provided written informed consent.

This study includes data from Menstrual Calendar sub-study participants at four study sites (Boston, southern Michigan, Oakland, and Los Angeles). Of the 1950 women enrolled at these sites, 1883 (96.6%) participated in the menstrual calendar sub-study. To be eligible for this analysis, women had to have an observed FMP as the study indexes women's symptom experience in relation to the date of the FMP. A total of 959 (52.3%) women had an observed FMP in the Menstrual Calendar sub-study. A woman's FMP was not observed if she had a hysterectomy or double oophorectomy, was lost to follow-up prior to her FMP or had not reached her FMP by 2006, or when her FMP was masked by HT use.

Menstrual and Symptom Calendar.

Participants filled out the menstrual calendars daily to capture days when spotting or bleeding occurred. On the last day of each month women answered questions about HT use and gynecological procedures which could affect their bleeding reports and completed a short questionnaire about whether they had experienced six symptoms in the past month including the three symptoms that are the focus of this analysis – hot flashes or flushes, night sweats, and trouble sleeping. Women were asked to complete the menstrual calendar monthly for at least 2 years after their last menstrual bleed.

The final menstrual period (FMP) was defined as the first day of the bleeding episode that was followed by at least 12 months of amenorrhea. For women who had missing calendars

during the 12 months of amenorrhea, we accepted the FMP observed in the menstrual calendar if the date was less than 31 days different from the FMP date identified by retrospective recall in the annual interview or if there were two or fewer missing calendars during the 12 months of amenorrhea. In this analysis time is indexed to the FMP, as months before or after the FMP. Hot flashes or flushes, night sweats, and trouble sleeping were coded as a binary variables (yes/no) for each month of observation. HT use was time-varying, with current use (yes/no) coded for each month of observation.

Baseline Covariates.

Ethnicity was self-defined as African American, Chinese, Japanese, or white. Women were asked about their highest level of education (high school graduate/GED or less than high school versus at least some college), their smoking status (never, current, past). Financial strain was ascertained by the question “how hard is it to pay for basics” (very hard, somewhat hard, or not hard). Height and weight were measured without shoes, and in light indoor clothing and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Analysis.

The 959 women contributed a total of 64,501 monthly calendars. We excluded 1858 observations that were >8 years prior to or >4 years after the FMP due to data sparseness and 64 post-hysterectomy observations, leaving 62,579 eligible observations from 955 women. Seventeen women were missing baseline covariate data, leaving 938 women eligible for the adjusted regression analyses. Additional observations were excluded in analyses for each outcome due to the missingness in the outcome variable (hot flash n=1327; night sweats n= 1542, and trouble sleeping n=1392) leaving 58553 observations from 935 women for the hot flash analyses, and 58338 and 58488 observations from 934 women for the night sweats and trouble sleeping analyses, respectively.

In descriptive analyses, we plotted frequency of symptoms by calendar month and by ovarian age (time before and after the FMP). Plots by calendar month suggested seasonality and plots by ovarian age suggested a sharp change in probability of symptoms coincident with the FMP. We modeled the log-odds of presence of a given symptom each month using a logistic mixed effects models. For ovarian age, we assumed a 3^{rd}-order (cubic) polynomial before FMP and a different 3^{rd}-order polynomial after FMP. For calendar month, we assumed sine and cosine functions for month of the year normalized to lie between 0 and 2π by multiplying month (January=1, February=2, etc.) by $2\pi/12$. We graph this effect of season to facilitate interpretation of the magnitude of the seasonal effect modelled by the sine and cosine functions. We allowed for the cubic polynomial to be disjoint at the time of FMP to assess whether there was evidence of a rapid change in probability of a symptom at the first month after FMP. To account for correlation between observations from the same subject we included subject-specific random effects through the 2^{nd}-degree (quadratic) polynomial before and after FMP.

We assessed the effect of concurrent exogenous reproductive hormone use on the likelihood of having a symptom after controlling for time trends and seasonality (Models 1 in Table 2).

