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Menopausal Hormone Therapy and Sleep-Disordered Breathing: Evidence for a Healthy-User Bias

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Abstract

Purpose—Observational studies suggest that menopausal hormone therapy protects against sleep-disordered breathing, but such findings may be biased by a "healthy-user effect." When the Women's Health Initiative Study reported in 2002 that estrogen-progestin therapy increases heart disease risk, many women discontinued hormone therapy. We investigate healthy-user bias in the association of hormone therapy with sleep-disordered breathing in the Sleep in Midlife Women Study.

Methods—228 women age 38–62 were recruited from the Wisconsin Sleep Cohort Study. They underwent polysomnography to measure apnea-hypopnea index, at home semiannually from 1997–2006, and in the sleep laboratory every four years (N=1,828 studies). Hormone therapy was recorded monthly. Linear models with empirical standard errors regressed logarithm of apnea-hypopnea index on hormone use with a pre/post-July 2002 interaction, adjusting for menopause and age.

Results—The association of hormone therapy and sleep-disordered breathing was heterogeneous ($p<0.01$); apnea-hypopnea index among users was 15% lower in the early period (95% confidence interval: −27%, −1%), but similar to non-users in the late.

Conclusions—Hormone therapy was negatively associated with sleep-disordered breathing only until the Women's Health Initiative results were publicized. Hormone therapy may have been a marker for healthfulness in the early period, creating a spurious association with sleep-disordered breathing.

Keywords

Sleep Apnea Syndromes; Sleep Apnea; Obstructive; Women's Health; Menopause; Estrogen Replacement Therapy; Bias (Epidemiology)

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INTRODUCTION

Before the halting of the Women's Health Initiative Study's estrogen-progesterone trial was announced in July 2002 [1], the association of hormone therapy with sleep-disordered breathing was an active area of investigation, in which several observational studies found that midlife women using hormone therapy had less sleep-disordered breathing than nonusers. Estrogen therapies have since become a widely-cited example of an exposure whose effects appear different when investigated by observational studies or by randomized controlled trials. The most famous results from the Women's Health Initiative suggested that observational studies linking hormone therapy use to reduced risk of coronary heart disease had been biased by a healthy-user effect, in which healthier subjects self-selected into the user group or sicker subjects selectively dropped out. However, some of the study's other findings, including that hormone therapy reduced risk of hip fracture [2] and colorectal cancer [3], were consistent with the observational literature. Sleep outcomes were not measured in detail in the Women's Health Initiative Study or any other large randomized trial, so there are no results with which to compare observational study estimates. Therefore it is unclear whether the seeming protective effect of hormone therapy on sleep-disordered breathing can be explained by a healthy-user bias.

The most common manifestation of sleep-disordered breathing, obstructive sleep apnea, is a disorder in which the airway repeatedly narrows or closes during sleep, leading to decreased airflow and a drop in oxyhemoglobin saturation. Typically, the brain responds by arousing the sleeper, allowing the airway to reopen. Breathing is intermittently impaired and sleep is fragmented, throughout the night. Obstructive sleep apnea has health consequences that include greater risk of hypertension, coronary heart disease, stroke, depression, cognitive impairment and motor vehicle accidents, as well as greater mortality [4–9].

Among younger adults, the prevalence of sleep-disordered breathing in men is roughly twice the prevalence in women [10,11], but among older adults, women's prevalence approaches men's [12]. Lower sex hormone levels among older women could explain this pattern, and as a corollary it has been suggested that exogenous estrogen could prevent or treat sleep-disordered breathing. Since coronary heart disease is an observed outcome of obstructive sleep apnea, for women predisposed to sleep-disordered breathing the benefit of preventing or treating the disorder could in theory outweigh the harm of hormone therapy. Several clinical trials have attempted to test this hypothesis directly, but all were small, several studied male subjects, the quality of the study design was variable, and results were conflicting [13–21]. The strongest evidence supporting the hormone hypothesis has come from population-based observational studies [22–24].

