Sleep Health and the Menopausal Transition among Participants in the Sleep in Midlife Women Study

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[*] Mom, please don't be alarmed, but this dissertation contains graphs.

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List of Abbreviations

AHI: Apnea-hypopnea index

BMI: Body mass index

HT: Menopausal hormone therapies

PAP: Positive airway pressure

SDB: Sleep-disordered breathing

WASO: Wake after sleep onset

WHI: Women's Health Initiative Study

Abstract

This dissertation investigates the relationship of sleep-disordered breathing (SDB) in midlife women to the menopausal transition, to menopausal hormone therapies, and to insomnia symptoms, using longitudinal data from the Sleep in Midlife Women Study.

I. Menopause is widely believed to cause sleep disorders, but evidence is inconclusive, and attributing all sleep problems to menopause may lead to underdiagnosis of treatable sleep disorders. This dissertation finds that later menopausal stage is associated with SDB, independent of age and body habitus.

II. Observational studies have suggested that menopausal hormone therapy (HT) protects against SDB, but findings may be biased by a "healthy-user effect." When the Women's Health Initiative Study reported in July 2002 that estrogen-progestin therapy increases heart disease risk, many women discontinued HT. This dissertation finds evidence of a healthy-user bias in the association of HT with SDB. HT use was associated with SDB only until July 2002; after that the association disappeared.

III. Many studies of sleep clinic patients indicate that obstructive sleep apnea and insomnia often co-occur, particularly among women, which may suggest that women are prone to a more complex SDB phenotype. Population-based studies have been lacking, however, so it is unclear whether referral patterns could explain the co-occurrence. This dissertation finds that SDB is not associated with insomnia, and that most subjects with SDB reported typical symptoms.

Conclusions: Menopausal women are at risk for SDB, and treatments for menopausal discomforts do not improve this sleep disorder. There is no evidence that midlife women experience atypical SDB symptoms.

Chapter 1. Introduction

The perception that menopause is an established cause of sleep problems such as sleep-disordered breathing (SDB) is widespread despite inconclusive evidence, and this misunderstanding may lead to midlife women with primary sleep disorders going undiagnosed. The overarching goal of this dissertation is to characterize SDB in midlife women. It will investigate the role of menopause and menopausal hormone therapies in SDB, and whether SDB in midlife women diverges from the classic clinical portrait of obstructive sleep apnea, which was once thought to be primarily a man's disease.

Young women have lower risk of SDB than young men, but the effect of gender on prevalence diminishes in older populations. One possible explanation for this pattern is that premenopause is a protective state, and that the transition to menopause is associated with risk of SDB. Some studies have suggested an association between menopausal stage and SDB, but since menopause is an aging process, and age is a powerful predictor of SDB in all genders, many of these study findings are confounded by age. Menopause is also associated with changes in body habitus, including factors such as weight gain and central adiposity that could mediate an association with SDB. Thus it is unclear whether menopause is an independent risk factor for SDB.

Lower levels of sex hormones are one feature of menopause that could plausibly affect SDB. If lower levels of estrogens or progesterones cause SDB, it follows that the use of exogenous hormone could protect against SDB. Menopausal hormone therapy (HT), commonly prescribed for complaints such as hot flashes and vaginal dryness, has shown a protective association with

SDB in several observational studies. It is unclear, however, whether that association represents a causal relationship, or an artifact stemming from a “healthy user bias.”

Many clinic-based studies have found that women with SDB are more likely than men to present with symptoms of insomnia, which can create further barriers to correct diagnosis. The explanation for this association, however, is also unclear. It may suggest that women with SDB have a different disease biology, but it may also suggest that women with insomnia symptoms are more likely to obtain care at a sleep clinic. It is possible that men tend to be referred for less severe sleep pathology, so that the women who are referred are sicker on average. There have been few studies on population-based samples that could examine the true pattern of co-occurrence between these two common sleep disorders.

Using detailed longitudinal data on sleep health and menopausal health, from a population-based cohort of participants in the Sleep in Midlife Women Study and the Wisconsin Sleep Cohort Study (WSCS), this dissertation describes the associations of menopause, menopausal hormone therapies, aging, body habitus, and insomnia symptoms, with SDB.

Chapter 2. Specific Aims

Specific Aim 1. To determine the association of the transition through menopause with risk and severity of SDB, I test the following hypotheses:

1A. That risk and severity of SDB increase with each successive menopausal stage, accounting for aging and changes in body habitus

1B. That the association of menopausal status with SDB is positively confounded by chronologic age.

1C. That the association of menopausal stage with SDB is mediated by BMI.

1D. That the association of menopausal stage with SDB is modified by age, body habitus, and time in menopause

Specific Aim 2. To determine whether hormone therapy modifies the association of menopausal stage with SDB, I will test the following hypotheses:

2A. That HT use reduces risk and severity of SDB, independent of menopausal stage

2B. That where HT use is associated with risk or severity of SDB, the association is modified by time period, demarcated by the date July 2002, which marked a major change in prevalence of HT use among US women following the halting of the Women's Health Initiative trial

2C. That this period effect is associated with changes to patterns of HT use, including timing of medication initiation, duration of use, dose, and type of medication

2D. That in the early period, HT use is associated with markers of healthiness including education level, income, physical activity, and measures of cardiovascular health

Specific Aim 3. To determine whether midlife women with SDB experience symptoms of insomnia rather than classical SDB symptoms, I will test the following hypotheses:

3A. That SDB in midlife women is associated with insomnia symptoms, accounting for age, menopausal status, and depression symptoms

3B. That SDB in midlife women is associated with classical symptoms of sleep apnea

3C. That where SDB is associated with insomnia symptoms, the relationship is modified by menopausal status

3D. That SDB in midlife women is associated with canonical symptoms of sleep apnea such as snoring and daytime sleepiness.

Chapter 3. Background and Literature Review

3.1 The Menopausal Transition

The menopausal transition is at once a mundane experience universal to women who survive to middle age, and an elusive concept that resists definition, quantification, and study. There has always been tension around the meaning of menopause. In different eras, cultures, and contexts, menopause has been framed as a socially neutral feature of healthy aging, a shift in identity and societal standing ("the change of life"), a personal tragedy, a release from the afflictions of fertility, and a medical disease state. For research purposes, menopause has no consensus definition. Where fertility is a primary focus, any person who attained and then lost childbearing capability may be said to have completed the transition. But menopause is an aging process with much broader relevance beyond reproduction.

Though often characterized as a binary state of premenopause vs. postmenopause, menopause does not occur at a single time point; it is a transition over time. Menopause is often framed as ovarian aging, but this too is somewhat reductive as endocrine changes do not fully capture the process. Efforts to define progression through menopause on the basis of hormonal biomarkers such as estrogen and progesterone levels, or levels of follicle-stimulating hormone and luteinizing hormone, have largely been frustrated by wide normal variation in hormone levels and in hormonal changes over time. Menopause is an experience that results from the overlap of multiple continuous aging processes, some of them unmeasured and unmeasurable.

The qualitative experience of menopause is also extremely heterogeneous. One person may experience menopause as a barely noticeable cessation of menses, while another person may

endure intense physical and mental discomforts, and another may experience it primarily as recovery from a gynecologic surgery. Some may experience it as a linear progression, and for others the transition may be sporadic or regressive. As the endocrinology of menopause is characterized with greater sophistication, clusters of different hormone levels are becoming linked to different menopausal phenotypes.[1] Efforts to quantify menopause as a single, universal experience have major conceptual limitations.

Even where a working definition of menopause is accepted, research into the menopausal transition is plagued by measurement error. In the absence of reliable biomarkers for menopause, the most important criterion for research purposes is menstrual history,[2] which relies on subjects' recall. Retrospective reports of last menstrual period or cycle changes are often unreliable. Furthermore many women begin menopause after decades of irregular menses, hysterectomies and oophorectomies, or other reproductive features that require secondary criteria be used to classify their status.

Despite these challenges, or because of them, the study of menopause remains extremely important. It is intrinsic to aging for women, and a factor in many health outcomes. Over fifty million women were over the age of 45 at the last U.S. census,[3] and the relevance of menopause to public health is clear.

Menopause has long been associated with sleep problems, but there has been little evidence base to support this connection. Furthermore it is unclear whether sleep problems among menopausal women are a feature of normal menopausal discomforts, such as hot flashes and night sweats, which are temporary and well treated by exogenous estrogen and/or

progesterone therapies. Menopause may represent a state of increased risk of primary sleep disorders, which require clinical recognition and specific appropriate treatments. The misapprehension that menopause is an established, evidence-based cause of sleep problems and sleep disorders may lead to misdiagnosis, inappropriate prescription of menopausal hormone therapies, and gender disparities in sleep health outcomes in midlife populations.

3.2 Sleep-Disordered Breathing and Obstructive Sleep Apnea

Sleep-disordered breathing is a disorder in which the airway repeatedly narrows or closes during sleep, leading to a decrease in airflow and drop in oxyhemoglobin saturation. Typically, the brain responds by producing an arousal from sleep, thus allowing the airway to reopen. Breathing is intermittently impaired and sleep is fragmented throughout the night. The most clinically significant form of SDB is obstructive sleep apnea, the health consequences of which include increased risk of hypertension, coronary heart disease, stroke, depression, cognitive impairment and motor vehicle accidents, as well as mortality.[4–9] Well-demonstrated risk factors for sleep-disordered breathing and obstructive sleep apnea include male gender, age, and adiposity. If diagnosed correctly, obstructive sleep apnea is treatable by the use of a positive airway pressure (PAP) mask to maintain an open airway during sleep.

The most accurate tool to assess sleep-disordered breathing is polysomnography, including measurements of airflow, blood oxygen levels, and respiratory effort. The relatively high prevalence of SDB in population-based studies suggests that underdiagnosis remains common, and that referral to sleep medicine specialists remains socially patterned.[10–13]

3.3 Sleep-Disordered Breathing and the Menopausal Transition (Specific Aim #1)

Among younger people, the prevalence of sleep apnea in men is roughly three times the prevalence in women, but the effect of gender is smaller among older people.[12,14–16] A possible explanation for the contrast in aging patterns between genders is that SDB risk increases with the transition to menopause. Several studies that have attempted to investigate the association between menopausal status and sleep-disordered breathing, but many have had important methodological limitations.

Studies are rarely designed to measure both menopausal status and SDB accurately. In addition to the challenges inherent to measuring menopausal status, the measurement of SDB presents unique challenges. Since the disease manifests during sleep, when patients are rarely observed by doctors and cannot observe themselves at all, underdiagnosis is common. Self-report of diagnosis is therefore of limited value, and likely to introduce bias as some groups of people are more likely than others to receive a correct diagnosis.

Many studies have failed to account for confounding, especially by age. Menopause is inherently an aging process, and since age is a powerful predictor of sleep apnea risk and severity, it is important to distinguish whether menopause itself is associated with greater risk of sleep apnea or whether it simply captures an aging process similar to that in men. Some studies found that more advanced menopausal stage is associated with sleep-disordered breathing, but failed to account for the effect of age.[17–22]

A further consideration is that if menopausal status does affect breathing during sleep, it could do so primarily through changes in body habitus. Postmenopausal women tend to have higher

BMI and central adiposity,[23] both of which are strongly associated with SDB.[24] If any association between menopausal stage and sleep-disordered breathing can be explained either by body habitus changes or by aging itself, then there is little immediate clinical utility in identifying menopausal status as a risk factor—knowing a patient's age and BMI would suffice to assess her risk.

Among the more rigorous studies that have accounted for both age and body habitus, results have been contradictory. Two physiology studies used experimentally-induced apneas to study whether menopausal status predicted the tendency for airways to close during sleep. One found that premenopausal women were more resilient to apneas induced by hypocapnia,[25] but the other found no association between menopausal status and apneas induced by nasal occlusion.[26]

Population-based epidemiologic studies have also yielded somewhat conflicting results. Bixler et. al. sampled over 1,000 subjects and found that women in postmenopause had over four times greater odds of obstructive sleep apnea than women in premenopause, but only among women not using menopausal hormone therapies.[27] More recently Polesel et. al. studied a Brazilian cohort of over 400 subjects and found an exposure-response relationship between later menopausal status and SDB severity, in which women in early postmenopause had six times greater odds of obstructive sleep apnea than premenopausal women, and women in late postmenopause had eight times greater odds.[28] However women in perimenopause and women using menopausal HT were excluded from that analysis.

Both of these studies were cross-sectional. The only prior study that has followed the same women through different menopausal stages rather than relying on cross-sectional comparisons across different women is an analysis of Wisconsin Sleep Cohort data. Young et. al. found that compared to premenopause odds of obstructive sleep apnea were slightly higher in perimenopause, nearly 3.5 times higher in postmenopause, and three times higher in subjects in whom it could not be determined whether they were in perimenopause or postmenopause.[29] This analysis also found an exposure-response relationship in the odds of having any mild to severe sleep-disordered breathing. These three studies all adjusted for age and BMI, but relied on retrospective recall of menstrual history to define menopausal status.

3.4 Menopausal Hormone Therapies and Sleep-Disordered Breathing (Specific Aim #2)

There are many mechanisms by which menopausal status might affect SDB, but the aspect of the menopausal transition that has received the most attention from researchers as a potential determinate of SDB is the decrease in sex hormone levels associated with progression through menopause. A natural corollary to that hypothesis is the idea that introducing exogenous hormone in the form of medication would make perimenopausal and postmenopausal women more like premenopausal women, and thus protect against SDB. If HT protects against SDB, then the treatment most likely to be offered for menopausal complaints is also beneficial for SDB, and the issue of misdiagnosis is less pressing. If there is no causal association, however,

then women with primary sleep disorders may be inappropriately exposed to the risks of menopausal hormone therapies while their true disorder goes undiagnosed.

3.4.1 A brief history of menopausal hormone therapies

Different kinds of exogenous sex hormone have been used to manage menopausal discomforts or symptoms since at least the late 19th century.[30,31] Premarin, the estrogen formulation produced by Wyeth Pharmaceutical, was approved in 1942. The 1960s best-seller *Feminine Forever* popularized the concept of menopause as a hormone deficiency. The term "hormone replacement therapy," which had been used to describe treatments for endocrine insufficiencies such as hypothyroidism, came to be synonymous with the use of estrogens to mimic a premenopausal state in midlife women and older. As the book's title suggested, the drugs could be prescribed indefinitely. Although this terminology is still in widespread use, I have not used it in this dissertation, as it implicitly accepts the model of menopause as an endocrine disorder.

The popularity of hormone therapy continued to rise for decades, with a brief dip when Premarin was shown to increase risk of endometrial cancer. [30,32] However the addition of small amounts of progesterone to the estrogen regimen appeared to offset that risk, so estrogen-progesterone combination therapy became common in women with intact uteruses. These drugs had FDA approval for treatment of vaginal dryness and hot flashes, but they were regularly prescribed for off-label uses.

Chief among these off-label uses was prevention of chronic disease. There was a large and remarkably consistent body of observational studies suggesting that hormone therapy users

experienced less osteoporosis, dementia, and most importantly cardiovascular disease.[33] Reviewing the evidence in 1991, one of the investigators on the Nurses' Health Study, which had been particularly influential in the shift to using HT to prevent heart disease, concluded that HT was overwhelmingly beneficial, and that "this effect is unlikely to be explained by confounding factors or selection."[34] A decade later, those words would become famous.

While there had been a randomized trial of hormone therapy's effectiveness at treating menopausal symptoms, and a trial of its effectiveness at preventing osteoporosis, until the WHI study was established in the early 1990s to study estrogen and estrogen/progesterone therapy, (the industry-sponsored HERS trial quickly followed), there had never been a trial of HT's effectiveness at preventing heart disease.[31] Nonetheless HT for preventive indications gradually became the standard of care. As a preventive therapy, hormones could reasonably be prescribed to any woman approaching menopause, and at one point 40% of all women over 50 in the U.S. were estimated to have been prescribed hormone therapy.[35]

On July 9, 2002, the announcement came that the WHI study was being halted because it had shown that, contrary to the prevailing wisdom, estrogen-progesterone combination therapy modestly *increased* risk of cardiovascular disease. This news was a shock to several different systems. A doctor told a New York Times reporter that it was "the biggest bombshell that ever hit in my 30-something years in the menopause area."[36]

Prescribing practices changed almost literally overnight. A newspaper polled physicians ten days after the announcement and found that half of all patients using hormone therapy had been instructed to quit.[32] Within a month the American College of Obstetricians and

Gynecologists was recommending that women taking HT solely to prevent heart disease take themselves off their medications without waiting to consult with a doctor.[37] The popularity of hormonal medications plummeted,[35] and the new standard of care became to prescribe these medications only for menopausal discomforts, for short periods of time, and at the minimum dose necessary.

3.4.2 The Healthy-user effect

The reason for the discrepancy between the WHI findings on heart disease and the observational studies that preceded it has been the topic of much scholarly theorizing and empirical investigation. One popular explanation is the healthy-user effect. If women who were predisposed to good cardiovascular health were more likely to choose or be prescribed hormonal therapies, or women who were less healthy were more likely to discontinue them, non-causal associations could arise between HT use and any number of health outcomes.

There is some empirical evidence that HT use is associated with both SES and many correlates of good general and cardiovascular health. Several studies predating the halting of WHI suggested that healthier women were more likely to self-select into the hormone therapy user category,[38–41] while women who got sick stopped using hormone therapy earlier.[42] After WHI, several studies found that socioeconomic status, exercise habits, and alcohol use had predicted HT use.[40,43–45] In a systematic review, Lawlor et. al. found that what distinguished observational studies that had found HT beneficial for heart disease from those that had showed it to be harmful, was the quality of the measures used to adjust estimates for socioeconomic status.[44]

Competing explanations have also emerged, however. A Nurses' Health Study investigator defended the study's findings by arguing that WHI subjects had been older and more adipose at the start of the trial than women in the general population tended to be when they initiated hormone therapy, and that they were thus more susceptible to the prothrombotic effects of estrogen.[46] In other words it was not that hormone users' comparative good health biased its association with hormone therapies, it was that hormone therapy was only beneficial to the healthiest women. Another paper argued that the hormone users in WHI were more likely to receive rigorous testing for cardiovascular diseases, leading to detection bias.[47]

Most notably Hernán et. al. argued that the discrepancy could be explained by a prevalent user bias.[48] They pointed out that within WHI, most adverse cardiovascular events occurred within a year of initiating hormone therapy. Observational studies on the other hand, tended to include women who had been using HT for years before the study began. In that population, most of the women who were vulnerable to the prothrombotic effects of hormonal medications had already had cardiovascular events and stopped taking HT before entering the study. Thus the study design created a survivor effect that made CVD rare among HT users. They reanalyzed the Nurses' Health data, restricting the sample to subjects who would have met the criteria at the start of the WHI, including a multi-year washout period for HT, and found that this approach brought observational estimates into agreement with the WHI estimates.

The WHI trial results dropped a proverbial bombshell specifically because of the findings on cardiovascular disease. Importantly, however, the results of the WHI trial were consistent with the weight of the observational research with respect to many of the study's other endpoints. It

confirmed the findings that hormonal therapies effectively treated menopausal discomforts, that they prevented hip fracture and colon cancer, and that they increased risk of breast cancers. Therefore other outcomes that had been associated with HT use in observational studies, but that were not rigorously investigated in the WHI or HERS trials, had therefore to be viewed with new uncertainty. Their findings could not be interpreted without suspicion of bias, but neither had they been disproven. As the WHI and HERS findings made the conduct of further randomized trials unlikely to be ethical, it was unlikely they ever would be.

3.4.3 Menopausal hormone therapies and SDB

Before the halting of the WHI, the association of hormone therapy with sleep-disordered breathing was an active area of investigation, in which several observational studies had found that midlife women using hormone therapy had less sleep-disordered breathing than nonusers. Sleep outcomes were not measured in detail in the WHI or HERS trials, and the literature that has investigated the relationship of SDB to estrogen and progesterone has been based on small physiology experiments, and a handful of large observational epidemiologic studies.

Many physiology studies have investigated the short-term effects of exogenous progesterone on breathing during sleep, each in a small number of subjects. Some have found progesterone to be beneficial in women[49–51] or men,[52] and others have found no effect or a mixed effect in women,[53] men,[54,55] or both.[56,57] Estrogen and estrogen/progesterone combination therapy has been more consistently associated with beneficial effects on sleep breathing,[25,58–60] but has received less study. One study conducted at a sleep clinic found lower spontaneously occurring serum levels of progesterones and estrogens among patients with higher AHI.[61] Another study

in premenopausal women experimentally suppressed sex hormone levels to mimic the hormonal milieu of menopause, and found no change in AHI.[62] These studies raise interesting hypotheses, but conclusions are limited by their small sample sizes and short follow-up times.

Two small randomized trials (on 50-70 subjects) of estrogen therapy alone, in women with history of hysterectomy, found that estrogen reduced the frequency of breathing events during sleep.[63,64] However both these studies were restricted to women without sleep apnea, and followed subjects for only three months.

The most persuasive evidence for a connection between menopausal hormone therapy and SDB comes from three observational epidemiologic studies. As will be explained in Chapter 6, Bixler et. al. found that HT use modified the association of menopausal status to SDB in a large cross-sectional study.[27] Among nonusers, postmenopausal women had four times greater odds of sleep apnea than premenopausal women, but among HT users, no association with menopausal status was apparent. Using repeated measures from the Sleep Heart Health Study, Shahar et. al. found that estrogen or estrogen/progesterone combination therapy were associated with roughly 25% lower AHI and roughly half the odds of SDB.[65] However this analysis was not adjusted for menopausal status. Lastly, in an exploratory analysis on in-laboratory data from the Wisconsin Sleep Cohort Study, Young et. al. found that HT users had slightly lower risk of SDB (Odds ratio 1.38 for users and 1.75 for nonusers), and that HT use modified the association with menopausal status.[29] All three of these population-based studies were well conducted, but all used data from 2001 or earlier, predating the halting of the WHI.

In retrospect it is unclear whether these associations could be explained by a healthy-user effect.

3.5 Co-occurrence of Sleep-Disordered Breathing and Insomnia Symptoms (Specific Aim #3)

The third specific aim relates to the first two through the issue of misdiagnosis, and whether midlife women with sleep-disordered breathing experience atypical symptoms. Sleep-disordered breathing and insomnia are often treated as independent disorders with distinct or mutually exclusive etiologies, but the overlap between them is a complex phenomenon worthy of its own study. Since both disorders are common in the general population, even if the disorders were unrelated, chance alone would suggest that some proportion of the population would have both conditions. Yet because excessive sleepiness is a cardinal symptom of sleep-disordered breathing, while insomnia is by definition a state of insufficient sleepiness, it is also possible that their symptoms could mask one another, making the prevalence of the two disorders together appear to be lower than expected from chance. Many studies of sleep clinic patients, however, have found the opposite—that sleep-disordered breathing and insomnia co-occur unexpectedly often in clinic populations.

If the two disorders co-occur more often than would be expected as a matter of chance, several interesting hypotheses arise. Sleep scientists have proposed that sleep-disordered breathing produces arousals that cause nighttime awakenings,[66] that sleep breathing events increase sympathetic tone, leading to hyperarousal and insomnia,[67,68] or that both are caused by an unknown upstream condition. These issues are particularly relevant to women's health, as

insomnia alone is more prevalent among women,[69] and several clinic-based studies have observed greater co-occurrence in women than in men.[70–75] This gender effect raises the possibility that women with SDB experience different symptoms from men with SDB, and that the historical misapprehension of SDB a man's disease has obscured a different etiology in women.

However, while more than twenty studies have shown either unexpectedly high prevalence of sleep-disordered breathing in insomniacs,[66,76–85] or unexpectedly high prevalence of insomnia among people with sleep-disordered breathing,[71,72,86–92] few of these studies have used a control group to allow comparison of SDB prevalence in subjects without insomnia, or of insomnia prevalence in subjects without SDB in that same study population. Without an estimate of the prevalence of each disease alone, it is difficult to conclude whether or not the prevalence of both diseases together is truly higher than expected.

