Menopausal Status and Sleep-disordered Breathing in the Wisconsin Sleep Cohort Study

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Menopause is considered to be a risk factor for sleep-disordered breathing, but this hypothesis has not been adequately tested. The association of premenopause, perimenopause, and postmenopause with sleep-disordered breathing was investigated with a population-based sample of 589 women enrolled in the Wisconsin Sleep Cohort Study. Menopausal status was determined from menstrual history, gynecologic surgery, hormone replacement therapy, follicle-stimulating hormone, and vasomotor symptoms. Sleep-disordered breathing was indicated by the frequency of apnea and hypopnea events per hour of sleep, measured by in-laboratory polysomnography. Multivariable logistic regression was used to estimate odds ratios for having 5 or more and 15 or more apnea and hypopnea events per hour. Odds ratios (95% confidence interval), adjusted for age, body habitus, smoking, and other potential confounding factors, for 5 or more apnea and hypopnea events per hour were 1.2 (0.7, 2.2) with perimenopause and 2.6 (1.4, 4.8) with postmenopause; odds ratios for 15 or more apnea and hypopnea events per hour were 1.1 (0.5, 2.2) with perimenopause and 3.5 (1.4, 8.8) with postmenopause. The menopausal transition is significantly associated with an increased likelihood of having sleep-disordered breathing, independent of known confounding factors. Evaluation for sleep-disordered breathing should be a priority for menopausal women with complaints of snoring, daytime sleepiness, or unsatisfactory sleep.

Keywords: sleep apnea; obstructive sleep apnea; women; epidemiology; hormone replacement therapy

Menopause is widely considered to be a risk factor for sleep-disordered breathing (SDB), a condition of repeated breathing pauses during sleep, but this hypothesis has not been adequately tested. The threefold higher prevalence of SDB in men relative to women and clinic observations that most women diagnosed with SDB are postmenopausal suggest direct or indirect effects of diminishing estrogenic hormones as a likely mechanism (1, 2). Because virtually all women living beyond the age of 55 years will experience menopause, it is important to understand whether menopausal changes contribute to the development or progression of SDB, which is associated with significant morbidity, including daytime impairment (3, 4) and cardiovascular morbidity (5–7). Furthermore, if depletion of estrogen and progesterone has a causal role in SDB, hormone replacement therapy (HRT) may reduce the incidence and severity of this condition.

Findings from comparisons of SDB prevalence by menopausal status (8–11), age trends (12), and clinical trials of HRT (13–16) do not consistently support a role of menopause in SDB. However, interpretation of the findings collectively is difficult because of differing methodologic shortcomings of the studies, including clinic referral bias, small sample sizes, imprecise categorization on menopausal status, and other measurement issues.

Only one population study focused primarily on the relationship between menopause and SDB. Bixler and colleagues (1) reported a higher prevalence of SDB in menopausal compared with premenopausal women (3.9 and 0.6%, respectively), but these estimates were not adjusted for age or body habitus. In multivariable models to adjust for these and other confounding factors, the association of postmenopause *per se* was not analyzed; only categories of postmenopause with and without HRT were investigated as predictors of SDB. Postmenopause without HRT use was associated with SDB (odds ratio = 4.3, 95% confidence interval = 1.1, 17.3), whereas postmenopause with HRT was not (odds ratio = 0.9, 95% confidence interval = 0.1, 5.8). The results indirectly suggest that menopause is associated with an increased risk of SDB and that HRT reverses the risk, but caution is needed in interpreting these findings as evidence for an independent association of menopause and SDB. HRT use is a marker for overall health and other factors related to a lower SDB risk, and thus, categorization of postmenopausal women on HRT use may dichotomize the sample on SDB risk for reasons other than actual HRT exposure. Consequently, results of this study and those of others do not adequately address the role of menopause in SDB occurrence.

