

# Hormone Replacement Therapy and Sleep-disordered Breathing

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Disordered breathing during sleep is more common among postmenopausal women than among their premenopausal counterparts, possibly because of declining levels of estrogen and progesterone. We examined the relationship between the use of replacement hormones and sleep-disordered breathing in a sample of 2,852 non-institutionalized women, 50 years of age or older, who participated in the Sleep Heart Health Study. The frequency of apneas and hypopneas per hour of sleep (apnea-hypopnea index) was determined by unattended, single-night polysomnography at the participant's home. The prevalence of sleep-disordered breathing (apnea-hypopnea index of 15 or more) among hormone users (61 of 907) was approximately half the prevalence among nonusers (286 of 1,945). Multivariable adjustment for known determinants of the disorder, including age, body mass index, and neck circumference, has attenuated the association, but only moderately (adjusted odds ratio, 0.55; 95% confidence interval, 0.41 to 0.75). The inverse association between hormone use and sleep-disordered breathing was evident in various subgroups and was particularly strong among women 50 to 59 years old (adjusted odds ratio, 0.36; 95% confidence interval, 0.21 to 0.60). If the observed associations are causal, hormone replacement therapy could have a role in preventing or alleviating sleep-disordered breathing.

**Keywords:** sleep apnea; sleep; menopause; estrogen; progesterone

For reasons that are not completely understood, disordered breathing during sleep is more common among postmenopausal women than among their premenopausal counterparts (1–3). Estimates of the prevalence of this condition among women in their sixth or seventh decade of life range from 4% to as high as 22% (3–6), depending on the definition used and the study population. Along with other biologic sequelae of aging, the transition to the postmenopausal period and the associated hormonal changes might increase the risk of developing sleep-disordered breathing or might

exacerbate a pre-existing disorder. These hypotheses are still debated (3, 6–9), however, because of paucity of data and the difficulty of distinguishing an effect of the menopause from the effects of other age-related factors (10, 11).

If low levels of estrogen and progesterone indeed increase the risk of disordered breathing during sleep, replacement hormones may partially negate this risk and offer preventive and therapeutic benefits to postmenopausal women. To date, two observational studies reported an inverse association between hormone use and sleep-disordered breathing, but in both studies, relatively few women were classified as having the disorder (3, 12). Several pilot trials, the largest of which enrolled 15 women, reported conflicting results (13–16). We examined the relationship of sleep-disordered breathing to the use of replacement hormones in a sample of nearly 3,000 noninstitutionalized women.

## METHODS

### Subjects

The Sleep Heart Health Study is a cohort study of the cardiovascular consequences of sleep-disordered breathing. The study design is described in detail elsewhere (17). In brief, between November 1995 and January 1998, 6,441 subjects, with an age of 40 years or older, were recruited for the study from population-based cohorts in the United States. Only three exclusion criteria were specified, reflecting conditions that pose technical difficulties for monitoring sleep physiology or can alter the natural history of sleep-disordered breathing: treatment of sleep apnea with continuous positive airway pressure or an oral device, oxygen treatment at home, and open tracheostomy. Frequent snoring (3 nights per week or more frequently) was somewhat more prevalent in the Sleep Heart Health Study cohort than in the source population (39% vs. 33%) because of self-selection and some intentional over-recruitment of middle-aged habitual snorers. The study protocol was approved by the institutional review boards of the participating institutions. All subjects provided written consent.

### Polysomnography

Participants underwent unattended, single-night polysomnography at home using a Compumedics Portable PS-2 System (Abottsville, Australia). On the night of the sleep study, certified technicians placed the sensors on the participant, calibrated the signals, instructed the participant about handling the equipment, and gathered other types of study data. Nine categories of physiologic or physical signals were recorded on the sleep monitor: thoracic and abdominal excursions (inductive plethysmography bands); airflow, detected by a nasal-oral thermocouple (Protec, Woodinville, WA); oxyhemoglobin saturation, measured by finger pulse oximetry (Nonin, Minneapolis, MN); electroencephalogram (C4/A1, C3/A2); bilateral electro-oculogram; bipolar submental electromyogram; electrocardiogram (using a bipolar lead); body position (using a mercury gauge sensor); and ambient light (on/off, by a light sensor secured to the recording garment). The sleep studies were stored in real time on Personal Computer Memory Card International Association

(Received in original form October 29, 2002; accepted in final form January 12, 2003)

Supported by National Heart, Lung and Blood Institute cooperative agreements UO1HL53940 (University of Washington), UO1HL53941 (Boston University), UO1HL53938 (University of Arizona), UO1HL53916 (University of California, Davis), UO1HL53934 (University of Minnesota), UO1HL53931 (New York University), UO1HL53937 (Johns Hopkins University), UO1HL63463 (Case Western Reserve University), and UO1HL63429 (Missouri Breaks Research).

