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SCIENTIFIC INVESTIGATIONS

Sleep symptoms signaling the menopausal transition

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Study Objectives: To describe changes in sleep quality and associated sleep symptoms as women begin menopausal transition compared with premenopausal controls.

Methods: In a repeated-measures design, we analyzed data collected every 2–6 months from a community-based sample of 223 women aged 40–50 (45.6 ± 2.3) years old over a 2-year period. Each 6-month visit included urinary follicle-stimulating hormone (FSH) as a marker of ovarian function and the Pittsburgh Sleep Quality Index (PSQI) and other questionnaires (Center for Epidemiological Studies–Depression Scale; Perceived Stress Scale). Menstrual cycle and vasomotor symptoms (Seattle Women's Health Symptom Checklist) were tracked every 2 months by phone. For women entering menopausal transition (n = 68) we used data from the two consecutive visits prior to their FSH rise and the next two visits. Data from the last four consecutive visits were used for controls remaining premenopausal (n = 155).

Results: The transition group did not differ from controls on age, vasomotor symptoms (hot flashes/night sweats), stress, or depression but did have a higher body mass index. Measures were stable over time for controls. However, the transition group experienced an increase in PSQI scores (initial PSQI = 5.7 ± 3.2 and final PSQI = 6.3 ± 3.8; P = .030) and frequency of trouble sleeping because of feeling too hot (P = .016), which lagged the FSH rise by 6 months with no notable change in report of hot flashes/night sweats.

Conclusions: Trouble sleeping because of feeling too hot, distinct from awareness of vasomotor symptoms, was the only uniform contribution to higher PSQI scores after the initial FSH increase and may signal the onset of the menopausal transition.

Keywords: sleep quality, insomnia, depression, race, vasomotor symptoms, hot flashes, night sweats, pain, PSQI, menopause

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Research on menopausal transition and sleep involves primarily either cross-sectional studies comparing women by menopausal stage or longitudinal studies with assessments typically on an annual basis over long periods of time. To our knowledge, there are no longitudinal data looking intensively, every few months, at changes in sleep symptoms at the point of the transition from late reproductive stage to early perimenopausal stage.

Study Impact: We identify a sentinel sleep-disturbance symptom, trouble sleeping because of feeling too hot, rather than hot flashes or night sweats, that potentially signals menopausal transition and risk for poor sleep quality. Early recognition of this symptom could lead to more effective therapy for insomnia in midlife women.

INTRODUCTION

Poor sleep is a significant problem for midlife women, with an estimated prevalence of approximately 30%.[1] It is unclear if worsening of sleep in midlife is a function of aging alone, menopause-related factors, or a combination of these.[2] Longitudinal studies have shown variable patterns of change in sleep, with gradual worsening as women progress through the menopausal transition,[3] worsening from the late pre- to early perimenopausal transition,[4] worsening from the late perimenopausal transition to postmenopausal stage,[5] or no clear relationship with menopausal stage.[6] Two studies indicated that sleep quality in the premenopausal stage predicted sleep quality during menopausal transition[1,4] and another described four different trajectories: stable patterns of either low or moderate difficulty maintaining sleep and two patterns of increasing difficulty maintaining sleep that start from either a low prevalence or an already high prevalence.[7] Factors associated with poor sleep quality and continuity include hot flashes,[1,3–6] rise in follicle-stimulating hormone (FSH),[3,5] decrease in estradiol,[3] age,[5] anxiety,[5] and depression.[5,6] These studies convey long-term trends from data collected typically every 12 months with variable years of follow-up assessments.

Based on these previous reports, it remains unclear when or specifically how sleep symptoms change at the time of the menopausal transition. We performed a longitudinal study with measures every 2–6 months and hypothesized that poor sleep quality would occur at the onset of the menopausal transition when a rise in FSH signals that ovarian function is beginning

to diminish. In our previous cross-sectional analysis of sleep symptoms comparing premenopausal with perimenopausal women at one point in time without regard for the timing of the initial rise in FSH, we reported that perimenopausal women had more sleep disturbances attributed to feeling too hot.[8] Thus, we also hypothesized that poor sleep quality would begin with trouble sleeping attributed to feeling too hot and that this would correlate with the onset or worsening of vasomotor symptoms of hot flashes and/or night sweats. In addition, based on associated factors noted in prior studies,[5,6] we also expected depressive symptoms and perceived stress to increase in association with worsening sleep quality when compared with women in the cohort who did not begin the menopausal transition.

METHODS

Sample and procedures

Women living in the San Francisco Bay area were recruited from the community between February 1996 and November 1997 if they were between 40 and 50 years of age and still experiencing regular menstrual cycles. Women were excluded if they were taking hormone therapy, were pregnant or breastfeeding, had a diagnosed sleep disorder, or endorsed any major health problem such as stroke, heart attack, emphysema, cancer, type I diabetes, ovarian cysts, or a psychiatric condition on a 12-item Comorbidity checklist.[9] There was attrition (n = 78) due to participant burden, health problems, or moving out of the region. Women who began hormone therapy, had surgical menopause, or became pregnant during the study were excluded (n = 25) from further participation in this longitudinal analysis.[10] Responses to Pittsburgh Sleep Quality Index (PSQI) items about breathing-related symptoms and the daytime dysfunction component were flagged at enrollment and followed up by a sleep specialist who referred women for further evaluation of obstructive sleep apnea if indicated. Details of recruitment for this sample from the University of California San Francisco (UCSF) Midlife Women's Health Study have been previously reported.[9,10] The UCSF Committee on Human Research approved the study, and all participants provided informed consent. Each participant had the same research associate for each contact during the study.