As the findings from the Women's Health Initiative received widespread publicity, many clinicians stopped prescribing hormone therapy for preventive indications in the months following July 2002, and many women abruptly discontinued their medications [25,26]. Thus behavioral correlates of hormone therapy use likely changed from healthy, to neutral or unhealthy. The present study compares data from before and after July 2002 from the Sleep in Midlife Women Study to investigate whether a healthy-user bias could explain the negative association of hormone therapy use with sleep-disordered breathing severity.

MATERIALS AND METHODS

Study design and population

The sample for the Sleep in Midlife Women Study was recruited from women participating in the Wisconsin Sleep Cohort Study. Full details of the Wisconsin Sleep Cohort Study design are described elsewhere [12]. Briefly, from 1989–1993 a random sample of state workers was recruited to participate in a mailed survey. A stratified random subsample of survey responders was chosen, with sampling weights based on self-report of snoring and other factors chosen to enrich the sample with subjects with sleep apnea. From 1989–2003 these responders were invited to participate in overnight polysomnography studies in the sleep lab. Participants were invited to return for in-laboratory studies approximately every four years through the present.

Beginning in 1996, all female Wisconsin Sleep Cohort Study participants who were over 47 years old or who had begun perimenopause were invited to participate in the Sleep in Midlife Women Study. The substudy was designed specifically to measure data relating to sleep health and the menopausal transition. Response rate was approximately 80%. Every six months on average through 2007, subjects underwent sleep studies in their own homes. During this time they also completed daily diaries. Data from the same subjects' lab visits for the parent study were also used for this analysis; any lab visit dates for which hormone therapy use and confounding factors were known were used. Protocols and informed consent documents for the Sleep in Midlife Women Study and Wisconsin Sleep Cohort Study were approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board.

Assessment of exposure, outcome, and covariates

Hormone therapy use was recorded in diaries, where subjects reported any hormonal medications they had used that month, along with daily menstrual bleeding and sleep symptoms [27]. Details of type of medications reported are available in the Appendix (Table A.1). When diary data was missing, hormone therapy use (including current use, past use, and start and stop dates) was assessed by questionnaire at the time of the sleep study. For this analysis, subjects with any hormone therapy use since their last sleep study were classified as current hormone therapy users.

Sleep-disordered breathing was assessed by measuring the apnea-hypopnea index to indicate the rate of breathing pauses during sleep. Polysomnography was used to measure arterial oxyhemoglobin saturation, oral and nasal airflow, nasal air pressure (in-laboratory only), and rib cage and abdominal respiratory motion. Apnea-hypopnea index was calculated by summing the number of apneas (air flow cessation ≥10 seconds) and hypopneas (discernable decrease in airflow or nasal pressure for ≥ 10 seconds, with oxygen desaturation of ≥ 4%), divided by objectively measured total sleep time.

In-home studies used a polysomnography monitor (P-series, Compumedics USA, Inc., Fridley, MN), including piezoelectric chest and abdominal bands to record breathing effort, nasal-oral thermistry to detect airflow, and finger-pulse oximetry to record arterial oxygen saturation. For in-lab studies, a 20-channel polysomnography digital sleep system

(Telefactor Heritage, Grass Instruments, Warwick, RI) was used. Oxyhemoglobin saturation was recorded by pulse oximetry (Datex-Ohmeda 3740, Madison, WI), airflow was recorded by thermocouples (Dymedix, Shoreview, MN) and a nasal pressure transducer (Protec, Andover, MA), and rib cage and abdominal excursions were recorded by respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, NY).

Wherever possible, menopausal status was categorized based on diary-reported menstrual bleeding pattern, an approach consistent with the Stages of Reproductive Aging Workshop criteria for research [28]. Different criteria were used for subjects taking medication that could prolong menstrual bleeding, including hormone therapy and hormonal contraceptives. Subjects who had undergone hysterectomy were categorized based on date and type of surgery in conjunction with circulating levels of follicle-stimulating hormone. Complete details of menopausal staging are available in the Appendix (Figure A.1).