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This article has an online supplement, which is accessible from this issue's table of contents online at [www.atsjournals.org](http://www.atsjournals.org)

Am J Respir Crit Care Med Vol 167, pp 1186–1192, 2003

Originally Published in Press as DOI: 10.1164/rccm.200210-1238OC on January 16, 2003

Internet address: [www.atsjournals.org](http://www.atsjournals.org)

cards, downloaded onto a computer, reviewed at the study site, and then shipped to a central reading center (Case Western Reserve University, Cleveland, OH), where they were reviewed again and scored. Technical details of the hook-up procedure, failure rates, scoring protocols, and quality control procedures are described elsewhere (18).

We defined an apnea as a complete, or nearly complete, cessation of airflow (amplitude of the thermocouple signal smaller than 25% of the baseline amplitude) for 10 seconds or longer. A hypopnea was defined as a decrease in the amplitude of a measure of flow (thermocouple signal) or a measure of volume (thoracic or abdominal inductance band signals) to amplitude smaller than 70% of the baseline amplitude for 10 seconds or longer. For this analysis, we considered only apneas and hypopneas that were associated with oxyhemoglobin desaturation of 4% or greater relative to the baseline.

We computed the apnea-hypopnea index, a widely used measure of sleep-disordered breathing, by dividing the total number of apneas and hypopneas (respiratory events) by the total sleep time in hours. To the extent possible, we distinguished obstructive events from central events; however, the contribution of the latter to the apnea-hypopnea index was small. Only 2% of the participants had an average of central events per hour of sleep that was greater than one. The interscorer reliability for the apnea-hypopnea index was high (intraclass correlation coefficient, 0.99) (19). Sleep stages were identified according to the guidelines of Rechtschaffen and Kales (20). Sleep stages 3 and 4 (slow-wave sleep) were combined.

### Use of Replacement Hormones

Participants were asked to gather all of the medications that they had taken during the 2 weeks before the night of the study. The name and the dose of each medication were transcribed by the study technicians and were matched with a computerized database of prescription and non-prescription medications (21). The duration of medication use was not recorded. We defined hormone users as users of estrogen or users of estrogen and progesterone. Most hormone users (82%) were taking Premarin.

### Other Measurements and Variables

Information about daytime sleepiness, snoring, and other sleep-related items was obtained from a self-completed questionnaire, which was provided to the participant during the recruitment contacts and was filled out before the night of the sleep study. Daytime sleepiness was assessed by a direct question: "How often do you feel excessively sleepy during the day?" It was also assessed by a summary score on the Epworth sleepiness questionnaire (22). The higher the Epworth questionnaire score, the greater the magnitude of reported daytime sleepiness. We defined five categories of snoring status: habitual (6 to 7 nights per week), frequent (3 to 5 nights per week), light (up to 2 nights per week), no snoring, and unknown.

Medical history was recorded on the night of the study using an interviewer-administered questionnaire. Body weight was measured in kilograms on a portable digital scale. Neck circumference was measured in centimeters at the level of the laryngeal prominence (23) and rounded to the nearest 0.5 of an integer. Because the participants were recruited from ongoing cohort studies, the parent study provided the values of the following variables: date of birth, race, height, waist circumference, and hip circumference. Race was classified as white, African American, American Indian, or "other" (primarily Hispanic origin). We computed the body mass index (the weight in kilograms divided by the square of the height in meters) and the waist-to-hip ratio.