Over a 2-year period, we enrolled 347 women and conducted telephone interviews every 2 months for menstrual cycle and symptom data. In-person health assessments were conducted every 6 months over the next 3 years or until 1 year after the last menstrual period, at which point the women were excluded from further data collection.[10] For this longitudinal analysis, only participants with complete data for four consecutive in-person time points were included (see **Figure 1** for the participant flowchart). In order to minimize potential historical threats to validity we used 1 year of data before the initial rise in FSH and 1 year after the initial rise in FSH in the perimenopausal group to examine differences in sleep quality and specific symptoms related to menopause transition, which required a minimum of two visits prior to a rise in FSH. This resulted in a cohort of 68 women who entered the menopausal transition and 155 women who remained premenopausal for at least 2 years.

Measures

Study visits at 6-month intervals included validated self-report questionnaires described below, any changes in demographic characteristics (such as marital status and income), a morning urine sample for FSH as an indicator of reproductive stage and ovarian function, and anthropometric measurements that consisted of weight and height to calculate current body mass index (BMI) and waist and hip circumferences to calculate waist-hip ratio. These 6-month visits were supplemented every 2 months with telephone surveys (Seattle Women's Health Diary) about their symptoms, including hot flashes, night sweats, and their menstrual cycle length, duration, and menstrual bleeding.[5]

Stages of Reproductive Aging Workshop (STRAW) criteria[11] were used to categorize reproductive status based on FSH levels and menstrual cycle regularity. For this analysis, the onset of menopausal transition was determined by the first point at which the FSH value was above 2.5 IU/dL on a first-morning urine sample (Esoterix Endocrinology Services Laboratory, Calabasas Hills, CA, USA) based on STRAW criteria adjusting for the difference in FSH concentration in urine vs serum.

Sleep quality

The PSQI is a self-report assessment of sleep quality over the past month. The PSQI yields seven components of sleep (including sleep disturbance and sleep duration) based on 19 items referencing the previous 1-month time period.[12] Scores range from 0 to 21 and a score above 5 indicates poor sleep quality. Validity for the PSQI in this sample of healthy midlife women has been reported, with internal consistency reliability differing slightly by reproductive stage (Cronbach alpha = .705 for premenopausal women and .771 for perimenopausal women).[13] There are seven items in the PSQI sleep disturbance component that ask about reasons for trouble sleeping during the night, including feeling too hot, feeling too cold, pain, and using the bathroom. These items are coded as a frequency from 0 (not in the past month) to 3 (> 3 times/week).