Furthermore, nearly all of these studies have been conducted in samples drawn from sleep clinic patients or have used physician diagnosis of sleep apnea[75] to measure SDB. Therefore it is unclear whether high co-occurrence of sleep-disordered breathing and insomnia among clinic patients reflects equally high co-occurrence in the general population, or whether it reflects a selection bias in which patients with comorbid sleep conditions are more likely to be referred to sleep specialists.[93]

A small number of studies conducted on population-based samples, or on primary care patients presenting with concerns other than sleep, have shown no evidence of a positive association between sleep-disordered breathing and insomnia, and no evidence that gender predicts co-

occurrence. Using a single sleep study and longitudinal insomnia data from the Penn State sleep cohort, Singareddy et. al. found that sleep apnea was associated with slightly lower odds of subsequent insomnia, though with wide confidence intervals (OR 0.75, 95% CI [0.41, 1.38]).[94] A case-control study by Gooneratne et. al., using adults over 65 sampled from clinics and the general population found that subjects with insomnia had roughly half the odds of SDB.[95] However this study did not adjust for potential confounders such as age. Both studies relied on a single measurement of sleep-disordered breathing.

One interpretation of co-occurring SDB and insomnia symptoms in women is that insomnia may be an atypical symptom of sleep apnea, which women are more likely to experience. This supports the idea that women are underdiagnosed because they experience SDB differently. However high co-occurrence in clinic populations could reflect a social process in which women with classic sleep apnea symptoms are less likely to receive the correct diagnosis.[93] A prior study of the Wisconsin Sleep Cohort, comparing male and female subjects with similar SDB severity, found that women with SDB were no less likely than men to experience classical symptoms.[96] Therefore it is unclear whether women experience SDB differently from men.

3.6 The Sleep in Midlife Women Study

Data for this dissertation are taken from the Sleep in Midlife Women Study. This study offers several unique opportunities to investigate sleep health in midlife women. The study is designed to take high-quality measures of both sleep health parameters and menopausal health parameters, allowing a detailed longitudinal analysis of the association between the two.

This study is also unique in its timespan, bridging the years before and after prescription of hormone therapy underwent a paradigm shift away from preventive indications, creating natural "experiment" that allows us to observe many of the same women before and after the social correlates of menopausal hormone therapies changed. Lastly the detailed data on insomnia allows us to examine associations between primary sleep disorders, and assess whether women in midlife experience an atypical SDB phenotype in a population-based sample.

Chapter 4. Methods

4.1 Study Design

Subjects for the Sleep in Midlife Women Study subjects were recruited from among female participants in the Wisconsin Sleep Cohort Study. The parent study's design is described in full elsewhere.[15] Briefly, Wisconsin state workers were sampled at random and recruited to participate in a mailed questionnaire from 1989-1993. Among questionnaire responders, a stratified random sample was selected for further study. Sampling was weighted so that questionnaire responders with risk factors for sleep apnea were more likely to be selected. From 1989-2003, this subsample of responders was invited to undergo in-laboratory polysomnography, and to return for sleep studies approximately every four years, continuing through the present.

From 1996-2005, all female subjects who were at risk of menopause (defined as having begun Perimenopause or being over 47 years old) were invited to participate in the Sleep in Midlife

Women Study. The response rate was approximately 80%. Because the median age in the overall cohort was 47 at the start of recruitment for the substudy, many women had already begun the menopausal transition, and there was a limited window of time during which they could be observed before entering postmenopause. Thus early recruitment prioritized women already in perimenopause, and women in premenopause did not begin to enter the study until 1999.

Subjects completed monthly diaries (Appendix 1), that included questions about medication use, and specifically menopausal hormone therapies. Monthly diaries also included calendars, on which subjects marked sleep data and menstrual symptoms every day (9.2Appendix 2). Diary data was collected from 1996-2007, in three versions. Every six months on average, from 1999-2006, subjects underwent sleep studies in their own homes. Data from the same subjects' laboratory visits for the parent study were also used for some parts of this analysis (see Appendix 5).

4.2 Measurement

Wherever possible, menopausal stage was measured using menstrual history, based on daily menstruation data reported on sleep calendars. Criteria used to define menopausal stages are discussed in Section 6.1.2. Hormonal medication usages were based on data taken from monthly sleep diaries.

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, 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 (25% decrease in airflow, or interruption in flow pattern, 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), which included piezoelectric chest and abdominal bands to record breathing effort, nasal-oral thermistry to detect airflow, and finger-pulse oximetry to record arterial oxygen saturation.

Insomnia was assessed several different ways. Daily report of sleep problems taken from sleep calendars was used to calculate number of symptom days. Self-reported total sleep time and sleep latency data was also taken from interviews conducted on the day of the sleep study.

Weight, waist girth, and neck girth were measured on the day of the sleep study. Subjects were weighed twice to the nearest half kilogram, wearing light clothing but not shoes. Two measurements each of waist and neck girth were taken by tape measure, to the nearest half centimeter. Waist measurements were taken under clothing unless volunteers requested it be taken over clothing. The average of each set of two weight, neck, and waist measurements was used. Height was not measured at in-home visits, so for this analysis, height at the most recent laboratory visit was used to calculate BMI as kg/m^2. The morning following the in-home sleep study, Zung depression score[97] and use of sedatives or alcohol on the day of the sleep study, were assessed by questionnaire. Habitual alcohol and smoking data were collected by interview.

4.3 Descriptive analyses

Categorical variables were described using frequencies and percentages. Continuous variables at baseline were described using means and standard deviations. Across multiple observations, continuous variables were described by taking the mean for each individual subject, and then finding the population-level mean of those individual-level means, and the standard deviation across subjects. Distributions of important continuous variables were described graphically with histograms or kernel density plots.

The variation in AHI over time was also described graphically. To represent AHI over time in the entire sample, a scatter plot and naïve marginal regression line were used. To represent AHI over time within individuals, each individual's AHI was plotted as a scatter, with the x axis representing time since entry into the study.

The variables used in analyses for this dissertation are described in Tables 4-1 through 4-3 (p. 24-26).

Table 4-1. List of variables used in analyses: SDB and Menopausal status

	Variable	Unit	Categories	Measurement	Chapters
Sleep-Disordered Breathing	AHI	Breathing events per hour		PSG	5-8
	log(AHI+1)	Natural log of breathing events per hour		PSG	5-8
	AHI ≥ 15		AHI < 15 (ref.) AHI ≥ 15	PSG	5-8
	AHI ≥ 30		AHI < 30 (ref.) AHI ≥ 30	PSG	5-8
	REM AHI	Breathing events per hour		PSG	8
	STOP-BANG score		0-2: low risk 3-7: moderate to high risk	Interview, in-person measurements	8
Menopausal Status	*A priori* menopausal stage		Premenopause (ref.) Early Perimenopause Late Perimenopause Postmenopause	Diaries, interviews	6
	Combining premenopause with early perimenopause		Pre/Early Perimenopause (ref.) Late Perimenopause Postmenopause	Diaries, interviews	6,8
	Combining early perimenopause with late perimenopause		Premenopause (ref.) Perimenopause Postmenopause	Diaries, interviews	6
	Adding a category for undetermined peri-postmenopause		Premenopause (ref.) Perimenopause Postmenopause Peri-Postmenopause (undetermined)	Diaries, interviews	6-7
	Continuous time in menopause	Years		Diaries, interviews	6-7

Table 4-2. List of variables used in analyses: Menopausal Hormone Therapy and Insomnia

	Variable	Unit	Categories	Measurement	Chapters
Menopausal hormone therapy	HT Use		No Use (ref.) Current Use	Diaries	6-8
	Type		Estrogen Progesterone Estrogen/Progesterone Combination Other	Diaries	7
	Dose	Variable		Diaries	7
	Duration of use	Months		Diaries	7
Insomnia	Symptom days with trouble getting to sleep	Days		Diaries	
	Trouble getting to sleep (DSM criteria)		<3 times per week for 3 months (ref.) ≥3 times per week for 3 months	Diaries	8
	Trouble getting to sleep (looser criteria)		<3 times per month for 3 months (ref.) ≥3 times per month for 3 months	Diaries	8
	Long sleep latency	Minutes		Interview	8
	Symptom days with trouble staying asleep	Days		Diaries	
	Trouble staying asleep (DSM criteria)		<3 times per week for 3 months (ref.) ≥3 times per week for 3 months	Diaries	8
	Trouble staying asleep (looser criteria)		<3 times per month for 3 months (ref.) ≥3 times per month for 3 months	Diaries	8
	Wake After Sleep Onset (WASO)	Minutes		PSG	8
	Short total sleep time		≥6 hours or satisfied with sleep (ref.) <6 hours + dissatisfied with sleep	Interview	8

Table 4-3. List of variables used in analyses: Covariates and Mediators

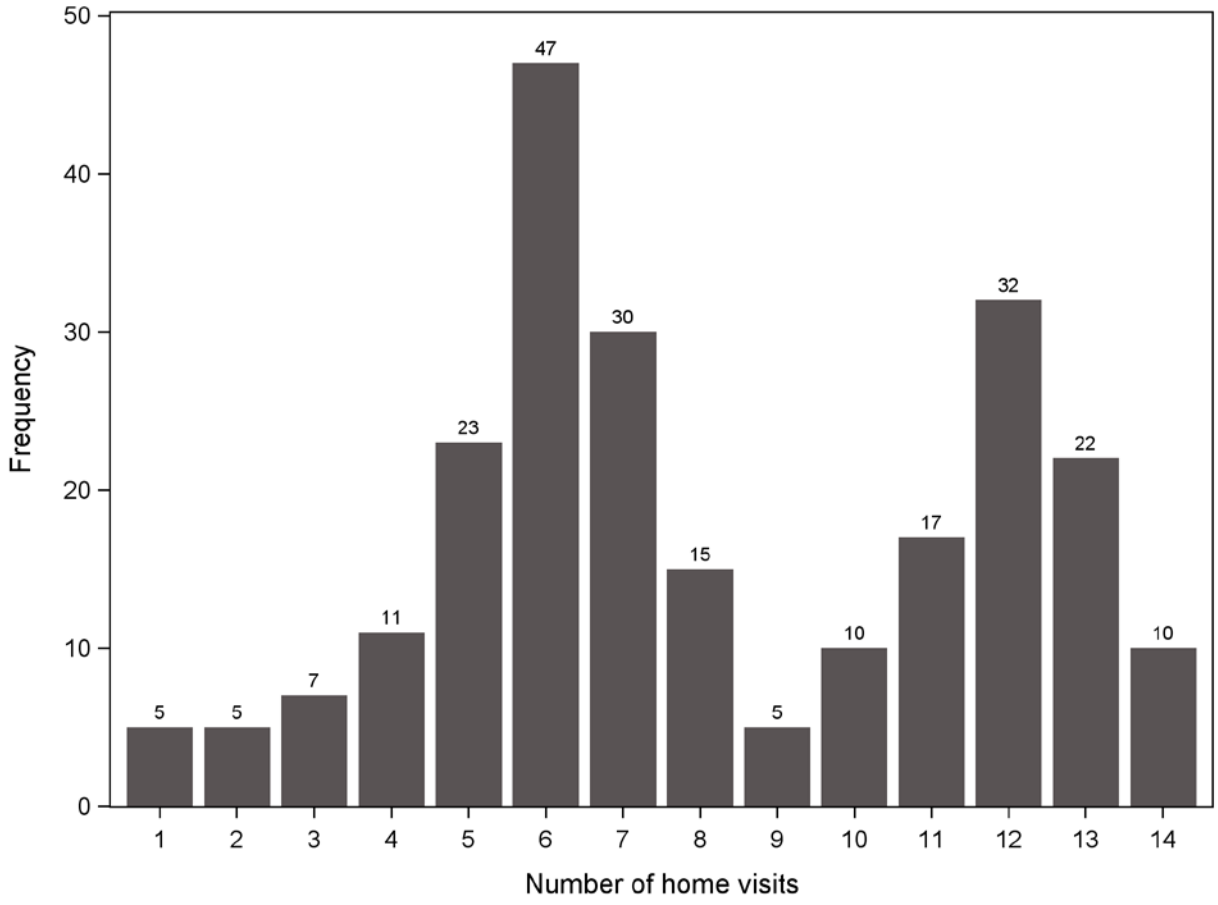
	Variable	Unit	Categories	Measurement	Chapters
Covariates	Age	Years		Interview	5-8
	BMI	kg/m^2		In-home measure	5-8
	Waist girth	cm		In-home measure	5-7
	Neck girth	cm		In-home measure	5-7
	Zung depression score	Unit		Survey instrument	5,8
	Alcohol Use	Drinks/week		Interview	5-8
	Smoking history		Never (ref.) Former Current	Interview	5-8
Potential mediators of a healthy hormone-user effect	Income	$5		1989 WSC Survey	7
	Education		High school graduate or less (ref.) Some college Bachelor's degree from college Postgraduate work in college	1989 WSC Survey	7
	Mean Arterial Blood Pressure	mmHg		In-laboratory measure	7
	Total Cholesterol	mg/dL		In-laboratory measure	7
	LDL Cholesterol	mg/dL		In-laboratory measure	7
	Triglycerides	mg/dL		In-laboratory measure	7
	Physical Activity	Hours/week		1989 WSC Survey	7

Chapter 5. Sample Characteristics and Descriptive Statistics on Apnea-Hypopnea Index

5.1 Sample Characteristics

259 women were recruited for the Sleep in Midlife Women Study. Of these, 249 completed at least one diary, 238 yielded at least one usable sleep study, and 224 contributed at least one of each. Subjects completed sleep studies at 1-14 home visits (Figure 5-1, p. 28). The median number of visits was seven and mode was six. A total of 1,943 sleep studies were completed.

Figure 5-1 Number of home visits per subject



5.2 Descriptive Statistics on Apnea-Hypopnea Index

The overall distribution of AHI was skewed toward zero, as was expected in this relatively healthy population (Figure 5-2, p. 29). Taking the natural logarithm of AHI produced a more normal distribution (Figure 5-3, p. 29). Figure 5-4 (p. 26) shows each subject's AHI values over time in the study. AHI remained relatively stable for most subjects, but others showed upward or downward trends over time, and others varied with no obvious pattern (Figure 5-4, p. 30). AHI overall went up over time, as expected (Figure 5-5, p. 31).

Figure 5-2. Overall distribution of apnea-hypopnea index

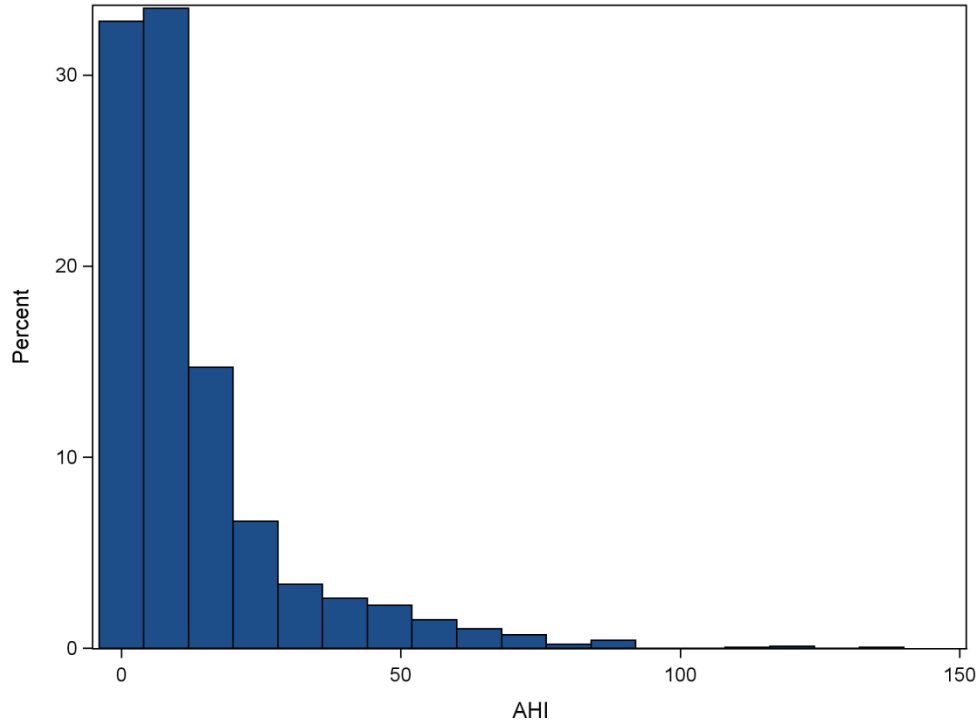


Figure 5-3. Overall distribution of logged apnea-hypopnea index. The curve represents a normal distribution.

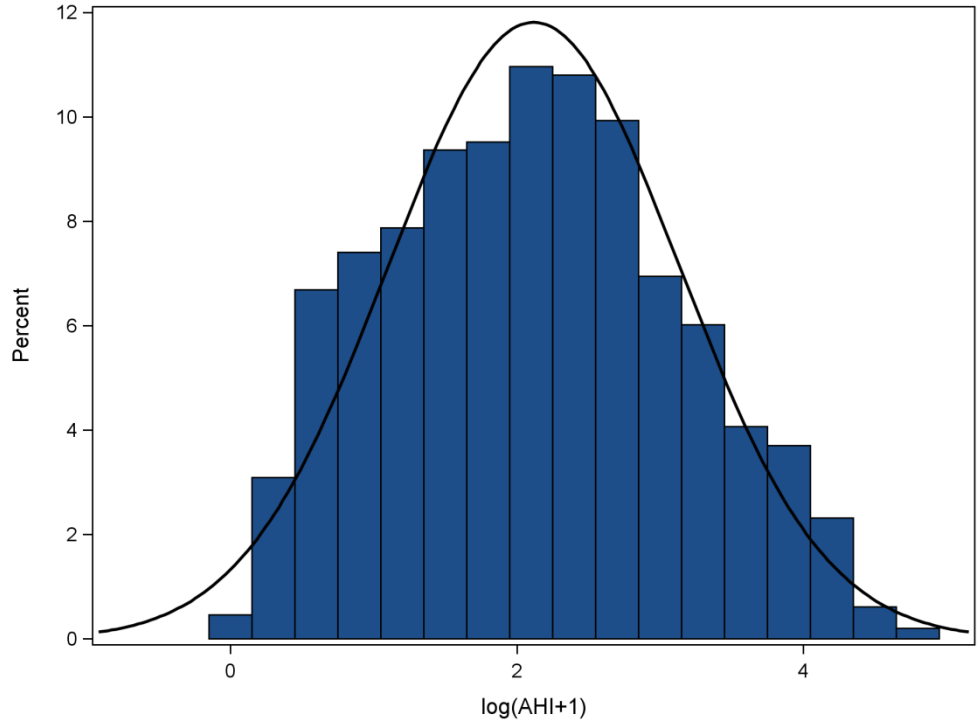


Figure 5-4 AHI over time in 238 subjects

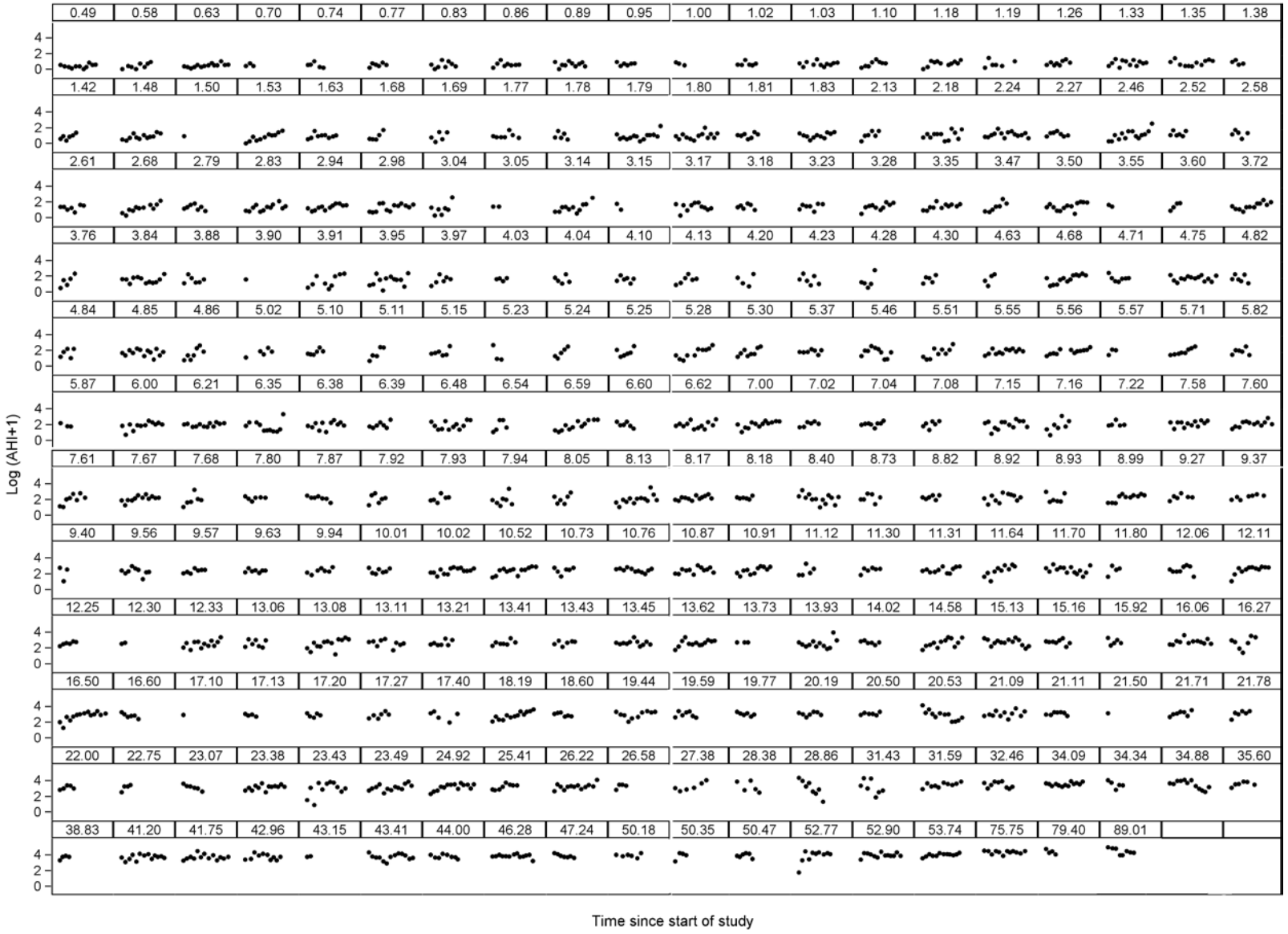
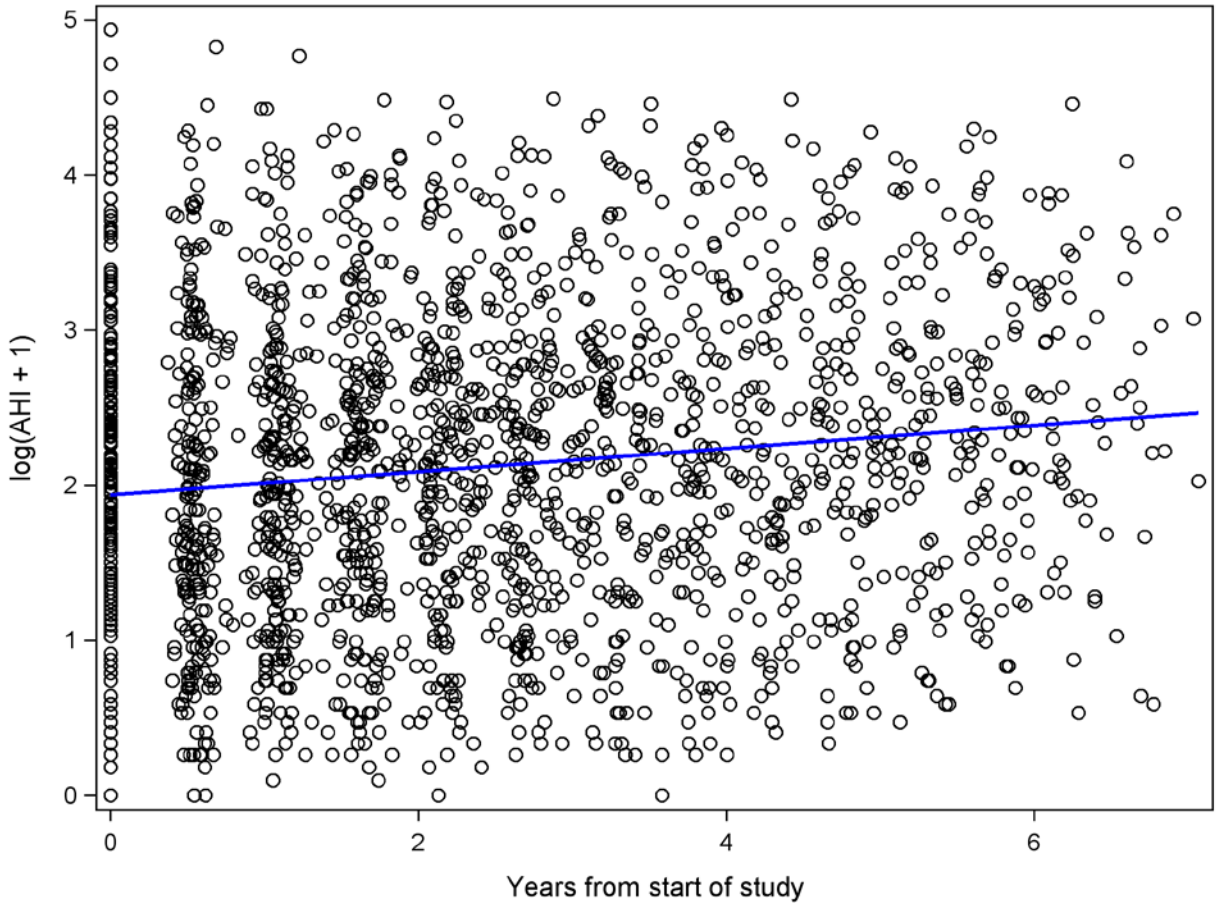


Figure 5-5. AHI over time over the whole study population. Line represents a naïve linear regression that does not take repeated measures into account.