We next constructed models adjusted for covariates, retaining in the final model variables that had a statistically significant impact ($p<0.05$) on the probability of at least one of the three symptoms after controlling for time to FMP, seasonality and HT use (Models 2 in Table 2). We tested potential interactions between season and site and season and race/ethnicity. Finally, we tested whether the effect of concurrent HT use interacted with menopausal status (before/after FMP).

RESULTS

The 955 women included in this analysis had a mean age at FMP of 51.6 years (standard deviation (SD) = 0.08) and a mean BMI of 26.5 kg/m^2 (SD = 0.23). Baseline characteristics of the participants are presented in Table 1. Reflecting the race/ethnic distribution of the enrolled cohort, 42% of participants were white, 26% were black, 15% were Chinese and 17% were Japanese. Approximately one-quarter of the women had only a high school education or less, one-third had some college, and 45% had completed college or higher. One third of the women reported having a very or somewhat hard time paying for basics. One quarter were past smokers and 15% were current smokers. Over the study period, HT use was reported by 22% of women.

Difference in latitude across sites is small ranging from 34.0 in Los Angeles to 42.3 in Boston and southeast Michigan. Average July temperatures vary from 12 to 19 degrees Celsius (lows) and 19 to 29 degrees (highs). Average January temperatures vary more, from −7 to 9 degrees (lows) and 0 to 20 degrees (highs).

Figure 1 presents the prevalence of women reporting hot flashes, night sweats and trouble sleeping by month before and after the FMP. Approximately 20% of women report hot flashes five to eight years prior to the FMP. The prevalence began rising approximately four years before the FMP reaching about 48% of women reporting hot flashes each month in the year before the FMP. A sharp rise in reporting occurred at the time of the FMP as approximately 60% reported hot flashes each month in the year after the FMP. The prevalence declined slowly thereafter. A similar baseline prevalence and pattern of change was observed for night sweats, although the increase in prevalence was less, being approximately 30% and 40% immediately before and after the FMP, respectively. For trouble sleeping, the baseline prevalence was higher, approximately 40%, and the magnitude of the rises before and after the FMP were smaller than for either hot flashes or night sweats.

Table 2 presents the results of the regression analyses estimating the monthly odds of reporting each symptom. For each symptom, we present the models incorporating only time, season, and HT use (Model 1) as well as models additionally adjusted for age at menopause, race/ethnicity, smoking status and BMI (Model 2). Reporting of all three symptoms varies by season as is indicated by the significant odds ratios (OR) for the sine and co-sine terms with the magnitude of this seasonal effect illustrated in Figure 2. A peak in hot flash reports was observed in July and a trough in January consistent with the timing of the solstices, with peaks in night sweats occurring about one month earlier. The peak and trough for trouble sleeping were observed at approximately the same times as hot flashes but were of smaller magnitude. Women had a 66% greater odds of a hot flash at their seasonal peak versus their

seasonal minimum in both the unadjusted model and the model adjusted for smoking, race, age at FMP, and BMI, since season is observed for each woman throughout follow-up and is largely independent of other factors. The corresponding percentages for night sweats and sleep problems were 50% and 24%, respectively. We detected an interaction between season and ethnicity such that a stronger seasonal effect for hot flashes observed among Japanese women (cosine OR=0.67, sine OR=0.79, p<0.0001) and stronger seasonal effects for night sweats observed among Japanese (cosine OR=0.64, sine OR=0.88, p<0.0001) and, to a lesser extent, Chinese women (cosine OR=0.76, sine OR=0.88, p<0.0001).

The odds of reporting all three symptoms increased as women approach the FMP as evidenced by the significant squared and cubed terms for time before the FMP. To provide a visual interpretation of these regression results accounting for seasonal effects, Figure 3 illustrates the estimated within-woman trend in the probability of reporting each symptom in relation to time to the FMP by smoking status at baseline, by race/ethnicity, and by the time-varying current HT use. The odds of symptom reporting jumped sharply at the time of the FMP, as evidenced in Table 2 by the second intercept for the post-FMP time variable, with the odds then declining with increasing time post the FMP. An interaction was present between HT and time in relation to the FMP. HT was associated with a decreased odds of hot flashes before the FMP, and an even stronger decrease in the odds of hot flashes, after the FMP [OR prior to FMP=0.58 (95% CI= 0.45, 0.75); OR post FMP=0.10 (95% CI= 0.06, 0.15)] (red lines Figure 3C). Prior to the FMP, HT was not associated with the odds of night sweats or sleeping trouble, but it was associated with decreased odds of reporting these symptoms after the FMP [OR for night sweats post FMP=0.29 (95% CI= 0.18, 0.47) and for trouble sleeping post FMP=0.26 (95% CI= 0.17, 0.39)].