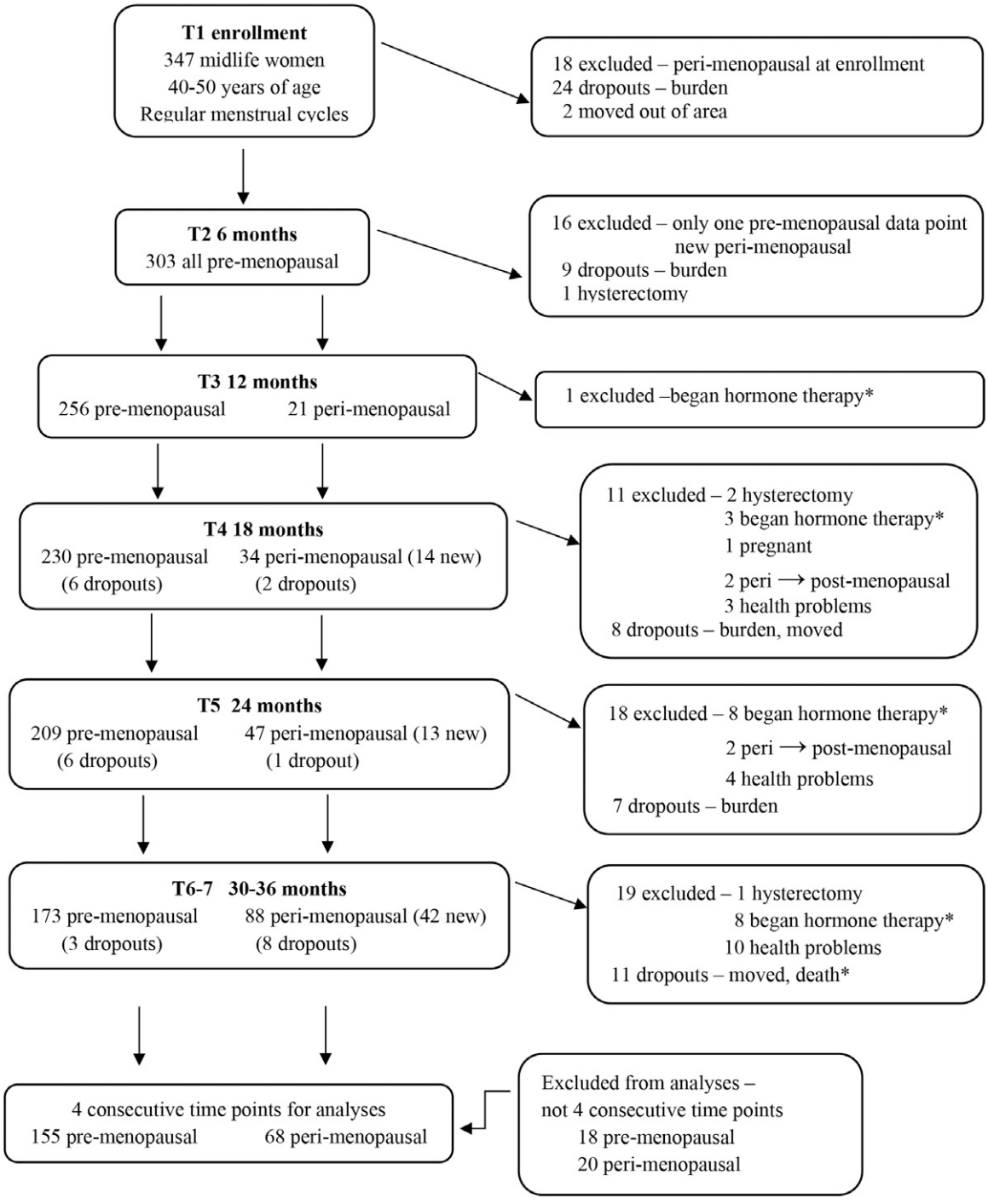
Depressive symptoms

The 20-item Center for Epidemiologic Studies–Depression scale (CES-D) is used to screen for depressive symptoms in the general population.[14] The CES-D asks participants to indicate how often they experienced a particular symptom in the past week, from 0 (rarely/none of the time or less than one day) to 3 (most/all of the time or 5–7 days). Scores can range from 0 to 60; 16 or higher is considered at risk and in need of clinical evaluation. In this sample of healthy midlife women, the Cronbach alpha was .91.

General health and stress measures

The 36-item Short-Form Health Survey (SF-36) question about general health perception was used for participants to rate their overall health as excellent (1), very good (2), good (3), fair (4), or poor (5).[15] Participants were also asked to consider the past week and rate their levels of health, stress, and tension using 0 (low) to 10 (high) numerical rating scales (NRSs). The 10-item version of the Perceived Stress Scale (PSS-10) was also used to measure participants' perception of general stress.[16] Items are rated from 0 (never) to 4 (very often) for a possible total score of 40;

Figure 1—Flowchart of participant attrition over time.



*Hormone therapy includes estrogen replacement or oral contraceptives; death due to terminal cancer (n = 4), stroke (n = 2).

higher scores indicate higher levels of general stress during the past month. The internal consistency reliability of the PSS-10 was .88 for both the control and transition groups. We also asked about specific sources of stress associated with work, family issues, physical health, personal stress, and their perception of overall stress, with responses ranging from 1 (none) to 4 (a lot) with an investigator-developed measure. The PSS-10 was significantly ($P \leq .001$) correlated with both the stress NRS ($r = .567$) and the tension NRS ($r = .635$).

Menstrual cycle patterns and vasomotor symptoms

The Seattle Women's Health Diary was used to track participants' monthly symptoms and menstrual cycle experiences.[17] Of the 52 symptoms in this diary, the two symptoms of interest

in this analysis were vasomotor symptoms of hot flashes and night sweats. Each symptom has a severity score from 0 (not present) to 4 (extreme). Symptoms at these 2-month time points were averaged for each 6-month interval.

Statistical analysis

Each participant with data at four consecutive 6-month time points was categorized as either being premenopausal or in early perimenopausal transition. For the premenopausal controls, the last four consecutive in-person visits (T1, T2, T3, T4) were used. Data from these time points were then compared with data from four consecutive 6-month time points for the transition group surrounding the rise in FSH that included two time points before an elevated FSH was detected (T1, T2), the first time point at which an elevated FSH is detected signaling onset of perimenopausal transition (T3), and the next time point 6 months later (T4). Demographic comparisons of the two groups when regularly menstruating at the first of the four time points (T1) included independent *t* tests for continuous data and chi-square tests for categorical data.

Longitudinal analysis included repeated-measures analysis of variance by group (two factors) and time (four factors). To meet normality assumptions, the seven reasons for trouble sleeping itemized in the PSQI were recoded as 0 (not in the past month), 1 (less than once/week), or 2 (at least once/week); and square root transformations were sufficient to normalize PSQI and CES-D scores. For repeated-measures analysis of variance, covariates included race and baseline values for BMI, sleep duration, and pain during the night based on known associations with sleep quality or our group differences at baseline with $P \leq .10$. All analyses were performed using SPSS version 22.0 software (IBM Corporation, Armonk, NY).

RESULTS

Demographic and clinical characteristics

Demographic characteristics are compared in **Table 1**. At T1, the mean age was 45.6 ± 2.3 years and did not differ between the transition group and premenopausal controls. The transition group had a significantly higher BMI than the control group ($P = .033$). The proportion of Black participants was significantly higher in the transition group compared with controls ($P = .009$). Participants were similar on all other nonsleep clinical characteristics, including self-reported presence and severity of night sweats and hot flashes. Both groups were also similar on perceived health, depressive symptoms, and multiple stress measures at T1.

Sleep-related symptoms

Sleep quality measures are also compared by group at T1 in **Table 1**. There were no statistically significant differences in mean PSQI score between groups ($P = .101$). Sleep quality was poor (PSQI score > 5) for 53% of the transition group and 40% of the premenopausal group, but this difference was not significant ($P = .073$). The premenopausal group self-reported habitual sleep duration of 6.9 ± 1.1 hours and the transition group self-reported less sleep at night (6.6 ± 1.1 hours), but this difference also did not reach statistical significance ($P = .064$). The groups did not differ on frequency per week of experiencing sleep latencies > 30 minutes ($P = .109$), perception of sleep quality ($P = .938$), or use of sleep medication ($P = .145$).

Table 2 compares groups on specific reasons for trouble sleeping at the baseline T1 visit. Although there was no significant group difference in the frequency of trouble sleeping because of pain ($P = .094$), 32% of women in the transition group indicated trouble sleeping due to pain on at least 1 night in the past week compared to only 19% of the premenopausal control group ($P = .026$).

Longitudinal changes in sleep quality

The multivariate time-by-group analysis for PSQI scores is depicted in **Figure 2**. Controlling for race and baseline BMI, sleep duration, and pain during the night, PSQI scores (square root transformed) did not differ significantly for the omnibus test (Wilks' Lambda=.965, $F_{[3,207]} = 2.47$, $P = .063$). Estimated marginal means in adjusted PSQI scores fluctuated between 5.3 and 5.5 for the overall sample, and between-group differences were not significant. However, in the post hoc analysis, there was a significant increase in PSQI scores (transformed) between T3 and T4 for within-subject comparisons ($F_{[1,209]} = 4.52$, $P = .035$) as seen in **Figure 2**, which was only seen in the transition group ($F_{[1,60]} = 4.93$, $P = .030$).