Subjects were weighed and underwent neck girth measurement at every sleep study visit; details of the protocol are publicly available. [29] measured height was taken from most recent lab visits to calculate BMI (kg/m^2). Number of alcoholic drinks per week and smoking history were assessed by interview.

Statistical analysis

Descriptive statistics of the sample were obtained by averaging values for each subject, and then obtaining the mean and standard deviation across all subjects.

Because most subjects were healthy, the distribution of the apnea-hypopnea index was expected to be skewed toward zero. To produce a more normal distribution of outcome values, we transformed the apnea-hypopnea index by taking a natural logarithm, adding one to allow use of zero values. That is, transformed apnea-hypopnea index is equal to ln(*apnea-hypopnea index* + 1).

Transformed apnea-hypopnea index was used as the outcome in mixed linear regression models, with random intercepts for each subject to account for repeated measures, and empirical standard errors. Regression parameters were then exponentiated, so that results may be interpreted as the ratio of (*apnea-hypopnea index* + 1) compared to the relevant reference. Potential confounders were chosen *a priori* based on previous literature and available data, including menopausal status, age, BMI, neck girth, alcohol, and smoking.

To examine whether the association of hormone therapy use with sleep-disordered breathing differed before and after July 2002, models were fit on data from all years, including as independent variables hormone therapy use, a pre/post indicator, and their product term. Other potential modifiers of the association between hormone therapy use and sleep-disordered breathing were examined by the same method, including age, menopausal status, time in postmenopause, and duration of hormone therapy use.

Apnea-hypopnea index values calculated from in-home measurements were systematically higher than values calculated from in-laboratory measurements. There is a linear relationship between apnea-hypopnea index measured in the laboratory and apnea-hypopnea index measured at the closest home visit in time (Pearson correlation 0.65, $p<0.01$). To account for

the systematic difference, our regression models also adjusted for study venue. Further models excluded in-lab values, as a check against information bias.

To investigate whether July 2002 was in fact a demarcation point between two different paradigms in the use of hormone therapy, and not merely an indicator for unrelated secular trends, we conducted a further sensitivity analysis. Mixed linear models were fitted using time points other than July 2002 to mark different Before and After periods. These models were adjusted for menopausal status and age, and were limited to the in-home data. We compared the estimated magnitude of the product term from each model (interpretable as the difference between the association of sleep-disordered breathing with hormone use before the cutoff date and the association with hormone use after that date). All dates for which 30 or more observations were available in each category of hormone use were used.

All statistical analysis was conducted using SAS v9.3 software (SAS Institute; Cary, NC). PROC MIXED was used for linear regression models.

RESULTS

Participant characteristics and hormone therapy use

239 subjects participated in the Sleep in Midlife Women Study. Subjects underwent 1–14 home visits each (median number of visits was 7), for a total of 1,949 in-home sleep studies. Eleven subjects were excluded from this analysis: two did not yield usable sleep studies, seven could not be categorized with respect to menopausal status at the time of their sleep studies, and two were concurrently participating in the Women's Health Initiative study so their hormone therapy use was unknown. 203 subjects had one or more sleep studies before July 2002, and 228 subjects had one or more sleep studies after July 2002. Characterization of hormone therapy use and all confounders was possible for 1,502 in-home sleep studies, plus an additional 326 sleep studies conducted in-laboratory (1–4 per subject), yielding a total sample of 1,828 studies. Characteristics of the 228 included study participants are shown at baseline in Table 1 and across all visits in Table 2.

Hormone therapy use showed a temporal pattern, rising from 1990–1999, remaining relatively flat until July 2002, then sharply declining, and remaining low thereafter. Figure 1 shows hormone therapy use over the course of the Sleep in Women's Health substudy as reported in monthly diaries.

Seven subjects (3%) used hormone therapy throughout their study visits, 69 subjects (30%) had at least one sleep study using and at least one not using, and 152 subjects (67%) never used hormone therapy. Of the 69 subjects who used hormone therapy over the course of the study, 47 were prevalent users at baseline (Table 1). In the early period, mean duration of hormone therapy use was 17.9 months (SD 18.5); in the later period mean duration was 15.6 months (SD 19.4).