Adjusting for additional covariates had little impact on the odds ratios for season or time but the odds ratio for HT use prior to the FMP was attenuated in the hot flash model. Additional factors associated with symptom reporting were smoking, race/ethnicity, age, and BMI. Specifically, current smoking was associated with more than a two-fold increase in the odds of hot flashes and night sweats, and an 80% increase in the odds of trouble sleeping. Reporting of all three symptoms are more likely among current smokers (green lines Figure 3A). Compared to White women, Black women had an 80% increase in the odds of reporting hot flashes, Japanese women had a 50% to 70% decrease in the odds of reporting symptoms, while Chinese women were 50% less likely to report night sweats. Similar symptom patterns are present by race/ethnicity, but Black women (blue lines Figure 3B) are most likely and Japanese women (brown lines) are least likely to report hot flashes and night sweats, whereas white women (red lines) are most likely to report trouble sleeping across time. The odds of hot flashes increased also with age at FMP and with higher BMI.

DISCUSSION

Based on prospectively recorded monthly reports of menopausal symptoms in the SWAN Menstrual Calendar sub-study, this analysis documented that the reporting of hot flashes, night sweats and trouble sleeping varied by season, with peaks in reporting occurring around the time of the summer solstice (longest period of daylight) and troughs occurring around the time of the winter solstice (shortest period of daylight). Notably, we also documented

prospectively a sharp increase in symptom occurrence coincident with the FMP. As expected, HT was associated with decreased odds of hot flashes, however the magnitude of this effect was stronger after than before the FMP while only use after the FMP was associated with decreased odds of night sweats and trouble sleeping.

Despite a large body of work documenting seasonal variation in many aspects of reproductive function, few studies have examined seasonality of menopausal symptoms. One multi-country study reported that hot flashes were more frequent in regions with colder mean temperatures and greater temperature variation, consistent with latitudes having greater variability in daylight hours (13). Another multi-country study found that hot flash reporting was associated with higher temperatures (14). Two single country studies reported no association with temperature or temperature variation (15–16). One national study from the US reported that some, but not all, women reported more symptoms in the summer (17).

The literature on seasonal variability in sleep problems is inconsistent and dependent on the dimension of sleep examined. In two Norwegian studies, adults reported increased difficulty initiating sleep in December compared to June (18, 19). A Finnish study reported worse sleep quality in the summer (20), while another Norwegian study reported no monthly variation in reported insomnia (21). In contrast to our findings, a cross-sectional analysis of a subset of pre-menopausal women only in SWAN found that women assessed in the November-January quarter reported more trouble sleeping than did women assessed in the May-July quarter (22). Data on seasonality of menopausal sleep complaints are lacking.

Availability of prospectively recorded monthly symptom information from the SWAN Menstrual Calendar sub-study for up to 10 years permitted us to evaluate the impact of season on symptom reporting within-women longitudinally. We observed seasonal patterns in reporting of hot flashes, night sweats and trouble sleeping, with peaks in the summer near the solstice, consistent with results for hot flashes in the national US study (17) and for sleep quality in the Finnish study (20). The four sites in our study have little variation in latitude but meaningful variation in temperature, especially in the winter months.

Notably, although the underlying physiology of hot flashes and night sweats are not fully understood, leading models indicate that they are thermoregulatory events, or dramatic heat dissipation events in the context of altered hypothalamic thermoregulatory functioning in symptomatic menopausal women (24). Thus, higher ambient temperature may increase the likelihood of hot flashes and night sweats, with some laboratory data supportive of that hypothesis (25). However, effects of season did not differ by site (which varied markedly in temperature), suggesting that the observed seasonality in symptom reporting was not driven solely by temperature alone. Other potential stimuli include temperature changes rather than absolute levels, or changes in light.