### Statistical Analysis

A total of 3,399 women participated in the study. Because menopausal status was not recorded on the night of the sleep study, we restricted the sample to women who were 50 years old or older ( $n = 2,994$ ), assuming that most women in this age range were postmenopausal and that a small proportion were perimenopausal. As shown later, setting the cutoff for age that was even higher (55 years) had no material effect on the results. We excluded 12 women who were taking progesterone but not estrogen, 4 women with missing information on hormone use, and 126 women with missing data on key covariates. The final sample included 2,852 observations. An analysis of sleep stages was based on a similar sample size ( $n = 2,854$ ) but a slightly different sample because

of different criteria of acceptable polysomnograms for the scoring of sleep stages.

Characteristics of hormone users and nonusers were compared by computing mean values, SDs, and percentiles (of continuous variables) or proportions (for categorical variables). In addition, we compared the distribution of the apnea-hypopnea index in hormone users and nonusers by displaying the proportion of women from each group in deciles of the index distribution in the entire sample (users and nonusers combined).

The distribution of the apnea-hypopnea index was skewed, but log transformation of the index (adding 0.1 to allow transformation of a zero value) generated an approximately normal distribution. Adjusted mean values of the log-transformed apnea-hypopnea index among hormone users and nonusers were estimated from multiple linear regression models (analysis of covariance) that included known determinants of sleep-disordered breathing: age, race, body mass index, waist-to-hip ratio, and neck circumference. Adjusted geometric means (often approximating median values) were computed by back transformation (taking the antilogarithm). Similarly, back transformation of the difference between the mean of log-transformed apnea-hypopnea index among hormone users and nonusers has yielded the ratio of the geometric means (24). Confidence intervals for the geometric mean ratio were computed by back transforming the 95% confidence bounds for the mean difference (24).

To examine further the association of hormone use with sleep-disordered breathing, we fit multivariable logistic regression models, dichotomizing the apnea-hypopnea index at a value of 15 for our principal analysis and at a value of 20 for sensitivity analysis. To examine the relationship of hormone use to nocturnal hypoxemia, an important consequence of sleep-disordered breathing, we computed the percentage of sleep time during which the oxyhemoglobin saturation declined below 90%, used two cutoff values—5% and 10% of the total sleep time—and fit multivariable logistic regression models.

The association of hormone use with sleep stages was examined in multiple linear regression models. Because of considerable skewness of the distributions, the proportions of sleep time (P) in stage 1 and stages 3 and 4 combined were transformed according to the formula  $-\log(-\log[P + 0.001])$  with back transformation of the least-square estimates. The distributions of the proportion of sleep time in stage 2 and rapid eye movement sleep were approximately normal.

## RESULTS

A total of 907 women (32%) were using replacement hormones, of whom 525 were taking estrogen alone and 382 were taking estrogen and progesterone. The frequency of hormone use declined across ascending age groups, from 46% among women 50 to 59 years old to 33% among women 60 to 69 years old to 18% among women 70 years old or more. Compared with women who did not use hormones, hormone users were more likely to be of white descent than African American or American Indian descent and tended to be thinner (1.1 kg/m<sup>2</sup> mean difference of body mass index) and healthier (*see* Table E1 in the online supplement). A larger proportion of hormone users than nonusers reported feeling excessively sleepy during the day and often taking a medication for sleep. Although other sleep-related symptoms ("not getting enough sleep" and "waking up during the night") were as prevalent among hormone users as among nonusers, the former group scored slightly higher on the Epworth sleepiness scale. A similar proportion of women in each group reported frequent or habitual snoring (25% of users and 23% of nonusers), but snoring status remained unknown for a greater proportion of nonusers than users. The distribution of both the apnea-hypopnea index and the hypoxemia index among users of replacement hormones was shifted to the left as compared with the distribution of these variables among nonusers (Table E1 and Figure 1).

Table 1 contrasts the adjusted geometric mean of the apnea-hypopnea index among hormone users with the corresponding mean among nonusers, in the entire sample and in subgroups