Mean apnea-hypopnea index from home visits was 11.8 (SD 13.4). As a result of using different equipment, mean apnea-hypopnea index from lab visits was lower, at 5.2 (7.5). Overall mean apnea-hypopnea index was 10.9 (13.0).

Association of hormone therapy and sleep-disordered breathing

Hormone therapy users had lower apnea-hypopnea index at baseline (Table 1). Across all observations, hormone therapy users had lower mean apnea-hypopnea index before July 2002, but after July 2002 apnea-hypopnea index was similar between users and nonusers (Table 2). Hormone users were also younger in the early period, whereas in the later period users and nonusers were the same age on average.

In all regression models, the association of hormone therapy with sleep-disordered breathing was heterogeneous between the two time periods, showing hormone therapy associated with lower apnea-hypopnea index before July 2002, but no meaningful association after July 2002 (Figure 2). The product term *P*-value was equal to or below 0.01 in all models. Table 3 shows results from a multivariable model regressing transformed apnea-hypopnea index on hormone therapy use before and after July 2002, adjusting for menopausal status, age, BMI, neck girth, alcohol use and smoking history. The relationship of hormone therapy to apnea-hypopnea index was not modified by age, menopausal status, time in postmenopause, or duration of hormone therapy use.

Before July 2002, hormone therapy use was associated with 15% lower apnea-hypopnea index (95% confidence interval [−27%, −1%]) as estimated by the fully adjusted model. After July 2002, apnea-hypopnea index was similar among users and nonusers. Exclusion of data obtained at in-lab studies reduced power but did not change the pattern of association between hormone therapy use and apnea-hypopnea index across time periods.

Sensitivity analysis

There were 58 dates (April 2000–February 2005) before and after which there were at least 30 in-home sleep studies among both hormone users and non-users in both time periods. The date chosen *a priori*, July 2002, showed the strongest contrast between the association of hormone therapy use with sleep-disordered breathing before and after (Figure 3). Time points closest to July 2002 showed greater positive contrasts, and earlier and later time points showed smaller or negative contrasts, suggesting a systematic pattern.

DISCUSSION

Our findings suggest that hormone therapy use was associated with less severe sleep-disordered breathing before July 2002, and was no longer associated with sleep-disordered breathing after that date. Were there a true biological mechanism for the effect of hormone therapy on breathing during sleep, that association would be expected to persist irrespective of time period. A healthy-user bias, however, could explain the period effect. Before the halting of the Women's Health Initiative trial, hormone therapy use may have been a marker for overall healthfulness, confounding its relationship with sleep health. After the risks of hormone therapy were made public, when hormone therapy use was no longer perceived as a healthy behavior, it was no longer associated with sleep-disordered breathing.

Hormone therapy use in our sample comprised many different types of medication, including synthetic estrogens, progesterones, and combination therapies, as well as over-the-counter remedies such as black cohosh which have no known relationship to sleep-

disordered breathing and whose effectiveness at treating the symptoms of menopause is debated [30]. Though sample size did not allow us to examine effect modification by medication type, the finding that these substances with different mechanisms of action are on average associated with lower sleep-disordered breathing only until July 2002 makes a biological effect less plausible and a bias effect more so.

Several mechanisms for a healthy-user effect are possible. Previous studies using data from before 2002 have suggested that healthier women select into the hormone therapy user category [31–33], while women who get sick stop using hormone therapy [34]. While development of sleep-disordered breathing itself is unlikely to be a reason for stopping hormone therapy use, some of its sequelae could be. Furthermore, socioeconomic status, exercise, and alcohol use have been shown to be predictors of hormone therapy use [33,35–37]. Our measures of socioeconomic status and exercise were too limited to allow us to model whether they were associated with hormone therapy initiation or maintenance, but alcohol and smoking were weak predictors of hormone therapy use.