Freedman and colleagues suggest women experiencing VMS have a smaller thermoneutral zone compared to those with no VMS (26), thus small temperature changes may easily provoke hot flashes or night sweats in symptomatic women. Hot flashes have been linked to sleep disturbances, particularly early in the night. One hypothesis is that rapid eye movement (REM) sleep stages may reduce thermoregulatory responses leading to reduced VMS (27).

The circadian regulation of body temperature, a highly complex system influenced by numerous factors, is increasingly unstable with aging (28).

Notably, the hypothalamus houses not only thermoregulatory centers but also the superchiasmatic nucleus, a pacemaker which is entrained in part by light, and integrally involved in the control of circadian rhythms across a range of physiologic processes. Light inhibits secretion of melatonin. Melatonin helps regulate the circadian clock and thus sleep. Melatonin also plays an important, although not fully understood, role in neuroendocrine regulation. It down regulates reproductive function, inhibits luteinizing hormone and may inactivate the gonadotropin releasing hormone pulse generator (29–31). Longer winter nights are associated with increased and more prolonged melatonin secretion, thus susceptible women may experience changes in melatonin-regulated phenomena associated with lengthening hours of daylight (31). With aging and with the transition to menopause, melatonin levels decrease, especially at night (29, 30, 32). Thus, the increase in sleep complaints during this lifestage may in part be attributable to this decrease in melatonin levels (29,30). Evidence for a direct effect of melatonin on vasomotor symptoms is lacking (30,31) but may be associated with the increase in sleep disorders. Advances in scientific understanding of the underlying physiology of vasomotor symptoms may shed further light on how seasonality influences these menopausal symptoms.

Longitudinal data from annual interviews in SWAN estimated the average duration of hot flashes (time between first reported and last reported period of hot flashes occurring 6 or more days over a 2 week period) to be 7.4 years (33). The Penn Ovarian Aging (POA) study reported an average hot flash duration of 10.2 years (34). Both studies documented important differences in duration based on timing of onset in relation to stage of reproductive aging. The duration for women who first experienced hot flashes in the late transition/postmenopause was 3.4 and 3.8 years, respectively. SWAN (35) and other studies (36) have documented that subgroups of women differ in the timing and trajectory of their hot flash experience while the POA study reported a correlation between FSH variability and women’s hot flash trajectories (37). In future studies, longitudinal assessment of melatonin levels in SWAN using stored urine specimens may enhance understanding of relationships between change in melatonin levels with ovarian aging and risk of menopausal symptoms.

Availability of monthly calendar data made it possible to model the trajectory of change in symptoms in relation to proximity of the FMP more precisely. The current analysis of monthly symptom data again documents that a significant proportion of women experienced symptoms many years before the FMP, yet we identified a sharp increase in the prevalence of symptom reporting coincident with the FMP. This large jump in prevalence is particularly notable since symptoms were recorded prospectively and women would not have been aware when they reported symptoms that the menstrual period reported in a given month was in fact their FMP. This finding provides further evidence that the FMP is a salient marker of menopause, associated with an observable impact on symptom reporting in the month the FMP occurs. Notably, HT use was associated with a stronger reduction in hot flashes, night sweats and trouble sleeping after the FMP than before. This pattern of symptom onset and varying responsiveness to HT use suggests that attribution of symptoms to menopause, while clearly appropriate for some women, may not be an appropriate attribution for the symptom

experience of all women. Future studies should evaluate alternative explanations and biological mechanisms for vasomotor symptoms and sleep complaints that begin several years before and continue several years after the menopause.

Consistent with other studies of midlife women (33, 34), current smokers were more likely to report all three symptoms, Black women were more likely and Japanese women were least likely to report hot flashes and night sweats, and white women were most likely to report trouble sleeping across time. However, none of these covariates significantly influenced the observed seasonal variation.

This study has some limitations. We indexed symptom experience to the date of FMP, thus included only women observed to have a natural menopause. Women whose FMP was masked by HT use, who are likely to have been the most symptomatic, were excluded which may have resulted in selection bias. We had information on occurrence but not severity of symptoms. Nonetheless, this study had several strengths including the availability of prospectively recorded and frequent monthly assessment of symptoms for up to 10 years, the ability to index symptoms by months before and after the FMP, and ability to control for other risk factors for menopausal symptoms.