The multivariate time-by-group analysis for "trouble sleeping because of feeling too hot" is depicted in **Figure 3**. RMANOVA with covariates of race, baseline BMI, sleep duration, and pain showed a between-group difference over time in the omnibus test (Wilks' Lambda = .954, $F_{[3,214]} = 3.50$, $P = .016$). Estimated marginal means fluctuated between 0.81 and 0.94 for the overall sample. The only significant within-subject difference was an increase in feeling too hot between T3 and T4 ($F_{[1,216]} = 10.25$, $P = .002$). The post hoc analysis showed that the increase between T3 and T4 was seen only in the transition group and was significant ($F_{[1,67]} = 7.39$, $P = .008$).

In contrast to feeling too hot, the experience of hot flashes and night sweats did not differ by group or time. The time-by-group difference in hot flashes (**Figure 4**) was not significant (Wilks' Lambda = .969, $F_{[3,214]} = 2.27$, $P = .082$). The time-by-group difference in night sweats (**Figure 5**) was also not significant (Wilks' Lambda = .986, $F_{[3,214]} = 0.99$, $P = .398$) at any time point.

The frequency of "trouble sleeping because of pain" did not change over time for either group (Wilks' Lambda = .992, $F_{[3,215]} = 0.60$, $P = .613$), as shown in **Figure S1** in the supplemental material. There were no other time-by-group differences in other reasons for trouble sleeping within the PSQI sleep disturbance component, including reasons such as "cannot breathe comfortably" or "cough or snore loudly." There was no difference by group or time in PSQI self-reported sleep duration (Wilks' Lambda = .996, $F_{[3,208]} = 0.31$, $P = .818$) (**Figure 6**), CES-D depressive symptom scores (Wilks' Lambda = .994, $F_{[3,214]} = 0.46$, $P = .709$) (**Figure S2**) or other measures of psychological health including stress, tension, and general health perception. There was an increase in BMI over time that was similar for both groups and no difference over time in other

Table 1—Unadjusted participant characteristics by menopause status at T1.

Characteristics at T1	Premenopausal Control Group	Menopausal Transition Group	Statistical Test	*P*
	(n = 155)	**(n = 68)**		
Age, y	45.6 ± 2.4	45.6 ± 2.3	*t* = 0.08	.934
FSH, IU/dL	0.66 ± 0.56	0.71 ± 0.55	*t* = 0.64	.520
Body mass index, kg/m^2	27.2 ± 6.9	29.3 ± 6.0	*t* = 2.15	.033
Exercise, days/wk	2.3 ± 2.1	2.2 ± 2.2	*t* = 1.27	.207
Depressive symptoms (CES-D)	11.7 ± 9.0	13.0 ± 11.0	*t* = 0.80	.423
General health perception	2.3 ± 0.90	2.4 ± 0.94	*t* = 0.64	.524
Menstrual cycle length, d	27.0 ± 4.5	31.9 ± 7.0	**t* = 1.51	.137
Current smoker	13 (9%)	7 (13%)	χ^2 = 0.8	.361
Ethnicity			χ^2 = 9.4	.009
White	85 (55%)	28 (41%)		
Black	26 (17%)	24 (35%)		
Latina	44 (28%)	16 (24%)		
Education (college graduate)	93 (60%)	42 (62%)	χ^2 = 0.1	.804
Partnered/married	87 (56%)	34 (50%)	χ^2 = 0.7	.398
Has child living at home	98 (63%)	49 (72%)	χ^2 = 1.6	.200
Currently employed	132 (85%)	62 (91%)	χ^2 = 1.5	.219
Current smoker	13 (9%)	7 (13%)	χ^2 = 0.8	.361
Income adequacy	20.6 ± 4.9	20.9 ± 5.1	*t* = 0.40	.687
Hot flashes (severity)	0.27 ± 0.79	0.25 ± 0.77	*t* = 0.18	.856
Yes (%)	21 (14%)	9 (13%)	χ^2 = 0.0	.950
Night sweats (severity)	0.42 ± 0.98	0.35 ± 0.97	*t* = 0.49	.626
Yes (%)	29 (19%)	10 (15%)	χ^2 = 0.5	.469
	(n = 153)	**(n = 26)**		
Perceived stress (PSS-10)	16.8 ± 6.7	15.7 ± 6.4	*t* = 0.64	.524
	(n = 155)	**(n = 52)**		
Stress past week (0–10)	5.8 ± 2.5	6.0 ± 2.7	*t* = 0.57	.571
Tension past week (0–10)	5.2 ± 2.6	5.4 ± 2.9	*t* = 0.54	.590
Healthy past week (0–10)	7.3 ± 4.3	6.9 ± 2.2	*t* = 0.79	.428
	(n = 155)	**(n = 68)**		
PSQI global score	5.2 ± 3.0	5.8 ± 3.4	*t* = 1.65	.101
PSQI > 5	62 (40%)	36 (53%)	χ^2 = 3.2	.073
Fairly bad or very bad quality sleep	25 (16%)	12 (18%)	χ^2 = 0.1	.942
Onset > 30 min > 1/wk	33 (21%)	17 (25%)	χ^2 = 0.4	.541
Use sleep medication > 1/wk	5 (3%)	7 (10%)	χ^2 = 3.1	.381
Sleep duration < 6 h	25 (16%)	15 (24%)	χ^2 = 1.1	.288
Sleep duration, h	6.9 ± 1.1	6.6 ± 1.1	*t* = 1.86	.064

Values are n (%) or mean ± SD. **t* Test for unequal variance. CES-D = Center for Epidemiological Studies– Depression scale, FSH = follicle-stimulating hormone, PSQI = Pittsburgh Sleep Quality Index, PSS-10 = 10-item Perceived Stress Scale, SD = standard deviation, T1 = time 1 (6 months before T2).

measures of physical health that included waist-hip ratio and exercise days per week.

