Predictors of Sleep Quality in Women in the Menopausal Transition

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Study objectives: To determine associations between menopausal status, reproductive hormone levels, menopausal symptoms, and poor sleep quality.

Design: The present study examines subjective sleep quality over an 8-year period in participants in an ongoing longitudinal study of ovarian aging in a randomly identified cohort of African American and Caucasian women.

Participants: The Penn Ovarian Aging Study, a population-based cohort of 436 women from Philadelphia County who were 35 to 47 years of age and had regular menstrual cycles at enrollment.

Interventions: N/A.

Measurements and results: The primary outcome measure was the Sleep Quality factor score, derived from the St. Mary's Hospital Sleep Questionnaire, which was adapted for this population and collected at each assessment period over the 8-year follow-up. Associations between menopausal status, reproductive hormone levels, menopausal symptoms, sleep quality, age, and race were examined in multivariable linear mixed regression models for repeated measures. Menopausal status was not significantly associated with sleep quality (P = 0.12). In the adjusted model, independent predictors of sleep quality were hot flashes (P < 0.0001), Center for Epidemiological Studies Depression Scale scores (P < 0.0001) and levels of the reproductive hormone inhibin B (P = 0.05).

Conclusions: Sleep quality was predicted by hormone levels and symptoms that occur in the menopausal transition but did not worsen with advancing menopausal status alone. Lower inhibin B levels, hot flashes, and symptoms of depression were all strong and independent predictors of difficulty sleeping. Race was not a significant contributor to sleep quality. Together, the findings demonstrate that women who experience other perimenopausal symptoms are likely to experience sleep problems during the menopausal transition.

Keywords: Sleep, sleep disorders, menopause, middle-aged

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PROBLEMS WITH SLEEP ARE WIDELY REPORTED AMONG MIDDLE-AGED WOMEN AND HAVE COMMONLY BEEN ATTRIBUTED TO THE MENOPAUSAL transition or cited as a symptom of menopause.[1-7] In several large, cross-sectional, community-based surveys, higher rates of self-reported difficulty sleeping have been observed among perimenopausal and postmenopausal women compared with premenopausal women.[2,4,6-8] For instance, in a survey of nearly 1500 Scottish women aged 45 to 54, the prevalence of sleep problems among perimenopausal and postmenopausal women was 40% and 35% respectively, compared to 22% among premenopausal women.[6] Data from the multiethnic, community-based sample comprising the Study of Women's Health Across the Nation (SWAN) have also demonstrated significantly higher rates of sleep difficulty among perimenopausal and postmenopausal women, compared with premenopausal women[2]; in this study, vasomotor symptoms were a strong and consistent predictor of trouble sleeping.

Nevertheless, whether difficulty sleeping increases among women in the late reproductive years and occurs due to symptoms of the menopausal transition, particularly hot flashes and night sweats, or whether the aging process itself causes an increase in sleep problems that is incorrectly attributed to menopause is not well understood. In addition, given the integral relationship between reproductive hormones and menopausal status, the impact on sleep of hormones such as estradiol, which is secreted by the ovary to support developing follicles and any subsequent pregnancy, and inhibin B, which is a hormone produced by ovarian granulosa cells and falling levels of which precede the menopausal decline in estradiol levels and are a marker of the early menopausal transition,[9] is also of interest. However, how reproductive hormone levels affect sleep quality has not been extensively examined.

The present study examines subjective sleep quality over an 8-year period in the Penn Ovarian Aging Study, an ongoing longitudinal study of ovarian aging in a population-based cohort. The aim of our study was to determine associations among menopausal status, reproductive hormone levels, menopausal symptoms, and sleep quality. Based on our earlier study in this cohort,[10] we hypothesized that women would experience worsened sleep quality during the menopausal transition, compared with the premenopausal and postmenopausal states, and that lower levels of reproductive hormones such as estradiol and inhibin B, which decrease with ovarian aging, would be associated with poorer sleep quality during the transition to menopause.

Disclosure Statement

This was not an industry supported study. Dr. Sammel has consulted for Wyeth Pharmaceuticals. Dr. Freeman has received research support from Wyeth and has participated in speaking engagements for Wyeth and Phoenix Pharmaceuticals. The other authors have indicated no financial conflicts of interest.