5.3 Assessment for Participation Bias

Tables 5-1 (p. 33) and 5-2 (p. 34) present results of a comparison between participants in the Sleep in Midlife Women Study and female participants in the Wisconsin Sleep Cohort Study who did not join the women's substudy, using data from the parent study. Continuous variables are reported as each individual's mean across all laboratory visits during the period of time during which subjects were entering the women's study (May 1996-September 2005). Categorical variables are reported as ever reporting having the characteristic at any visit over that period.

Women who joined the substudy had, on average, lower AHI than women who did not join, were less likely to use menopausal hormone therapies, and had a slightly lower mean Zung score (i.e. had fewer depressive symptoms). Participants were slightly less likely to report having difficulty falling back asleep, waking repeatedly, or waking too early.

Menopausal status is not assessed here, because as described in section 4.1, women who had already begun the menopausal transition were intentionally prioritized for recruitment. Overall this analysis does not suggest that participation bias is likely to cause spurious associations in these data. It is possible that associations between AHI and insomnia outcomes could be biased toward the null, but given the small differences in frequency of insomnia between participants and non-participants, the magnitude of such a bias is likely to be small.

Table 5-1. Comparison of Sleep in Midlife Women Study participants with female Wisconsin Sleep Cohort Study participants who did not join the substudy: continuous variables. Variables are presented as means over all laboratory visits during the period in which new substudy participants joined.

	Sleep in Midlife Women Study Participant				All	
	No		Yes			
	Mean	(SD)	Mean	(SD)	Mean	(SD)
AHI	10.80	(19.5)	7.59	(13.4)	9.58	(17.5)
log(AHI+1)	1.74	(1.1)	1.53	(0.9)	1.66	(1.0)
Alcoholic drinks per week	2.42	(4.1)	2.32	(2.9)	2.38	(3.7)
BMI	32.35	(8.1)	31.87	(8.0)	32.17	(8.1)
Neck girth (cm)	35.96	(3.5)	35.98	(3.3)	35.96	(3.4)
Waist girth (cm)	95.24	(17.5)	93.94	(16.7)	94.75	(17.2)
Zung score	34.11	(6.7)	31.75	(6.1)	33.22	(6.6)

Table 5-2. Comparison of Sleep in Midlife Women Study participants with female Wisconsin Sleep Cohort Study participants who did not join the substudy: categorical variables. Variables are presented as frequencies over all laboratory visits during the period in which new substudy participants joined.

	Sleep in Midlife Women Study Participant				All	
	No		Yes			
	N	(%)	N	(%)	N	(%)
HT Use						
No	182	(56%)	156	(76%)	338	(64%)
Yes	145	(44%)	49	(24%)	194	(36%)
Difficulty sleeping						
No	123	(38%)	78	(38%)	201	(38%)
Yes	204	(62%)	127	(62%)	331	(62%)
Trouble falling back asleep						
No	105	(32%)	80	(39%)	185	(35%)
Yes	222	(68%)	125	(61%)	347	(65%)
Early awakening						
No	144	(44%)	102	(50%)	246	(46%)
Yes	183	(56%)	103	(50%)	286	(54%)
Awakening Repeatedly						
No	79	(24%)	59	(29%)	138	(26%)
Yes	248	(76%)	146	(71%)	394	(74%)
Antidepressant Use						
No	213	(65%)	141	(69%)	354	(67%)
Yes	114	(35%)	64	(31%)	178	(33%)
Smoking						
No	171	(52%)	103	(50%)	274	(52%)
Yes	156	(48%)	102	(50%)	258	(48%)
All	327	(100%)	205	(100%)	532	(100%)

Chapter 6. Menopausal Stage and Sleep-Disordered Breathing (Specific Aim #1)

6.1 Analytic Methods

6.1.1 Descriptive statistics

Descriptive statistics were performed as described in Section 4.3. Number of studies at each menopausal stage was assessed numerically. Distribution of AHI at different menopausal stages was also assessed graphically.

6.1.2 Defining menopausal status

Menopausal status was assigned based on the criteria outlined in Table 6-1 (p. 37). Subjects were assumed to be in premenopause until meeting one of the criteria for early perimenopause, then assumed to continue in early perimenopause until meeting one of the criteria for late perimenopause, etc.

Menopausal stage was classified using criteria consistent with the Stages of Reproductive Aging Workshop.[2] Menstrual history was used wherever possible. Because hormonal contraceptives and menopausal hormone therapies can affect bleeding, menstruation criteria were modified for subjects using those medications. Among women with a history of hysterectomy and/or oophorectomy, dates of surgery were used. Where menstrual and surgical histories were either missing or uninformative, criteria based on chronological age were used.

Since menopause is a continuous process with no clear boundaries (see Section 3.1), the categorization of this process is to some extent arbitrary. Therefore menopausal status was

categorized several different ways for the purposes of this analysis. First all four categories were treated as independent states. Then premenopause was combined with early perimenopause. A third categorical definition combined early perimenopause and late perimenopause into a single perimenopause category. Lastly, a continuous variable for time since the start of perimenopause was created, for an analysis restricted to observations on subjects in perimenopause or postmenopause.

Menopausal status was missing at many observations, primarily because the date of postmenopause was unknown. Several methods of multiple imputation were attempted, but none were successful (see Appendix 4). So to avoid losing those observations, two approaches were taken for this analysis: mean imputation and the creation of a separate category for women with undetermined menopausal status. Mean imputation is described in section 8.1. Analyses presented in this chapter followed the approach taken by Young et. al.,[29] and a category of menopausal status was created for women whose age at postmenopause was unknown. This category included any sleep study at which a subject was known to have started perimenopause, but at which it could not be determined whether or not the subject had progressed to postmenopause.

Table 6-1. Criteria for defining menopausal status. After meeting one of the criteria, subjects were assumed to continue in that stage until one of the criteria for the next stage was met.

Early Perimenopause	Late Perimenopause	Postmenopause
First incidence of no flow with no hormonal contraception	3 months of no flow	12 months of no flow
Change in cycle length ≥7 days with no hormonal contraception	Starting hormone therapy	6 months of no flow with hormone therapy
First incidence of hot flashes or night sweats while using hormonal contraception	Ovary-sparing surgery with FSH <10 6 or more months ago	Hormone therapy for ≥12 months
Ovary-sparing surgery with FSH <10 under 6 months ago and first incidence of hot flashes or night sweats	FSH >40 prior to ovary-sparing surgery	60th Birthday
	Ovary-removing surgery within last 6 months	55th Birthday with hormone therapy
		FSH>40 after ovary-sparing surgery
		Ovary-removing surgery 6 or more months ago

6.1.3 Regression models

The association between menopausal status and sleep-disordered breathing was assessed using regression models, with different models run for each definition of menopause as outlined in section (6.1.2). Linear models regressed log(AHI +1) on menopausal status, and logistic models regressed log odds of having AHI ≥ 15. PROC MIXED was used for linear models, with empirical standard errors to account for repeated measures. Compound symmetry was assumed throughout the model building process, until the final model was run using unstructured covariance and AR(1). The covariance structure with the smaller BIC value was chosen. PROC

GENMOD was used for logistic models, using Generalized Estimating Equations[98] to account for repeated measures. Compound symmetry was assumed for all logistic models.

Models were run unadjusted, and adjusting for age, BMI, waist girth, neck girth, use of menopausal hormone therapy, alcohol consumption, and smoking history. Potential confounding introduced by each covariate was assessed by backwards deletion, in which the covariate that produced the smallest magnitude of change to the regression parameter on any menopause category was sequentially removed. To account for a possible non-linear age effect, an additional model was run including a B-spline for age. Effect modification of the association between menopausal status and AHI by age, hormone therapy use, and BMI was assessed by running linear and logistic models including product terms, and adjusted for all other covariates.

6.2 Descriptive Statistics

The frequencies of sleep studies performed at different menopausal stages is reported in Figure 6-1 (p. 41). Because the study design prioritized recruitment of women already in perimenopause (see section 4.1), only 42 observations were gathered on subjects in premenopause. Roughly half of all sleep studies occurred during postmenopause. Nearly a fifth of all sleep studies were completed on women whose menopausal stage could not be defined at the time of the study.

The distribution of AHI within each category of menopausal status is shown in Figure 6-1 (p. 41). The right tail of the distribution is shorter in premenopause than the other categories. The distribution in the early perimenopause category was similar to the distribution in the late

perimenopause category. There were notably fewer values close to zero during postmenopause.

The logged distribution was close to normal in every category except for premenopause, where sample size was small. Combining the premenopause and early perimenopause category produced a single category with a distribution close to normal (Figure 6-2, p. 42), but as only 14% of observations in this category come from women in premenopause, this approach essentially discards information contributed by those observations. Moreover the distribution in the early perimenopause category appears more similar to the distribution in late perimenopause than to the distribution in premenopause. Thus combining premenopause with early perimenopause is more appealing for its modeling properties, but combining the two perimenopause categories is more appealing from the perspective of describing menopausal status precisely. In this chapter, where menopause was the primary predictor of interest, the two perimenopause categories were combined. In Chapter 8, where menopausal status is of interest only as a confounder, I opted to combine premenopause with early perimenopause.

The addition of a category for studies at which perimenopause could not be distinguished from postmenopause yielded a distribution with a long right tail (Figure 6-3, p. 42), and a proportion of near-zero values in between that of perimenopause and postmenopause.

Participant characteristics are described at baseline in Table 6-2 (p. 44), and over all observations in Table 6-4 (p. 48). Mean AHI was relatively high, reflecting the fact that the in-home polysomnography equipment and scoring measured AHI systematically higher than laboratory equipment (see Appendix 5). Women who had progressed further through

menopause by the beginning of the study were older and had higher mean AHI. Women with undetermined peri-postmenopausal status had lower mean BMI at baseline than women in perimenopause, but over all observations mean AHI was in between that of women in perimenopause and women in postmenopause. Women in premenopause had smaller mean waist circumference, but there were no meaningful differences in BMI or neck circumference. Women in premenopause also reported more alcohol consumption, and less history of smoking. Of the 42 observations on subjects in premenopause, only 25 had complete covariate data.

Figure 6-1. Distribution of log(AHI+1) over four categories of menopausal status.

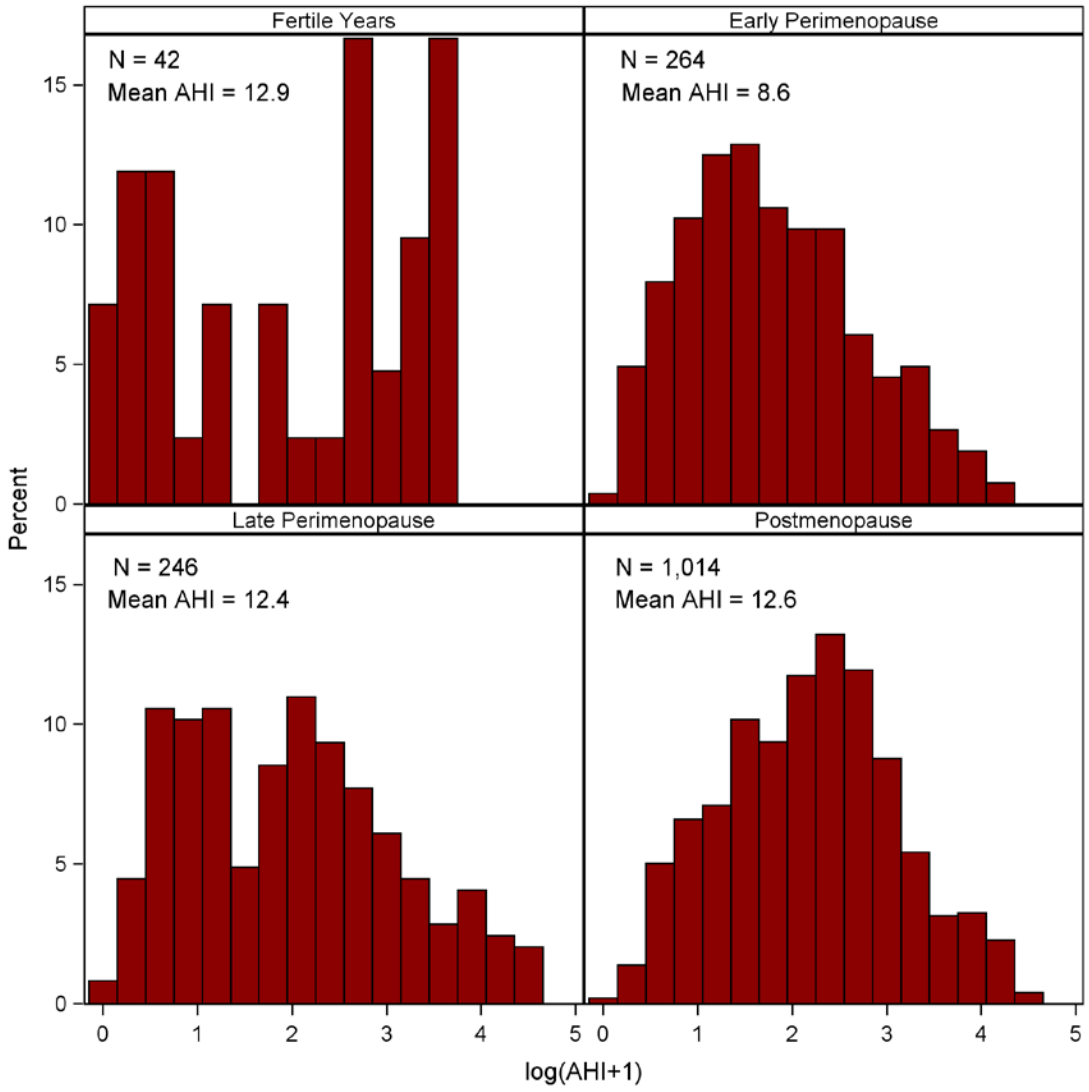


Figure 6-2. Distribution of log(AHI+1) over three categories of menopausal status, in which premenopause and early perimenopause have been combined.

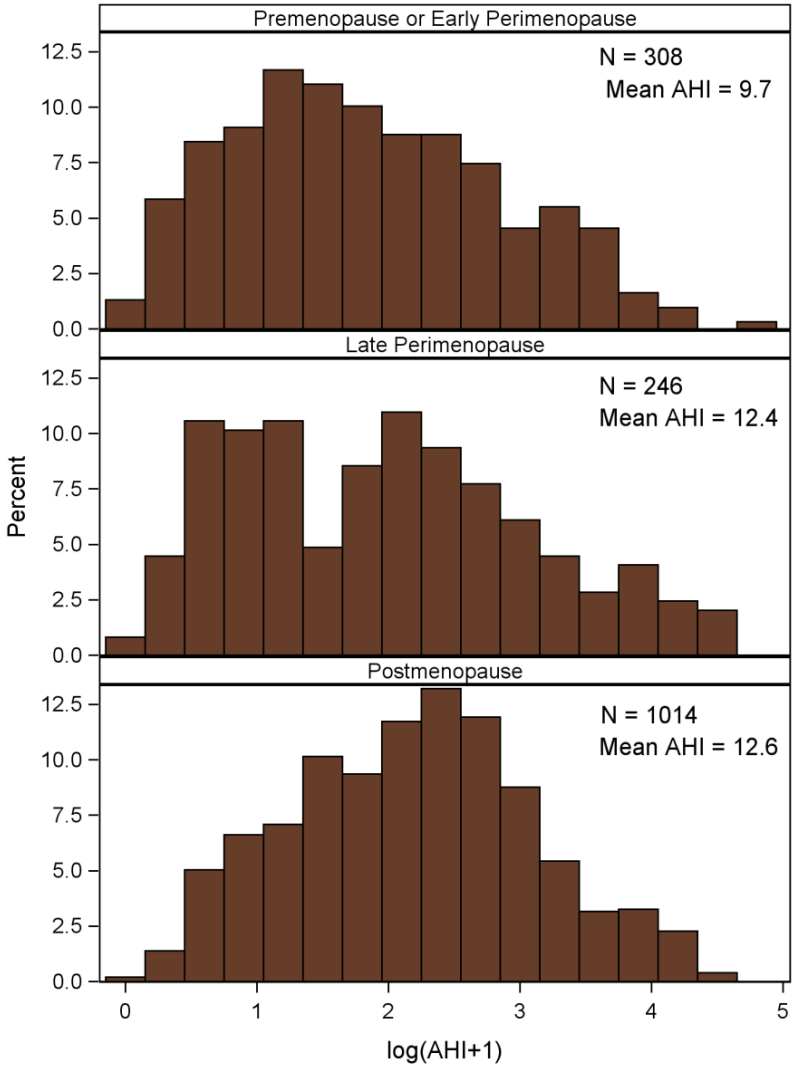


Figure 6-3. Distribution of log(AHI+1) over 3 categories of menopausal stage, plus a category for observations at which perimenopause could not be distinguished from postmenopause.

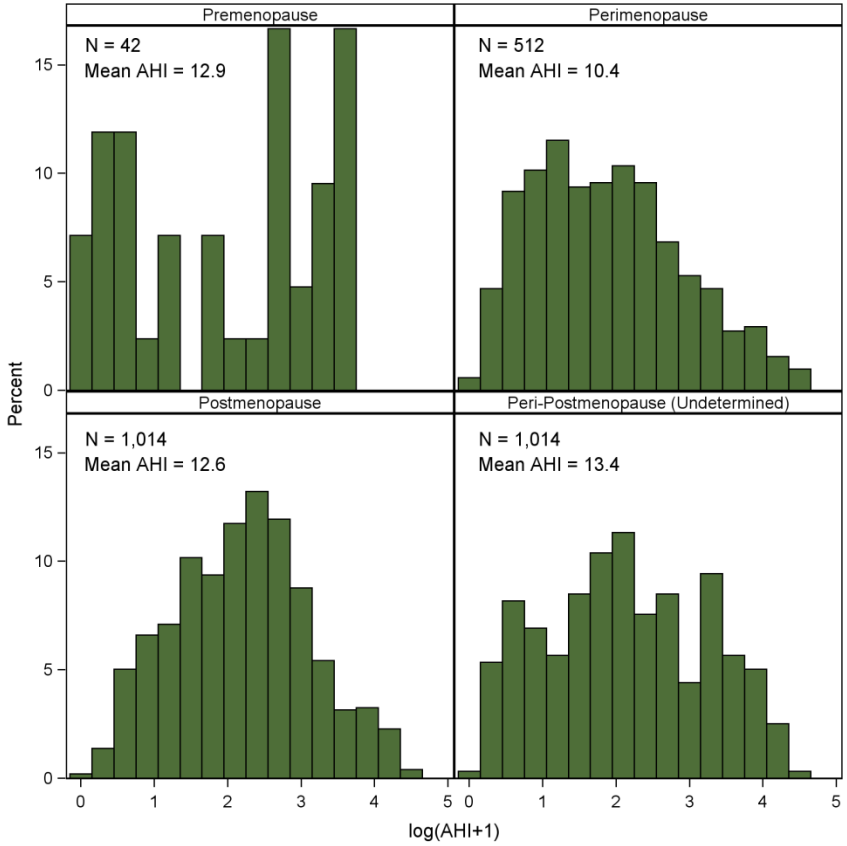


Figure 6-4. Continuous menopause: distribution of sleep studies by months elapsed since start of perimenopause at each sleep study.

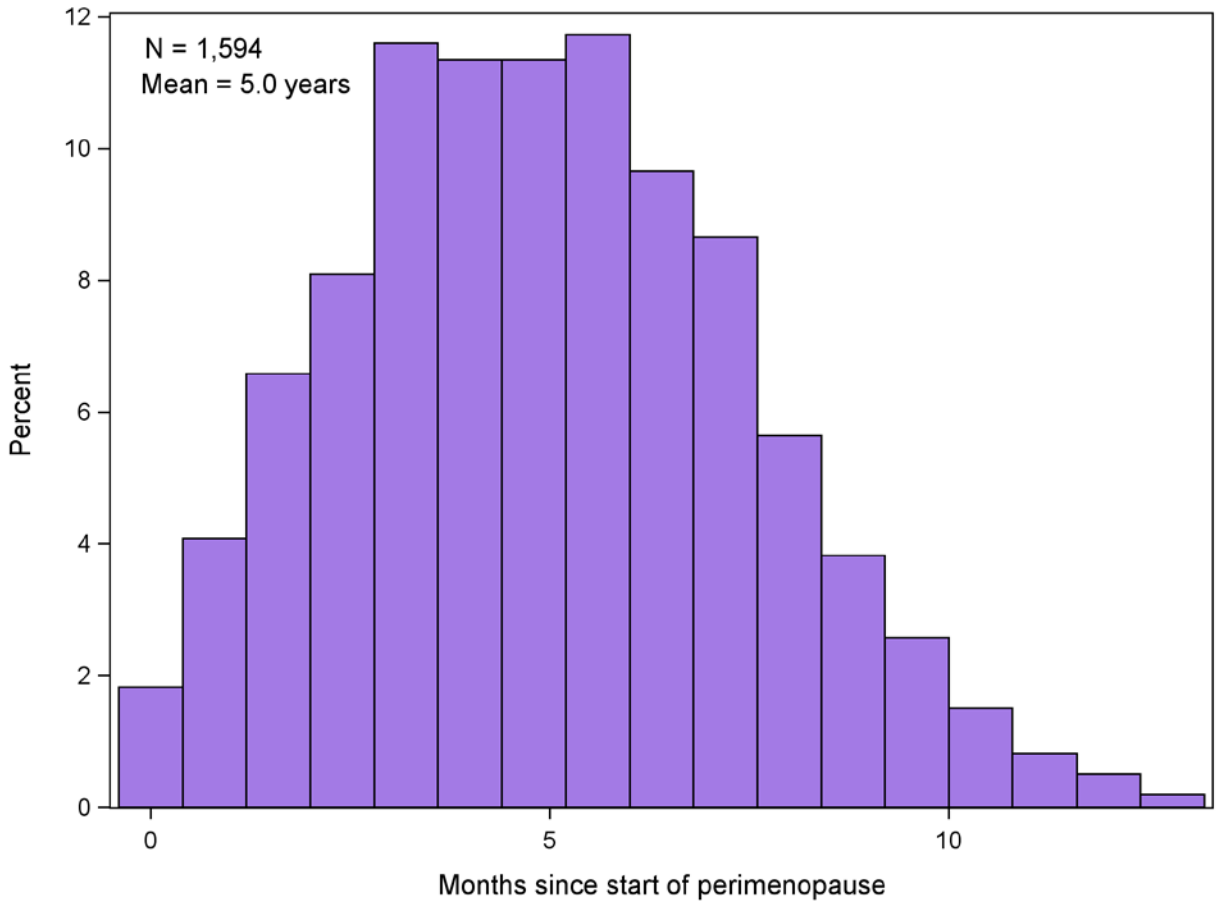


Table 6-2. Participant characteristics at baseline, by menopausal status.