Three previous population-based studies have found evidence of varying strength that hormone therapy use is associated with healthier breathing during sleep [22–24]. However, they all used data collected before 2002, when hormone therapy use was more common among healthy women. Our study suggests that a healthy-user effect may explain those findings. Though the question remains relevant, few studies have been conducted since the halting of the Women's Health Initiative trials. Our data is unique in its timespan, bridging the years before and after prescription of hormone therapy underwent a paradigm shift away from preventive indications.

Alternative secular trends could explain the difference between the Before and After periods rather than a healthy-user effect. Prescribing practices changed in response to the Women's Health Initiative findings, including reducing the dose of hormone therapy [38]. It is possible that hormone therapy is effective at lowering the apnea-hypopnea index only at high doses. It is also possible that hormone therapy is most effective at preventing sleep-disordered breathing in women who are otherwise healthy, and that as the pool of hormone therapy users become on average less healthy overall, the medications were less effective. A chance association is also possible.

This study's generalizability is also limited. The Wisconsin Sleep Cohort sample included almost exclusively Caucasians, and thus it is not possible to investigate whether race or ethnicity would affect the relationships observed here.

The relationship of hormone therapy to sleep-disordered breathing may represent an interesting case study of healthy-user bias. The conversation sparked by the Women's Health Initiative results brought the concept of a healthy-user bias to renewed prominence. Competing explanations for the discrepancy between trial results and observational results have also been advanced, however, including non-representativeness of the Women's Health Initiative study population [39], and the sampling of prevalent users among the observational studies [40]. Our findings support the theory that hormone therapy was once a marker for healthfulness, potentially biasing studies of its preventive indications.

The apparent lack of association between hormone therapy and sleep-disordered breathing since July 2002 is also relevant because the evidence base to guide prescription of hormone therapy for sleep complaints in menopausal women remains weak. Several studies have suggested that sleep complaints may be symptoms of underlying sleep-disordered breathing in female sleep clinic patients [41,42]. When a gynecology or primary care clinician misdiagnoses sleep-disordered breathing as a temporary disruption caused by menopausal discomforts, a patient may receive a prescription for a hormonal medication. Our findings suggest that these drugs are unlikely to benefit such a patient's sleep health.

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ABBREVIATIONS

BMI Body-Mass Index

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APPENDIX A

Table A1

Type of menopausal hormone therapy used before and after July 2002 in the Sleep in Midlife Women Study, Madison, WI, 1990–2009. N=3,899 out of 17,010 diaries

	Before July 2002	After July 2002
Estrogen, conjugated (Cenestin, Premarin)	464	186
Estrogen, esterified (Estratab, Menest)	48	0
Estradiol (Alora, Climara, Esclim, Estrace, Estraderm, Estring, FemPatch, Gynodiol, Innofem, Vagifem, Vivel le, Vivelle-dot)	430	322
Estradiol & Norethindrone (Activelle, Combipatch, Femhrt)	29	34
Estrogen & Medroxyprogesterone (Premphase, Prempro)	795	115
Estrone/Estradiol/Progesterone compound	25	17

	Before July 2002	After July 2002
Medroxyprogesterone acetate (Amen, Androderm, Curretab, Cycrin, Depo-Provera, Provera)	435	182
Estrogen & Methyltestosterone (Estratest, Menogen)	99	49
Selective Estrogen-receptor modulators (Droloxifene, Raloxifene(Evista), Tamoxifen, Tiboline(Livial))	27	34
Herbal and OTC preparations (Black Cohosh, Promensil, flax seed, yam extracts)	167	101
Estrogen (Version 1 diary only[a])	192	N/A
Progesterone (Version 1 diary only[a])	148	N/A

[a]Diaries used through May 1998 offered only two options to describe hormonal medications, “Estrogen” or “Progesterone.” Later versions of the diary offered more categories of medication, as well as a blank space to specify those not on the list.