DISCUSSION

Focusing on midlife women with completed assessments at 2- and 6-month intervals over a 2-year period, we compared sleep quality and sleep symptoms of women entering the menopausal transition with women who remained premenopausal according to the STRAW criteria.[11] Controlling for race and baseline BMI, sleep duration, and pain during the night, sleep quality worsened with the change in reproductive stage but the worsening was not simultaneous with the rise in FSH and lagged the increase in FSH by 6 months. The only sleep-related symptom that increased was feeling too hot, which was not seen

Table 2—Unadjusted PSQI-delineated reasons for trouble sleeping by menopause status.

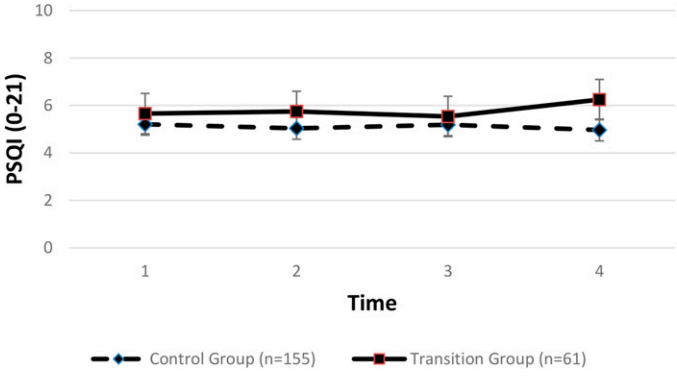
Reasons at T1*	Premenopausal Control Group (n = 155)	Menopausal Transition Group (n = 68)	Statistical Test	*P*
Use the bathroom (0–2)	1.43 ± 0.75	1.34 ± 0.82	t = 0.84	.403
(yes, in past week)	92 (59%)	38 (56%)	χ^2 = 0.2	.694
Feel too hot (0–2)	0.78 ± 0.82	0.91 ± 0.82	t = 0.96	.334
(yes, in past week)	39 (25%)	20 (29%)	χ^2 = 0.4	.508
Cough or snore loudly (0–2)	0.56 ± 0.81	0.62 ± 0.85	t = 0.20	.839
(yes, in past week)	35 (23%)	16 (24%)	χ^2 = 0.0	.877
Feel too cold (0–2)	0.56 ± 0.76	0.59 ± 0.78	t = 1.01	.313
(yes, in past week)	31 (20%)	12 (18%)	χ^2 = 0.2	.682
Pain (0–2)	0.55 ± 0.79	0.76 ± 0.92	t = 1.69	.094
(yes, in past week)	29 (19%)	22 (32%)	χ^2 = 5.0	.026
Bad dreams (0–2)	0.50 ± 0.68	0.49 ± 0.66	t = 0.44	.658
(yes, in past week)	17 (11%)	6 (9%)	χ^2 = 0.2	.629
Not breathing comfortably (0–2)	0.27 ± 0.60	0.31 ± 0.63	t = 0.20	.839
(yes, in past week)	14 (9%)	6 (9%)	χ^2 = 0.0	.960

Values are n (%) or mean ± SD. *Recoded as: 0 = not in past month; 1 = less than once/week; 2 = 1 or more nights/week. PSQI = Pittsburgh Sleep Quality Index, SD = standard deviation, T1 = time 1 (6 months before T2).

at the initial rise in FSH (T3) but at the subsequent time point (T4) 6 months later. We conclude that trouble sleeping because of "feeling too hot" is a sentinel symptom of the menopausal transition.

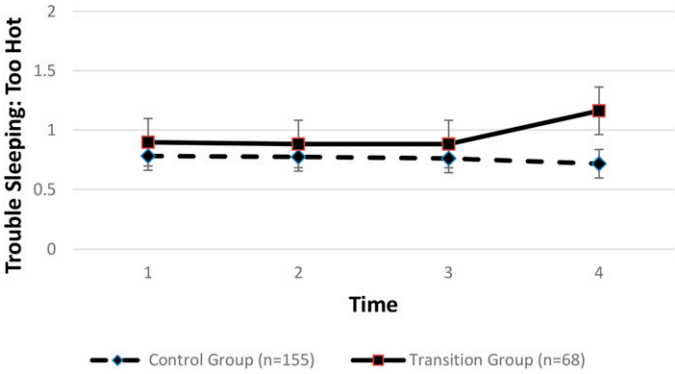
An increase in sleep disturbance because of feeling too hot occurred in the absence of any change in the experience of hot flashes or night sweats. One possibility is that awakening from feeling too hot is the onset of a continuum of vasomotor symptom severity that is not recognized as frank "hot flashes," either because the woman is not aware she is entering the transition or is not aware of the variable intensity of hot flashes. This is consistent with prior research showing that, while objective hot flashes are associated with nocturnal awakenings,[18,19] women are not always aware of hot flashes.[20] The detrimental

Figure 2—Longitudinal changes in PSQI scores* by menopausal stage.