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METHODS

Study Cohort

Subjects were identified by random-digit dialing to households in Philadelphia County for participation in a longitudinal study of hormonal, clinical, behavioral, and demographic factors associated with ovarian aging. Recruitment of the cohort has been described in detail elsewhere[10-12] and was stratified to enroll equal numbers of African American and Caucasian women. Eligibility criteria for enrollment included age between 35 and 47 years, menstrual cycles in the normal range (22-35 days) for the previous 3 months, and presence of the uterus and at least 1 ovary. Exclusion criteria included current use of psychotropic or hormone medications (including hormonal contraception and replacement therapies), pregnancy or lactation, serious health problems known to compromise ovarian function (e.g., diabetes, liver disease, breast or endometrial cancer), abuse of alcohol or drugs within the past year, and non-English speakers. The study was approved by the University of Pennsylvania Institutional Review Board, and all participants provided written informed consent.

A total of 436 women (75% of those eligible) were enrolled in the cohort (218 African American and 218 Caucasian), of whom 422 had usable baseline questionnaire data. At the 10th assessment period, approximately 8 years after study inception, data were obtained from 311 participants. Comparisons of baseline data from the participants in the present study and individuals who discontinued participation revealed no significant differences in demographic background variables or any of the variables in this report. Reasons for attrition from the cohort include relocation (n = 8), medical or personal problems (n = 10), withdrawal of consent (n = 58), time constraints (n = 18), death (n = 4), and loss to follow-up (n = 27).

Assessment Periods

Data were collected at approximately 9-month intervals in the first 5 years of the study and annually in the last 4 years over an 8-year period. During each assessment period, 2 visits were scheduled between days 1 and 6 of 2 consecutive menstrual cycles, to obtain blood samples for hormone assays. The narrow visit window was selected to assess hormone levels in the early follicular phase, when levels are the most reliable[13,14] and changes associated with ovarian aging are most pronounced.[15]

Assessments of Study Variables

At each visit, a trained research interviewer conducted a standardized interview, collected blood samples for hormone assays, and measured height and weight to determine body mass index. The interview focused on overall health and included demographic background information, menstrual-cycle dates, reproductive history, general health status, behaviors (including medications, smoking, alcohol and caffeine consumption, and history of depressive disorders), and common menopausal symptoms. Participants completed self-administered standard questionnaires, which included the St. Mary's Hospital Sleep Questionnaire (SMHSQ)[16] at study enrollment and at 6 follow-up assessment periods over the 8-year time span. All study questionnaires were completed within the first 6 days of the menstrual cycle, as were the hormone assessments.

Hormone Measurements

Nonfasting blood samples for the hormone assays were collected between days 1 and 6 of the menstrual cycle in 2 consecutive cycles (or at monthly intervals in noncycling women) during each assessment period. The samples were centrifuged and frozen in aliquots at -80° C. Assays were conducted in the General Clinical Research Center in batches that included 4 visits per subject to reduce the within-subject variability due to assay conditions. Estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone, dehydroepiandrosterone sulfate, and testosterone were measured by radioimmunoassay using Coat-A-Count commercial kits (Diagnostic Products; Los Angeles, CA). Assays were performed in duplicate for all hormones and repeated if values differed by more than 15%. The interassay and intraassay coefficients of variation calculated from the assays were less than 5%. Dimeric inhibin B was measured in serum by Dr. Patrick Sluss at the Massachusetts General Hospital using a sensitive, 2-site, nonisotopic immunoassay (OxforD BioInnovation; London, UK). The intraassay and interassay coefficients of variation were less than 8% and less than 20%, respectively, for concentrations of 50 to 500 pg/mL; the analytical sensitivity was 15 pg/mL.

Symptom Measures

We adapted the SMHSQ[16] for use in our cohort by adding items to assess the etiology of nocturnal awakenings, the frequency of sleep medication use, and whether the previous night of sleep was comparable to usual sleep and by deleting questions about bedtime, fall-asleep time, wake time, time out of bed, and the "depth" of sleep; this resulted in a total of 20 items (see Appendix A).

Additional self-report symptom measures that were completed by the study participants at each assessment period included the following:

- The Center for Epidemiologic Studies – Depression Scale is a well-established epidemiologic measure of depression that assesses depressive symptoms over the past week.[17] Participants rated 20 items related to depressed mood from 1 (not at all) to 4 (most of the time). Positive item scores were reversed and the item ratings were summed to yield a total score, with higher scores indicating more depressed mood.
- The Zung Anxiety Scale is a validated measure that is sensitive to the frequency of anxiety symptoms.[18] Participants rated the 5 affective and 15 somatic symptoms on a 4-point scale ranging from 0 (none) to 4 (all the time) for their severity over the past week. Ratings were summed to yield a total score, with higher scores signifying greater anxiety.
- The Perceived Stress Scale is a 14-item validated measure of the degree to which situations are considered to be stressful.[19] Participants rated the items on a 5-point scale from 0 (never) to 4 (very often). Total scores were obtained by re-

verse scoring the 7 positive items and summing all ratings to indicate the severity of stress during the past month. The Perceived Stress Scale has been correlated with depression, physical symptomatology, and anxiety and has been shown to measure an independently predictive construct of appraised stress.