CONCLUSIONS

It is estimated that 40–80% of women report vasomotor symptoms during the menopausal transition with the potential for significant adverse impact on quality of sleep and quality of life. (11, 27, 38, 39) Prospectively collected monthly symptom reports allowed us to account for seasonal variation of menopausal symptom reporting and to examine change in reporting closely aligned to the date of the FMP. These data revealed for the first time the temporal impact of the FMP per se on symptom experience, with trouble sleeping, night sweats and most notably hot flashes increasing sharply at the time of the FMP. Modelling of seasonal variation revealed increases in symptom reporting associated with the summer solstice and troughs with the winter solstice. These data underscore the need for clinicians to consider the summer as critical time with respect to the occurrence of symptoms and needs for their management. Reducing current gaps in knowledge of the factors and mechanisms related to experience of menopausal symptoms are central to the development of interventions and of treatment to reduce these symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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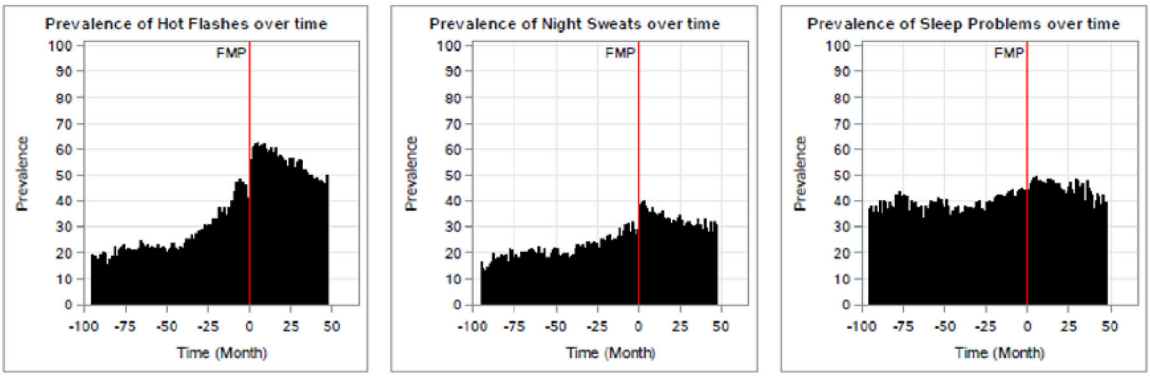

Figure 1:

Histograms of the monthly prevalence of hotflashes, night sweats, and trouble sleeping in relation to time before and after the final menstrual period (FMP): the Study of Women's Health Across the Nation (SWAN) (n=955).