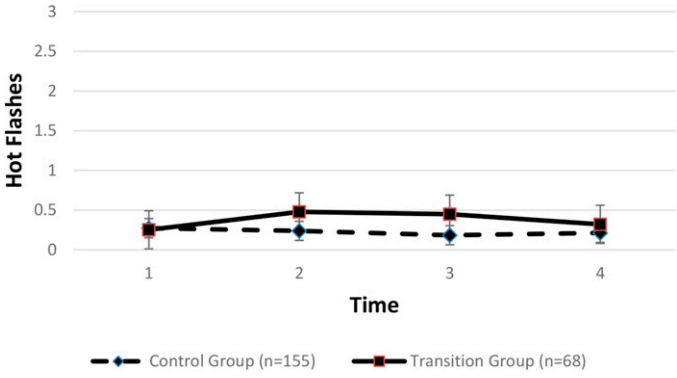
Covariates appearing in the model are evaluated at the following values: BMI = 27.8 kg/m^2; race (Black, yes = .22; White, yes =.52); PSQI pain = .61; sleep duration hours = 6.83. *Note that PSQI scores were square-root transformed for analysis but absolute PSQI values are displayed here. Estimated marginal means and error bars representing 95% CIs for PSQI scores are displayed on the *y* axis after controlling for covariates. The Transition Group (—) and Control Group (- - -) are compared at each of the four time points. The overall group-by-time model did not reach statistical significance (Wilks' Lambda = .965, $F_{[3,207]}$ = 2.47, P = .063). BMI = body mass index, CI = confidence interval, PSQI = Pittsburgh Sleep Quality Index.

Figure 3—Longitudinal changes in "trouble sleeping due to feeling too hot" by menopausal stage.



Covariates appearing in the model are evaluated at the following values: BMI = 27.8 kg/m^2; race (Black, yes = .23; White, yes = .52); PSQI pain = .61; sleep duration hours = 6.82. Estimated marginal means and error bars representing 95% CIs for "trouble sleeping due to feeling too hot" are displayed on the *y* axis after controlling for covariates. The Transition Group (—) and Control Group (- - -) are compared at each of the four time points. The overall group-by-time model was statistically significant (Wilks' Lambda = .954, $F_{[3,214]}$ = 3.50; P = .016). BMI = body mass index, CI = confidence interval, PSQI = Pittsburgh Sleep Quality Index.

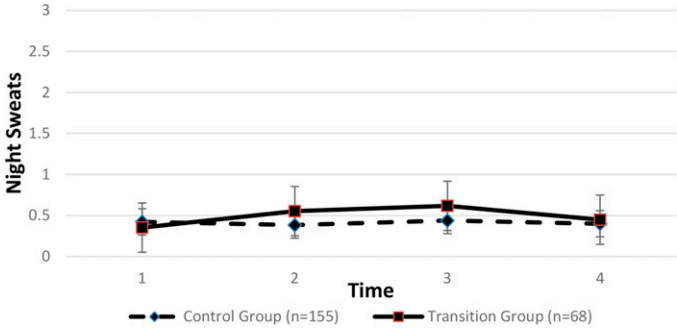
Figure 4—Longitudinal changes in hot flashes by menopausal stage.



Covariates appearing in the model are evaluated at the following values: BMI = 27.8 kg/m^2; race (Black, yes = .23; White, yes = .52); PSQI pain = .61; sleep duration hours = 6.82. Estimated marginal means and error bars representing 95% CIs for hot flash severity are displayed on the *y* axis after controlling for covariates. The Transition Group (—) and Control Group (- - -) are compared at each of the four time points. The overall group-by-time model did not reach statistical significance (Wilks' Lambda = .969, $F_{[3,214]}$ = 2.27, P = .082). BMI = body mass index, CI = confidence interval, PSQI = Pittsburgh Sleep Quality Index.

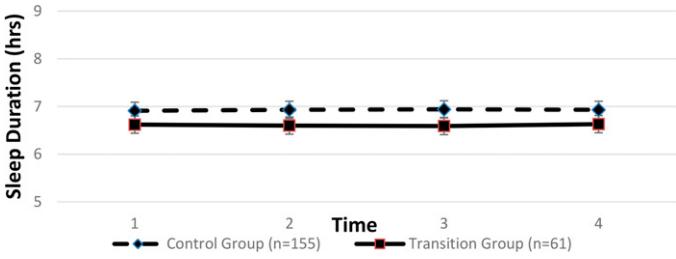
effect of perceived hot flashes on women's self-reported[21] and objective sleep quality[19] has been previously demonstrated. Thus, any symptom potentially indicating the onset of hot flashes can be critical in directing a woman's overall care, particularly as vasomotor symptom burden can be associated with depression, anxiety, and worsening physical health and quality of life.[22] We posit that the onset of menopause-related autonomic neurovascular dysregulation in some cases may initially be perceived

Figure 5—Longitudinal changes in night sweat severity by menopausal stage.



Covariates appearing in the model are evaluated at the following values: BMI = 27.8 kg/m^2; race (Black, yes = .23; White, yes = .52); PSQI pain = .61; sleep duration hours = 6.82. Estimated marginal means and error bars representing 95% CIs for night sweat severity are displayed on the *y* axis after controlling for covariates. The Transition Group (—) and Control Group (- - -) are compared at each of the four time points. The overall group-by-time model was not statistically significant (Wilks' Lambda = .986, $F_{[3,214]}$ = 0.99, P = .398). BMI = body mass index, CI = confidence interval, PSQI = Pittsburgh Sleep Quality Index.

Figure 6—Longitudinal changes in sleep duration by menopausal stage.



Covariates appearing in the model are evaluated at the following values: BMI = 27.8 kg/m^2; race (Black, yes =.22; White, yes = .52); PSQI pain = .61. Estimated marginal means and error bars representing 95% CIs for sleep duration (hours) are displayed on the *y* axis after controlling for covariates. The Transition Group (—) and Control Group (- - -) are compared at each of the four time points, and the overall group-by-time model did not reach statistical significance (Wilks' Lambda = .996, $F_{[3,208]}$ = 0.31, P = .818). BMI = body mass index, CI = confidence interval, PSQI = Pittsburgh Sleep Quality Index.

as simply awakening feeling too hot and is the initial sleep-related symptom of the menopausal transition. This is consistent with results from the extensive and complex literature on midlife women's sleep synthesized by Shaver and Woods,[23] who conclude that hypothalamic-pituitary-ovarian hormone fluctuations with resultant vasomotor instability is a major cause of poor sleep during the menopausal transition.