Outcome Variables

The primary outcome measure was the Sleep Quality factor identified from the factor analyses of the adapted SMHSQ (below). Higher scores indicated better sleep quality. The secondary outcome variable was a single item from the SMHSQ, "How well did you sleep last night," which was used as a primary outcome measure in previous analyses in this cohort.[10] Subjects rated this item on a scale from 1 ("very badly") to 6 ("very well").

Menopausal Status

Menopausal status was determined from the data on menstrual bleeding, which included the menstrual dates at each study interview (conducted within 6 days of onset of bleeding), the dates of the 2 previous menstrual periods recorded at the interview, the number of menstrual periods between assessments, cycle length, and the menstrual dates recorded in the individual's daily symptom diaries. At each assessment period, each participant was assigned to 1 of the following categories based on bleeding patterns established by the PENN-5 criteria,[20] which extend the STRAW criteria by differentiating between 1 observed change in cycle length (late premenopause) and 2 observed changes in cycle length (early transition). The definitions are as follows:

- Premenopausal: regular cycles in the normal range (21-35 days)
- Late premenopausal: 1 observed change in cycle length of at least 7 days in either direction compared with the subject's own baseline at enrollment
- Early transition: at least 2 cycles with cycle length changes of at least 7 days in cycle length in either direction compared with the subject's own baseline or ≥ 60 days amenorrhea
- Late transition: greater than or equal to 3 months of amenorrhea
- Postmenopausal: greater than or equal to 12 months of amenorrhea and no hysterectomy

Predictor Variables

The selection of predictor variables was based on their significance in previous studies and the goals of this project. Predictor variables included menopausal status,[1-5,7,8,21] race (African American or Caucasian),[22] baseline age (35-39, 40-44, or 45-49 years),[23] Center for Epidemiological Studies Depression Scale scores,[24] Zung scores,[25] presence of hot flashes,[26,27] number of living children,[28] marital status,[29] smoking status,[30] time, body mass index,[31] alcohol use,[32] education level,[33] and symptoms of premenstrual syndrome.[34] Hormone levels included estradiol,[10] testosterone, dehydroepiandrosterone sulfate, inhibin B, follicle-stimulating hormone, and luteinizing hormone.

Statistical Analysis

Factor Analysis

We first conducted an exploratory factor analysis of the SMHSQ that was administered to participants at baseline to determine the factor structure and to select the most appropriate outcome variable for the sleep-quality analyses. Using all data from the first assessment period, the factor structure was examined using a principal components factor analysis, followed by varimax and promax rotations. Because we assumed that the sleep factors were correlated, a solution using the oblique promax rotation was selected. Various factor structures were investigated, with the first set conducted on all 20 questionnaire items. The remaining sets were conducted with subsets of these items, as suggested by the initial analyses. Three factors that had eigenvalues greater than 1 were identified. Parallel models were generated in SAS (SAS, Inc., Cary, NC; version 9.1), which assumes all outcomes were normally distributed, and in MPLUS (v2.13, Muthén and Muthén, Los Angeles, CA), which treats ordinal responses as coming from a cumulative probit distribution. The individual items loaded on the factors similarly; however, the weights (or loadings) of the factors were generally larger for the MPLUS models.

The factor analysis identified 3 factors: Sleep Quality, Sleep Complaints, and Sleep Latency. The Sleep Quality factor score explained 37% of the total variability in all items, whereas the Sleep Complaints factor explained 9.8% and the Sleep Latency factor score explained 9.2% of variability. The Sleep Quality factor, which explained the largest proportion of variability in responses and was estimated consistently regardless of the assumed number of factors, was used as the primary study outcome variable. A confirmatory factor analysis was then performed using data from the final assessment period (8 years later) and yielded results similar to the developmental factor analysis, indicating that the factors appeared stable.