	Premenopause		Perimenopause		Postmenopause		Peri-Postmenopause (undetermined)		All	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
Apnea-Hypopnea Index (AHI)	6.9	(7.9)	9.3	(13.7)	10.9	(14.4)	8.1	(9.6)	9.6	(13.2)
Age (years)	47.5	(3.0)	49.6	(3.3)	53.2	(3.9)	45.2	(3.8)	50.3	(4.5)
BMI	31.5	(7.8)	31.5	(8.4)	31.1	(7.5)	31.4	(6.6)	31.3	(7.7)
Neck circumference (cm)	35.6	(3.7)	35.5	(3.5)	35.8	(3.7)	35.5	(3.4)	35.6	(3.5)
Waist circumference (cm)	91.7	(14.7)	94.3	(19.0)	95.3	(16.1)	94.4	(15.7)	94.5	(17.2)
Alcoholic drinks per week	4.4	(6.7)	2.4	(3.5)	2.5	(3.4)	2.7	(3.3)	2.6	(3.7)
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**		
Apnea-Hypopnea Index										
< 15	12	(86%)	78	(83%)	64	(77%)	25	(89%)	179	(82%)
≥ 15	2	(14%)	16	(17%)	19	(23%)	3	(11%)	40	(18%)
Menopausal Hormone Therapy										
No	14	100%)	87	(93%)	43	(52%)	28	100%)	172	(79%)
Yes	0	(0%)	7	(7%)	40	(48%)	0	(0%)	47	(21%)
Smoking history										
Never	9	(64%)	50	(53%)	41	(49%)	15	(54%)	115	(53%)
Past	5	(36%)	27	(29%)	34	(41%)	11	(39%)	77	(35%)
Current	0	(0%)	17	(18%)	8	(10%)	2	(7%)	27	(12%)
Total Subjects	14		94		83		28		219	

Table 6-3. Participant characteristics over all home visits, by menopausal status. Means were calculated as the mean of all subjects' individual means over multiple observations. Standard deviations are across individual mean values.

	Premenopause		Perimenopause		Postmenopause		Peri-Postmenopause (undetermined)		All	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
Apnea-Hypopnea Index (AHI)	8.7	(10.8)	10.1	(13.6)	11.5	(11.8)	11.1	(12.3)	10.9	(12.4)
Age (years)	47.7	(3.0)	50.7	(3.0)	54.4	(3.5)	48.2	(3.5)	51.9	(4.2)
BMI	31.7	(7.9)	31.3	(8.3)	31.6	(8.8)	32.0	(6.5)	31.6	(8.3)
Neck circumference (cm)	35.8	(3.8)	35.3	(3.4)	35.5	(3.5)	35.7	(3.1)	35.5	(3.4)
Waist circumference (cm)	91.5	(14.9)	93.8	(18.8)	95.1	(17.8)	94.8	(14.6)	94.5	(17.5)
Alcoholic drinks per week	4.5	(6.3)	2.1	(3.0)	2.2	(3.0)	2.5	(3.5)	2.3	(3.3)
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Apnea-Hypopnea Index										
< 15	17	(68%)	398	(82%)	663	(75%)	205	(74%)	1283	(77%)
≥ 15	8	(32%)	85	(18%)	225	(25%)	73	(26%)	391	(23%)
Menopausal Hormone Therapy										
No	25	100%)	451	(93%)	631	(71%)	274	(99%)	1381	(82%)
Yes	0	(0%)	32	(7%)	257	(29%)	4	(1%)	293	(18%)
Smoking history										
Never	17	(68%)	256	(53%)	477	(54%)	142	(51%)	892	(53%)
Past	8	(32%)	138	(29%)	313	(35%)	111	(40%)	570	(34%)
Current	0	(0%)	89	(18%)	98	(11%)	25	(9%)	212	(13%)
Total subjects[a]	14		102		155		51		219	
Total Observations	25		483		888		278		1674	

[a]Subjects may contribute observations to more than one category of menopausal status

6.3 Regression models using complete case analysis

Fully adjusted regressions using the four-category definition of menopause are shown in Table 6-4 (p. 48). Both linear and logistic models showed a monotonic increase in AHI as menopausal status advanced, but the tests for trend were not persuasive, and confidence intervals were wide, particularly in the logistic model. Age, BMI, waist girth, neck girth, and alcohol remained predictors of higher AHI.

Fully adjusted regressions in which premenopause was combined with early perimenopause are shown in Table 6-5 (p. 49). There were two observations at which the subject's menopausal status could not be classified as either Premenopause or Early Perimenopause. However, neither observation had complete covariate data, and thus sample size did not increase in the fully adjusted model when these two categories were combined. The similarity between early perimenopause and late perimenopause was evident in these models, and the contrast between perimenopause and postmenopause was small. The monotonic pattern across menopausal status was not observed in the logistic model.

There were also two observations at which the subject's menopausal status could not be classified as either early or late perimenopause. One of these observations had complete covariate data, and was included in the models shown in Table 6-6 (p. 50). Combining the two perimenopause categories brought the relationship of menopausal status to AHI closer to a linear trend at P=0.07. The confidence interval for perimenopause compared to premenopause included one, but the confidence interval for postmenopause, which was associated with 30% higher AHI, did not. The logistic model did not show any evidence of linearity, and confidence

intervals remained broad. The small number of observations in the premenopause category made all the logistic models particularly unstable, and difficult to interpret.

Models using continuous time in menopause are presented in Table 6-7 (p. 51). Time in menopause showed a stronger relationship to continuous AHI than chronological age. Even when adjusted for chronological age, both variables were associated independently with AHI. Logistic models showed an even stronger association with odds of having AHI ≥ 15, although with confidence intervals including one. This logistic model is more informative than the unstable models using categorical menopause.

Age, BMI, waist girth, neck girth, and alcohol remained associated with higher AHI in all models. There was no evidence of a non-linear age effect.

Table 6-4. Regressions of AHI on four categories of menopausal status. Fully adjusted regression linear (outcome = log(AHI+1)and logistic (outcome = AHI ≥ 15) regression models.

	Linear	**Logistic**
	AHI Ratio (95% CI)	**Odds Ratio (95%CI)**
	N=1,390	**N=1,390**
Menopausal status		
Premenopause	**1.00 (ref.)**	**1.00 (ref.)**
Early Perimenopause	**1.22 (0.96, 1.54)**	**0.85 (0.56, 1.27)**
Late Perimenopause	**1.21 (0.94, 1.55)**	**0.96 (0.54, 1.71)**
Postmenopause	**1.30 (1.00, 1.68)**	**1.06 (0.26, 4.28)**
Overall F	***P* = 0.22**	***P* = 0.84**
Test for trend	***P* = 0.12**	***P* = 0.83**
Age (years)	1.06 (1.03, 1.07)	1.10 (1.02, 1.18)
BMI	1.02 (1.00, 1.05)	1.06 (0.99, 1.14)
Neck circumference (cm)	1.05 (1.02, 1.07)	1.08 (0.97, 1.19)
Waist circumference (cm)	1.01 (1.01, 1.02)	1.04 (1.01, 1.07)
Menopausal Hormone Therapy		
No	1.00 (ref.)	1.00 (ref.)
Yes	0.98 (0.87, 1.09)	0.85 (0.47, 1.54)
Alcoholic drinks per week	1.01 (1.00, 1.02)	1.05 (1.00, 1.12)
Smoking history		
Never	1.00 (ref.)	1.00 (ref.)
Past	0.86 (0.73, 1.02)	0.62 (0.32, 1.18)
Current	0.97 (0.80, 1.16)	0.78 (0.35, 1.74)

Table 6-5. Regressions of AHI on three categories of menopausal status, with premenopause and early perimenopause combined. Fully adjusted linear (outcome = log(AHI+1)and logistic (outcome = AHI ≥ 15) regression models.

	Linear	**Logistic**
	AHI Ratio (95% CI)	**Odds Ratio (95%CI)**
	N=1,390	**N=1,390**
Menopausal status		
Premenopause or Early Perimenopause	**1.00 (ref.)**	**1.00 (ref.)**
Late Perimenopause	**1.00 (0.90, 1.12)**	**0.88 (0.55, 1.40)**
Postmenopause	**1.07 (0.95, 1.21)**	**1.04 (0.58, 1.85)**
Overall F	***P* = 0.38**	***P* = 0.66**
Test for trend	***P* = 0.21**	***P* = 0.78**
Age (years)	1.06 (1.04, 1.08)	1.10 (1.02, 1.18)
BMI	1.02 (1.00, 1.05)	1.06 (0.99, 1.14)
Neck circumference (cm)	1.05 (1.02, 1.07)	1.08 (0.97, 1.19)
Waist circumference (cm)	1.01 (1.01, 1.02)	1.04 (1.01, 1.07)
Menopausal Hormone Therapy		
No	1.00 (ref.)	1.00 (ref.)
Yes	0.98 (0.87, 1.11)	0.85 (0.47, 1.53)
Alcoholic drinks per week	1.01 (1.00, 1.02)	1.06 (1.00, 1.12)
Smoking history		
Never	1.00 (ref.)	1.00 (ref.)
Past	0.86 (0.73, 1.02)	0.62 (0.32, 1.18)
Current	0.97 (0.81, 1.16)	0.78 (0.35, 1.73)

Table 6-6. Regression of AHI on three categories of menopausal status, with early and late perimenopause combined. Fully adjusted linear (outcome = log(AHI+1)and logistic (outcome = AHI ≥ 15) models.

	Linear	**Logistic**
	AHI Ratio (95% CI)	**Odds Ratio (95% CI)**
	N=1,391	**N=1,391**
Menopausal stage		
Premenopause	**1.00 (ref.)**	**1.00 (ref.)**
Perimenopause	**1.22 (0.96, 1.54)**	**0.88 (0.25, 3.13)**
Postmenopause	**1.30 (1.01, 1.68)**	**1.01 (0.26, 3.90)**
Overall F	***P* = 0.11**	***P* = 0.78**
Test for trend	***P* = 0.07**	***P* = 0.60**
Age (years)	1.06 (1.04, 1.07)	1.09 (1.02, 1.18)
BMI	1.02 (1.00, 1.05)	1.06 (0.99, 1.14)
Neck circumference (cm)	1.05 (1.02, 1.07)	1.08 (0.97, 1.19)
Waist circumference (cm)	1.01 (1.01, 1.02)	1.04 (1.01, 1.07)
Menopausal Hormone Therapy		
No	1.00 (ref.)	1.00 (ref.)
Yes	0.98 (0.87, 1.09)	0.84 (0.47, 1.51)
Alcoholic drinks per week	1.01 (1.00, 1.02)	1.06 (1.00, 1.12)
Smoking history		
Never smoker	1.00 (ref.)	1.00 (ref.)
Past smoker	0.87 (0.73, 1.03)	0.62 (0.32, 1.20)
Current smoker	0.97 (0.81, 1.16)	0.79 (0.35, 1.76)

Table 6-7. Regressions of AHI on continuous menopause. Fully adjusted linear (outcome = log(AHI+1)and logistic (outcome = AHI≥15) regressions on years in menopause. Observations on subjects in premenopause were excluded.

	Linear **AHI Ratio (95% CI)** **N=1,391**	**Logistic** **Odds Ratio (95% CI)** **N=1,391**
Years since start of perimenopause	**1.04 (1.02, 1.06)**	**1.07 (0.97, 1.18)**
Age (years)	1.03 (1.01, 1.05)	1.07 (0.99, 1.16)
BMI	1.02 (0.99, 1.05)	1.04 (0.97, 1.11)
Waist circumference (cm)	1.02 (1.01, 1.03)	1.10 (1.01, 1.21)
Neck circumference (cm)	1.03 (1.01, 1.05)	1.05 (1.02, 1.08)
Menopausal Hormone Therapy		
No	1.00 (ref.)	1.00 (ref.)
Yes	0.98 (0.88, 1.09)	0.74 (0.38, 1.41)
Alcoholic drinks per week	1.00 (0.99, 1.01)	1.02 (0.95, 1.09)
Smoking history		
Never smoker	1.00 (ref.)	1.00 (ref.)
Past smoker	0.88 (0.74, 1.03)	0.51 (0.26, 0.98)
Current smoker	0.94 (0.78, 1.13)	0.68 (0.31, 1.47)

6.4 Regression models using a category for undetermined menopausal status

Full results of multivariable regressions using a definition of menopause that includes a category for undetermined peri-postmenopausal status are presented in Table 6-8 (p. 52). An additional 276 observations with complete covariate data were gained. Compared to premenopause, the associations of perimenopause and postmenopause with AHI were similar to the models presented in Table 6-8 (p. 52). The overall *F*-test produced a *P*-value of 0.03. The monotonic pattern continued to be observed.

Table 6-8. Regressions of AHI on menopausal status with a category for undetermined per-postmenopause. Fully adjusted linear (outcome = log(AHI+1)and logistic (outcome = AHI ≥ 15) models.

	Linear	**Logistic**
	AHI Ratio (95% CI)	**Odds Ratio (95% CI)**
	N=1,667	**N=1,667**
Menopausal stage		
Premenopause	**1.00 (ref.)**	**1.00 (ref.)**
Perimenopause	**1.21 (0.96, 1.54)**	**1.13 (0.31, 4.13)**
Postmenopause	**1.31 (1.02, 1.68)**	**1.31 (0.33, 5.15)**
Peri- to Postmenopause (undetermined)	**1.41 (1.08, 1.82)**	**1.52 (0.39, 5.87)**
Overall *F* test	***P* = 0.03**	***P* = 0.63**
Age (years)	1.05 (1.03, 1.07)	1.09 (1.03, 1.16)
BMI	1.03 (1.00, 1.05)	1.07 (1.00, 1.14)
Neck circumference (cm)	1.04 (1.02, 1.06)	1.09 (1.00, 1.19)
Waist circumference (cm)	1.01 (1.01, 1.02)	1.04 (1.01, 1.07)
Menopausal Hormone Therapy		
No	1.00 (ref.)	1.00 (ref.)
Yes	0.96 (0.86, 1.08)	0.83 (0.46, 1.49)
Alcoholic drinks per week	1.00 (0.99, 1.02)	1.04 (0.98, 1.10)
Smoking history		
Never	1.00 (ref.)	1.00 (ref.)
Past	0.90 (0.77, 1.04)	0.61 (0.34, 1.09)
Current	0.95 (0.80, 1.13)	0.69 (0.33, 1.44)

6.5 Effect modification

There was no evidence of effect modification by age, or by menopausal hormone therapy use, on the relationship of menopausal status to SDB in any model (Table 6-9, p. 54). Nor was there evidence for an interaction between menopausal stage and time in menopause (*P* = 0.14).

There was some evidence of effect modification by BMI. In the model using categorical menopausal stage, the cross-product term on BMI and postmenopause had a borderline *P*-value of 0.06. The coefficient on the cross product term was negative, indicating that the effect of time in menopause on SDB was attenuated in women with higher BMIs.

In the model excluding observations on subjects in premenopause, and using time in menopause as the predictor of interest, the cross product term had a *P*-value of 0.01. Here, too, the coefficient was negative, and clinical significance was small. For every five units of BMI, the menopause ratio diminished by 0.01. In this model, each additional year in menopause was associated with an AHI ratio of 1.07 among women with a BMI of 20, 1.06 at a BMI of 25, 1.04 at a BMI of 30, 1.03 at a BMI of 35, and 1.02 at a BMI of 40. The effect of each additional year in menopause rounded to the null at a BMI of 48. This is potentially meaningful, as it falls within the range of BMIs observed in this sample; mean BMI ranged from 17.6 to 52.3, in addition to one outlier with a mean BMI of 74.4.

Table 6-9. Testing for interaction: *P*-values for cross-product terms from models testing interaction between each covariate indicated and menopausal stage.

	Age		BMI		Hormone Therapy[a]		Time in menopause[b]	
	Linear	Logistic	Linear	Logistic	Linear	Logistic	Linear	Logistic
Perimenopause	0.24	0.63	0.21	0.53	--	--	--	--
Postmenopause	0.34	0.48	0.06	0.61	0.32	--	0.58	0.44
Peri-Postmenopause (undetermined)	0.42	0.62	0.46	0.58	0.20	--	0.23	0.18
Years since start of perimenopause	0.57	0.14	0.01	0.82	0.77	0.63	--	--

[a]Because HT was not used during premenopause, the reference category for these interaction terms is perimenopause. The logistic model including these interaction terms did not converge.
[b]This analysis excluded observations at which subjects were in premenopause. Thus the reference category was perimenopause.

6.6 Mediation and Confounding

The only covariate with a substantial empirical confounding effect was age (Table 6-10, p.55). Waist girth showed the next highest impact. However, while BMI, waist circumference, and neck circumference were all associated with higher AHI, there was no evidence that body habitus mediates the association between menopausal stage and AHI. Dropping all three body habitus measures from the linear regression model made little change to the estimated association of any menopausal stage with AHI (Table 6-11, p 56).

Table 6-10. Impact of adjustment for covariates: linear regression parameters from models regressing log(AHI+1) on menopausal status, with adjustment for different combinations of covariates.

Premenopause	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Perimenopause	0.31	0.24	0.16	0.17	0.18	0.18	0.18	0.19
Postmenopause	0.58	0.44	0.33	0.34	0.35	0.35	0.35	0.27
Peri-postmenopause (undetermined)	0.49	0.30	0.28	0.28	0.29	0.31	0.30	0.34
Covariates Included								
Age		●	●	●	●	●	●	●
Waist girth			●	●	●	●	●	●
Menopausal hormone therapy				●	●	●	●	●
Alcoholic drinks per week					●	●	●	●
Neck girth						●	●	●
BMI							●	●
Smoking								●

Table 6-11. Regression of AHI on menopausal status, dropping body habitus measures from linear regression models (outcome = log(AHI+1)).

	AHI Ratio (95% CI) **N=1,671**
Menopausal stage	
Premenopause	**1.00 (ref.)**
Perimenopause	**1.22 (0.99, 1.49)**
Postmenopause	**1.34 (1.07, 1.68)**
Peri- to Postmenopause (undetermined)	**1.39 (1.08, 1.79)**
Overall F test	***P* = 0.02**
Age (years)	1.06 (1.03, 1.08)
Menopausal Hormone Therapy	
No	1.00 (ref.)
Yes	0.97 (0.85, 1.09)
Alcoholic drinks per week	1.00 (0.99, 1.01)
Smoking history	
Never	1.00 (ref.)
Past	0.99 (0.85, 1.14)
Current	1.05 (0.84, 1.30)

6.7 Discussion

6.7.1 Summary

In these data, menopause was a risk factor for sleep-disordered breathing, independent of age and body habitus. Progression through menopause was associated with worse AHI in all linear models. Regardless of which covariates were included or how menopause was categorized, a monotonic increase in AHI was observed across the menopausal transition, and this pattern was confirmed in models using continuous time in menopause. This suggests an exposure-

response relationship between further progression through menopause and sleep-disordered breathing.

Logistic models did not show as clear an association, but given the width of the confidence intervals, they do not contradict it either. However, the small number of observations on women in premenopause made these models particularly unstable, and less interpretable than the linear models.

The observed association between menopausal stage was not entirely explained by age or body habitus. Age and waist were important empirical confounders in this analysis, underscoring the importance of accounting for chronologic age in all studies of menopause and SDB. However, while age and menopausal status remain necessarily intertwined, adjusting for age did not entirely remove the effect of menopause. Neither is the relationship evidently mediated by changes in BMI or any other measure of body habitus, as adjustment for these covariates made little difference to the estimated association between menopause and SDB.

Surprisingly, the most severe sleep-disordered breathing was observed in the group with undetermined menopausal status. If this group represents a mix of subjects whose “true” menopausal status is perimenopause and subjects in “true” postmenopause, we would expect the estimated association with AHI to fall in between that of perimenopause and postmenopause. It is unclear why this group should be at especially high risk of sleep apnea.

One possibility is that women who had irregular menses or oligomenorrhea throughout adulthood may have been difficult to classify on the basis of their menstrual histories, or may have had particularly long perimenopauses that lasted beyond the end of the study, leading to

right-censoring. This could represent a qualitatively different experience of menopause, with some inherent biological importance. Our study did not collect data on polycystic ovary syndrome (PCOS), and this is one known predictor of irregular menses. Several studies of women with PCOS have found that they are at greater risk of obstructive sleep apnea, independent of age and BMI.[99]

It is a potentially interesting finding that progression through menopause seems to have the most important effect for women at lower BMI. This is relevant to the issue of diagnosis, because BMI is a well-recognized predictor of sleep apnea, and women with extremely high BMI are as likely as anyone to be correctly diagnosed. Leaner women with SDB are more likely to be missed. However a simpler interpretation of the observed statistical interaction might be that at higher BMIs, the effect of adiposity overwhelms the effect of postmenopause. A type of survivor effect may be at play--subjects who are resilient to SDB at high BMIs may not be vulnerable to developing it at any menopausal stage.

Any of these interpretations are plausible. However, there is no existing literature that supports this particular type of interaction between BMI and menopausal stage, and this finding should be interpreted with caution. Furthermore, the magnitude of the modified association between menopausal status and SDB is only substantially different at extremes of BMI. In this sample, 90% of subjects had BMIs between 23 and 44, a range over which the interacted estimates of the association of menopausal status and SDB were close to the uninteracted estimate. Most of the sample was well represented by the main estimate.

6.7.2 Strengths and Limitations

This study has several important strengths that distinguish it from existing studies of the association between menopausal stage and SDB. Very few studies have been designed to both measure menopause well and to measure SDB well. First, measurement of menopause was measured with unusual precision, with subjects reporting menstrual and symptom data daily, and AHI measured by polysomnography. Second, the measurements used to define menopausal status were collected prospectively, which addresses the issue of recall bias that has limited existing studies on this topic. A third strength is the length of follow-up time, which allowed many subjects to be observed at different stages of the menopausal transition, rather than relying solely on comparisons across different women. This study is also notable for its ability to control for factors associated with menopause, including age, body habitus measures, and health behaviors such as alcohol and smoking.

While it was necessary to prioritize women who had already begun perimenopause for recruitment as discussed above, the paucity of observations on subjects in premenopause is a major limitation of this analysis. It poses practical limitations, such as making the logistic models unstable, and also limits the range of the menopausal transition over which these findings can be generalized.

The observational nature of this study also poses threats to the internal validity of these estimates. While there are few factors that are known to influence menopausal stage, unmeasured confounders could bias the observed associations. Subjects may also have selected

into the study population on the basis of unknown factors that could affect both menopausal stage and SDB.

Lastly, while our method of characterizing menopause was able to describe a process that was associated with SDB, the boundaries between menopausal stages are always somewhat arbitrary. This limitation could be conceptualized as a type of measurement error, but that assumes that each subject has a "true" menopausal status, which could in theory be measured with great precision. The heterogeneity of the menopausal experience, however, challenges that assumption. Any attempt to quantify and categorize menopause as a single, universal process is always inherently limited.

6.7.3 Importance

This project's findings present the most comprehensive study of menopause and SDB to date. They confirm that for a given woman, progression through menopause is associated with greater risk of SDB, and add that the association is not mediated by changes in body habitus.

These findings agree with much of the published literature in finding a positive association between later menopausal status and SDB. However they are able to add greater nuance to these estimates, and give stronger support to a causal association. In contrast to the studies by Bixler et. al[27] and Polesel et. al.,[28] this study used repeated measures that allow regression modeling to control for time-invariant personal characteristics that could bias a cross-sectional association. One notable different between these studies and this one is that the magnitude of the associations found in this analysis were substantially smaller.