In this study, we tested the hypothesis that menopause is an independent risk factor for SDB using in-laboratory polysomnography and detailed data on stage of menopause, duration of postmenopause, HRT use, history of hysterectomy and oophorectomy, vasomotor symptoms, and serum follicle-stimulating hormone from a population-based sample of 589 midlife women. The protocol was approved by the University of Wisconsin Internal Review Board, and informed consent was obtained from all participants. Some of the results from preliminary analyses of data from this study have been previously reported in the form of an abstract (17).

METHODS

Sample and Data Collection

The sample comprised all women, ages 30–60 years, enrolled in the Wisconsin Sleep Cohort Study, an ongoing longitudinal study of sleep disorders (18). Employees of four diverse Wisconsin state agencies were surveyed by mailed questionnaire to provide a sampling frame for recruiting a probability sample of participants for overnight studies at 4-year intervals. A baseline study was completed by 618 women, 364 of whom had completed up to two follow-up studies. After exclusions (described later), 1,035 studies from 589 women were available for analysis.

Data were collected during an overnight in-laboratory protocol. Before polysomnography, a structured questionnaire on lifestyle and medical, menstrual, and menopausal history was administered, and several body habitus measures were taken using standard anthropometric methods (19). A blood sample was drawn in the morning.

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TABLE 1. SAMPLE CHARACTERISTICS

Characteristic	Menopausal Status			
	Premenopause	Perimenopause	Perimenopause/ Postmenopause	Postmenopause
Number of observations	498	125	37	375
Age, yr, mean (SD)*	42.6 (5.1)	48.4 (4.6)	51.6 (3.7)	56.8 (5.8)
Use of hormone replacement				
Current, n (%)	0 (0)	20 (16.3)	18 (48.7)	177 (47.3)
Past, n (%)	0 (0)	9 (7.3)	7 (18.9)	54 (14.4)
Never, n (%)	498 (100)	94 (76.4)	12 (32.4)	143 (38.3)
AHI of 5 or more, n (%)	54 (10.8)	23 (18.4)	10 (27.0)	109 (29.1)
AHI of 15 or more, n (%)	18 (3.6)	9 (8.1)	4 (12.9)	33 (11.0)
Hysterectomy with and without oophorectomy, n (%)	31 (6.2)	15 (12.0)	29 (78.4)	129 (34.4)

Definition of abbreviation: AHI = apnea–hypopnea index.
* Not adjusted for correlation.

Menopausal Status

Status at each visit was categorized as follows.

Premenopause. Defined as having had a menstrual period within 3 months and no HRT use or having had a hysterectomy with at least one ovary intact, no HRT use, and follicle-stimulating hormone less than 10 mIU/ml.

Perimenopause. Defined as having had amenorrhea for at least 3 but less than 12 months and no current HRT use or having current HRT use for less than 1 year.

Postmenopause. Defined as having had amenorrhea for at least 12 months or bilateral oophorectomy at least 6 months previous.

Perimenopause/postmenopause. (The distinction between perimenopause and postmenopause could not be made). Defined as having had HRT for over 1 year with a bleeding cycle within the previous year or having had a hysterectomy without bilateral oophorectomy and vasomotor symptoms.

The results of classification according to these definitions were examined for concordance with age, follicle-stimulating hormone, length of HRT use, vasomotor symptoms, and date of last menstrual period. Discrepancies were individually adjudicated considering all available data. Sleep studies of women who had unknown ovarian status (n = 49) or missing data on menstrual status (n = 10) were excluded.

Full overnight polysomnography with an 18-channel recording system (Model 78; Grass Instruments, Quincy, MA) was performed. Records were scored using published criteria (20, 21), without knowledge of menopausal status. Studies with less than 4 hours of adequate data were excluded (n = 12). Apnea was defined as no airflow for 10 or more seconds and hypopnea by a discernable reduction in respiratory effort for 10 or more seconds associated with an oxyhemoglobin desaturation of 4% or more. SDB was summarized using the average number of abnormal breathing events per hour of sleep (apnea–hypopnea index [AHI]).