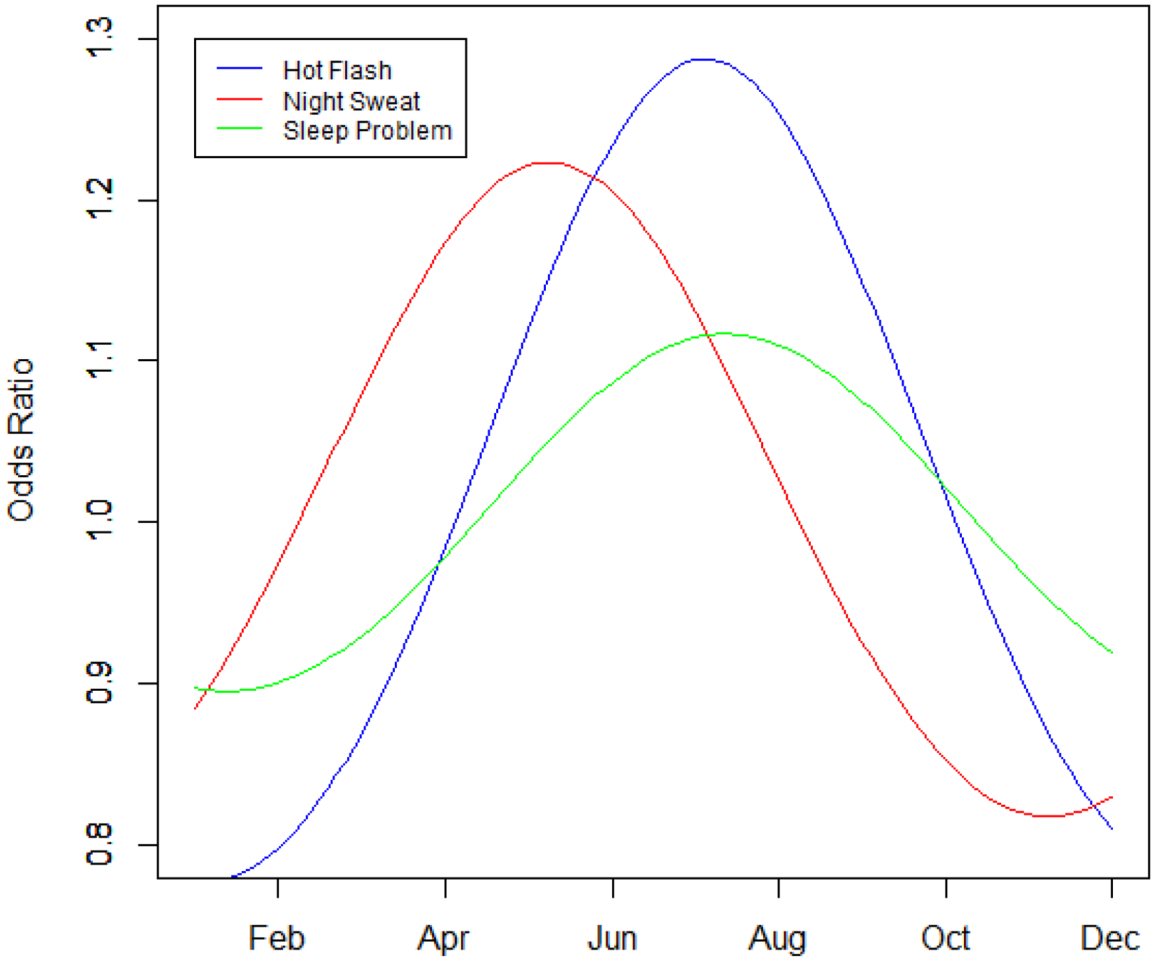

Figure 2.

Odds ratio for reporting of hot flash, night sweats, and trouble sleeping by month, the Study of Women's Health Across the Nation (SWAN) (n=955). Peaks for hot flash and trouble sleeping reporting occur in July and for night sweats in May while troughs occur in January and November, respectively.