Summary outcomes were constructed from the SMHSQ factors by assigning each item to the factor on which its factor loading was the highest. Factor scores were computed by summing the participants' severity ratings of the items in each factor (i.e., assuming equal weighting of the items within the specific factor). To assess the validity of the Sleep Quality factor, correlations with other standard symptom measures were calculated using data from the last assessment period. The Sleep Quality factor had modest correlations (r = 0.33-0.38) with standard measures of mood, anxiety, and stress (the Center for Epidemiological Studies Depression Scale [CES-D], Zung, and Perceived Stress Scale questionnaires), indicating that the measure of sleep was not simply a measure of these mood domains. The correlation with the Women's Health Initiative Insomnia score[35] (administered at the 8-year follow-up assessment) was r = 0.57, indicating a moderate similarity of the 2 measures; moderate correlations with questions from a menopausal symptom list[36] about the frequency and severity of difficulty sleeping were also observed, ranging between 0.44 and 0.50. Cronbach coefficient α for the Sleep Quality factor, which included 7 items from the questionnaire, was 0.76, indicating strong internal consistency of the component items. For the Sleep Complaints and Sleep Latency factors,

Table 1—Subject Characteristics at Baseline and 8-Year Follow-Up

	Baseline (n = 422)	Follow-up (n = 292)
Menopausal status, n (%)		
Premenopausal	422 (100)	96 (32.9)
Late premenopausal	0	10 (3.4)
Early transition	0	75 (25.7)
Late transition	0	53 (18.2)
Postmenopausal	0	58 (19.9)
Race, n (%)		
African American	210 (49.8)	141 (48.3)
Caucasian	212 (50.2)	151 (51.7)
Age, n (%)		
35-39 years	154 (36.5)	0 (0)
40-44 years	188 (44.6)	49 (16.8)
45-49 years	80 (19.0)	131 (44.9)
50-54 years	0	107 (36.6)
55-59	0	5 (1.7)
Employment, n (%)		
Unemployed	77 (18.3)	53 (18.2)
Employed	345 (81.8)	239 (81.9)
Hot flashes, n (%)		
Flashes	174 (41.2)	153 (52.4)
No flashes	248 (58.8)	139 (47.6)
Hormones, mean (SD)		
Estradiol, pg/mL	42.3 (27.8)	44.5 (41.1)
Testosterone, ng/dL	12.6 (12.4)	17.7 (11.3)
FSH, mIU/mL	8.2 (5.2)	33.4 (28.2)
Inhibin B, pg/mL	78.9 (41.4)	33.7 (52.1)
Caffeine, #/wk (SD)	18.9 (21.1)	17.6 (19.1)
Smoking, n (%)		
Yes	157 (37.2)	88 (30.1)
No	264 (62.6)	204 (69.9)
Zung Anxiety Scale, mean (SD)	34.7 (7.8)	31.5 (6.7)
CES-D Scale, mean (SD)	15.0 (10.6)	11.7 (9.2)
Perceived Stress Scale, mean (SD)	21.2 (7.8)	19.3 (8.8)
PMS symptoms, n (%)		
Yes	86 (20.4)	28 (9.6)
No	336 (79.6)	264 (90.4)

FSH refers to follicle stimulating hormone; CES-D, Center for Epidemiological Studies Depression Scale; PMS, premenopausal syndrome.

which each incorporated 2 questionnaire items, the Cronbach α values were 0.94 and 0.32, respectively.

Regression Models for Sleep Quality over Time

The linear regression analyses included all available data from the study participants (2619 total observations on 422 study participants). Each participant could contribute up to 7 observations, depending on the number of follow-up visits completed. All variables were measured at each assessment period. The distribution of the outcome variable (the Sleep Quality factor score) was first examined at each assessment period to ensure that normality assumptions were met. A general linear mixed-regression model for repeated measures was used to estimate the unadjusted and adjusted associations of each study variable on sleep quality, as assessed by the Sleep Quality score. Results were summarized using means and SEMs for categorical variables and regression coefficients (slopes) and standard errors for continuous measures.