Statistical Analysis

Odds ratios for an AHI of 5 or more versus less than 5 and 15 or more versus less than 5 with menopausal status were estimated with multivariable logistic regression modeling using the generalized estimating equation method (22, 23). All variables, including menopausal status, were time varying. The generalized estimating equation estimates combine cross-sectional and longitudinal associations, adjust for correlation within women, and produce robust standard errors for testing hypotheses and computing confidence intervals. The addition of terms to discriminate the longitudinal and cross-sectional components allowed separate estimates and the ability to test whether the cross-sectional and longitudinal associations differed (24). Associations were expressed as odds ratios with 95% confidence intervals. Beta coefficients were assessed with Wald chi-square tests, with $p < 0.05$ indicating statistical significance (additional details on the methods are available in the online supplement).

RESULTS

The distribution of the sample by menopausal status is given in Table 1. The prevalence of SDB, indicated by AHI cut points of 5 and 15 to reflect severity categories commonly used in epidemiology studies, increased across menopausal categories: 10.8, 18.4, 27, and 29.1% of premenopausal, perimenopausal, perimenopausal/postmenopausal, and postmenopausal women, respectively, had SDB indicated by an AHI of 5 or more. There was a similar trend for an AHI of 15 or more, but the smaller number of women with SDB at this level was a limiting factor for analyses with further stratification. The crude odds ratios for an AHI of 5 or more with perimenopausal, perimenopausal/postmenopausal, and postmenopausal categories (versus premenopause) were 1.66, 2.82, and 3.22, respectively (Table 2). After adjusting for age, body habitus, alcohol use, smoking, hypertension, exercise, cardiovascular disease, and health status in logistic regression models, the odds ratios dropped to 1.23, 1.80, and 2.60, respectively; odds ratios for AHI of 15 or more dropped slightly for perimenopause versus premenopause but increased and remained statistically significant for the other categories of perimenopause/postmenopause and postmenopause.

Because age and body mass index (BMI) are strong confounding factors with respect to menopause and SDB, we examined the trends in prevalence of AHI of 5 or more in premenopausal, perimenopausal, and postmenopausal women by plotting moving prevalence averages by 5-unit increments over the age and BMI range of the sample. Figures 1 and 2 give no indication that the higher odds of SDB in perimenopausal and postmenopausal women are due primarily to differences between these groups in age or BMI distribution. For virtually every age between 32 and 53 years and at every BMI level, SDB prevalence is higher for perimenopausal and postmenopausal women compared with premenopausal women. The completeness of controlling for confounding factors depends on adequate overlap of the comparison groups. The BMI range (Figure 2) was similar in both premenopausal and postmenopausal women, but for age (Figure 1), the overlap was restricted to the age range of 32–53 years. The total number of observations in the overlapping age range included 483 women in premenopause and 219 women in perimenopause and postmenopause.

The lower odds ratio for an AHI of 5 or more with perimenopause compared with the odds ratio with postmenopause, given in Table 2 suggests that as the menopausal transition progresses, the risk for SDB increases. Consistent with this hypothesis, when perimenopausal and postmenopausal women were stratified on years since last menstrual period, we saw a statistically significant linear trend ($p = 0.01$) toward increasing odds ratios for an AHI of 5 or more with increasing duration of postmenopause up to 5 years, after which point the odds ratios slightly decreased. Compared with premenopause, the odds ratios (95% confidence

TABLE 2. ASSOCIATION OF MENOPAUSAL STATUS AND SLEEP-DISORDERED BREATHING DEFINED BY FREQUENCY OF APNEA AND HYPOPNEA EPISODES PER HOUR OF SLEEP (APNEA–HYPOPNEA INDEX)*