The other notable finding was the lag time from the initial rise in FSH for significant worsening of sleep quality and specifically for feeling too hot. It is possible that this lag is a function of the rate of FSH rise, the need to reach a particular absolute FSH value, or fluctuations in FSH due to "sputtering" in response to the negative feedback from declining production of ovarian estrogen. The lag may also be inherent in the sampling interval, as we were not able to obtain more frequent samples to document the exact month of rise in FSH or worsening in sleep quality. Previous investigators have noted a complex relationship between FSH levels and sleep, whether self-reported or objectively measured. Greater difficulty staying asleep has been associated with rising FSH levels,[3] and worse sleep quality (PSQI) with higher FSH level at baseline and a more rapid rise in FSH.[24] These self-reports of worse quality sleep stand in contrast to a 6-year longitudinal study[25] showing no association between FSH levels during and after the menopausal transition with polysomnographic measures of poor sleep, such as arousals or awakenings, although a subsequent continuation of that study showed that longer sleep latency was associated with higher FSH levels.[26]

Even before the change in FSH levels signifying the onset of the menopausal transition, significantly more women in the transition group endorsed pain as a reason for trouble sleeping compared with controls who remained premenopausal. However, the experience of pain in our sample did not change over time for either group and was generally low compared with other midlife women in the SWAN cohort.[27] Kravitz et al[27] noted that 64% of the pre- and early perimenopausal women reported at least 1 night of pain on any of 15 to 30 nights of

actigraphy monitoring. This is a much higher prevalence of pain than was present in both our control group (16%) and transition group (32%). However, their cohort was somewhat older (mean: 51.6 years) than our sample and perhaps age-related chronic musculoskeletal conditions might explain the difference. Without knowing the etiology of their pain, it is unclear why more women in our transition group experienced trouble sleeping due to pain at the same age as controls and even before the rise in FSH. Potential explanations could include the higher BMI in the transition group associated with more musculoskeletal pain or the type of pain, such as vaginal dryness associated with intercourse, menstrual cramping, or pain due to fibroids. Replication of this finding is needed, and further research on the type of pain and the onset of pain in premenopausal women is warranted to better understand how pain impacts sleep quality. Furthermore, actigraphy is influenced by movement, and when in pain, people tend to move less, so in this case the use of a self-reported sleep measure can help us gain more insight.

None of the stress measures or depressive symptom scores differed by time or reproductive stage group in our analysis, and our perceived stress scores were similar to normative data for women between 45 and 54 years of age.[17] Our sample entering the menopausal transition had a higher percentage of Black participants, which may reflect an earlier age at onset of the menopausal transition in this ethnic group.[28] Controlling for BMI, race, sleep duration, and pain, there were also no changes in self-reported symptoms that would suggest sleep apnea, such as coughing or snoring loudly or trouble sleeping because of not breathing comfortably.

Strengths and limitations

Our findings over an intensive 2-year time frame minimize the threat to validity that could occur with longer time frames or less-frequent assessments. Nevertheless, our findings require replication in larger samples of midlife women. Although general health perception and perceived stress remained stable over time and did not differ by reproductive stage, a health problem may have developed during this limited 2-year time frame that had an impact on sleep quality and was not noted.

Our measures for sleep and vasomotor symptoms were self-reported. Although potential participants were screened and excluded if diagnosed with a sleep disorder such as obstructive sleep apnea or periodic limb movement disorder, we did not use a validated questionnaire or polysomnography. We did, however, control for BMI in the analyses, and breathing-related symptoms suggestive of obstructive sleep apnea in the PSQI were rare (as shown in **Table 2**). The absence of polysomnography and actigraphy also prevented assessment of sleep stages and objective sleep fragmentation. However, we previously validated the PSQI against actigraphy in this population.[13] We cannot definitively extrapolate from "feeling too hot" to an assumption of frank hot flashes as we did not have an objective measure of sweating such as skin conductance to verify the presence of a vasomotor hot flash. We do not have information on sleeping environment conditions to rule out external causes of awakening feeling too warm, such as extra bedding or ambient temperature; however, data collection for all participants, including controls, occurred across all seasons, participants did not differ in awakening from feeling too cold, and they were from one geographic area (ie, San Francisco) where it tends to be cool at night even during summer. We only measured FSH and did not have assays of other hormones, such as estradiol, progesterone, or luteinizing hormone, as they are specific to menstrual cycle phase and not specific for indicating menopausal stage. Finally, our sample of midlife women was from one geographic location and was racially diverse, but results cannot be generalized to all racial/ethnic groups or other geographic locations.

CONCLUSIONS

The earliest sleep symptom associated with the menopausal transition may be an awareness of feeling too hot without the more characteristic symptoms of night sweats or hot flashes. Thus, clinicians should routinely ask a midlife woman if she is experiencing nighttime awakenings in association with feeling too hot and, if so, have a high clinical suspicion that she may be entering the menopausal transition to prompt a more extensive evaluation of her hormonal status and symptoms that could represent hot flashes, the treatment of which may improve sleep continuity and quality. Further research is warranted to establish if "feeling too hot" without an awareness of vasomotor symptoms is indicative of hot flashes, as that could potentially guide therapy.