These findings are more congruent with the findings of Young et. al. using the Wisconsin Sleep Cohort.[29] However one important finding from this analysis contradicts the earlier analysis. In the present study, menopausal hormone therapy did not modify the association of menopausal stage and AHI. This discrepancy may be explained by the fact that data analyzed in the parent study was collected prior to 2002, the year in which prescribing practices for menopausal hormone therapies changed dramatically. This issue is explored in depth in Chapter 7.

Chapter 7. Menopausal Hormone Therapies and Sleep-Disordered Breathing (Specific Aim #2)

7.1 Analytic Methods

The relationship of menopausal hormone therapies to SDB overall is shown Chapter 6. This chapter investigates evidence for a period effect in that relationship, dichotomizing time into periods before and after July 2002. In addition to the descriptive statistics described in Section 4.3, more detailed descriptive statistics on hormone therapy use were performed. The number of subjects who had used HT, and when they initiated HT use, was calculated. HT use over time was also represented graphically, based on diary data, both for each subject and for the entire cohort.

Frequencies of medication type were calculated, and medications were categorized into estrogen only, progesterone only, estrogen-progesterone combination, and other; these medication categories were also used to assess HT use over time graphically. Because the earliest version of the monthly diaries only allowed HT to be described as estrogen or progesterone, these are treated as separate types of medication. The dose of estrogen and/or progesterone medications was calculated as means before and after July 2002.

Initially, interaction between time period and HT use was assessed by regressing log(AHI+1) on the cross-product of HT use and the time period indicator, using the in-home data only, and adjusted for menopausal status (including the undetermined category), age, BMI, neck girth, waist girth, alcohol use, and smoking history. The *P*-value was assessed on the cross-product

term. In subsequent analyses, the predictor was coded as a single four-level variable, defined by the combination of HT use and time period. Since duration of HT use may be a mechanism for a period effect, a model was run using months of HT use as the predictor variable.

Two factors that have been implicated as possible mechanisms for a healthy-user effect are an intrinsic tendency to adopt health-promoting behaviors, and socioeconomic status. Neither the Sleep in Midlife Women Study nor the Wisconsin Sleep Cohort study was designed to measure socioeconomic parameters or health behaviors in great depth, so my ability to examine these mechanisms empirically was quite limited. A crude analysis was attempted, however, to answer these questions as clearly as possible with the available data. Two sets of models were run regressing either odds of ever using HT or odds of using HT before July 2002, on factors relating to first cardiovascular health at baseline and then to socioeconomic status at baseline. Complete data on these parameters was available on only a subset of subjects.

Education status was taken from the first Sleep Cohort survey, in which subjects were asked, "What is the highest level of formal school you completed?" Answers were categorized into high school or less, some college, bachelor's degree from college, and postgraduate work from college. Hourly income was taken from state payroll records used to sample subjects. Hours of exercise was a taken from the first mailed survey sent to Wisconsin state office workers at the beginning of the Wisconsin Sleep Cohort Study. Subjects were asked, "About how many hours per week—if any—do you spend at regular planned exercise (such as jogging, sports, exercise class, workouts at home or a gym)?" Levels of total cholesterol, low-density lipoprotein, and triglycerides were taken from blood samples taken at each subject's first overnight sleep study

in the laboratory. Seated diastolic and systolic blood pressures were taken from the same laboratory visit, averaged over two measures, and mean arterial pressure was calculated as two times diastolic plus systolic over three.

In addition to these baseline factors, smoking history and alcoholic drinks per week were reported at the time of each sleep study. To assess the impact of adjusting for these covariates, a backwards selection process was used, as described in section 6.1.3.

A further sensitivity analysis was conducted to test whether the cut point of July 2002 indicated a change following the halting of the WHI study as assumed, or whether it was merely capturing continuous secular trends. Models adjusted for menopausal status and age were run interacting HT use with different time period indicators. A model was run using data before and after every date over the course of the study at which 30 or more observations were available in each category of HT use.

Last, because subjects by definition did not use menopausal hormone therapies in premenopause, a further sensitivity analysis was performed, excluding observations on women in premenopause, most of which occurred in the later period as a result of the recruitment design discussed in section 4.1.

7.2 HT Use over time

Among subjects who contributed sleep studies, 103 (43%) reported HT use in at least one diary, and 76 (33%) had at least one sleep study at which they were using HT (Table 7-1, p. 67). Forty-two subjects were already using hormone therapy at their first diary. Another 34 subjects

initiated hormone therapy over the course of the study, exactly half beginning before July 2002 and half beginning after.

Menopausal hormone therapy use showed a strong temporal pattern. As shown in Figure 7-1 (p. 68), HT use rose from 1990-1999, remained relatively flat until July 2002, then sharply declined, and remained low thereafter.

Subjects used many different types of hormonal medication (Table 7-2, p. 69). The most common were the types studied in the Women's Health Initiative trial, conjugated estrogen and estrogen/medroxyprogesterone compound. The most dramatic drop in hormone use after July 2002 was observed in the estrogen/progesterone combination therapy group (Figure 7-2, p. 70), which makes sense since it was the combination therapy arm of the trial that was halted at that time. However all categories of hormone therapy declined rapidly between 2002 and 2004. There is no evidence that subjects preferentially switched from one type of hormonal therapy to another; use of all types declined over that two year period.

As Figure 7-3 (p. 71) demonstrates, fewer of the subjects using hormonal medications after July 2002 used them for long periods of time, consistent with changes to recommended prescribing practices. However, there was no clear period effect in dosage. Mean doses of medications containing estrogen and progesterone are shown in Table 7-3 (p. 72). The dosage of some medication types went down after July 2002, but others went up.

Mean time in menopause at the time of initiation was 4.3 years before July 2002, and 5.2 years after. Thus it does not appear that in the later period subjects initiated menopausal hormone therapies earlier in the menopausal transition.

Table 7-1. Total sample of subjects using HT at the time of one or more sleep studies

	Sleep Studies	
	N	**Percent**
Always using HT	7	3%
Using and not using	69	30%
Subtotal	76	33%
Never Using	152	67%
Total	228	

Figure 7-1. Menopausal hormone therapy use over time in all subjects completing diaries. May 1996 is excluded due to small sample size: N=20, 5 HT users (25%).

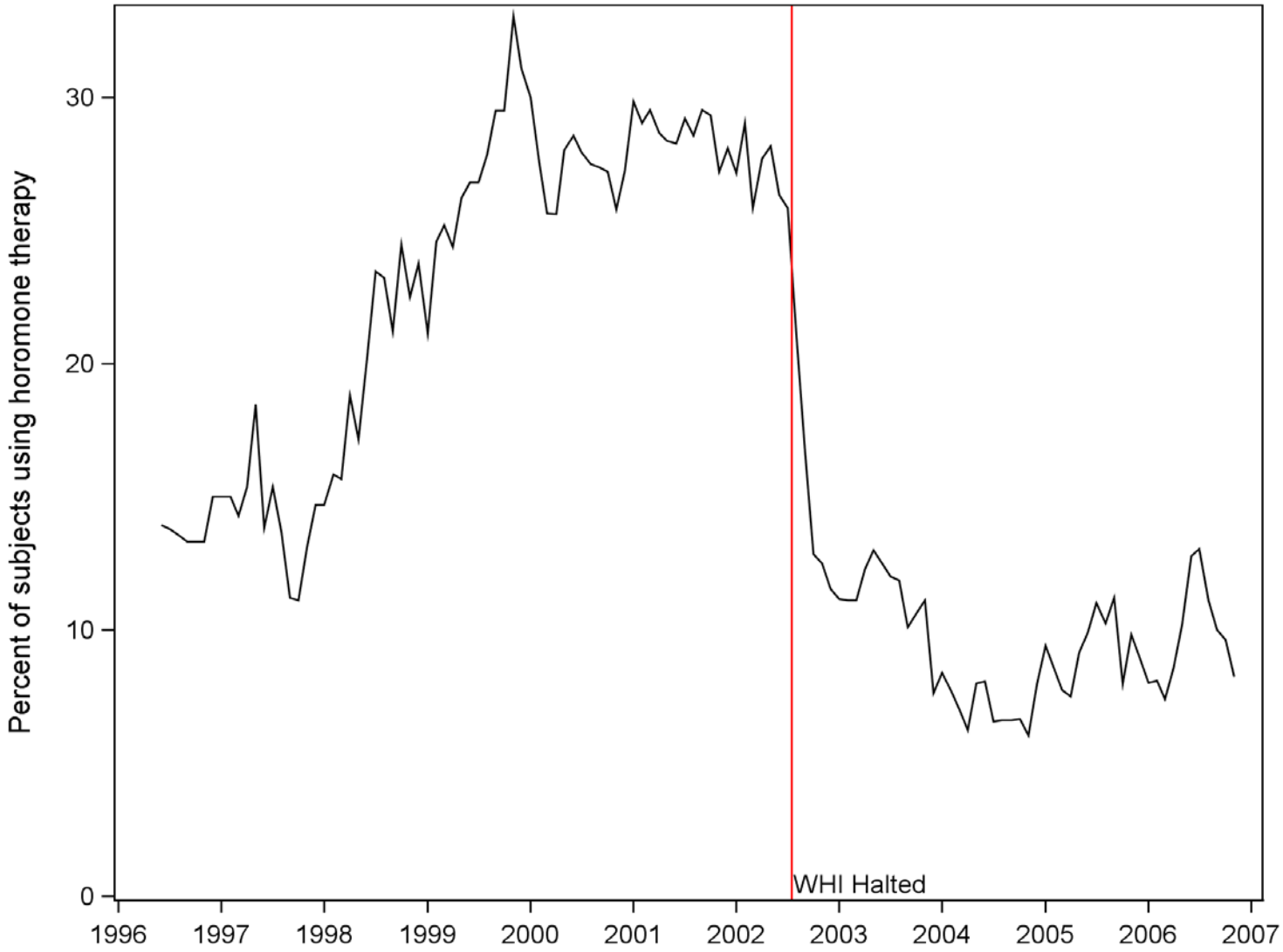


Table 7-2. Menopausal hormone therapy by type of drug. N=3,899 out of 17,010 diaries.

		Before July 2002		After July 2002	
		N	**(%)**	**N**	**(%)**
Estrogen Only	Estrogen, Conjugated	464	(16%)	186	(18%)
	Estrogen, Esterified	48	(2%)	0	(0%)
	Estradiol	430	(15%)	322	(31%)
	Estrogen (Version 1 Diary only)	192	(7%)	0	(0%)
	Subtotal	1134	(40%)	508	(49%)
Estrogen and Progesterone Combination	Estradiol & Norethindrone	29	(1%)	34	(3%)
	Estrogen & Medroxyprogesterone	795	(28%)	115	(11%)
	Estrone/Estradiol/Progesterone Compound	25	(1%)	17	(2%)
	Subtotal	849	(30%)	166	(16%)
Progesterone Only	Medroxyprogesterone Acetate	435	(15%)	182	(18%)
	Progesterone (Version 1 diary only)	148	(5%)	0	(0%)
	Subtotal	583	(20%)	182	(18%)
Other	Estrogen & Methyltestosterone	99	(3%)	49	(5%)
	Selective Estrogen Receptor Modulators	27	(1%)	34	(3%)
	Herbal and OTC preparations	167	(6%)	101	(10%)
	Subtotal	293	(10%)	184	(18%)
All		2859	(100%)	1040	(100%)

Figure 7-2. Menopausal hormone therapy use over time by type of hormone. Red lines represent the halting of the WHI study.

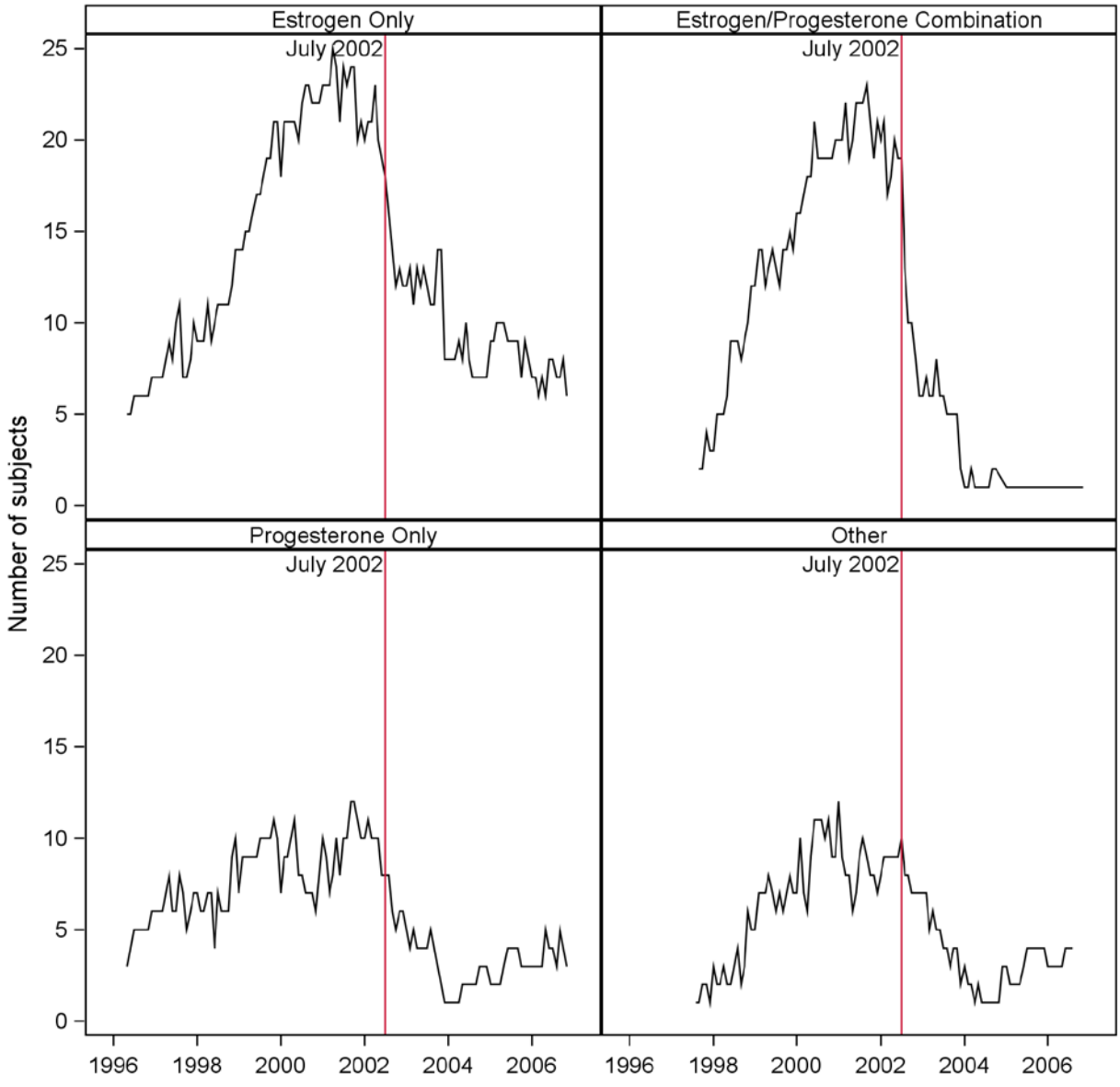


Figure 7-3. Menopausal hormone therapy use over time in individual subjects. Each line represents one subject.

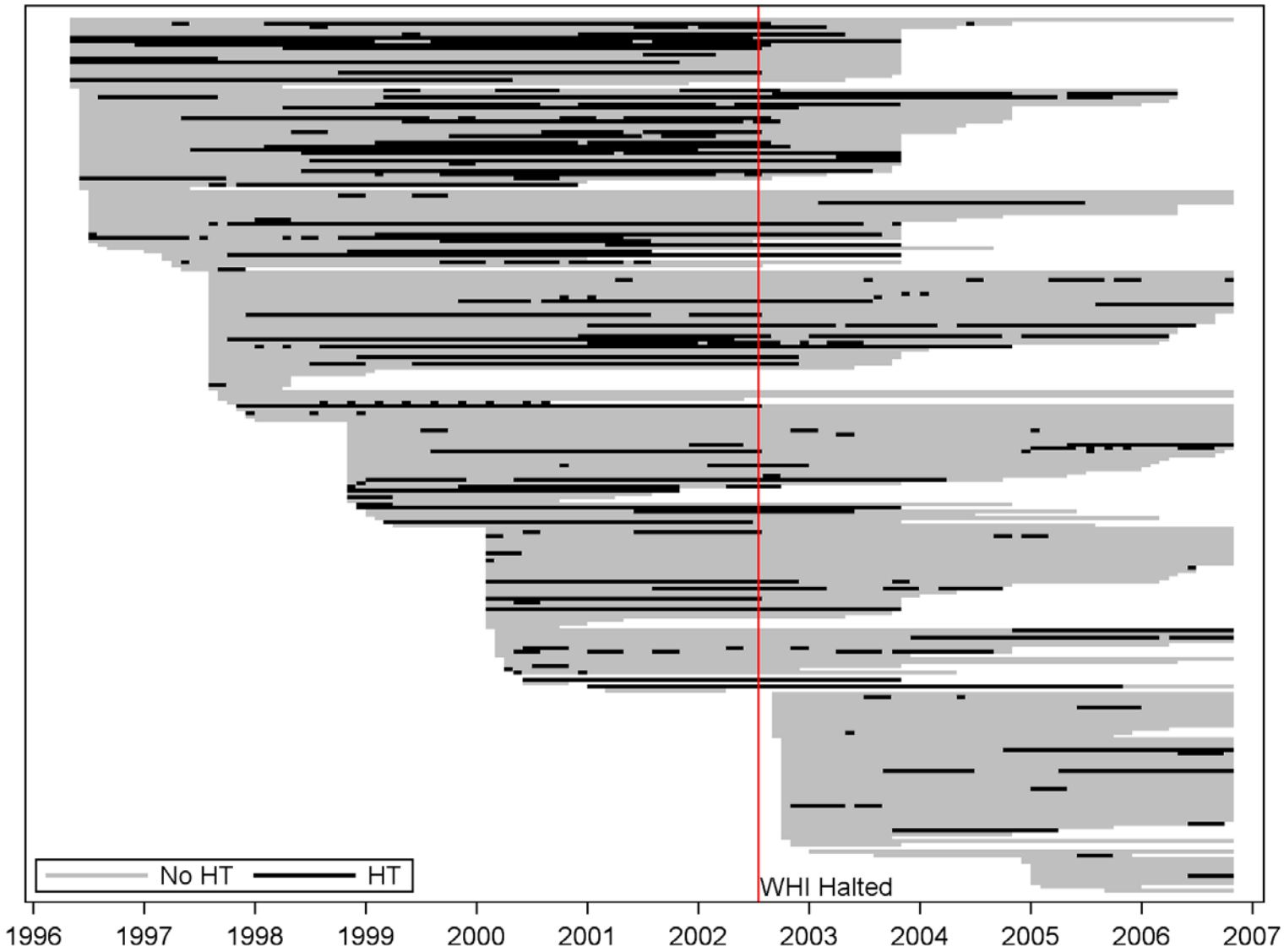


Table 7-3. Mean dose of estrogen and progesterone medications before and after July 2002

	Before July 2002		After July 2002	
	Estrogen Dose(mg)	**Progesterone Dose (mg)**	**Estrogen Dose(mg)**	**Progesterone Dose (mg)**
Estrogen (Version 1 Diary only)	0.91	--	--	--
Estrogen, Conjugated	0.77	--	0.89	--
Estrogen, Esterified	0.63	--	--	--
Estradiol	0.96	--	0.62	--
Estradiol & Norethindrone	0.22	0.18	0.05	0.18
Estrogen & Medroxyprogesterone	0.71	3.25	1.57	3.69
Estrone/Estradiol/Progesterone Compound	0.17	100.00	0.27	85.29
Progesterone (Version 1 diary only)	--	5.04	--	--
Medroxyprogesterone Acetate	--	5.37	--	11.45

7.3 Descriptive Statistics

Characteristics of subjects at baseline by HT use are presented in Table 7-4 (p. 73). AHI was similar among users and non-users, but slightly lower among users, with a similar proportion of AHI over 15. Only one of the subjects who began the study after 2002 was using HT at the time. As expected, users were more likely to be in postmenopause, and were three years older on average. Surprisingly, a similar proportion of users and nonusers were current smokers. Users drank fewer alcoholic beverages per week on average.

Subjects' characteristics are shown over all observations by menopausal status before and after July 2002 in Table 7-5 (p. 74). Overall, AHI remained slightly lower in the HT user category, but only in the early period. AHI went up in both categories across period, as expected given that the cohort aged. Duration of HT use at the time of the sleep study was two months shorter in the later period.

Table 7-4. Subject characteristics at baseline, by HT use.

	No HT		HT		All	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
AHI	9.7	(13.5)	9.1	(12.4)	9.6	(13.2)
Age (years)	49.7	(4.4)	52.5	(4.0)	50.3	(4.5)
BMI	31.5	(7.8)	30.8	(7.5)	31.3	(7.7)
Neck girth (cm)	35.6	(3.6)	35.8	(3.5)	35.6	(3.5)
Waist girth (cm)	94.3	(17.6)	95.2	(15.9)	94.5	(17.2)
Alcoholic drinks per week	2.8	(3.9)	1.8	(2.7)	2.6	(3.7)
	N	**(%)**	**N**	**(%)**	**N**	**(%)**
AHI						
<15	141	(82%)	38	(81%)	179	(82%)
≥15	31	(18%)	9	(19%)	40	(18%)
Time period						
Before July 2002	123	(72%)	46	(98%)	169	(77%)
After July 2002	49	(28%)	1	(2%)	50	(23%)
Menopausal stage						
Premenopause	14	(8%)	0	(0%)	14	(6%)
Perimenopause	87	(51%)	7	(15%)	94	(43%)
Postmenopause	43	(25%)	40	(85%)	83	(38%)
Peri-Postmenopause (undetermined)	28	(16%)	0	(0%)	28	(13%)
Smoking history						
Never	89	(52%)	26	(55%)	115	(53%)
Past	61	(35%)	16	(34%)	77	(35%)
Current	22	(13%)	5	(11%)	27	(12%)
Total observations	172		47		219	

Table 7-5. Subject characteristics over all observations, by hormone therapy status before and after July 2002. Means were calculated as the mean of all subjects' individual means over multiple observations. Standard deviations are across individual mean values.

	Before July 2002				After July 2002				All	
	No HT		HT		No HT		HT			
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
AHI	9.8	(12.7)	9.0	(9.7)	11.5	(12.5)	12.1	(11.7)	10.7	(12.2)
Age (years)	49.6	(6.6)	53.5	(3.9)	53.7	(5.1)	54.0	(3.6)	52.3	(5.7)
BMI	31.2	(8.1)	30.5	(8.3)	32.1	(8.5)	32.1	(8.5)	31.6	(8.4)
Neck girth (cm)	35.5	(3.6)	35.3	(3.4)	35.7	(3.3)	35.7	(3.3)	35.6	(3.4)
Waist girth (cm)	94.2	(18.2)	93.4	(17.2)	95.0	(17.2)	95.5	(18.9)	94.6	(17.7)
Alcoholic drinks per week	2.5	(3.3)	2.1	(2.6)	2.3	(3.1)	2.3	(3.3)	2.3	(3.1)
Duration of HT use (months)	--	--	17.9	(18.5)	--	--	15.6	(19.4)	17.1[b]	(18.8)[b]
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
AHI										
<15	385	(75%)	169	(83%)	660	(76%)	65	(74%)	1279	(77%)
≥15	127	(25%)	35	(17%)	203	(24%)	23	(26%)	388	(23%)
Menopausal stage										
Premenopause	17	(3%)	0	(0%)	8	(1%)	0	(0%)	25	(1%)
Perimenopause	264	(52%)	21	(10%)	185	(21%)	11	(13%)	481	(29%)
Postmenopause	168	(33%)	182	(89%)	461	(53%)	74	(84%)	885	(53%)
Peri-Postmenopause (undetermined)	63	(12%)	1	(0%)	209	(24%)	3	(3%)	276	(17%)
Smoking history										
Never	256	(50%)	116	(57%)	465	(54%)	54	(61%)	891	(53%)
Past	185	(36%)	70	(34%)	289	(33%)	24	(27%)	568	(34%)
Current	71	(14%)	18	(9%)	109	(13%)	10	(11%)	208	(12%)
Total subjects[a]	133		60		186		41		219	
Total observations	512		204		863		88		1667	

[a]Subjects may contribute observations to more than one category

[b]Among HT users only

7.4 Investigation of Evidence for a Period Effect

There was strong evidence in all regression models that the association between HT use and SDB was modified by period. In the model regressing log(AHI+1) on HT use interacted with the time period indicator, the *P*-value on the cross-product term was less than 0.01. Results of that regression are shown in Table 7-6 (p. 76). HT use is associated with 11% lower AHI in the early period, but 7% *higher* AHI in the later period. Confidence intervals included the null in all cases, but the overall *F* test yielded a *P*-value of 0.01. Postmenopause and undetermined peri-postmenopause remained associated with higher AHI, as did age, and all body habitus measures. Duration of HT use was not associated with continuous AHI, and adjustment for duration of use did not remove the observed pattern.