	Odds Ratio (*95% CI*)	
	AHI of 5 or More versus AHI of Less Than 5	AHI of 15 or More versus AHI of Less Than 5
Unadjusted model		
Premenopause	Reference category	
Perimenopause	1.66 (1.05, 2.60)	1.18 (0.83, 1.69)
Peri/Postmenopause	2.82 (1.41, 5.65)	1.82 (1.04, 3.21)
Postmenopause	3.22 (2.23, 4.66)	2.59 (1.64, 4.09)
Adjusted model*		
Premenopause	Reference category	
Perimenopause	1.23 (0.68, 2.22)	1.07 (0.52, 2.20)
Peri/postmenopause	1.80 (0.79, 4.12)	3.13 (1.06, 9.20)
Postmenopause	2.60 (1.41, 4.81)	3.49 (1.38, 8.78)
Age, 5 yr	1.17 (0.98, 1.38)	1.10 (0.82, 1.48)
BMI, kg/m^2	1.14 (1.11, 1.17)	1.20 (1.15, 1.25)

Definition of abbreviation: AHI = apnea–hypopnea index; BMI = body mass index.

* Model is also adjusted for alcohol, education, smoking, hypertension, exercise, cardiovascular disease, and self-rated evaluation of health; further adjustment with body habitus measures other than BMI did not alter the odds ratios. Covariates were all modeled as continuous, with the exception of variables for hypertension (yes = systolic blood pressure of 140 or more, diastolic blood pressure of 90, or more or using hypertensive medication) and cardiovascular disease (yes = self-reported myocardial infarction, coronary artery disease, atherosclerosis, heart failure), and smoking (current = yes).

interval) for an AHI of 5 or more were 1.21 (0.6, 2.3) for women with 1 year or less since the last menstrual period, 1.77 (0.7, 4.6) for 1–3 years, 3.72 (1.7, 8.1) for 3–5 years, 2.45 (1.1, 5.5) for 5–10 years, and 1.93 (0.8, 4.8) for greater than 10 years. A term for "years of duration squared" to describe a plateau effect was of borderline statistical significance ($p = 0.06$) when added to the regression model. Estimation of the change in odds ratio for an AHI of 15 or more with duration of menopause was not possible because of the lower prevalence of SDB at this level.

In an exploratory analysis of a possible modifying effect of HRT, we found HRT users did have a lower odds of SDB at an AHI of 5 or more in comparison with those for perimenopausal and postmenopausal nonusers, suggesting a small protective effect of HRT. The odds ratio (95% confidence interval) for an AHI of 5 or more was 1.38 (95% confidence interval = 0.76, 2.49) for perimenopausal and postmenopausal women with HRT use and 1.75 (1.05, 2.91) for perimenopausal and postmenopausal women without HRT use. However, the confidence intervals are wide, and the difference in odds ratios by HRT use is not statistically significant. When we considered the years of HRT use, we found no indication of an acute effect of HRT use on the menopause–SDB association. The odds ratio (95% confidence interval) for an AHI of 5 or more with HRT for less than 1 year was 2.05 (0.70, 5.97), whereas the odds ratio with HRT use for more than 1 year was 1.31 (0.70, 2.46). We also found no indication that HRT use had a long-term modifying effect that continued after HRT was stopped. The odds ratio (95% confidence interval) for past HRT users was 2.34 (1.09, 5.03).

DISCUSSION

Our findings represent the first firm data to show that the menopausal transition is associated with an increased likelihood of SDB indicated by the AHI level after controlling for age, body habitus, and several lifestyle factors. Compared with premenopausal women, postmenopausal women were 2.6 times more likely to have SDB defined by an AHI of 5 or more and 3.5 times more likely with SDB defined by an AHI of 15 or more. Perimenopausal women did not have statistically significantly increased odds of having SDB, as defined by the AHI cut points.