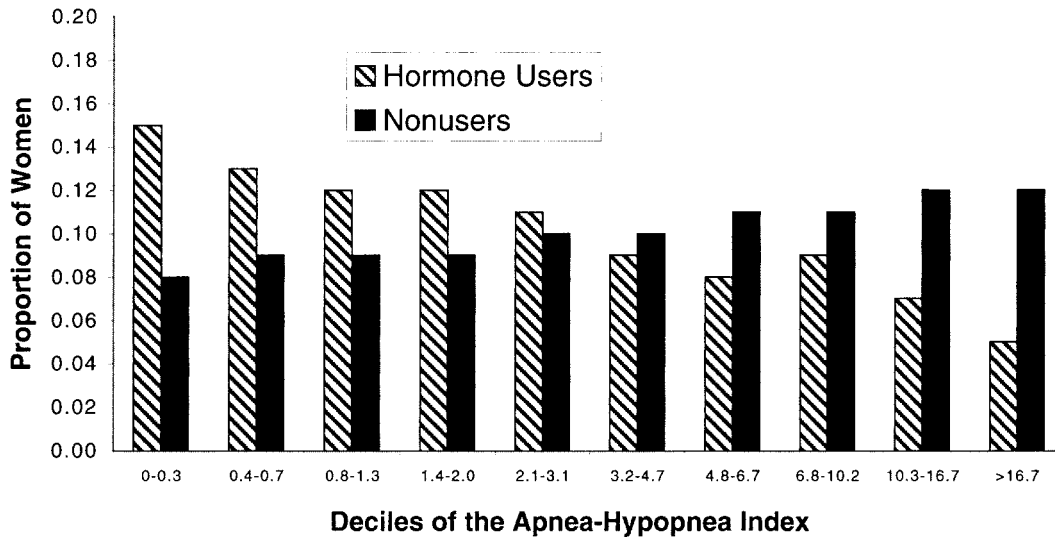


Figure 1. Distribution of the apnea-hypopnea index according to use of replacement hormones. Deciles correspond to the distribution of the index in the entire sample (users and nonusers combined).

of women (see a complete version of Table 1 in the online supplement: Table E2). In most of the models, the adjusted geometric mean among users of hormones was 25 to 30% lower than among nonusers, and the majority of the estimates were fairly precise (upper-to-lower 95% confidence bound ratio smaller than 1.5). The inverse association between use of replacement hormones and the apnea-hypopnea index was attenuated with aging (test for interaction:  $p = 0.03$ ) but was very similar in women classified as normal weight (body mass index of less than 25 kg/m<sup>2</sup>), overweight (body mass index of 25 to 30 kg/m<sup>2</sup>), and obese (body mass index of more than 30 kg/m<sup>2</sup>). Likewise, the point estimates did not vary much across subgroups defined by self-reported general health or after the exclusion of women

with several major clinical conditions (Table E2). In most cases, departure from the “typical” geometric mean ratio in this sample (ranging from 0.68 to 0.76 in most subgroups) was related to small-size strata. The association of hormone use with the apnea-hypopnea index was similar for users of estrogen alone and users of estrogen and progesterone (geometric mean ratio of 0.71 and 0.75, respectively). We found nearly identical associations of hormone use with rapid eye movement-related apnea-hypopnea index and non-rapid eye movement-related apnea-hypopnea index. Of note, the estimates were derived from linear regression models that fit the data reasonably well (all  $r^2 > 0.19$ ).

As shown in Table 2, 347 women (12% of the sample) had an apnea-hypopnea index of 15 or more. Of these, 61 women

TABLE 1. RELATIONSHIP OF HORMONE REPLACEMENT THERAPY TO THE APNEA-HYPOPNEA INDEX\*

Characteristic	n	Adjusted Log (Apnea-Hypopnea Index)	Adjusted Geometric Mean	Adjusted Geometric Mean Ratio	95% Confidence Interval
All women					
Users	907	0.83 ± 0.04	2.3	0.73	0.65-0.81
Nonusers	1945	1.15 ± 0.03	3.2		
Age group, years					
50-59					
Users	430	0.85 ± 0.09	2.3	0.66	0.55-0.78
Nonusers	498	1.27 ± 0.09	3.5		
60-69					
Users	292	0.88 ± 0.08	2.4	0.71	0.59-0.85
Nonusers	593	1.23 ± 0.05	3.4		
≥ 70					
Users	185	0.86 ± 0.12	2.4	0.87	0.70-1.06
Nonusers	854	1.00 ± 0.09	2.7		
Body mass index, kg/m <sup>2</sup>					
< 25					
Users	292	0.81 ± 0.09	2.2	0.76	0.63-0.91
Nonusers	530	1.09 ± 0.08	3.0		
25-30					
Users	345	0.76 ± 0.07	2.1	0.73	0.61-0.86
Nonusers	696	1.08 ± 0.05	3.0		
> 30					
Users	270	0.92 ± 0.09	2.5	0.70	0.58-0.84
Nonusers	719	1.28 ± 0.07	3.6		
Type of hormone					
Estrogen only					
Users	525	0.81 ± 0.06	2.3	0.71	0.63-0.81
Nonusers	1945	1.15 ± 0.03	3.2		
Estrogen and progesterone					
Users	382	0.86 ± 0.07	2.4	0.75	0.64-0.87
Nonusers	1945	1.15 ± 0.03	3.2		