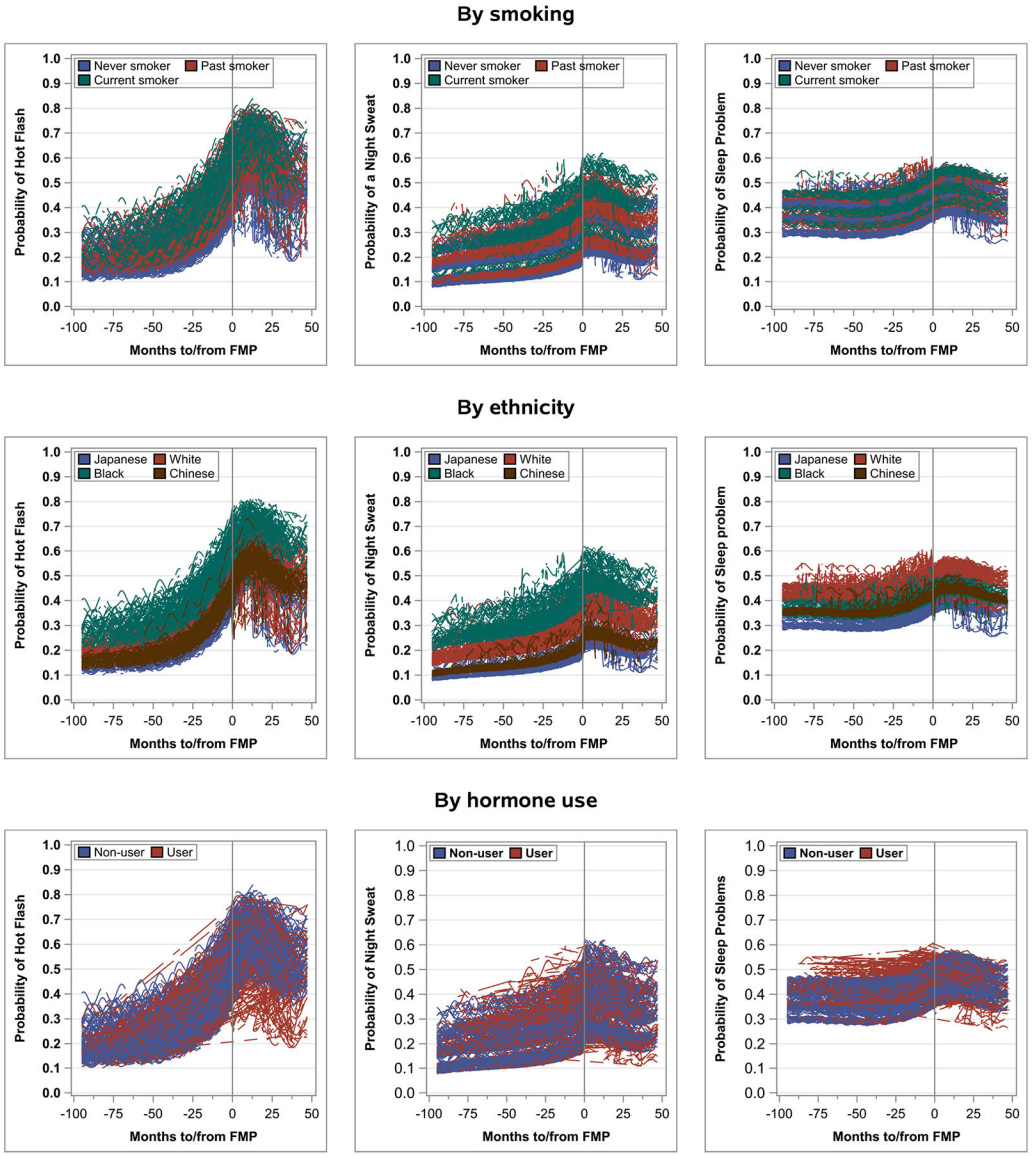

Figure 3.

Estimated within-woman trends in the probability of reporting hot flashes, night sweats and trouble sleeping in relation to time before and after the final menstrual period (FMP) by smoking status at baseline, race/ethnicity and ever hormone use, the Study of Women's Health Across the Nation (SWAN) (n=955).

Table 1:

Descriptive Characteristics of Study Participants, the Study of Women's Health Across the Nation (SWAN) Menstrual Calendar substudy (n=955).

	Frequency	
	N	**Percent**
Race/Ethnicity		
Black	245	25.7%
White	401	42.0%
Chinese	147	15.4%
Japanese	162	17.0%
Education		
Less than High School	54	5.7%
High School	161	17.0%
Some Post High School	308	32.5%
College	216	22.8%
Post College	208	22.0%
Missing	8	
Difficulty Paying for Basics		
Very Hard	73	7.8%
Somewhat Hard	267	28.4%
Not Hard	599	63.8%
Missing	16	--
Smoking		
Never Smoker	578	60.8%
Past Smoker	227	23.9%
Current Smoker	145	15.3%
Missing	5	--
HT use during study period		
No	748	78.4%
Yes	206	21.6%
Missing	1	
Site		
Michigan	245	25.7%
Boston	217	22.7%
Oakland	241	25.2%
Los Angeles	252	26.4%

Table 2:

Logistic mixed effects regression of the monthly odds of reporting hot flashes, night sweats and sleep problems, the Study of Women's Health Across the Nation (SWAN) Menstrual Calendar substudy (n=955).