ABBREVIATIONS

BMI, body mass index
CES-D, Center for Epidemiological Studies–Depression scale
FSH, follicle-stimulating hormone
PSQI, Pittsburgh Sleep Quality Index
STRAW, Stage of Reproductive Aging Workshop
SWAN, Study of Women Across the Nation
T1, time 1 (6 months before T2)
T2, time 2 (last visit before rise in FSH)
T3, time 3 (first visit at which rise in FSH is detected and 6 months after T2)
T4, time 4 (6 months after T3 and 12 months after T2)

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SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

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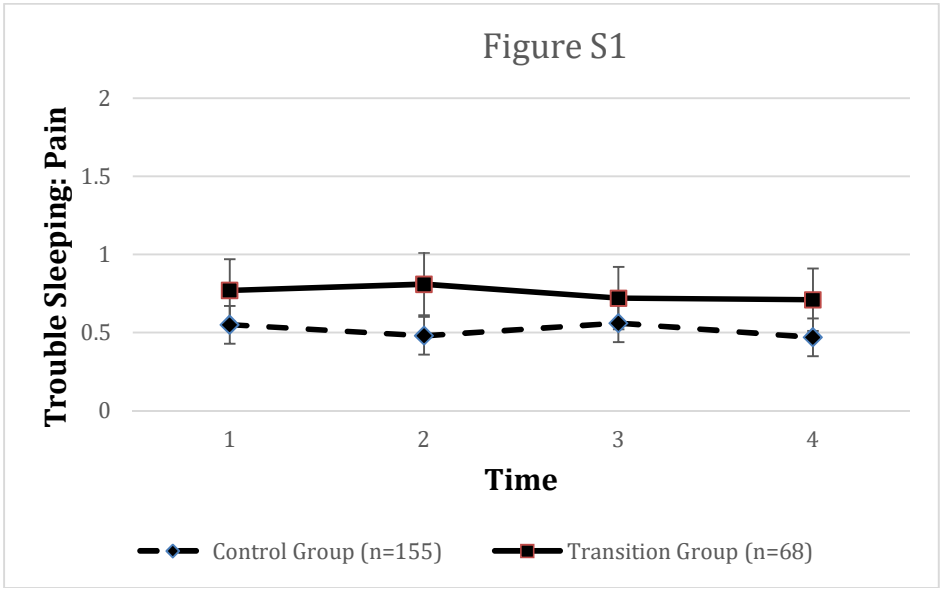
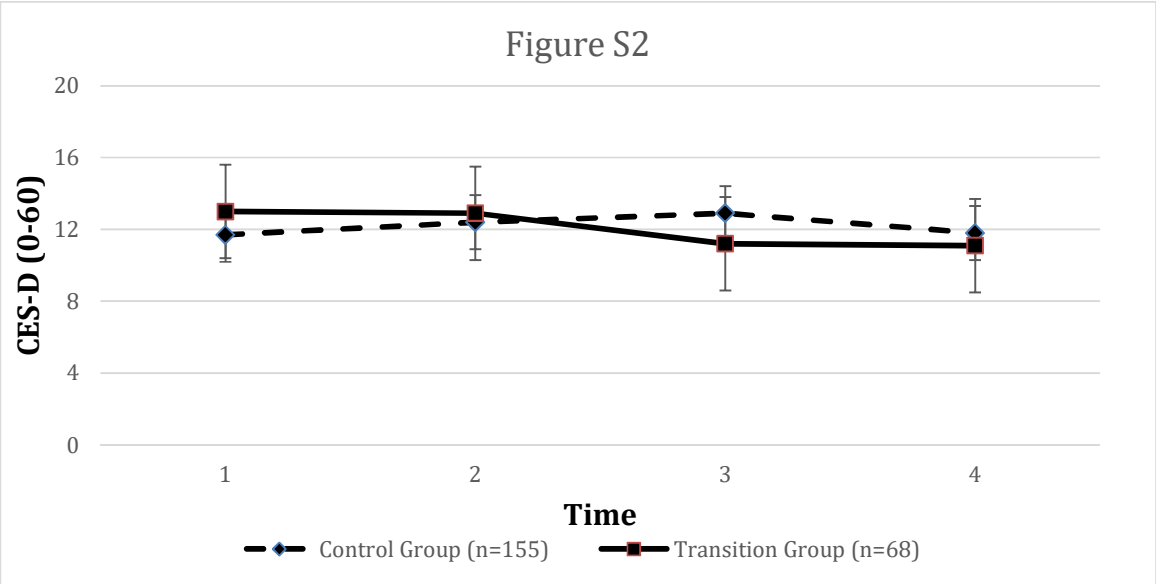
Figure S1. Longitudinal Changes in “Trouble Sleeping due to Pain” by Menopausal Stage.



Covariates appearing in the model are evaluated at the following values:
BMI=27.8; race (Black yes=.23, White yes=.52); sleep duration hours=6.82.

Estimated marginal means and error bars representing 95% CI for frequency of “trouble sleeping due to pain” are displayed on the Y axis after controlling for covariates that included race and baseline values for BMI and sleep duration. The Transition Group (—) and Control Group (- - -) are compared at each of the four time points, and the overall group-by-time model was not statistically significant (Wilks’ Lambda= .992, $F_{[3,215]}$=0.60, p=.613).

Figure S2. Longitudinal Changes in Depressive Symptoms (CES-D*) by Menopausal Stage.



Covariates appearing in the model are evaluated at the following values:
BMI=27.8; race (Black yes=.23, White-yes=.52); PSQI pain=.61; sleep duration hours=6.8.

Estimated marginal means and error bars representing 95% CI for depressive symptom scores on the CES-D are displayed on the Y axis after controlling for covariates that included race and baseline values for BMI, sleep duration and pain during the night. The Transition Group (—) and Control Group (- - -) are compared at each of the four time points, and the overall group-by-time model did not reach statistical significance (Wilks' Lambda=.994, $F_{[3,214]}$=0.46, p=.709.

*Note that CES-D scores were square-root transformed for analysis but absolute CES-D values are displayed here.