\* Estimates were derived from linear regression models that included age, body mass index, waist-to-hip ratio, neck circumference, and race group as covariates. All covariates, except race group, were entered as continuous variables. To minimize residual confounding, age (continuous) and body mass index (continuous) were also included in models that examined the relation of hormone replacement therapy to sleep-disordered breathing within categories of age or body mass index. Plus-minus values are means of log-transformed apnea-hypopnea index ± SEM. Geometric mean ratio is the ratio of the geometric mean of the apnea-hypopnea index among users of replacement hormones to the geometric mean among nonusers.

**TABLE 2. ADJUSTED ODDS RATIOS FOR PREVALENT SLEEP-DISORDERED BREATHING COMPARING USERS OF REPLACEMENT HORMONES WITH NONUSERS\***

Characteristic	Number of Cases/ Number of Users	Number of Cases/ Number of Nonusers	Adjusted Odds Ratio	95% Confidence Interval
All women	61/907	286/1945	0.55	0.41–0.75
Only whites	53/775	200/1436	0.64	0.46–0.90
Age, 55 years or older	57/755	261/1723	0.59	0.43–0.82
Age group, years				
50–59	22/430	72/498	0.36	0.21–0.60
60–69	18/292	83/593	0.55	0.32–0.95
≥ 70	21/185	131/854	0.86	0.52–1.43
Body mass index, kg/m <sup>2</sup>				
< 25	12/292	46/530	0.59	0.30–1.14
25–30	15/345	62/696	0.60	0.33–1.08
> 30	34/270	178/719	0.52	0.34–0.79
Type of hormone				
Estrogen only	38/525	286/1945	0.53	0.36–0.76
Estrogen and progesterone	23/382	286/1945	0.60	0.38–0.96

\* Sleep-disordered breathing was defined as an apnea–hypopnea index of 15 or more. Estimates were derived from logistic regression models that included age, body mass index, waist-to-hip ratio, neck circumference, and race (except for a model for whites alone) as covariates. To minimize residual confounding, age (continuous) and body mass index (continuous) were also included in models that examined the relationship of hormone replacement therapy to sleep-disordered breathing within categories of age or body mass index.

were taking hormones and 286 were not. The prevalence of sleep-disordered breathing among hormone users (61 of 907) was approximately half the prevalence among nonusers (286 of 1,945), and adjustment for known determinants of sleep-disordered breathing only moderately attenuated the magnitude of this association (adjusted odds ratio 0.55; 95% confidence interval, 0.41 to 0.75). Similar to the geometric mean ratio, the estimated odds ratio did not vary significantly across several subgroups and participants' characteristics except age (test for interaction,  $p = 0.013$ ). The inverse relationship between hormone use and sleep-disordered breathing was particularly strong among women 50 to 59 years old (odds ratio, 0.36; 95% confidence interval 0.21 to 0.60), was weaker but still strong among 60 to 69 year olds (odds ratio, 0.55; 95% confidence interval, 0.32 to 0.95), and was weakest among the oldest age group (odds ratio, 0.86; 95% confidence

interval 0.52 to 1.43). In most of the models, the use of replacement hormones was associated with approximately 40 to 50% lower odds of having an apnea–hypopnea index of 15 or more after adjustment for determinants of sleep-disordered breathing. (see Table E3 in the online supplement.) The associations were similar and, in some cases, stronger when the apnea–hypopnea index was dichotomized at 20.