Table A.2

Criteria used to define menopausal stage in the Sleep in Midlife Women Study, Madison, WI, 1990–2009. For the present analysis, subjects who had not met criteria for late perimenopause were classified as premenopause/early perimenopause. Subjects meeting the criteria for late perimenopause were classified as being in late perimenopause until meeting criteria for postmenopause. Hormonal medications in this context include menopausal therapies and hormonal contraceptives.

Criteria		Start of Late Perimenopause	Start of Postmenopause
Menstrual Bleeding	No Hormonal Medication Hormonal Medication	Beginning of 3 months of no flow	Beginning of 12 months of no flow Beginning of 6 months of no flow
Surgical History and FSH Level	Ovary-Sparing Surgery	Hot flashes or night sweats, where FSH>10 for 6 months or more FSH>40 prior to surgery	FSH>40 any time after surgery
	Ovary-Removing Surgery	Surgery <6 months ago	Surgery ≥6 months ago
Medication History		Initiation of menopausal hormone therapy	12 months of menopausal hormone therapy
Age	No Hormonal Medication Hormonal Medication Any Medication History		60th birthday 55th birthday 573 days past start of late perimenopause, where no other criteria are available

HIGHLIGHTS

- We studied bias in menopausal hormone therapy's effect on sleep-disordered breathing.
- When the Women's Health Initiative ended in July 2002, many women quit these drugs.
- Before July 2002, hormone users had lower apnea-hypopnea index.
- After July 2002, the association disappeared.
- A healthy-user effect may have caused a spurious association in the early period.

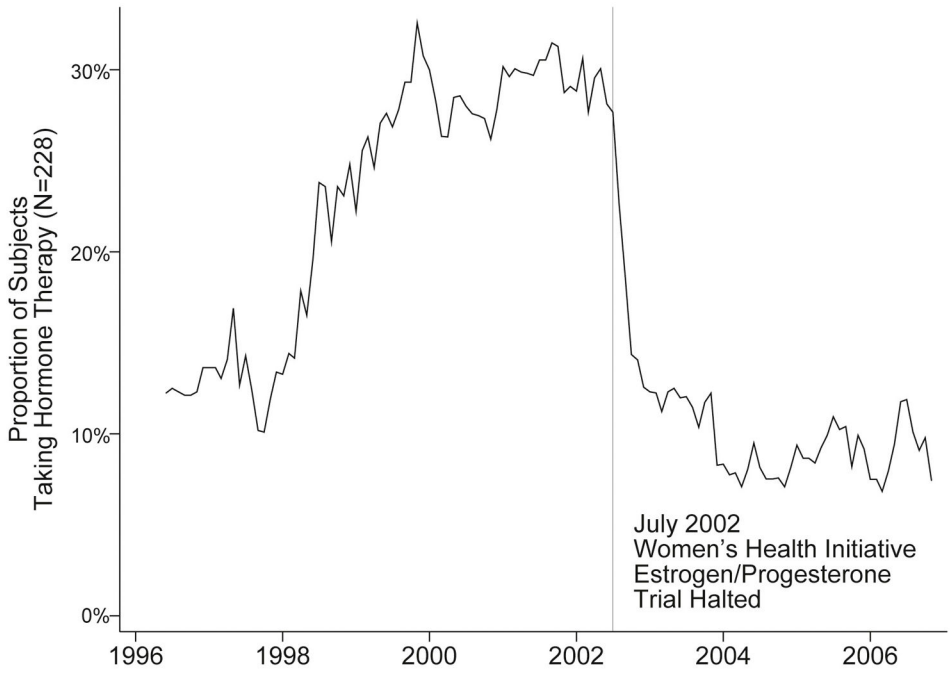

Figure 1.

Hormone therapy use among 228 participants in the Sleep in Midlife Women Study, Madison WI, as reported monthly in diaries. Figure excludes May 1996 due to small sample size: N=15, 5 hormone therapy users (33%).

Figure 2.

Estimated ratio of apnea-hypopnea index plus one in each group compared to hormone therapy non-users before July 2002, among participants in the Sleep in Midlife Women Study (N= 1,828 observations from 228 subjects), from mixed multivariable regression model with empirical standard errors, adjusting for menopausal stage, age, BMI, neck girth, smoking history, and alcohol use. Product term between hormone therapy use and time period: $p<0.01$. Madison, WI, 1990–2009.

