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Original article

# 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:* A total of 228 women aged 38 to 62 years were recruited from the Wisconsin Sleep Cohort Study. They underwent polysomnography to measure apnea-hypopnea index, at home semiannually from 1997 to 2006, and in the sleep laboratory every four years ($n = 1828$ studies). Hormone therapy was recorded monthly. Linear models with empirical standard errors regressed logarithm of apnea-hypopnea index on hormone use with a pre- or post-July 2002 interaction, adjusting for menopause and age.
*Results:* The association of hormone therapy and sleep-disordered breathing was heterogeneous ($P < .01$); apnea-hypopnea index among users was 15% lower in the early period (95% confidence interval, −27% to −1%), but similar to nonusers 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.


## 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

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[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. As 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 after 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 to 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 to 2003, these responders were invited to participate in overnight polysomnography studies in the sleep laboratory. 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 aged more than 47 years 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' laboratory visits for the parent study were also used for this analysis; any laboratory 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 A1). When diary data were 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 (airflow cessation $\geq$10 seconds) and hypopneas (discernable decrease in airflow or nasal pressure for $\geq$ 10 seconds, with oxygen desaturation of $\geq$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-laboratory 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 (Table A2).

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 laboratory visits to calculate body mass index (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 preindicator and/or postindicator,