We assumed that the sleep quality measures for each woman's repeated measures were equicorrelated, and statistical tests for covariate associations were adjusted using generalized estimating equation methodology.[37] This specialized statistical technique is similar to repeated-measures analysis of variance in that the point-in-time associations between the covariates of interest (menopausal status, hormone level, etc) and outcome (sleep quality) are averaged over time, i.e., combine cross-sectional (between women) and longitudinal (within woman) estimates of association and correct statistical tests for the correlation due to multiple measures within women. This method is more flexible than repeated-measures analysis of variance, as it does not require each woman to have the same number of repeated measurements, as long as missing information can be assumed missing-at-random, i.e., missing data do not depend upon the unobserved sleep quality measures. Reproductive hormone levels and all other covariates associated with poor sleep quality in the unadjusted analyses at $p < 0.20$ were included in the model selection process for the multivariable models. Hypothesized interactions between time, hormone levels, and menopausal status were examined given the potential impact of time on reproductive hormone levels and menopausal status and the assumed relationship between hormone levels and menopausal status. The final selection of covariates was guided by whether each variable remained statistically significant at $P \leq 0.05$ or whether its inclusion modified other significant associations in the model by 15% or more.[38] In addition to the final explanatory model, we also considered the possibility that depressive symptoms and/or hot flashes could mediate (i.e., explain how the relationship between an independent and dependent variable occurs[39,40]) the observed association of menopausal status and inhibin B levels on sleep quality by creating models with and without the hypothesized mediators and examining the magnitude of these relationships. For all models, observations during the study were censored for subjects who were using hormone therapy or oral contraceptives, were pregnant or breastfeeding, or had had a hysterectomy or an ovariectomy (83 censored observations).

The SAS statistical software package, version 9.1, was used for all analyses. Statistical tests were 2-tailed, with P values ≤ 0.05 considered significant.

RESULTS

Study Subjects

Characteristics of the cohort at baseline and at the final assessment 8 years later are shown in Table 1. At enrollment, the mean (SD) age of the cohort was 41 (3.5) years, and all participants were premenopausal. At the study endpoint, the mean age was 48.8 (3.5) years; 36% were premenopausal, 44% were in the menopausal transition, and 20% were postmenopausal.

Table 2—Unadjusted and Adjusted Associations between Menopausal Status, Other Study Variables, and Sleep Quality Factor Scores

Variable	Unadjusted Sleep Quality Factor Scores (SE)[b]	P value	Adjusted Sleep Quality Factor Scores (SE)[c]	P value
Menopausal Status		0.27		0.12
Premenopausal	-0.05 (0.14)	—	-0.22 (0.14)	—
Late Premenopausal	0.27 (0.24)	0.17	0.17 (0.25)	0.10
Early Transition	0.26 (0.21)	0.12	0.17 (0.22)	0.07
Late Transition	0.06 (0.33)	0.75	0.17 (0.33)	0.25
Postmenopausal	0.69 (0.49)	0.13	0.66 (0.45)	0.06
Race		0.23		0.56
African American	-0.10 (0.20)		0.26 (0.20)	
Caucasian	0.23 (0.18)	—	0.12 (0.21)	—
Hot flashes		<0.0001[a]		<0.0001[a]
Yes	-0.50 (0.19)		-0.20 (0.21)	
No	0.45 (0.14)		0.58 (0.17)	—
Baseline Age		0.15		0.35
35-39	-0.21 (0.23)	—	0.14 (0.23)	—
40-44	0.35 (0.20)	0.06	0.43 (0.21)	0.29
45-49	-0.04 (0.31)	0.65	0.00 (0.28)	0.67
Employment		0.06		
Unemployed	-0.50 (0.34)			
Employed	0.20 (0.14)			
Caffeine Use	-0.01 (0.01)	0.15		
Current Smoking		0.03[a]		
Smoking	-0.27 (0.22)			
Not smoking	0.25 (0.15)			
Zung Anxiety Scale	-0.17 (0.01)	<0.0001[a]		
CES-D Scale	-0.12 (0.01)	<0.0001[a]	-0.12 (0.01)	<0.0001[a]
PSS	-0.10 (0.01)	<0.0001[a]		
PMS		<0.0001[a]		
Yes	-0.94 (0.28)			
No	0.25 (0.14)			
Hormones				
Estradiol, pg/mL	0.03 (0.12)	0.79		
Testosterone, ng/dL	0.06 (0.10)	0.50		
FSH, mIU/mL	-0.02 (0.13)	0.89		
Inhibin B, pg/mL	0.07 (0.11)	0.48	0.21 (0.11)	0.05[a]
Time	0.02 (0.03)	0.53		

[a]P value ≤ 0.05. P values are from linear regression models for repeated measures, with variance parameters adjusted for correlation within subjects over time using generalized estimating equation sandwich variance estimates. Pairwise comparisons for subgroups are reported for menopausal status (compared to premenopausal women) and baseline age (compared to 35-39 years of age).