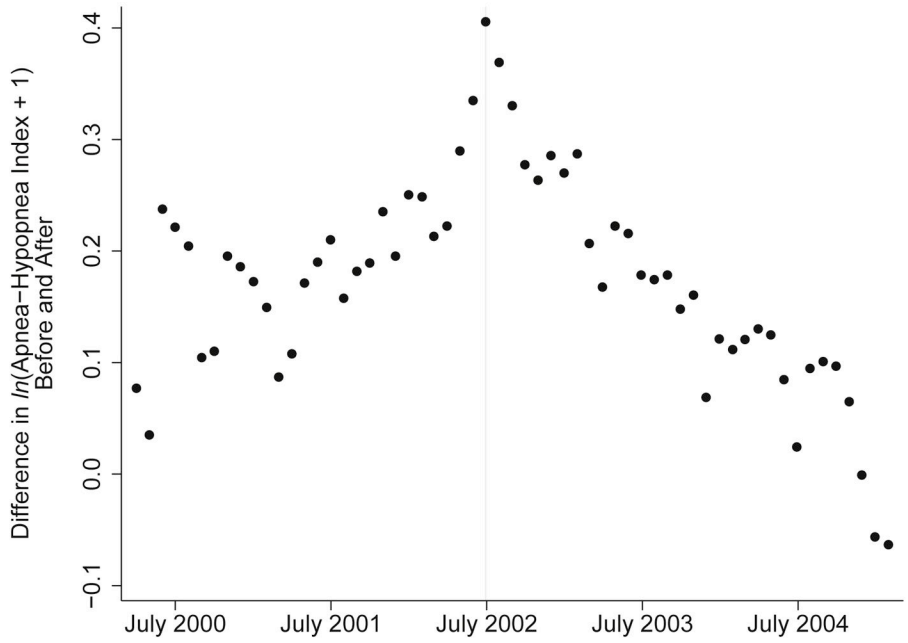

Figure 3.

Results of sensitivity analysis, in which 58 linear mixed models regressed *ln*(Apnea-Hypopnea Index+1) on hormone therapy use before and after a cutoff date, among 228 subjects in the Sleep in Midlife Women Study, Madison, WI, 1990–2009. Each model used a different date. Each data point is the estimated difference between the effect of hormone therapy use before and after the date shown. Models were adjusted for menopausal stage and age. In-home visits only were used (N=1,519 observations).

Table 1

Baseline Characteristics of 228 Participants in the Sleep in Midlife Women Study, Madison, WI, 1990–2009

	Mean	(SD)
Apnea-Hypopnea Index	8.8	(12.9)
Age (years)	48.5	(6.9)
BMI	31.0	(7.8)
Neck girth (cm)	35.6	(3.5)
Alcoholic drinks per week	2.3	(3.2)
	N	**%**
Date of first sleep study		
Before July 2002	195	(86%)
After July 2002	33	(14%)
Hormone Therapy		
Nonuser	181	(79%)
User[a]	47	(21%)
Menopausal stage		
Premenopause or Early Perimenopause	105	(46%)
Late Perimenopause	36	(16%)
Postmenopause	87	(38%)
Smoking history		
Never smoker	117	(51%)
Past smoker	75	(33%)
Current smoker	36	(16%)
Venue		
Home	172	(75%)
Lab	56	(25%)
All	228	

[a]One of the subjects using hormone therapy at baseline entered the study after July 2002. All other baseline users entered the study in the early period.

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Table 2

Characteristics of Sleep in Midlife Women Study Participants, Madison, WI, Over 1–18 Sleep Studies from 1990–2009.