Table 7-6. Results of linear and logistic regressions of AHI on menopausal hormone therapy interacted with a post-July 2002 indicator

	AHI Ratio (95% CI) N=1,667	**Odds Ratio (95% CI) N=1,667**
HT Use Pre/Post		
No HT Before	**1.00 (ref.)**	**1.00 (ref.)**
HT Before	**0.89 (0.76, 1.03)**	**0.68 (0.31, 1.52)**
No HT After	**0.98 (0.90, 1.06)**	**1.00 (0.69, 1.45)**
HT After	**1.07 (0.94, 1.21)**	**1.32 (0.70, 2.50)**
Overall F test	***P* = 0.01**	***P* = 0.39**
HT After vs. No HT After	**1.09 (0.99, 1.21)**	**1.32 (0.75, 2.30)**
Menopausal stage		
Premenopause	1.00 (ref.)	1.00 (ref.)
Perimenopause	1.23 (0.98, 1.55)	1.17 (0.33, 4.20)
Postmenopause	1.34 (1.04, 1.72)	1.36 (0.35, 5.38)
Peri-Postmenopause (undetermined)	1.44 (1.11, 1.88)	1.54 (0.40, 6.02)
Age (years)	1.05 (1.03, 1.06)	1.08 (1.02, 1.15)
BMI	1.03 (1.00, 1.05)	1.06 (1.00, 1.13)
Neck girth (cm)	1.04 (1.02, 1.06)	1.09 (1.00, 1.19)
Waist Girth (mean cm)	1.01 (1.01, 1.02)	1.04 (1.02, 1.07)
Alcoholic drinks per week	1.00 (0.99, 1.02)	1.04 (0.98, 1.10)
Smoking history		
Never	1.00 (ref.)	1.00 (ref.)
Past	0.90 (0.77, 1.04)	0.58 (0.32, 1.05)
Current	0.95 (0.80, 1.13)	0.65 (0.31, 1.36)

Table 7-7. Effect of duration of HT use. Results of linear models of AHI on months of menopausal hormone therapy.

	Ratio (95% CI)
Months of HT use	**1.00 (0.99, 1.01)**
Menopausal Stage	
Premenopause	1.00
Perimenopause	1.07 (0.88, 1.32)
Postmenopause	1.17 (0.93, 1.46)
Peri-Postmenopause (Undetermined)	1.26 (1.02, 1.57)
Age (years)	1.05 (1.03, 1.06)
BMI	1.03 (1.00, 1.06)
Neck girth (cm)	1.04 (1.02, 1.06)
Waist Girth (cm)	1.01 (1.01, 1.02)
Alcoholic drinks per week	1.00 (0.99, 1.01)
Smoking history	
Current	1.00
Past	0.96 (0.83, 1.12)
Never	1.05 (0.88, 1.26)

7.5 Investigation of Evidence for a Healthy-user effect

Socioeconomic and health characteristics of hormone users at baseline are shown in Table 7-7 (p. 77). HT users before July 2002 had lower total cholesterol and higher hourly income, but lower LDL, higher triglycerides, and higher blood pressure. Exercise and education level were similar in users and nonusers.

Few subjects had complete data on socioeconomic status or cardiovascular health (Table 7-8, p. 79). Evidence for or against a healthy user hypothesis was mixed. Though confidence intervals were broad, each $5 increase in hourly wage was associated with 1.44 (95% CI [0.77, 2.70])

times the odds of using HT before July 2002, consistent with the healthy user hypothesis. However women with more than a high school education, after adjusting for income, were less likely to use HT, which would contradict the healthy user hypothesis. Higher mean arterial blood pressure at baseline was associated with greater odds of ever using HT, which would also contradict a healthy-user effect. The effect was less clear on odds of using HT before July 2002, however.

As shown above, HT users consumed fewer drinks before July 2002 and were less likely to be current or former smokers (Table 7-5, p. 74), but after July 2002 HT users were no more or less likely to be drinkers or smokers. This pattern is suggestive of a healthy-user effect, but adjustment for alcohol and smoking made little impact on the estimated association of HT with continuous AHI (Table 7-9, p. 80). The only covariate with a substantial empirical confounding effect was age. It appears that failure to adjust for age biased the estimated association between HT use before July 2002 and AHI toward the null, in contrast to what was observed in age's relationship to the association between menopausal status and age (see section 6.5). It does not appear that alcohol and smoking are responsible for a healthy-user effect, but as general markers of health behaviors, the observed change after July 2002 may suggest that other unmeasured health behaviors may have changed, too.

Table 7-8. Socioeconomic and general health characteristics at baseline for the Wisconsin Sleep Cohort Study, by subsequent use of menopausal hormone therapies.

	HT Use Before July 2002				HT Use Ever				All	
	No		Yes		No		Yes			
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Mean arterial blood pressure (mmHg)	91.0	(9.3)	92.8	(10.8)	90.6	(9.2)	93.1	(10.7)	91.5	(9.8)
Total Cholesterol (mg/dL)	194.5	(38.1)	188.7	(33.9)	192.7	(37.1)	193.3	(37.1)	192.9	(36.8)
LDL (mg/dL)	120.9	(32.0)	112.5	(27.2)	119.4	(31.3)	117.3	(30.5)	118.7	(30.8)
Triglycerides (mg/dL)	117.6	(74.0)	142.0	111.9)	114.2	(72.7)	143.0	105.2)	124.2	(85.7)
Exercise (hours/week)	2.0	(2.6)	2.1	(1.9)	2.0	(2.6)	2.2	(2.2)	2.1	(2.4)
Hourly income	12.7	(3.9)	13.6	(3.6)	12.7	(3.9)	13.4	(3.5)	12.9	(3.8)
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Education level										
High school graduate or less	35	(25%)	16	(26%)	32	(25%)	19	(26%)	51	(25%)
Some college	45	(32%)	16	(26%)	40	(31%)	21	(28%)	61	(30%)
Bachelor's degree from college	31	(22%)	19	(31%)	30	(23%)	20	(27%)	50	(25%)
Postgraduate work in college	30	(21%)	11	(18%)	27	(21%)	14	(19%)	41	(20%)
All	141		62		129		74		203	

Table 7-9. Results of logistic regressions modeling odds of ever using HT and odds of using HT before 2002 on baseline measures of socioeconomic status and cardiovascular health

Subjects		Before July 2002	Ever
		Odds Ratio (95% CI)	Odds Ratio (95% CI)
N=81	Mean arterial pressure (10 mmHg)	1.49 (0.86, 2.58)	1.80 (1.10, 2.95)
	Total Cholesterol (10 mg/dL)	1.01 (0.52, 1.97)	1.00 (0.59, 1.71)
	LDL (10 mg/dL)	0.88 (0.42, 1.84)	0.95 (0.54, 1.69)
	Triglycerides (10 mg/dL)	1.01 (0.90, 1.14)	1.01 (0.92, 1.12)
	Hours of weekly exercise	1.01 (0.75, 1.35)	0.98 (0.77, 1.24)
N= 158	Education		
	High school or less	1.00 (ref.)	1.00 (ref.)
	Some college	0.40 (0.12, 1.26)	0.62 (0.23, 1.68)
	Bachelor's degree	0.86 (0.27, 2.70)	0.89 (0.31, 2.60)
	Postgraduate work	0.53 (0.13, 2.11)	0.77 (0.22, 2.66)
	Hourly income ($5)	1.44 (0.77, 2.70)	1.19 (0.68, 2.08)

Table 7-10. Impact of adjustment for covariates: Regression parameters from linear models regressing log(AHI+1) on HT use before and after July 2002 with different covariates included

No HT Before July 2002	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
HT Before July 2002	0.00	-0.10	-0.11	-0.12	-0.12	-0.12	-0.12	-0.11
No HT After July 2002	0.21	-0.03	-0.06	-0.04	-0.04	-0.04	-0.02	-0.03
HT After July 2002	0.25	0.04	0.02	0.04	0.05	0.05	0.06	0.04
Covariates Included								
Age		●	●	●	●	●	●	●
Menopausal status			●	●	●	●	●	●
BMI				●	●	●	●	●
Neck girth					●	●	●	●
Alcoholic drinks per week						●	●	●
Waist girth							●	●
Smoking history								●

7.6 Sensitivity Analyses

Of all dates that could have been chosen to define time period, the date chosen *a priori*, July 2002, showed the greatest contrast in the relationship of HT use to AHI (Figure 7-4, p. 82). These results support the dichotomization into two periods before and after the first halting of the WHI trial, and do not suggest that unrelated secular trends explain the period effect.

Excluding observations in premenopause (Table 7-10, p. 80) did not substantially change the association between HT and AHI, or the evidence for a period effect. Excluding the eight observations at which subjects were using exclusively over the counter or herbal preparations as a menopausal hormone therapy also had minimal impact, except that the confidence interval on the estimated *positive* association of HT use after July 2002 excluded one.

Figure 7-4. Comparison of period effect before and after different dates.

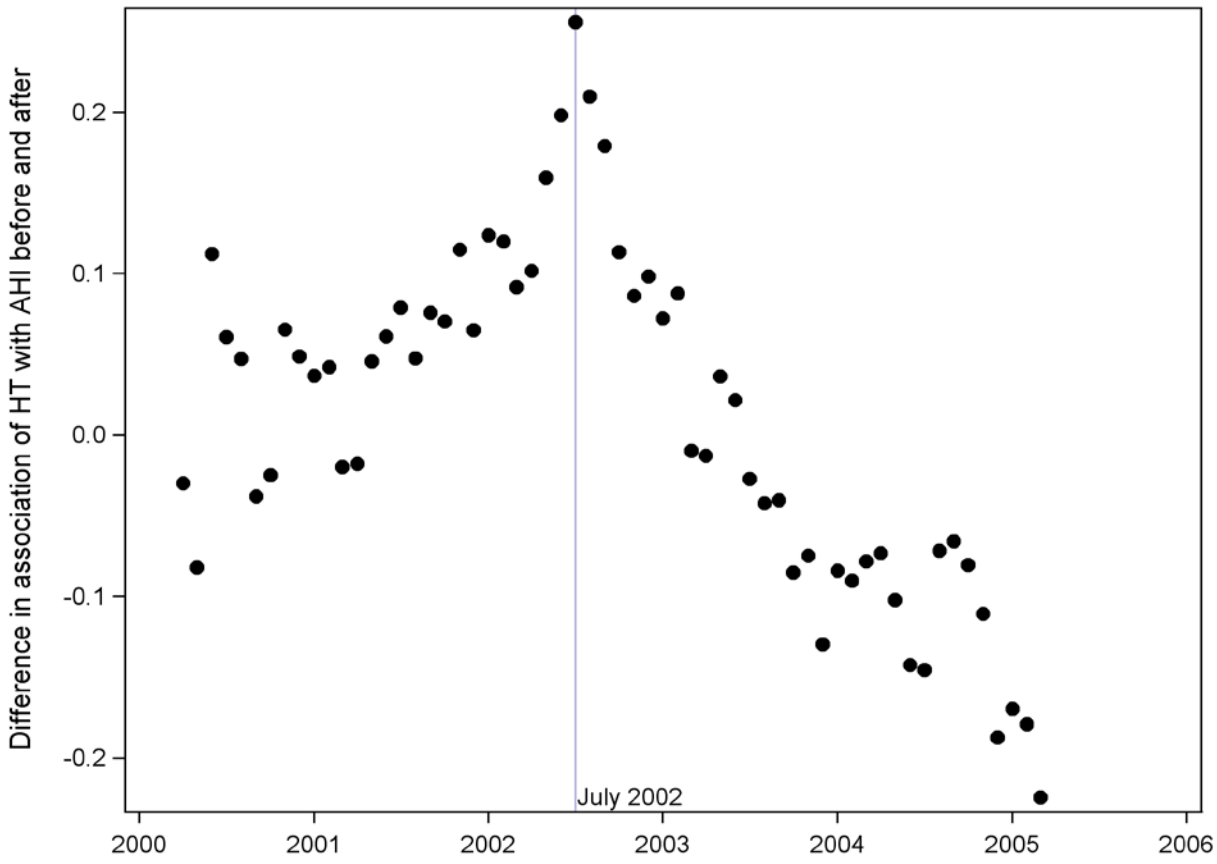


Table 7-11. Sensitivity analyses excluding observations on subjects in premenopause and excluding over the counter/herbal preparations from the definition of HT, from linear regression models (outcome = log(AHI+1).

	Excluding premenopause	**Excluding OTC/Herbal**
	AHI Ratio (95% CI)	**AHI Ratio (95% CI)**
	N=1,922	**N=1,658**
HT Use Pre/Post		
No HT Before	**1.00 (ref.)**	**1.00 (ref.)**
HT Before	**0.89 (0.76, 1.03)**	**0.87 (0.75, 1.01)**
No HT After	**0.97 (0.90, 1.05)**	**0.97 (0.90, 1.05)**
HT After	**1.06 (0.93, 1.20)**	**1.07 (0.95, 1.21)**
Overall *F* test	***P* = 0.01**	***P* <0.01**
HT After vs. No HT After	**1.09 (0.98, 1.21)**	**1.11 (1.00, 1.23)**
Menopausal stage		
Premenopause	--	1.00 (ref.)
Perimenopause	1.00 (ref.)	1.24 (0.98, 1.57)
Postmenopause	1.09 (0.99, 1.20)	1.35 (1.05, 1.73)
Peri-postmenopause (undetermined)	1.21 (1.03, 1.43)	1.44 (1.11, 1.88)
Age (years)	1.05 (1.03, 1.07)	1.05 (1.03, 1.06)
BMI	1.03 (1.00, 1.05)	1.03 (1.00, 1.05)
Neck girth (cm)	1.04 (1.02, 1.06)	1.04 (1.02, 1.06)
Waist Girth (mean cm)	1.02 (1.01, 1.02)	1.01 (1.01, 1.02)
Alcoholic drinks per week	1.00 (0.99, 1.02)	1.00 (0.99, 1.02)
Smoking history		
Never	1.00 (ref.)	1.00 (ref.)
Past	0.94 (0.82, 1.08)	0.94 (0.82, 1.08)
Current	1.06 (0.89, 1.26)	1.06 (0.90, 1.26)

7.7 Discussion

7.7.1 Summary

The findings presented in this chapter suggest that menopausal hormone therapies were associated with lower AHI only until July 2002. After that the association disappears. While it is plausible that HT could reduce AHI by a true biological mechanism, there is no clear explanation for why a biological relationship would be subject to a period effect. If HT truly improved breathing during sleep, that association would be expected to persist irrespective of time period. Moreover the finding that these heterogeneous medications with different mechanisms of action are on average associated with lower sleep-disordered breathing only until July 2002 makes a biological effect less plausible.

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.

No clear mechanism for a healthy-user effect emerged from this analysis. The Sleep in Midlife Women study was not designed to measure socioeconomic factors and health behaviors in detail, and the tools for directly testing a healthy user hypothesis were limited. There was a small amount of evidence that HT use in this sample was associated with some markers of overall healthfulness. Hourly income at baseline was associated with odds of using HT some time before July 2002, albeit with wide confidence intervals, but education level was associated

with lower odds of using HT after adjustment for income. Most baseline cardiovascular measures showed no association, but higher mean arterial pressure was associated with greater odds of HT use, a finding which contradicts the healthy user hypothesis. Descriptive analyses suggested that HT users in the early period were less likely to smoke and drank less alcohol, but neither behavioral factor appears to mediate the association between HT use in the early period and lower AHI.

These analyses found little evidence of other secular trends that could explain the period effect. Neither type of medication, dose of estrogen or progesterone, or time of medication initiation changed meaningfully after July 2002 in these data. Nor was any other date equivalent to July 2002 as a demarcation point, as might be expected if the dichotomization of time period merely captured a continuous change over time.

7.7.2 Strengths and Limitations

A major strength of this study is the time span of the data. All prior observational studies of HT and SDB used data collected before 2002, and thus may be vulnerable known and unknown factors analogous to those that, in hindsight, biased so many observational studies of HT and heart disease. This analysis had the ability to look at subjects in time periods when the social and health correlates of HT use were very different, and in many cases followed the same women in both periods.

The study's design offered further strengths. HT use was measured with unusual precision; medication use was captured at the level of the month, including medication type and dose. Collecting the data prospectively minimized recall bias, and taking repeated polysomnography

measurements over the course of the study allowed mixed regression models to control for time-invariant individual characteristics that could bias a cross-sectional association.

A major limitation of this analysis is the limited data on socioeconomic status and health behaviors that would have allowed more rigorous testing of the healthy user hypothesis. However it should be emphasized that healthy-user effects are by definition difficult to measure—if an easily measurable factor explains the tendency to use a type of medication, then adjustment for this factor would prevent a healthy user bias. It is the ill-defined intrinsic qualities of the user that cause the greatest potential for bias. Thus the lack of association between measurable qualities of "healthiness" and HT use does not rule out unmeasured confounding.

Alternative explanations for the observed period effect are possible. There was some evidence that after July 2002, subjects using HT did so for shorter periods of time. It is possible that hormone therapy is effective at lowering the apnea-hypopnea index only after prolonged exposure or at high doses, and thus these shorter intervals of HT use were less effective at lower AHI. However, duration of HT use was not associated with AHI in regression modeling, and adjustment for duration of HT use did not remove the observed pattern. Another possibility is 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. However there is no existing literature to support either of these speculations.

1.1.1 Importance

This analysis is unique in that it stratifies the effect of HT on SDB into a time before and after social and health correlates of menopausal hormone therapies changed. Importantly, these findings contradict those of three previous population-based studies, which found evidence of varying strength that hormone therapy use was associated with healthier breathing during sleep.[27,29,65] However all of these studies used data collected before 2001, when HT use was more common among healthy women. The evidence for a period effect suggests that a healthy-user effect may explain those findings.

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,[46] and the sampling of prevalent users among the observational studies.[48] 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.[70,100] When a gynecologist 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. The issue of interplay between sleep-disordered breathing and other sleep complaints is investigated in detail in Chapter 8.

Chapter 8. Sleep-Disordered Breathing and Insomnia Symptoms (Specific Aim #3)

8.1 Analytic Methods

This chapter focuses on AHI symptoms, with a focus on insomnia complaints. Subjects used monthly calendars (see Appendix 2) to report each night they had "trouble getting to sleep" or "trouble staying asleep." The calendar reports were used to derive the number of symptom days over the period between sleep studies. Modeling of total sleep time and hypnotic medication use are explored in Appendix 7 (p. 166) and Appendix 8 (p. 172) respectively.

In addition to continuous counts of symptom days, I created binary definitions of insomnia. I intended to define insomnia using DSM-5 criteria, as reporting a problem three nights per week for at least three months.[101] However, using this definition, sample size was too small to allow regression modeling (see Table 8-1, p. 95). So a looser definition was used, in which insomnia was defined as having a problem three nights per month for at least three months.

Sleep latency was derived from the interview question at which subjects were asked "About how many minutes does it usually take you to fall asleep at night?" Long sleep latency was defined as 30 minutes or more. Logistic regression was used to model this outcome.

One PSG-derived insomnia outcome was used. Minutes of Wake After Sleep Onset (WASO) was calculated as the total minutes spent awake after initially entering a sleep stage over the course of the night. Linear regression was used to model this outcome.

Descriptive statistics were performed as outlined in section 4.3.

Number of symptom days was modeled as a Poisson regression using number of diaries as an offset. I intended to also perform ordinal regressions using quartile of symptom days as an outcome. That analysis was not feasible, however, as described below in section 8.2. Logistic regressions modeled the odds of having insomnia from diary data (trouble getting to sleep, trouble staying asleep, or either kind of trouble), and from interview data (short sleep with dissatisfaction, short sleep with fatigue, or long sleep latency).

Models were adjusted for menopausal status (with premenopause and early perimenopause combined to avoid a small reference category), HT use, Zung depression score (modified to remove an item pertaining to trouble sleeping, so that possible scores ranged from 19-76), BMI, alcohol use, and smoking history.

In these models, menopausal status was defined as premenopause-early perimenopause, late perimenopause, or postmenopause. When date of postmenopause was missing, the date was imputed using mean time from the start of perimenopause to postmenopause (573 days). The main drawback to this mean imputation approach is that it may underestimate the variance in menopausal status,[102] but since it was primarily of interest for this analysis as a potential confounder, variance was a secondary concern.

Models were assessed for effect modification by menopausal status, by creating a cross-product term between AHI category and menopausal stage, in fully adjusted models. For the purposes of the effect modification analyses, menopausal stage was also dichotomized *post hoc* into pre-perimenopause vs. postmenopause. Mediation and confounding were assessed by a backwards deletion process as described in section 6.1.3.

Two sensitivity analyses examined the effect of excluding subjects who regularly used positive airway pressure masks—and whose AHI was therefore presumed to be higher on the night of the sleep study than it would be on nights they completed their diaries—and subjects who reported drinking alcohol within 24 hours of their sleep study.

Last, an analysis was conducted to assess whether women in this population with SDB exhibited classical SDB symptoms. Mimicking the STOP-BANG sleep apnea screening tool,[104] interview questions and measurement data were used to derive a seven-point score including snoring, tiredness/fatigue, observed apneas, blood pressure, BMI, age, and neck girth. The gender criterion was not used since everyone in the sample identified as female. Though interview questions were worded slightly differently from the questions on the screening tool, measurements captured the STOP-BANG criteria well.

Self-reported snoring, tiredness, and observed apneas were taken from interview data (Appendix 3). Subjects were asked how often they snore (question 34) and how loudly (question 35). Subjects were considered loud snorers if they reported that their snoring could be heard through a door. Subjects were also asked whether they or others had been aware of having breathing pauses during sleep (question 38), and answers were dichotomized as any vs. never or rarely. Subjects were also asked whether they usually experienced tiredness or fatigue (question 31). Blood pressure was taken from two seated measurements on the day of the sleep study; hypertension was classified as a mean systolic pressure of 140 mmHg or greater. BMI over 35, age over 50, and neck circumference over 40 cm were the final criteria. Sensitivity

to detecting an AHI of 15 or greater was calculated, using a STOP-BANG score of 3 or greater as a positive test.

8.2 Descriptive Statistics

The distribution of days with diary-reported insomnia outcomes was skewed toward zero (Figure 8-1, p. 94). Over all sleep studies with complete diary data, 765 (44%) were associated with a period of zero days of reported trouble getting to sleep, 594 (34%) were associated with zero days of reported trouble staying asleep, and 457 (30%) were associated with zero days reporting either kind of sleeping trouble. The high proportion of zero values makes the results of a straightforward linear regression of symptom days on AHI difficult to interpret. Furthermore the highest quartile of symptom days encompassed such a wide range of values (Table 8-2, p. 95) that an ordinal regression using quartiles as an outcome would not have been meaningful.

There were few observations at which subjects met the DSM criteria for insomnia (Table 8-1, p. 95). The looser definition was therefore used for modeling.