[b]For continuous variables (caffeine use; Zung, Center for Epidemiological Studies Depression Scale (CES-D), and Perceived Stress Scale (PSS) scores; hormone levels; and time), regression coefficients (SE) are given rather than mean values. Additional variables examined were number of living children, marital status, body mass index, alcohol intake, educational level, and levels of dehydroepiandrosterone sulfate and luteinizing hormone (all P values ≥ 0.20 in unadjusted analyses).

[c]N = 2619 observations used for this analysis. Variables included in the fully adjusted model were menopausal status, race, hot flashes, baseline age, and inhibin B levels.

Associations with Sleep-Quality Factor

Table 2 shows the unadjusted associations of study variables with sleep quality. Significant associations with poorer sleep included current smoking, current hot flashes, greater anxiety as assessed by the Zung scale, more depressed mood as assessed by the CES-D, greater stress as assessed by the Perceived Stress Scale, and severe symptoms of premenstrual syndrome.

Table 2 also shows the adjusted associations of the study variables with the Sleep Quality factor scores (each variable is adjusted for all other variables in the model). In the final adjusted model, independent predictors of sleep quality were hot flashes (P < 0.0001), CES-D scores (P < 0.0001), and inhibin B levels (P = 0.05). Women with hot flashes, more depressive symptoms, and lower inhibin B levels within any menopausal stage were more likely to report poor sleep quality. Although the anxiety scores were highly significant in unadjusted analyses, anxiety was not included in the final model because of collinearity with the CES-D, which was retained because of the clinical association of depressive symptoms with the menopausal transition. Similar associations were observed when anxiety was substituted for CES-D. We did not observe a statistically significant association of menopausal status, age, or race with sleep quality in either adjusted or unadjusted analyses. Despite

Table 3—Sleep Quality Factor Scores in Good and Poor Sleepers[a]

	Poor Sleepers		Good Sleepers		P value
	n (%)	Score (SD)	n (%)	Score (SD)	
Baseline	66 (15.6%)	-6.2 (3.2)	356 (84.4%)	1.2 (3.0)	< 0.0001
8-year Follow-up	59 (20.3%)	-6.3 (3.4)	232 (79.7%)	1.6 (3.1)	< 0.0001

[a]Responses to the single-item sleep quality measure from the St. Mary's Hospital Sleep Questionnaire were used to designate poor (slept "very badly," "badly," "fairly badly") and good (slept "fairly well," "well," "very well") sleepers. Unpaired t tests were performed.

the hypothesized relationships between reproductive hormone levels, menopausal status, and time, we did not observe significant interactions between these variables, suggesting that the magnitude of any such relationships is likely to be very small.

To examine the potential effects of depressive symptoms and hot flashes as mediators of the relationship between menopausal status, inhibin B levels, and sleep quality, we fit additional models omitting depressive symptoms and hot flashes both individually and together. In these models, the relationships between menopausal status and inhibin B levels (the independent variables) and sleep quality (the dependent variable) were stronger compared to the final model, consistent with our hypothesis of mediation. Removing the hot flash variable from the final model resulted in a 15% increase in the association estimate for inhibin B level (consistent with intensification of the relationship between inhibin B and sleep quality) and a statistically significant association for inhibin B ($P = 0.03$). Deleting hot flashes from the model also led to a 28% to 29% decrease in regression coefficients for the late transitional and postmenopausal stages, suggesting that in the later menopausal stages (when they are most common), hot flashes have a substantial negative impact on sleep quality. When CES-D scores were excluded, the association between menopausal status and sleep quality was strengthened but did not achieve conventional levels of statistical significance ($P = 0.09$). In this case, the change in estimated association with sleep quality ranged from -13% for women in late premenopause to +37% for postmenopausal women. These changes are consistent with the decreasing prominence of depressive symptoms in the late transition and postmenopause. Further analyses did not identify any significant interactions between menopausal status and depressive symptoms ($P = 0.28$) or between menopausal status and hot flashes ($P = 0.93$). Overall, these results indicate that the effects of menopausal status and inhibin B levels on sleep quality are attenuated in models that include symptoms of the menopausal transition that affect sleep quality as covariates in the final model.