Table 3 shows the adjusted odds ratios for experiencing hypoxemia (oxyhemoglobin saturation of less than 90%) during 5% or more of total sleep time (359 women) and during 10% or more of total sleep time (198 women). The results are largely consistent with those for the apnea–hypopnea index, especially among women 50 to 70 years old, but the estimates varied across the three strata of body mass index and the two case definitions. Modeling the odds of a more restrictive case definition (desat-

**TABLE 3. ADJUSTED ODDS RATIOS FOR TWO INDICES OF HYPOXEMIA DURING SLEEP, COMPARING USERS OF REPLACEMENT HORMONES WITH NONUSERS\***

Characteristic	Oxyhemoglobin Saturation Less than 90% during 5% or More of Sleep Time (n = 359)		Oxyhemoglobin Saturation Less than 90% during 10% or More of Sleep Time (n = 198)	
	Adjusted Odds Ratio	95% Confidence Interval	Adjusted Odds Ratio	95% Confidence Interval
All women	0.74	0.55–0.99	0.63	0.43–0.94
Only whites	0.81	0.59–1.12	0.67	0.43–1.03
Age, 55 years old or more	0.75	0.55–1.02	0.66	0.44–0.99
Age group, years				
50–59	0.59	0.35–0.99	0.41	0.19–0.89
60–69	0.59	0.35–1.01	0.44	0.21–0.92
≥ 70	1.03	0.66–1.63	1.09	0.62–1.91
Body mass index, kg/m <sup>2</sup>				
< 25	0.85	0.46–1.55	0.99	0.48–2.05
25–30	0.59	0.32–1.08	0.83	0.39–1.79
> 30	0.77	0.52–1.14	0.44	0.25–0.79
Type of hormone				
Estrogen only	0.79	0.56–1.10	0.75	0.48–1.15
Estrogen and progesterone	0.64	0.40–1.03	0.41	0.19–0.85

\* Estimates were derived from logistic regression models that included age, body mass index, waist-to-hip ratio, neck circumference, and race (except for a model for whites alone) as covariates. To minimize residual confounding, age (continuous) and body mass index (continuous) were also included in models that examined the relation of hormone replacement therapy to sleep-disordered breathing within categories of age or body mass index.

TABLE 4. RELATIONSHIP OF HORMONE REPLACEMENT THERAPY TO SLEEP ARCHITECTURE\*

	Users Adjusted Mean (95% CI)	Nonusers Adjusted Mean (95% CI)	p Value	Model $r^2$
Stage 1, percentage of sleep time	4.2 (4.0–4.4)	3.9 (3.8–4.1)	0.05	0.02
Stage 2, percentage of sleep time	54.8 (54.0–55.5)	53.1 (52.5–53.6)	0.0005	0.05
Stages 3–4, percentage of sleep time	18.6 (17.8–19.5)	21.1 (20.5–21.7)	< 0.0001	0.07
REM, percentage of sleep time	20.2 (19.7–20.6)	19.7 (19.4–20.0)	0.07	0.03

Definition of abbreviations: REM = rapid eye movement.

\* Adjusted estimates, 95% confidence intervals, and p values (two-sided tests) were derived from linear regression of percent of total sleep time in each stage on hormone replacement therapy status, age, race, body mass index, and smoking status. The proportion of sleep time (P) in stages 1 and stages 3 and 4 was log-log transformed according to the formula:  $-\log(-\log(P + 0.001))$ . Reported percentages were computed by back transformation.

uration during 10% or more of total sleep time) often yielded stronger associations. There was some suggestion of a stronger inverse relationship of the hypoxemia indices with use of estrogen and progesterone than with use of estrogen alone.

The distribution of sleep stages among hormone users tended to be similar to the distribution among nonusers or somewhat worse (Table 4). Users of replacement hormone spent a slightly greater percentage of their sleep time in stages 1 and 2 and a smaller percentage in deep, restorative sleep (stages 3–4). However, the mean percentage of sleep time in rapid eye movement stage was slightly greater among users of replacement hormones than among nonusers. In two cases (stage 2 and stages 3–4), there was strong statistical evidence against the null hypothesis of no association, but the estimated differences between the two groups were small. It should be noted that point estimates and related statistics were derived from regression models that did not account for much of the variance of the proportion of sleep time in any sleep stage ( $r^2 \leq 0.07$ ). We repeated the analyses of sleep stages using only 2,762 observations nested in the sample that was used for analyses involving the apnea-hypopnea index. The results were nearly identical (data not shown).