	Before July 2002				After July 2002				All	
	Hormone Therapy Nonuser		Hormone Therapy User		Hormone Therapy Nonuser		Hormone Therapy User			
	Mean[a]	(SD)	Mean[a]	(SD)	Mean[a]	(SD)	Mean[a]	(SD)	Mean[a]	(SD)
Apnea-Hypopnea Index	10.1	(14.2)	8.9	(9.3)	11.9	(13.2)	12.3	(11.4)	10.9	(13.0)
Age (years)	48.9	(7.3)	53.2	(3.9)	54.3	(4.7)	54.1	(3.5)	52.2	(6.1)
BMI	31.3	(8.3)	30.5	(8.1)	32.2	(8.8)	32.0	(8.5)	31.6	(8.5)
Neck girth (cm)	35.5	(3.7)	35.4	(3.5)	35.8	(3.4)	35.6	(3.4)	35.6	(3.5)
Alcoholic drinks per week	2.4	(3.2)	1.8	(2.4)	2.2	(3.0)	2.0	(2.9)	2.2	(3.0)
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	
Menopausal stage										
Premenopause or Early Perimenopause	253	(70%)	1	(0%)	108	(30%)	0	(0%)	362	
Late Perimenopause	128	(42%)	21	(7%)	142	(47%)	14	(5%)	305	
Postmenopause	214	(18%)	201	(17%)	648	(56%)	98	(8%)	1161	
Smoking history										
Never smoker	299	(30%)	126	(13%)	485	(49%)	72	(7%)	982	
Past smoker	199	(34%)	78	(13%)	289	(49%)	28	(5%)	594	
Current smoker	97	(38%)	19	(8%)	124	(49%)	12	(5%)	252	
Venue										
Home	472	(31%)	202	(13%)	736	(49%)	92	(6%)	1502	
Lab	123	(38%)	21	(6%)	162	(50%)	20	(6%)	326	
Total Observations	595	(33%)	223	(12%)	898	(49%)	112	(6%)	1828	
Total Subjects[b]	159		60		182		47		228	

[a] Mean values are the mean of each individual's mean; standard deviations represent the variation across individuals.

[b] Some subjects contributed observations as both users and non-users, and/or in both periods, thus the total number of subjects in each category sums to more than 228.

Table 3

Ratios of (Apnea-Hypopnea Index + 1) Among 228 Participants (1,828 Observations) in the Sleep in Midlife Women Study, Madison, WI, 1990–2009, from Mixed Multivariable Regressions Modeling *ln*(apnea-hypopnea index+1) with Random Intercepts and Empirical Standard Errors. Models are adjusted for all covariates shown, including age.

	Ratio	95% CI	Percent Difference	95% CI
Hormone Therapy Use[a,b]				
Before July 2002				
No Use	1.00		0	
Use	0.85	0.73, 0.99	−15	−27, −1
After July 2002				
No Use	0.97	0.90, 1.06	−3	−10, 6
Use	1.00	0.88, 1.13	0	12, 13
Menopausal status				
Premenopause or Early Perimenopause	1.00		0	
Late Perimenopause	1.07	0.97, 1.20	7	−3, 20
Postmenopause	1.15	1.02, 1.28	15	2, 28
Age (years)	1.05	1.03, 1.06	5	3, 6
BMI	1.05	1.02, 1.07	5	2, 7
Neck girth (cm)	1.06	1.03, 1.09	6	3, 9
Alcoholic drinks per week	1.01	1.00, 1.02	1	0, 2
Smoking history				
Never smoker	1.00		0	
Past smoker	0.89	0.74, 1.07	−11	−26, 7
Current smoker	1.01	0.84, 1.22	1	−16, 22
Venue				
Home	1.00		0	
Lab	0.68	0.64, 0.73	−32	−36, −27

[a] Of the 195 subjects that contributed one or more sleep studies in the early period, 60 (31%) were using hormone therapy at one or more of those visits. Of the 228 subjects contributing sleep studies in the late period, 47 (21%) were using hormone therapy at one or more visits.

[b] Estimated association of SDB with hormone therapy use after July 2002, compared to no use after July 2002, is ratio 1.03 (95% CI: 0.93, 1.14), percent difference 3 (95% CI: −7, 14)