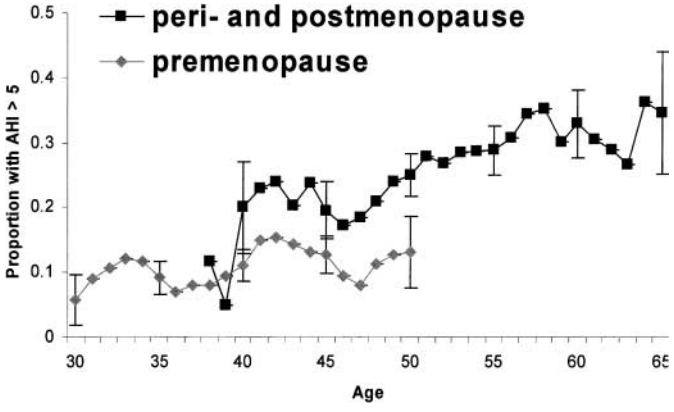

Figure 1. Prevalence of sleep-disordered breathing (SDB) indicated by apnea–hypopnea index (AHI) of 5 or greater for premenopausal women and perimenopausal plus postmenopausal women by age. Values represent a 5-year moving average.

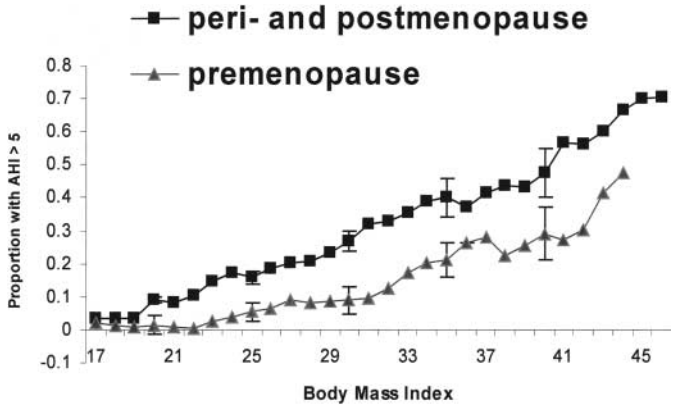

Figure 2. Prevalence of SDB indicated by an AHI of 5 or greater for premenopausal women and perimenopausal plus postmenopausal women by body mass index (BMI). Values represent a 5-unit moving average.

Confidence in our findings is strengthened with the use of a well-characterized probability sample, longitudinal data on women enrolled long enough for follow-up studies, in-laboratory polysomnography to measure SDB, and detailed classification on menopausal status. With longitudinal data on 60% of the sample and use of statistical methods for multiple measures over time, we were able to enhance the estimated associations with information on within-woman changes. Although the number of women who changed menopausal status over the 4-year intervals (n = 118) was not sufficient for performing exclusively longitudinal analyses, a generalized estimating equation modeling procedure allowed a comparison of the information provided by the longitudinal and cross-sectional components (*see* the online supplement for details). The estimates based on the cross-sectional data were similar to those based on the longitudinal data (odds ratio for an AHI of 5 or more and postmenopause was 2.26 for the cross-sectional component and 3.70 for longitudinal component). This consistency increases confidence in the validity of the cross-sectional data, which is generally considered to be more vulnerable to bias.

Our findings could be limited by potential participation bias due to women lost to follow-up. However, we were able to compare participants and nonparticipants among women eligible for follow-up and found no significant differences in age, menopausal status, BMI, or AHI. Another caveat is that our indicators for SDB, based on cut points of a continuum, may lack sensitivity and specificity. The cut points we have used (an AHI of 5 and 15) are commonly used and permit comparisons with findings from other studies. These cut points have also been recommended as indicators of mild and moderate SDB by a recent task force (21), but justification for this recommendation was based on consensus of opinion and sparse data.

Our study is unique in using cross-sectional and longitudinal data on menstrual history, HRT use, gynecologic surgery, and serum follicle-stimulating hormone to classify women on stage of menopause and years of postmenopause. Categorizing women on menopausal status based on age, the presence of regular menstrual cycles, or date of last menstrual period, as has been done in previous studies of menopause and SDB, lacks sensitivity and specificity (25–27) for women with cyclic bleeding due to HRT use who would otherwise have no bleeding and for women with hysterectomy but unknown ovarian status. It is possible that inconsistencies in previous study findings are due in part to misclassification on menopausal status.