Table 8-3 (p. 96) shows the co-occurrence of AHI above fifteen and either DSM-defined insomnia based on diary reports, or interview-reported insomnia, over all sleep studies. A relatively small proportion of the population overall had two co-occurring disorders, but a substantial proportion of subjects with insomnia did have AHI values above fifteen. Out of the 231 subjects completing both diaries and sleep studies, 35 (15%) had AHI ≥ 15 at one or more visits at which they also met at least one criterion for insomnia.

Complete diary and PSG data were available at one or more visits for 188 subjects. The characteristics of subjects at baseline are shown in Table 8-4 (p. 97). From diary data, more than a third of the sample had at least one type of insomnia, but few subjects met the criteria for insomnia based on interview data. There were no clear patterns in insomnia prevalence across AHI category. Trouble getting to sleep appeared to become more prevalent at higher AHI categories, but not consistently. Trouble staying asleep decreased at higher AHI categories.

Characteristics over all observations are shown in Table 8-5 (p. 98). The proportion of subjects with diary-reported insomnia was similar to baseline, as were patterns across AHI categories. Consistent with findings from Chapter 6, more women in postmenopause fell into the higher AHI categories. Mean BMI and weekly alcohol consumption were also higher in higher AHI categories.

Figure 8-1. Distributions of diary-reported trouble sleeping, as percent of all nights at which complaint was reported

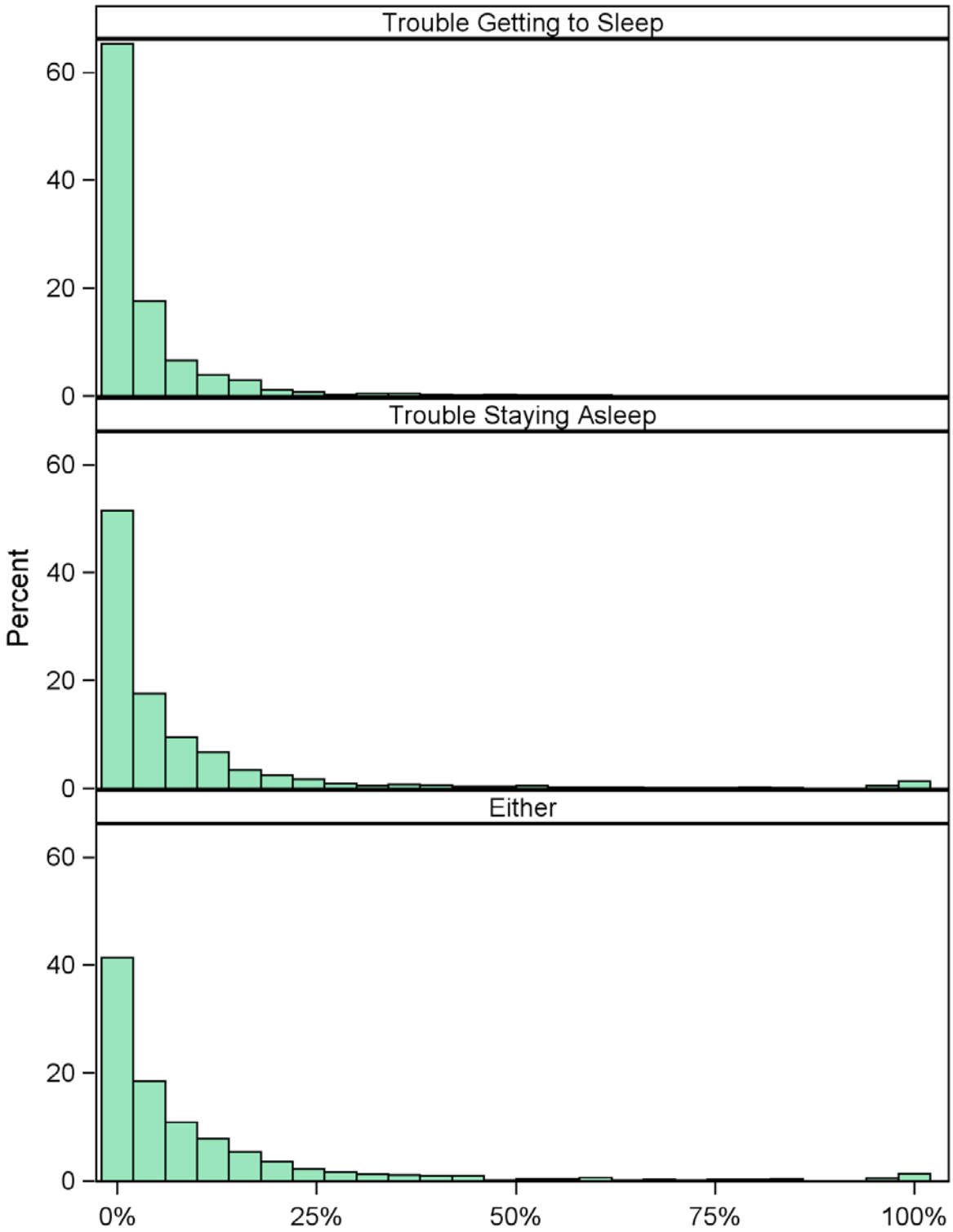


Table 8-1. Comparison of insomnia definitions using DSM criteria or looser criteria

	DSM Criteria					
	No		Yes		All	
	N	(%)	N	(%)	N	(%)
Trouble Getting to Sleep						
No	1445	(86%)	0	(0%)	1445	(87%)
Yes	214	(13%)	11	(1%)	225	(13%)
All	1659	(99%)	11	(1%)	1670	
Trouble Staying Asleep						
No	1261	(75%)	0	(0%)	1261	(76%)
Yes	322	(19%)	87	(5%)	409	(24%)
All	1583	(95%)	87	(5%)	1670	
Either						
No	1115	(67%)	0	(0%)	1115	(67%)
Yes	443	(27%)	112	(7%)	555	(33%)
All	1558	(93%)	112	(7%)	1670	

Table 8-2. Quartiles of diary-reported insomnia symptom days

	Trouble Getting to Sleep		Trouble Staying Asleep	
	Minimum	Maximum	Minimum	Maximum
Quartile				
1	0%	0%	0%	0%
2	0%	1%	0%	0%
3	1%	3%	2%	2%
4	3%	60%	8%	8%

Table 8-3. Co-occurrence, over all sleep studies, of AHI ≥ 15 and diary-reported insomnia (DSM criteria) or interview-reported insomnia

	AHI < 15		AHI ≥ 15		All	
	N	(%)	N	(%)	N	(%)
Trouble getting to sleep						
No	1286	(77%)	375	(22%)	1661	(99%)
Yes	8	(0%)	3	(0%)	11	(1%)
Trouble staying asleep						
No	1225	(73%)	360	(22%)	1585	(95%)
Yes	69	(4%)	18	(1%)	87	(5%)
All	1294	(77%)	378	(23%)	1672	
Long sleep latency						
No	1218	(76%)	349	(22%)	1567	(98%)
Yes	32	(2%)	7	(0%)	39	(2%)
All	1250	(78%)	356	(22%)	1606	

Table 8-4. Participant characteristics at baseline by AHI category.

	AHI									
	<5		5-<15		15-<30		≥30		All	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (years)	50.5	3.9	51.9	4.0	51.0	4.6	50.7	5.6	51.0	4.2
Zung score(modified)	30.2	7.4	29.0	6.2	31.0	6.0	31.8	7.4	30.1	6.9
BMI	28.1	6.3	32.2	7.3	38.0	8.6	42.1	6.9	31.6	8.2
Alcoholic drinks per week	2.6	3.2	2.7	3.6	2.1	5.3	2.9	4.6	2.6	3.7
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Trouble getting to sleep										
No	88	(93%)	48	(87%)	17	(81%)	14	(88%)	167	(89%)
Yes	7	(7%)	7	(13%)	4	(19%)	2	(13%)	20	(11%)
Trouble staying asleep										
No	68	(72%)	43	(78%)	16	(76%)	14	(88%)	141	(75%)
Yes	27	(28%)	12	(22%)	5	(24%)	2	(13%)	46	(25%)
Long Sleep Latency										
No	91	(96%)	53	(96%)	21	(100%)	16	(100%)	181	(97%)
Yes	4	(4%)	2	(4%)	0	(0%)	0	(0%)	6	(3%)
Menopausal stage										
Premenopause or Early Perimenopause	40	(42%)	16	(29%)	8	(38%)	4	(25%)	68	(36%)
Late Perimenopause	18	(19%)	11	(20%)	3	(14%)	4	(25%)	36	(19%)
Postmenopause	37	(39%)	28	(51%)	10	(48%)	8	(50%)	83	(44%)
Menopausal Hormone Therapy										
Yes	73	(77%)	40	(73%)	16	(76%)	14	(88%)	143	(76%)
No	22	(23%)	15	(27%)	5	(24%)	2	(13%)	44	(24%)
Smoking history										
Never smoker	51	(54%)	29	(53%)	13	(62%)	8	(50%)	101	(54%)
Past smoker	35	(37%)	18	(33%)	6	(29%)	4	(25%)	63	(34%)
Current smoker	9	(9%)	8	(15%)	2	(10%)	4	(25%)	23	(12%)
All	95		55		21		16		187	

Table 8-5. Subject characteristics by AHI category over all observations, continuous variables. Means are calculated as the mean of each subject's individual mean. Standard deviations are across subjects.

	AHI									
	<5		5-<15		15-<30		≥30		All	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (years)	52.1	3.9	53.1	3.8	53.3	4.0	52.4	4.8	52.7	4.0
Zung score(modified)	30.5	7.0	29.8	6.3	30.4	6.0	31.7	6.6	30.3	6.5
BMI	28.8	6.3	32.1	7.1	36.3	7.5	40.8	10.2	32.5	8.2
Alcoholic drinks per week	2.0	2.3	2.3	3.0	2.0	4.0	3.1	5.1	2.2	3.3
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Trouble getting to sleep										
No	469	(89%)	383	(87%)	144	(80%)	111	(87%)	1107	(87%)
Yes	57	(11%)	57	(13%)	35	(20%)	17	(13%)	166	(13%)
Trouble staying asleep										
No	388	(74%)	342	(78%)	140	(78%)	103	(80%)	973	(76%)
Yes	138	(26%)	98	(22%)	39	(22%)	25	(20%)	300	(24%)
Long Sleep Latency										
No	512	(97%)	427	(97%)	176	(98%)	124	(97%)	1239	(97%)
Yes	14	(3%)	13	(3%)	3	(2%)	4	(3%)	34	(3%)
Menopausal stage										
Premenopause or Early Perimenopause	143	(27%)	73	(17%)	27	(15%)	18	(14%)	261	(21%)
Late Perimenopause	115	(22%)	78	(18%)	29	(16%)	24	(19%)	246	(19%)
Postmenopause	268	(51%)	289	(66%)	123	(69%)	86	(67%)	766	(60%)
Menopausal Hormone Therapy										
Yes	421	(80%)	347	(79%)	138	(77%)	109	(85%)	1015	(80%)
No	105	(20%)	93	(21%)	41	(23%)	19	(15%)	258	(20%)
Smoking history										
Never smoker	287	(55%)	235	(53%)	99	(55%)	73	(57%)	694	(55%)
Past smoker	176	(33%)	138	(31%)	59	(33%)	31	(24%)	404	(32%)
Current smoker	63	(12%)	67	(15%)	21	(12%)	24	(19%)	175	(14%)
Total Subjects	117		125		61		21		187	
Total Observations	526		440		179		128		1273	

8.3 Investigation of Association between Sleep-Disordered Breathing and Trouble Getting to Sleep

There was some evidence that being in the highest AHI category was associated with trouble getting to sleep. In the multivariable Poisson and Logistic models (Table 8-6, p 101), there was no clear pattern across the lower severity categories, and neither tests for trend nor overall *F* tests suggested that AHI category overall was a good predictor of trouble getting to sleep. However the group with AHI ≥ 30 had more trouble getting to sleep in both models. In the Poisson model, the confidence interval excluded the null, and in both models the estimate had some clinical significance (1.62 times the number of symptom days and 1.95 times greater odds respectively). Age and modified Zung score were positively associated with symptom days, though effect sizes were small.

Paradoxically, being in the highest AHI category was also associated with the lowest odds of long sleep latency, though with broad confidence intervals. The test for trend was borderline significant ($P = 0.06$), with a negative relationship between AHI category and odds of long sleep latency. These two seemingly contradictory findings could be explained if subjects with higher AHI fell asleep more quickly on a typical night, but still had more atypical nights in which they had trouble falling asleep.

The impact of adjusting models of the association between AHI category and trouble getting to sleep are shown in Table 8-7 (p. 102) for the Poisson model, and in Table 8-8 (p.102) for the logistic model. Two noteworthy empirical confounders are menopausal status and Zung

depression score. In both models, exclusion of these covariates increased the magnitude of the estimated association between AHI and trouble getting to sleep.

The logistic models run without adjustment for Zung score is shown in (Table 8-9, p. 103, Model I). In the Poisson model of trouble getting to sleep, excluding Zung score had minimal effect on the observed pattern. In the logistic model, however, the highest AHI category was associated with more than twice the odds of trouble getting to sleep.

Over the course of the study, 23 subjects reported using PAP (continuous or bilevel), at 143 interviews. In sensitivity analyses (Table 8-9, p 103), excluding PAP users produced a similar model. Excluding subjects who reported using alcohol on their study night led to a higher estimated association with odds of trouble getting to sleep in all AHI categories above five, but with wide confidence intervals.

There was some evidence of effect modification by menopausal status in the logistic model (Table 8-10, p 104). Models interacting menopausal status with AHI category are shown in Table 8-11 (p 104). The observed association between high AHI and trouble getting to sleep was observed only in the pre-perimenopausal group. Postmenopausal subjects had more trouble getting to sleep overall, but AHI was not a predictor in this group.

Table 8-6. Association of AHI category with trouble getting to sleep. Poisson models report number of diary-reported symptom days, logistic models report odds of having symptoms three or more days per month for three months, and sleep latency reports self-reported time to fall asleep of 30 minutes or greater.

	Diary-Reported Trouble Getting to Sleep		Interview-Reported Long sleep latency
	Poisson	**Logistic**	**Logistic**
	N=1,303	**N=1,198**	**N= 1,336**
	Rate Ratio (95% CI)	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
AHI category			
<5	**1.00 (ref.)**	**1.00 (ref.)**	**1.00 (ref.)**
5-<15	**1.00 (0.76, 1.32)**	**1.10 (0.74, 1.62)**	**0.55 (0.23, 1.35)**
15-<30	**1.21 (0.82, 1.79)**	**0.91 (0.44, 1.89)**	**0.18 (0.02, 1.32)**
≥30	**1.62 (1.01, 2.59)**	**1.95 (0.77, 4.91)**	**0.15 (0.02, 1.43)**
Overall *F* test	***P* = 0.30**	***P* = 0.53**	***P* = 0.26**
Test for trend	***P* = 0.10**	***P* = 0.51**	***P* = 0.06**
Menopausal stage			
Premenopause or Early Perimenopause	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Late Perimenopause	1.07 (0.79, 1.45)	1.50 (0.84, 2.68)	1.72 (0.76, 3.90)
Postmenopause	1.23 (0.84, 1.78)	2.08 (1.12, 3.87)	1.47 (0.45, 4.86)
Age (years)	1.06 (1.01, 1.10)	1.07 (1.00, 1.14)	1.04 (0.86, 1.27)
Zung Score (modified)	1.03 (1.01, 1.05)	1.06 (1.03, 1.10)	1.03 (0.98, 1.09)
BMI	0.98 (0.96, 1.01)	0.98 (0.95, 1.02)	1.05 (0.98, 1.12)
Menopausal Hormone Therapy			
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	0.66 (0.50, 0.89)	0.51 (0.32, 0.80)	0.90 (0.43, 1.89)
Alcoholic drinks per week	0.97 (0.94, 1.01)	0.96 (0.90, 1.03)	0.94 (0.78, 1.13)
Smoking history			
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Past	0.97 (0.60, 1.55)	1.10 (0.51, 2.36)	1.69 (0.44, 6.50)
Current	1.29 (0.76, 2.19)	1.08 (0.51, 2.29)	3.37 (1.08, 10.51)

Table 8-7. Impact of adjustment for different confounders: Poisson parameters from models regressing trouble getting to sleep on AHI, with adjustment for different covariates.

AHI <5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
AHI 5-<15	0.15	0.14	0.11	0.11	0.13	0.14	0.14	0.15
AHI 15-<30	0.49	0.42	0.36	0.36	0.42	0.43	0.44	0.45
AHI ≥ 30	0.39	0.29	0.25	0.26	0.27	0.29	0.30	0.32
Covariates Included								
Zung score (modified)		●	●	●	●	●	●	●
Menopausal Status			●	●	●	●	●	●
Alcoholic Drinks per Week				●	●	●	●	●
Menopausal Hormone Therapy					●	●	●	●
BMI						●	●	●
Age							●	●
Smoking								●

Table 8-8. Impact of adjustment for different confounders: Logistic parameters from models regressing trouble getting to sleep on AHI category, with adjustment for different covariates

AHI <5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
AHI 5-<15	0.34	0.26	0.30	0.33	0.32	0.33	0.33	0.33
AHI 15-<30	0.39	0.26	0.34	0.37	0.34	0.37	0.38	0.38
AHI ≥ 30	0.85	0.78	0.96	0.87	0.80	0.81	0.81	0.83
Covariates Included								
Menopausal status		●	●	●	●	●	●	●
BMI			●	●	●	●	●	●
Zung score (modified)				●	●	●	●	●
Age					●	●	●	●
Smoking						●	●	●
Menopausal hormone therapy							●	●
Alcoholic drinks per week								●

Table 8-9. Comparison of different logistic regression models of odds of trouble getting to sleep ≥ 3 nights per month for three months. Model I does not adjust for Zung score, Model II excludes PAP users, Model III excludes subjects who reported using alcohol within 24 hours of their sleep studies.

	I. Not adjusting for depression	**II. Excluding PAP Users**	**III. Excluding night-of alcohol users**
	N= 1,187	**N=1,206**	**N=1,089**
	Odds Ratio (95% CI)	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
AHI category			
<5	**1.00 (ref.)**	**1.00 (ref.)**	**1.00 (ref.)**
5-<15	**1.34 (0.88, 2.03)**	**0.93 (0.61, 1.43)**	**1.47 (0.91, 2.39)**
15-<30	**1.39 (0.69, 2.79)**	**0.86 (0.42, 1.76)**	**1.41 (0.66, 3.00)**
≥30	**2.51 (1.03, 6.11)**	**1.37 (0.58, 3.25)**	**2.31 (0.93, 5.73)**
Overall *F* test	***P* = 0.41**	***P* = 0.79**	***P* = 0.41**
Test for trend	***P* = 0.09**	***P* = 0.90**	***P* = 0.13**
Menopausal stage			
Premenopause or Early Perimenopause	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Late Perimenopause	1.14 (0.64, 2.04)	1.37 (0.81, 2.33)	0.89 (0.51, 1.55)
Postmenopause	1.52 (0.83, 2.80)	1.93 (1.10, 3.39)	1.31 (0.73, 2.37)
Age (years)	1.06 (0.99, 1.13)	1.06 (0.99, 1.14)	1.07 (1.00, 1.15)
Zung score (modified)	--	1.05 (1.02, 1.08)	1.05 (1.02, 1.09)
BMI	0.99 (0.95, 1.03)	1.01 (0.96, 1.06)	0.99 (0.96, 1.03)
Menopausal Hormone Therapy			
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	0.82 (0.56, 1.21)	0.54 (0.34, 0.87)	0.76 (0.49, 1.20)
Alcoholic drinks per week	0.97 (0.91, 1.04)	0.97 (0.91, 1.03)	0.96 (0.89, 1.03)
Smoking history			
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Past	1.54 (0.71, 3.35)	1.30 (0.62, 2.69)	1.55 (0.70, 3.44)
Current	1.24 (0.59, 2.59)	1.31 (0.64, 2.66)	1.10 (0.50, 2.42)

Table 8-10. Testing for effect modification of AHI category by menopausal status in models of trouble getting to sleep. Each cell reports a *P*-value from the relevant cross-product term.

	Poisson Models			Logistic Models		
	AHI			AHI		
	5-<15	15-<30	≤30	5-<15	15-<30	≤30
Premenopause or Early Perimenopause	--	--	--	--	--	--
Late Perimenopause	0.69	0.60	0.80	0.85	0.04	0.96
Postmenopause	0.92	0.65	0.50	0.02	<0.01	0.05

Table 8-11. Results of regression models of trouble getting to sleep on AHI interacted with a postmenopause indicator. Logistic model outcome is odds of having trouble three nights per month for three months. Poisson model outcome is number of symptom days.

		Poisson Model Rate Ratio (95% CI) N=1,306	Logistic Model Odds Ratio (95% CI) N=1,299
Pre/Perimenopause	**AHI ≤5**	**1.00 (ref.)**	**1.00 (ref.)**
	AHI 5-<15	**1.73 (1.07, 2.78)**	**1.00 (0.73, 1.36)**
	AHI 15-<30	**1.41 (0.69, 2.85)**	**1.17 (0.85, 1.63)**
	AHI ≥30	**4.61 (2.02, 10.53)**	**2.08 (1.30, 3.33)**
Postmenopause	**AHI ≤5**	**2.52 (1.51, 4.21)**	**1.32 (0.98, 1.79)**
	AHI 5-<15	**1.99 (1.05, 3.78)**	**1.28 (0.90, 1.81)**
	AHI 15-<30	**2.06 (0.86, 4.93)**	**1.28 (0.90, 1.82)**
	AHI ≥30	**2.71 (1.02, 7.20)**	**1.18 (0.75, 1.84)**
Age (years)		1.04 (1.00, 1.07)	1.08 (1.01, 1.15)
Zung score(modified)		1.01 (1.00, 1.03)	1.06 (1.03, 1.09)
BMI		0.99 (0.97, 1.01)	0.99 (0.96, 1.03)
Menopausal Hormone Therapy			
Yes		1.00 (ref.)	1.00 (ref.)
No		0.86 (0.68, 1.09)	0.56 (0.35, 0.89)
Alcoholic drinks per week		1.01 (0.98, 1.03)	0.96 (0.90, 1.03)
Smoking history			
Never		1.00 (ref.)	1.00 (ref.)
Past		1.15 (0.84, 1.57)	1.32 (0.64, 2.71)
Current		1.29 (0.93, 1.78)	1.34 (0.67, 2.69)

8.4 Investigation of Association Between AHI and Trouble Staying Asleep

Results of logistic models regressing odds of having trouble staying asleep for three or more nights for three or more months are presented in Table 8-12 (p. 106). Multivariable Poisson models regressing symptom days with trouble staying asleep on AHI did not converge. As with models of trouble getting to sleep, there was some suggestion that subjects in the highest AHI category had more trouble staying asleep, but confidence intervals were broad.

Table 8-12 (p. 106) also shows results of multivariable linear models regressing minutes of WASO on AHI category. Higher AHI was associated with more waking minutes; both test for trend and overall *F* test were significant across AHI categories. Subjects in the highest AHI category had on average fifteen minutes more time awake overnight, with confidence intervals excluding zero.

Dropping Zung score from logistic models further reduced the magnitude of the association between AHI and trouble staying asleep (Table 8-13, p. 107). Excluding PAP users and subjects who reported alcohol use on the night of their sleep studies had minimal effect.

There was some evidence of effect modification by menopausal status (Table 8-14, p. 108). Among subjects in pre- or perimenopause, higher AHI category was associated with higher odds of trouble staying asleep (Table 8-15, p. 108). Among subjects in postmenopause, the opposite trend was observed. However confidence intervals were broad, and included the null for every estimate.

Table 8-12. Results of multivariable regressions of odds of reporting trouble staying asleep three nights per month for three months (logistic), and minutes of Wake After Sleep Onset (linear) on AHI category.