## DISCUSSION

We found an inverse association between use of replacement hormones in the postmenopausal period and sleep-disordered breathing. The association was consistent across various subgroups and was particularly strong among women 50 to 60 years old. To place our results in perspective, we compared the association of sleep-disordered breathing with hormone use to its association with body mass index, a key determinant of the disorder. In our main multivariable model of sleep-disordered breathing, the estimated odds ratio for hormone users as compared with nonusers (0.55) corresponded to the predicted effect of reducing body mass index by 6.8 kg/m<sup>2</sup>. Similarly, the estimated odds ratio for hormone use among women in their 6th decade of life (0.36) corresponded to the predicted effect of reducing body mass index by 11.6 kg/m<sup>2</sup>. If the observed associations are causal, hormone replacement therapy could have a significant role in the prevention or treatment of sleep-disordered breathing in postmenopausal women.

Although the magnitude of confounding appeared to have been moderate, residual confounding by one of the covariates is a possible explanation for our findings. Body fat distribution and body mass index were the principal confounders in this sample, presumably through the following mechanism: Because thinner women might be more likely to experience menopausal symptoms (25, 26) and are perhaps more health conscious than

heavier women, the former are more likely to take replacement hormones and are also expected to experience little or milder sleep-disordered breathing, regardless of any effect of replacement hormones. Three counterpoints should be considered, however. First, the inverse association between hormone use and sleep-disordered breathing was evident within three strata of body mass index, with further adjustment for body mass index, neck circumference, and other covariates within each stratum. Second, our findings were consistent across most strata of self-reported health, including the group of women who rated their general health as “very good” or “excellent.” This group was presumably fairly homogenous with respect to their health status. Third, the magnitude of confounding by the modeled covariates was moderate; most of the associations remained relatively strong after adjustment. Of course, we cannot exclude the possibility of confounding by an unknown, strong determinant of sleep-disordered breathing.

The use of replacement hormones was not uniformly associated with better sleep parameters, indicating, perhaps, that it was not a general marker of favorable sleep quality. In fact, hormone users were more likely than nonusers to report daytime sleepiness, to use a medication for sleep, and to have slightly worse sleep architecture (a smaller proportion of stages 3 and 4). Although subjective sleep problems and menopause-related sleep disruption could have led some women to seek medical attention and be treated with replacement hormones, this sequence of events is not expected to account for an inverse association between use of replacement hormones and sleep-disordered breathing. If at all, women who started taking hormones because they had perceived difficulty with sleep should have been more likely—not less likely—to suffer from sleep-disordered breathing.

A handful of small trials tested the effect of estrogen, progesterone, or both on sleep-disordered breathing in postmenopausal women, (13–16, 27), three of which reported a moderate to strong beneficial effect (13, 14, 16). Inference from these trials is severely constrained, however, by methodologic limitations such as a small sample size (13–16, 27), a lack of a control group or a control period (15, 16), the short duration of treatment (13, 15, 16, 27), the use of progesterone alone (27), and nonblinded treatment assignment (14–16). To our knowledge, only two observational studies have examined the issue. Bixler and colleagues compared the odds of prevalent sleep-disordered breathing (obstructive apnea-hypopnea index of 15 or more) among postmenopausal women and premenopausal women (3). Postmenopausal women who were not using replacement hormones had much greater odds of sleep-disordered breathing than premeno-

pausal women, but the odds of sleep-disordered breathing were very similar in postmenopausal hormone users and premenopausal women. The study estimates, however, were based on a small number of women with sleep-disordered breathing (fewer than 30). Young and colleagues reported similar preliminary results from a subset of the Wisconsin Sleep Cohort study (12).

Several postulated mechanisms could explain a causal connection between sleep-disordered breathing and low levels of circulating estrogen and progesterone, thereby explaining a putative benefit of hormone-replacement therapy.

Sleep-disordered breathing of the obstructive type is positively associated with indicators of central adiposity and is particularly related to the amount of fat in the neck (28, 29) and around the palatopharyngeal airspace (30–33), the typical site of airway obstruction. Although speculative, menopause-related changes in body fat distribution, from gynoid phenotype to android features (34–36), may also include deposition of fat around the upper airway. The effect of the menopause on body fat distribution is ascribed to declining levels of estrogen and progesterone and appears to be negated or attenuated by use of replacement hormones (37–40). If replacement hormones indeed protect against sleep-disordered breathing through this mechanism, our estimates of the effect size may be conservative because adjustment for neck circumference could have embedded some overadjustment.