Associations with Secondary Outcome Measure

We also examined associations between these same risk factors for poor sleep and the secondary outcome measure, the single item from the SMHSQ in which subjects were asked, "How well did you sleep last night," rated on a 6-point scale. Dichotomizing the single item for poor and good sleep, as we had done for a previous analysis,[10] demonstrated a large difference between the Sleep Quality factor scores at both the baseline and final assessment periods (Table 3). The correlation of this item with the Sleep Quality factor score was high ($r = 0.83$). Hot flashes, symptoms of premenstrual syndrome, and high anxiety, depression, and stress ratings all had detrimental effects on the sleep quality item in unadjusted analyses, consistent with the associations of these variables with the primary outcome measure. Lower inhibin B levels and higher FSH levels, which accompany the ovarian decline, were also strongly associated with this measure of sleep quality. In an adjusted model including the same covariates as the final model for the Sleep Quality factor score, hot flashes ($P < 0.0001$), CES-D scores ($P < 0.0001$), and mean inhibin levels ($P = 0.003$) were all significant and independent predictors of the single-item measure of sleep quality, consistent with results for the primary outcome measure.

DISCUSSION

This prospective study identified risk factors for poor sleep quality in a community-based cohort of late-reproductive-aged Caucasian and African American women. We found that self-reported sleep quality, as measured by the Sleep Quality factor score, did not decline during the menopausal transition. However, sleep quality was strongly affected by specific symptoms associated with menopause, including hot flashes and depressive symptoms. Thus, although many women in menopausal transition experience poor sleep, we observed that they do so primarily in association with other menopausal complaints that impact sleep quality.

Our results contrast with other studies measuring subjective sleep quality, which have observed that perimenopausal and postmenopausal women generally report worse sleep quality, compared with premenopausal women.[2,4,5,41] However, many of these studies failed to control for vasomotor symptoms when examining menopausal status as a predictor of sleep problems. In the SWAN, the investigators included both vasomotor symptoms and menopausal status when examining difficulty sleeping.[2] In this multiethnic multicenter study, both variables were significantly associated with sleep difficulties; women in late perimenopause were at greatest risk for difficulty sleeping. The prevalence of chronic insomnia was also highest among perimenopausal women in a recent survey of midlife women from California, compared with premenopausal and postmenopausal participants.[42] After adjustment for hot flashes, however, symptoms of insomnia were not consistently more common among perimenopausal and postmenopausal women; although advancing menopausal status was associated with difficulty maintaining sleep, global sleep dissatisfaction was *least* prevalent among perimenopausal women after adjusting for hot flashes and other variables. These study results imply that menopausal

status may be less important to sleep quality than the degree to which women are symptomatic with vasomotor or other symptoms of menopause, which is also suggested by our findings.

Few studies have examined whether levels of reproductive hormones in perimenopausal women predict difficulty sleeping or other symptoms of the menopausal transition.[3,10,43] Previously, when we examined associations between hormone levels and sleep quality in this cohort (after 2 years of data collection), lower mean levels of estradiol predicted difficulty sleeping among the oldest women in the cohort, who were 45 to 49 years of age at the time and still premenopausal.[10] In the current analyses, using a more in-depth measure of sleep quality and a longer time interval during which many subjects reached the late transitional and postmenopausal stages, we found that lower levels of inhibin B, a marker of the *early* menopausal transition, were a strong predictor of poorer self-reported sleep quality and also poor sleep, as was assessed in our previous report. Higher FSH levels were associated with poorer sleep, as assessed by the single-item measure but not the Sleep Quality factor, although we cannot determine reasons for this. However, the association among serum inhibin B levels, sleep quality, and poorer sleep is a novel finding that may be illuminated by recent results from another study of sleep difficulty and hormone levels.[3] In this study of a subset of SWAN participants, higher mean urinary log FSH levels (measured daily across the menstrual cycle) were associated with poor sleep in premenopausal and perimenopausal women in unadjusted analyses, but only with premenopausal women in multivariable analyses.[3] Since FSH stimulates the gonadal production of inhibin B, with inhibin B suppressing pituitary FSH secretion as part of a closed-loop feedback system, higher FSH levels are likely to result from a fall in inhibin B levels.[44] Thus, the findings from the SWAN investigators and the current study both suggest that changes in hormone levels along the FSH axis are likely to affect sleep quality.

Associations between hot flashes and sleep disturbance have been observed previously, both in studies of self-reported sleep quality[2,3,10,41,42] and in studies using objective measurements of sleep disturbance.[21,26] However, findings are conflicting, and, although hot flashes and difficulty sleeping frequently occur together, there may be no causal association. Postmenopausal women reporting hot flashes have been observed to have lower sleep efficiencies than postmenopausal women without vasomotor symptoms.[21,45] When changes in skin resistance and temperature were used to objectively measure hot flashes, the majority of hot flashes during sleep were associated with awakenings from sleep[26]; nevertheless, a more recent study failed to replicate this finding.[27] Other data suggest that poor sleep is explained by emotional factors and sleep deprivation.[46] Depression, as measured by the CES-D, was a strong predictor of poor sleep quality in our cohort, as has been previously reported in both menopausal[2] and general population studies.[47] Of note, depressed mood may be a consequence of the menopausal transition.[43,48] Therefore, it is possible that the effects of menopausal stage and hormone levels on sleep quality were underestimated in our study because of the inclusion in the model of depressive symptoms and hot flashes (another symptom of menopause), which had mediating effects on sleep quality.