	Hot Flashes Model 1[a] OR 95% CI	Model 2[b] OR 95% CI	Night Sweats Model 1 OR 95% CI	Model 2 OR 95% CI	Sleep Problems Model 1 OR 95% CI	Model 2 OR 95% CI
Season[c]						
CoSine	0.81(0.78, 0.84)	0.81 (0.78, 0.84)	0.83 (0.79, 0.86)	0.82 (0.79, 0.86)	0.92 (0.89, 0.95)	0.92 (0.89, 0.96)
Sine	0.87 (0.84, 0.91)	0.87 (0.84, 0.90)	1.08 (1.04, 1.12)	1.08 (1.04, 1.12)	0.93 (0.89, 0.96)	0.92 (0.89, 0.96)
Time Prior to FMP						
Intercept	1.13 (0.93, 1.37)	0.25 (0.10, 0.61)	.19 (0.15, 0.25)	0.21 (0.09, 0.48)	0.72 (0.56, 0.94)	0.61 (0.26, 1.45)
Time	2.96 (2.43, 3.61)	2.46 (2.04, 2.97)	1.25 (1.03, 1.51)	1.39 (1.15, 1.69)	1.37 (1.17, 1.62)	1.36 (1.16, 1.61)
Time squared	1.12 (1.06, 1.19)	1.10 (1.04, 1.16)	1.02 (0.96, 1.08)	1.04 (0.98, 1.10)	1.06 (1.01, 1.11)	1.05 (1.00, 1.11)
Time cubed	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Time After FMP						
Intercept	1.22 (0.99, 1.50)	0.31 (0.13, 0.78)	0.30 (0.23, 0.40)	0.29 (0.12, 0.66)	0.73 (0.55, 0.97)	0.62 (0.26, 1.47)
Time	4.61 (3.10, 6.88)	5.48 (3.51, 8.54)	0.82 (0.51, 1.33)	1.17 (0.73, 1.86)	1.77 (1.19, 2.63)	1.81 (1.22, 2.68)
Time squared	0.37 (0.28, 0.48)	0.34 (0.26, 0.46)	0.74 (0.55, 1.01)	0.61 (0.45, 0.83)	0.70 (0.54, 0.90)	0.70 (0.54, 0.90)
Time cubed	1.18 (1.12, 1.24)	1.19 (1.12, 1.25)	1.06 (1.00, 1.13)	1.09 (1.03, 1.16)	1.05 (1.00, 1.10)	1.05 (1.00, 1.10)
HT Use before FMP	0.58 (0.45, 0.75)	0.71 (0.55, 0.91)	0.87 (0.67, 1.11)	0.86 (0.67, 1.11)	0.94 (0.74, 1.21)	0.93 (0.73, 1.19)
HT Use after FMP	0.10 (0.06, 0.15)	0.10 (0.07, 0.16)	0.29 (0.18, 0.47)	0.35 (0.22, 0.57)	0.26 (0.17, 0.39)	0.26 (0.17, 0.39)
Age at FMP		1.10 (1.02, 1.18)		0.99 (0.93, 1.06)		1.04 (0.96, 1.12)
Race/Ethnicity						
Black		1.84 (1.12, 3.02)		1.15 (0.73, 1.82)		0.41 (0.26, 0.67)
Japanese		0.55 (0.32, 0.95)		0.28 (0.17, 0.47)		0.36 (0.22, 0.61)
Chinese		1.06 (0.59, 1.91)		0.45 (0.26, 0.79)		0.72 (0.41, 1.26)
White		Reference		Reference		Reference
Smoking Status						
Past Smoker		1.55 (0.98, 2.43)		1.29 (0.84, 1.97)		1.61 (1.03, 2.52)
Current Smoker		2.48 (1.41, 4.36)		2.84 (1.69, 4.77)		1.79 (1.03, 3.11)
Never Smoker		Reference		Reference		Reference
Body Mass Index		1.04 (1.01, 1.07)		1.01 (0.98, 1.03)		1.01 (0.98, 1.04)

[a] Model 1 For each symptom, Model one includes season (sine and cosine terms), time in months before and after the FMP (final menstrual period), and Hormone Therapy (HT) use.

[b] Model 2 includes the variables in Model 1 and age at menopause, race/ethnicity, smoking status and body mass index.

[c] The sine and cosine terms model seasonal effects which are graphed for ease of interpretation in Figure 2.