Menopause represents many physiologic changes over several years (28–30), and SDB is believed to develop over a period of years; thus, the effects of menopausal changes may not be evident in the short term. In view of this, we hypothesized that the strength of any association of menopause and SDB would be less in the earliest phase of the menopausal transition. The slightly elevated odds for SDB of perimenopausal women and increasing odds for up to 5-years postmenopause suggest there is a latent period for the effects of menopause. The lack of higher odds after 5 years of menopause may suggest that most of the increased SDB risk is realized by then. Alternatively, because the analysis is based on cross-sectional data, the change in odds may reflect a survivor bias.

Although we were able to investigate numerous factors for potential confounding, we do not expect our statistical adjustment to control for these factors completely. Of special concern is age, which is strongly correlated with menopause and with SDB. Our data showed that prevalence of SDB indicated by AHI cut points was higher in menopausal compared with premenopausal women after holding age constant. However, because the age range for premenopausal women is biologically limited, the contribution of menopause to SDB prevalence beyond that due to aging requires the assumption that the aging effect is linear over the entire age range. Only longitudinal data will clearly allow late-life aging and menopausal effects to be separated.

Confounding due to body composition differences by menopausal status is another serious concern. Menopause has been associated with weight gain, loss of muscle and bone mass, and increases in fat and in abdominal deposition of fat (31, 32), and high BMI and increased neck girth are strong risk factors for SDB (33). We investigated these and other measures of body habitus as potential confounders. After controlling for BMI, we found no difference in the strength or statistical significance of the association between menopause and SDB when body circumferences and skin fold thickness variables were added to the regression models. However, despite considering several different measures, it is possible that none adequately captured the aspect of body composition relevant to increased SDB risk.

In exploring a possible modifying effect of HRT, we found some suggestion that HRT may lower the risk of SDB. These findings, however, may be the result of a bias for women with lower SDB risk to use HRT (34). Women who seek and receive HRT are likely to be free of serious health problems, including heart disease, have a higher level of education, be more health conscious, thinner, younger, and in the earliest years of menopause (35–37), and women with these characteristics are also less likely to have SDB. Thus, our findings and those of other cross-sectional studies of decreased odds of SDB with HRT use may be spurious. We attempted to reduce confounding due to factors related positively to HRT but negatively to SDB by adjusting our estimates for several covariates, including exercise, self-rated health status, and prevalence of medical conditions that may influence use of HRT. However, our variables may not adequately reflect the relevant factors, and other unmeasured confounding factors may be operative.

Conclusion

Our major finding of an independent association of the menopausal transition with SDB is important as a basis for further prospective studies to establish causality and identify mechanisms. If causal, the possibility of modifying a menopause effect with HRT holds promise for reducing the occurrence of SDB in midlife women. However, HRT use is not without risks (38, 39), and solid evidence from well-designed clinical trials is needed to assess the degree of benefit with respect to lower SDB risk.

Of immediate clinical relevance, our findings do indicate that women who are undergoing menopause or are postmenopausal represent a subgroup at increased risk for SDB. Because sleep complaints in menopausal women are often considered by patients and healthcare providers to be a natural concomitant of vasomotor and other symptoms of menopause, underlying SDB may be overlooked. Indeed, based on comparisons of the male to female ratio for SDB in clinic versus general populations, women with SDB appear more likely to remain undiagnosed (40–42). A missed or delayed diagnosis may put women at a distinct health disadvantage: One study of diagnosed SDB patients reported a significantly higher mortality rate in women compared with men (43). Attention should be drawn to the need for SDB evaluation in perimenopausal and postmenopausal women with complaints of snoring, daytime sleepiness, or unsatisfactory sleep.

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