In our analyses, race was not a significant contributor to sleep quality or poor sleep. We retained this variable in the final model because the study was designed to examine differences between Caucasian and African American women and because of the previously identified differences between these 2 groups in reports of hot flashes, depression, and anxiety.[11,12,43]

In examining the relationship between the Sleep Quality factor and the single-item response for poor sleep, we found the correlation between the 2 measures to be high (0.83), suggesting that minimal information is lost by using the single-question format. Furthermore, the final adjusted model for the Sleep Quality factor closely predicted the single-item sleep-response measure, indicating that hot flashes, inhibin B levels, and depressive symptoms are similarly important in both measures of sleep.

Our study has several limitations. The analyses are based on self-reported data on sleep quality and cannot quantify sleep architecture, arousal index, or other objective measures of sleep. However, our measure of sleep quality is shown to be a valid tool with appropriate correlations to other sleep measures. Given the disparity between self-reported and objective sleep quality even when both endpoints have been measured,[8] we believe polysomnography does not fully capture the subjective elements contributing to the perception of a good night's sleep. Hormone measurements were made in the follicular phase when these hormone measures are believed to be most reliable but do not address the question of hormone effects on sleep quality over the luteal phase or the full cycle. Our subjects represent a community-based sample of healthy African American and Caucasian women, but the findings may not be generalizable to women in nonurban areas or to other racial or ethnic groups.

In summary, this study prospectively examined sleep quality at multiple points over 8 years in a well-characterized cohort of mid-life African American and Caucasian women. Sleep quality was significantly associated with hot flashes, depressive symptoms, and lower levels of the reproductive hormone inhibin B, which declines swiftly in the early menopausal transition. Menopausal stage was not significantly associated with sleep quality in this cohort, which may be due in part to the role of hot flashes and depressive symptoms as mediators of the effect of menopausal status on sleep quality. These findings demonstrate that women who experience other perimenopausal symptoms are also likely to experience sleep problems during the menopausal transition. The results challenge the popular perception that difficulty sleeping is simply due to the transition to the postmenopausal state and invite additional study to elucidate the relationships between hormone changes associated with ovarian decline and their impact on menopausal symptoms.

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APPENDIX A.

The Adapted St. Mary's Hospital Sleep Questionnaire

These questions refer to your sleep over the past 24 hours:

1. How much sleep did you have last night?
   (in hrs, mins)
2. How much did you sleep during the day (yesterday)?
   (in hrs, mins)
3. How well did you sleep last night?
   1) very badly 2) badly 3) fairly badly
   4) fairly well 5) well 6) very well
4. How clear-headed did you feel after getting up this morning?
   1) still very drowsy indeed 2) still moderately drowsy
   3) still slightly drowsy 4) fairly clear-headed
   5) alert 6) very alert
5. How satisfied were you with last night's sleep?
   1) very unsatisfied 2) moderately unsatisfied
   3) slightly unsatisfied 4) fairly satisfied
   5) completely satisfied
6. Were you troubled by waking early and being unable to get back to sleep again?
   1) Yes 0) No
7. How many times did you wake up last night?
   1) not at all 2) once 3) twice
   4) three times 5) four times 6) five times
   7) six times 8) more than six
8. Which of the following woke you up during the night?
   1) legs feel jumpy or jerk 2) hot flashes
   3) needing to go to the bathroom 4) noises
   5) physical discomfort or pain 6) worry or stress
   7) vivid dreams/ nightmares 8) other (specify)
   0) did not wake up at all last night
9. How much difficulty did you have in getting off to sleep last night?
   1) none or very little 2) some
   3) a lot 4) extreme difficulty
10. How long did it take you to fall asleep last night?
    (in hrs, mins)
11. How would you compare your sleep last night with your usual sleep?
    1) worse than usual 2) about the same as usual
    3) better than usual
12. During the past month, how often have you taken medicine (prescribed or over-the-counter) to help you sleep?
    1) not during the past month 2) less than once a week
    3) once or twice a week 4) three or more times a week