Upper airway patency during sleep is determined, in part, by the tonus of pharyngeal dilator muscles. Popovic and White found that the activity of the genioglossus muscle during wakefulness was lower in postmenopausal women than in premenopausal women, yet significantly increased in eight postmenopausal women after 2-week treatment with conventional doses of replacement hormones (41). Progesterone and possibly estrogen also play a role in the regulation of the ventilatory drive, raising the hypoxic ventilatory response (42) and stimulating ventilation in conditions of hypoventilation (43). Declining levels of these hormones might predispose some women to sleep-disordered breathing by lowering the ventilatory drive to the upper airway, which could lead to imbalance between forces that jeopardize upper airway patency and counteracting forces (44). Of the two hormones, progesterone is the principal stimulant of ventilation, but several studies point to synergistic effects of both hormones (42, 45, 46), perhaps because estrogen induces the formation of progesterone receptors (47). A role for progesterone in sleep-disordered breathing among postmenopausal women is supported, to some extent, by our finding of a stronger inverse association of indices of hypoxemia with combined use of estrogen and progesterone than with use of estrogen alone.

Finally, declining levels of estrogen and progesterone may contribute to nonsynchronized central nervous system activation of inspiratory muscles and pharyngeal dilator muscles, a possible mechanism of upper airway obstruction (44). This hypothesis gain support from physical proximity of central nervous system centers that regulate sleep physiology and centers that regulate body temperature (48, 49), both of which appear to be sensitive to estrogen levels and brain hypoestrogenism (48). Estrogen and progesterone can also modulate the levels or activity of certain neurotransmitters (47, 50); some of these factors may play a role in the regulation of sleep (51).

Several limitations of our study should be acknowledged. We did not have information on menopausal status at the time of the sleep study and, therefore, could not assess the effect of the menopause itself on sleep-disordered breathing nor verify that all of the women in the sample were postmenopausal. Nonetheless, if the sample included premenopausal women, they were likely younger women who were not taking hormones. Because younger women are expected to have a milder degree of sleep-

disordered breathing, the inclusion of premenopausal women in the group of nonusers is expected to attenuate the contrast between hormone users and nonusers and to lead to underestimation of the true association between hormone use and sleep-disordered breathing.

We could not draw inference on the relationship of hormone replacement therapy to snoring, a common manifestation of sleep-disordered breathing because the proportion of women who did not know whether they snored differed between hormone users and nonusers. Because information on the duration of hormone use was not available, we could not shed light on the time that it might take to observe an effect or about the effect of starting to take hormones at various ages. Data from small trials and postulated causal pathways suggest that the effect of replacement hormones, if any, should be evident after several weeks of treatment, but a much longer treatment period might be required to achieve maximal benefit via a mechanism such as redistribution of parapharyngeal fat. Finally, the cross-sectional nature of the sample precludes clear inference about the relationship of hormone use to self-reported sleep problems and sleep architecture because cross-sectional associations may reflect two historical effects: a tendency to prescribe replacement hormones to women who report disrupted sleep and a favorable effect, if any, of hormone use on sleep quality.

In summary, accumulating data suggest that replacement hormones could prevent or alleviate sleep-disordered breathing among postmenopausal women. In light of known consequences of symptomatic sleep apnea (52, 53) and possible consequences of mild-to-moderate sleep-disordered breathing (54–56), additional tests of this hypothesis are warranted.

**Acknowledgment:** The Sleep Heart Health Study acknowledges the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, the Framingham Heart Study, the Cornell/Mt. Sinai Worksite and Hypertension Studies, the Strong Heart Study, the Tucson Epidemiologic Study of Airways Obstructive Diseases, and the Tucson Health and Environment Study for facilitating the recruitment of members of their cohorts and for permitting data acquired by them to be used in the study. The authors are particularly grateful to members of these cohorts who agreed to participate in the Sleep Heart Health Study as well. The authors further acknowledge the investigators and staff who have contributed to the design and conduct of the study. A list of Sleep Heart Health Study investigators, staff, and participating institutions is available on the Sleep Heart Health Study website ([www.jhsph.edu/shhs](http://www.jhsph.edu/shhs)). The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the Indian Health Services.

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