	Trouble staying asleep **N=1,198** **Odds Ratio (95% CI)**	**WASO (minutes)** **N = 1,336** **Difference (95% CI)**
AHI category		
<5	**1.00 (ref.)**	**0.00 (ref.)**
5-<15	**0.98 (0.68, 1.41)**	**0.63 (-3.57, 4.82)**
15-<30	**0.86 (0.55, 1.34)**	**3.78 (-2.60, 10.16)**
≥30	**1.21 (0.70, 2.11)**	**15.59 (4.55, 26.63)**
Overall *F*-test	***P* = 0.52**	***P* = 0.05**
Test for trend	***P* = 0.93**	***P* = 0.02**
Menopausal stage		
Premenopause or Early Perimenopause	1.00 (ref.)	0.00
Late Perimenopause	1.52 (0.88, 2.64)	- 0.45 (-5.90, 4.99)
Postmenopause	1.43 (0.79, 2.59)	- 0.11 (-6.38, 6.15)
Age (years)	1.04 (0.98, 1.10)	0.95 (0.21, 1.70)
Zung Score (modified)	1.01 (0.98, 1.03)	0.17 (-0.20, 0.55)
BMI	0.98 (0.95, 1.01)	0.22 (-0.07, 0.50)
Menopausal Hormone Therapy		
No	1.00 (ref.)	0.00
Yes	1.18 (0.77, 1.80)	0.08 (-4.04, 4.20)
Alcoholic drinks per week	1.01 (0.95, 1.06)	0.09 (-0.57, 0.75)
Smoking history		
Never	1.00 (ref.)	0.00
Past	1.42 (0.81, 2.50)	0.44 (-7.51, 8.39)
Current	2.14 (1.08, 4.22)	0.92 (-7.08, 8.92)

Table 8-13. Comparison of different logistic regression models of odds of trouble staying asleep ≥ 3 nights per month for three months. Model I does not adjust for Zung score, Model II excludes PAP users, Model III excludes subjects who reported using alcohol within 24 hours of their sleep studies.

	I. Not adjusting for depression	**II. Excluding PAP Users**	**III. Excluding night-of alcohol users**
	N= 1,187	**N=1,206**	**N=1,089**
	Odds Ratio (95% CI)	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
AHI category			
<5	**1.00 (ref.)**	**1.00 (ref.)**	**1.00 (ref.)**
5-<15	**0.93 (0.63, 1.38)**	**0.94 (0.67, 1.32)**	**0.92 (0.61, 1.39)**
15-<30	**0.91 (0.56, 1.48)**	**0.86 (0.56, 1.33)**	**0.91 (0.54, 1.51)**
≥30	**1.18 (0.64, 2.18)**	**1.14 (0.66, 1.97)**	**1.21 (0.65, 2.27)**
Overall *F*-test	***P* = 0.77**	***P* = 0.72**	***P* = 0.67**
Test for trend	***P* = 0.09**	***P* = 0.89**	***P* = 0.86**
Menopausal stage			
Premenopause or Early Perimenopause	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Late Perimenopause	1.45 (0.79, 2.65)	1.70 (0.91, 3.17)	1.50 (0.86, 2.60)
Postmenopause	1.64 (0.87, 3.09)	1.87 (0.97, 3.61)	1.70 (0.94, 3.08)
Age (years)	1.03 (0.97, 1.09)	1.02 (0.96, 1.09)	1.02 (0.96, 1.08)
Zung depression score (modified)	--	1.00 (0.98, 1.03)	1.00 (0.97, 1.03)
BMI	0.98 (0.95, 1.01)	1.00 (0.96, 1.03)	0.98 (0.95, 1.01)
Menopausal Hormone Therapy			
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	1.11 (0.77, 1.59)	1.04 (0.72, 1.52)	1.06 (0.73, 1.55)
Alcoholic drinks per week	1.02 (0.96, 1.08)	1.01 (0.96, 1.06)	1.02 (0.96, 1.09)
Smoking history			
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Past	1.68 (0.93, 3.03)	1.59 (0.91, 2.77)	1.70 (0.94, 3.07)
Current	1.68 (0.84, 3.38)	1.88 (0.95, 3.70)	1.88 (0.94, 3.77)

Table 8-14. Testing for statistical interaction in models of trouble staying asleep: *P*-values from cross-product terms for AHI category and menopausal status

	Logistic Models			Poisson Models		
	AHI			AHI		
	5-<15	15-<30	≤30	5-<15	15-<30	≤30
Late Perimenopause	0.61	0.04	0.45	--	--	--
Postmenopause	0.64	<0.01	0.38	--	--	--

Table 8-15. Results of regression models of having trouble staying asleep three nights per month for three months on AHI interacted with a postmenopause indicator.

		Logistic Model Odds Ratio (95% CI) N=1,164
Pre/Perimenopause	**AHI ≤5**	**1.00 (ref.)**
	AHI 5-<15	**1.02 (0.55, 1.91)**
	AHI 15-<30	**1.25 (0.63, 2.46)**
	AHI ≥30	**1.99 (0.75, 5.28)**
Postmenopause	**AHI ≤5**	**1.55 (0.82, 2.93)**
	AHI 5-<15	**0.81 (0.41, 1.59)**
	AHI 15-<30	**0.61 (0.30, 1.24)**
	AHI ≥30	**0.41 (0.13, 1.26)**
Age (years)		1.04 (0.99, 1.10)
Zung score(modified)		1.00 (0.97, 1.03)
BMI		0.98 (0.95, 1.01)
Menopausal Hormone Therapy		
Yes		1.00 (ref.)
No		1.11 (0.78, 1.60)
Alcoholic drinks per week		1.02 (0.96, 1.08)
Smoking history		
Never		1.00 (ref.)
Past		1.67 (0.93, 3.00)
Current		1.72 (0.86, 3.46)

8.5 SDB and classical symptoms

Complete data for STOP-BANG criteria was available for 1,597 observations, at 224 of which subjects had AHI ≥ 30. Overall a score of three or greater had 91% sensitivity for detecting AHI ≥ 30. Table 8-16 (p. 109) shows the sensitivity of screening score by insomnia status over 82 observations where subjects had complete insomnia data.

Table 8-16. Sensitivity of the STOP-BANG screening tool to detect AHI ≥ 30 in subjects with and without insomnia. N=122 subjects with AHI ≥ 30 and complete insomnia data.

	STOP-BANG Score			
	0-2		3-7	
	N	(%)	N	(%)
Trouble getting to sleep				
No	8	(10%)	71	(90%)
Yes	4	(27%)	11	(73%)
Trouble staying asleep				
No	12	(16%)	64	(84%)
Yes	0	(0%)	18	(100%)
Long sleep latency				
No	12	(13%)	78	(87%)
Yes	0	(0%)	4	(100%)
All	12	(13%)	82	(87%)

8.6 Discussion

8.6.1 Summary

The proportion of visits at which subjects had co-occurring insomnia and SDB confirms that these two disorders are not mutually exclusive. However, overall this analysis presents little evidence to support the hypothesis that higher AHI is associated with greater risk of insomnia, or that women with SDB are likely to experience insomnia rather than classical SDB symptoms. Most effects were small, and no clear pattern emerged, suggesting that any association of SDB with insomnia symptoms may be the result of chance. AHI was not associated with odds of trouble staying asleep. There was a slight *negative* association between AHI and odds of long sleep latency.

There was, however, some evidence that AHI was associated with trouble getting to sleep. Though confidence intervals were wide in many models, the highest AHI category was consistently associated with more symptoms days and greater odds of having trouble getting to sleep. There was not consistent evidence of an exposure-response relationship between worse AHI and more trouble getting to sleep. But this association cannot be ruled out based on these analyses.

There was also some evidence that menopausal status modifies the relationship of AHI to both trouble getting to sleep and trouble staying asleep. It is possible that menopausal status is obscuring the association of AHI and trouble getting to sleep in the main effect models. However, as discussed in Chapter 6, these interaction results should be interpreted with caution. Here, as well, there is no literature to support the finding of effect modification by

menopausal status, and in the absence of replicating studies, a single finding of interaction is not highly persuasive.

The impact of adjustment for Zung depression score is potentially important. Depression was originally conceived as a confounder in this analysis, but it could plausibly mediate an association between SDB and insomnia. Several cross-sectional studies,[105,106] have assessed the relationship of SDB to depression, with conflicting results. Importantly, a longitudinal study in the Wisconsin Sleep Cohort[107] suggested that SDB was prospectively associated with depression symptoms. Links between insomnia and depression are well established, but the directionality of the relationship is not clear.[108,109] Another longitudinal analysis of the Wisconsin Sleep Cohort suggested that insomnia symptoms were associated with subsequent development of depression symptoms,[110] which raises the possibility that conditioning on depression could introduce a collider bias.

These different causal pathways are particularly difficult to disentangle given that adjustment for Zung score had different impacts on different models. For example adjusting for Zung score increased the association between AHI category and symptom days with trouble getting to sleep in the Poisson model, but diminished the association with odds of having trouble getting to sleep in the logistic model. In summary, this analysis is consistent with several possible causal relationships, and does not clarify the role of depression in comorbidity of SDB and insomnia.

The sensitivity analysis excluding habitual PAP users from logistic models of diary-reported insomnia produced slightly lower estimates, and changed the direction of the association of AHI 5-15 with odds of having trouble getting to sleep. There was minimal impact on models of other

insomnia outcomes. This finding is difficult to interpret, but it does not suggest that PAP use biased the estimated association toward the null.

Excluding alcohol use from logistic models had the opposite effect. With or without and interaction with menopausal status, models excluding alcohol use showed a stronger positive association between each AHI category and trouble getting to sleep. The effect was less pronounced on models of other insomnia outcomes.

While there was some evidence that high AHI could be associated with trouble getting to sleep, there was no evidence that women with both SDB and insomnia were less likely to have classical SDB symptoms. Overall, most subjects with SDB in this population were correctly classified by the STOP-BANG screening tool, whether or not they had co-occurring insomnia.

1.1.1 Strengths and Limitations

The major strength of this analysis is its use of a population-based sample. Much of the prior work on the co-occurrence of SDB and insomnia has been done in clinic populations, which are more vulnerable to selection bias. The discrepancy between the number of SDB cases with co-occurring insomnia that we found and the numbers reported in studies of patients referred for suspected sleep apnea emphasizes that difference.

The fact that this population was largely healthy is both a strength and a limitation. It makes these findings generalizable to a wider population, but it limited this analysis in that few subjects in the sample met the DSM criteria for insomnia, so regression modeling of those strictly-defined insomnia outcomes was not possible. While some models suggested a clinically significant association between AHI and trouble getting to sleep, those findings need to be

interpreted with the understanding that most of the subjects in the insomnia category would not be diagnosed with insomnia in a clinical setting. The finding that only the most severe SDB was associated with trouble getting to sleep raises the possibility that this association is only important in the sickest people. That is another possible explanation for the discrepancies in prevalence between our study and the clinic-based studies.

The prospective collection of insomnia data here is a strength in that it potentially limited recall bias (a comparison between diary-reported insomnia symptoms and symptoms reported retrospectively at interviews for the parent study is shown in Appendix 9 (p.176). The use of repeated measures, and modeling that allowed us to control for time-invariant individual effects, was another strength, as was the detailed covariate data that allowed us to adjust for potential confounders.

One covariate that could be limited by measurement error is the Zung depression score. Though the Zung scale is in widespread use, and was a reasonable choice for this study, it relies on self-report of depression symptoms rather than clinical analysis. It also was measured with less precision than the insomnia data, since it was given once every six months. It would be interesting to see whether the potential confounding or mediating effect of depression on the association between SDB and insomnia could be replicated in a study that was designed to gather more detailed mental health data.

8.6.2 Importance

These findings stand in contrast to many studies conducted on sleep clinic patients. Studies of patients referred for suspected sleep-disordered breathing have estimated the prevalence of

insomnia complaints in that population at anywhere from 17% to 78%, whereas this analysis found the prevalence among subjects with AHI over 15 to be 1-6%, depending on which insomnia outcome was used. Studies of patients referred for insomnia complaints have found obstructive sleep apnea prevalences ranging from 10%-75%,[77–81,83] and sleep-disordered breathing prevalences ranging from 25%-67%.[82–85] In this analysis, prevalence of AHI of 15 or greater was 17-29%, comparable with some of the low end of estimates in clinic populations. These descriptive findings emphasize that a history of insomnia does not preclude underlying SDB, and that whether or not the connection is causal, clinicians should be aware that the two disorders may coexist in the same patient.

In this study population, subjects with SDB generally showed typical SDB signs and symptoms. The STOP-BANG screening tool had a sensitivity comparable to its reported sensitivity to detecting moderate-severe sleep apnea in the Sleep Heart Health Study,[113] and was high compared to sensitivities reported in various comparative validation studies.[114] These analyses do not suggest that standard screening methods are less effective in midlife women. Though there was limited sample size with which to examine the effect of insomnia on sensitivity, there was little suggestion that the screening tool was especially likely to miss insomniacs with SDB.

The discrepancy between our study and the studies recruiting from clinic populations is important, because unlike clinic patients our study subjects were recruited by population-based sampling. This study design is less vulnerable to selection bias than those using clinic populations, in which patients self-select by seeking treatment, and/or are selected by physician referral patterns. It is notable as well that our null findings are consistent with several

studies obtained on other populations not defined with respect to their sleep health.[94,95,115] One population-based study that did find a link between the two disorders used physician diagnosis to measure both insomnia and obstructive sleep apnea, and thus may still be influenced by clinic referral bias.[75]

If patients with both insomnia and SDB do not for the most part experience SDB differently, then an alternative explanation is needed for the high proportion of patients with both disorders that has been consistently reported in sleep clinics. Patients with both SDB and insomnia might be more likely to be referred to a sleep clinic than patients with symptoms of only one disorder, either because the referring provider is more likely to recognize these symptoms as requiring a consultation with a sleep specialist, or because patients with comorbid disorders are more sick, and therefore more likely to seek care.

Chapter 9. Conclusions

9.1 Summary

The three analyses presented for this dissertation are united by the investigation of sleep-disordered breathing in midlife women. Implicit in the motivation for all these analyses is the issue of misdiagnosis. The recent history of estrogen and progesterone therapies teaches us that menopause is not a modifiable risk factor. While a connection between menopausal status and SDB suggests further interesting hypotheses, the immediate relevance in identifying such a connection and exploring its nuances is primarily to clinical diagnosis.

The analyses in Chapter 6 suggest that menopausal women, even with lean bodies and relatively young ages, have more breathing events during sleep. Thus sleep problems should not be attributed to normal processes of menopause without screening for primary sleep disorders. The analyses in Chapter 7 suggest that when sleep-disordered breathing is misdiagnosed as sleep disruption resulting from menopausal discomforts, treatments for those discomforts will not be effective for SDB. The analyses in Chapter 8 suggest that midlife women with sleep-disordered breathing in the general population are not much more likely to experience insomnia symptoms than other women, and that there is no evidence that sleep-disordered breathing is more likely to produce atypical signs and symptoms in this population. Overall this project demonstrates the importance of recognizing SDB in midlife women, of treating it as a primary sleep disorder rather than a feature of menopause, and of addressing factors that contribute to disparities in referral to sleep clinics.

9.2 Limitations and implications for future research

The dearth of observations on women in premenopause is a major limitation of this study. While the line between premenopause and perimenopause has an arbitrary element, future studies could provide a more complete picture of the spectrum of menopausal status. Further work remains to be done on the trajectory of sleep-disordered breathing, and whether menopausal status predicts progression from forms of the disease that are milder or more easily compensated-for, to a more severe disease phenotype.

All the challenges in measuring menopause accurately were challenges for this study, too. Because the menopausal transition occurs over a limited range of ages, the ability to control for chronologic age is limited. Like any observational study, this project is vulnerable to confounding by unknown and unmeasured factors. It is important to see whether the findings of interaction between BMI and menopausal status in predicting AHI, and between AHI and menopausal status in predicting insomnia, can be replicated in larger samples.

The heterogeneity in types of hormone use precluded an in-depth analysis of the effect of dose and duration of menopausal hormone therapies. The limited data available on socioeconomic and general health measures prevented in-depth assessment of potential mechanisms for a healthy-user effect.

It is theoretically possible that selection bias could explain some of the observed associations here. Subjects with less healthy sleep and more challenging experiences of menopause may have attributed their sleep problems to menopause, and thus been more likely to join the study.

This study's generalizability is limited by race and ethnicity. There has been much interesting scholarship around how race affects the experience of menopause, and whether differences across racial and ethnic categories can be attributed to other social factors. However the Wisconsin Sleep Cohort sample was overwhelmingly Caucasian, and the Sleep in Midlife Women Study included only seven women of color. Thus it was not possible to investigate whether race or ethnicity modified the relationships observed in this project. More research into how race and ethnicity interplay with issues of menopausal sleep health is needed.

This study is also limited to female-bodied subjects who identified as female. Recent research into the sleep health of transgender women[116] raises interesting possibilities for new ways to study the interactions of different aspects of gender and aging, and of exogenous hormone use, on sleep. Moving beyond gender as an unmodifiable binary trait has the potential to deepen our understanding of the causal mechanisms by which gender affects sleep health.

Despite these limitations, the projects presented for this dissertation represent the most thorough work to date on SDB and the menopausal transition. While menopausal stage itself is not a modifiable risk factor, the association between menopausal status and sleep-disordered breathing could generate many hypotheses about the mechanism of that association, some aspects of which could be modifiable. If we accept that menopausal women are at greater risk for primary sleep disorders such as obstructive sleep apnea, the most important next steps include hypotheses in the realm of health services research. Much need remains for empirical study into what causes social patterning in patients' willingness to seek care for sleep

complaints, primary care doctors' referral to sleep specialists, sleep clinicians' correct diagnosis of obstructive sleep apnea, and patients' adherence to treatments.

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Appendices

Appendix 1: Sleep Diary Questionnaires

Please answer these questions ***on the last day of the month***. (Circle one on each line)

1. Did you have any spotting or flow this month? No Yes

2. Did you take any birth control this month (pill/shot)? No Yes

3. Did you take any of the following for hormone replacement therapy (HRT) this month?
   a. Estrogen (Premarin/Estrace/Estradiol) No Yes: Dose_____
   b. Progesterone (Provera/Medroxyprogesterone/Cycrin) No Yes: Dose_____
   c. Other_____ Dose_____

4. Did you take melatonin this month? No Yes
   a. If **yes**, how much and how often?_____

5. Did you take any medications this month? No Yes
   a. If **yes**, what and how often? _____
   _____

6. Did you have any female or gynecologic surgery this month? No Yes
   a. If **yes**, what?_____

7. Did your period change at all this month? No Yes
   a. If **yes**, how?_____

8. Did you have any of these experiences this month? **If yes, how many days?**

a. Hot flashes	No	Yes:	1-2	3-5	6+
b. Night sweats	No	Yes:	1-2	3-5	6+
c. Feeling nervous, irritable or tense	No	Yes:	1-2	3-5	6+
d. Feeling down, blue or depressed	No	Yes:	1-2	3-5	6+
e. Trouble sleeping	No	Yes:	1-2	3-5	6+

9. Please answer the following questions about your sleep this month by **checking all that apply**.
   a. Sleep *disturbed* by:
      _____Hot flush/flashes
      _____Recent surgery, illness, or injury. Describe: _____
      _____Depression, stress, emotional upset
      _____Need to go to the bathroom
      _____Other. Please describe: _____

   b. Sleep habits changed:
      _____Got more sleep
      _____Got less sleep
      _____Other. Please describe: _____

   c. Sleep problems:
      _____Insomnia
      _____Nightmares/bad dreams
      _____Excessive sleeping (seem to sleep too much)
      _____Sleep was not refreshing
      _____Other. Please describe: _____

   d. Other changes in sleep:
      _____ Please describe: _____

Please use the following letters when filling out the calendar:

Menstrual Flow

Letter	Meaning
L	Light flow or spotting
M	Medium flow (change sanitary protection about every 3-4 hours)
H	Heavy flow (change sanitary protection about every 1-2 hours)
E	Extreme flow (change sanitary protection ***every hour for at least 3 hours***)

Please answer these questions ***on the last day of the month***. (Circle **one** on each line)

1. Did you take any birth control pills or have a birth control shot or implant this month? **N**o **Y**es

2. Did you take any hormone replacement therapy (HRT) this month? **N**o **Y**es **S**ame as last month

   a. If **yes**, what (refer to supplement pages)? _____**Dose:**_____

   Any HRT to add to our list?_____**Dose:**_____

3. Did you take any sleeping pills or other substance to help you sleep? **N**o **Y**es **S**ame as last month

   a. If **yes**, what and on how many nights did you take it?_____

   _____

4. Did you take any prescription medications this month? **N**o **Y**es **S**ame as last month

   a. If **yes**, what and on how many days/nights did you take it?_____

   _____

   _____

   _____

5. Did you take any herbal or over-the-counter medications this month? **N**o **Y**es **S**ame as last month

   a. If **yes**, what and on how many days/nights did you take it? _____

   _____

6. Did your period change at all this month? **N**o **Y**es **N**o period

   a. If **yes**, how?_____

7. Did you have any of these experiences this month? **If yes, how many days?**

-

   a. Feeling nervous, irritable or tense **N**o **Y**es: 1-2 3-5 6+

   b. Feeling down, blue or depressed **N**o **Y**es: 1-2 3-5 6+

— Please answer these questions **on the last day of the month**. (Circle **one** reply for each line) —

1. Did you take any birth control pills or have a birth control shot or implant this month? **No** **Yes**

2. Did you take any hormone replacement therapy (HRT) this month? **No** **Yes** **S**ame as last month

➔ If **yes**, what (refer to supplement pages)? _____ Dose**:**_____

_____ Dose**:**_____

Do you have any HRT to add to our list? _____ Dose**:**_____

3. Did you take any sleeping pills or other substance to help you sleep? **No** **Yes** **S**ame as last month

➔ If **yes**, what & on how many nights did you take it: _____

4. Did you take any prescription medications this month? **No** **Yes** **S**ame as last month

➔ If **yes**, please list the name of each drug and the number of days/nights it was taken:

Name of drug	#days/nights	Name of drug	#days/nights
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

5. Did you take any herbal or over-the-counter medications this month? **No** **Yes** **S**ame as last month

➔ If **yes**, please indicate what and the number of days/nights it was taken:

Name	#days/nights	Name	#days/nights
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

6. Did your period change at all this month? **No** **Yes** **No Period/menopause**

➔ If **yes**, how?_____

7. Did you have any of these experiences this month? **If yes, how many days?**

a. Feeling nervous, irritable or tense? **No** **Yes** Ž 1-2 3-5 6+

b. Feeling down, blue or depressed? **No** **Yes** Ž 1-2 3-5 6+

Appendix 2: Sleep Calendars

** Mark the calendar ***on each day you have menstrual flow even if it's just a little,*** by circling the letter that best describes your flow.

On the day you consider ***your first day* of your menstrual period, please ***circle the date*** to indicate the day your menstrual period started.

Letter	Meaning
L	Light flow or spotting
M	Medium flow (change sanitary protection about every 3-4 hours)
H	Heavy flow (change sanitary protection about every 1-2 hours)
E	Extreme flow (change sanitary protection ***every hour for at least 3 hours***)

MAY 1997

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1 L M H E	2 L M H E	3 L M H E
4 L M H E	5 L M H E	6 L M H E	7 L M H E	8 L M H E	9 L M H E	10 L M H E
11 L M H E	12 L M H E	13 L M H E	14 L M H E	15 L M H E	16 L M H E	17 L M H E
18 L M H E	19 L M H E	20 L M H E	21 L M H E	22 L M H E	23 L M H E	24 L M H E
25 L M H E	26 L M H E	27 L M H E	28 L M H E	29 L M H E	30 L M H E	31 L M H E
						
→ → → →	PLEASE TURN OVER TO ANSWER QUESTIONS. THANK YO					☺

MARK CALENDAR:

Menstrual Flow

- Circle date your menstrual flow started.
- Circle letter for heaviness of flow each day of period (see codes on back page).

Sleep Problems

- Write in code for sleep problem.
- Put the code on the day you woke up.
- Codes:

F-PM	Nighttime hot flashes
F-AM	Daytime hot flashes
I-1	Insomnia (getting to sleep)
I-2	Insomnia (staying asleep)
NM	Nightmares/Bad dreams
R	Restless sleep

June 1999

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1 L M H E	2 L M H E	3 L M H E	4 L M H E	5 L M H E
6 L M H E	7 L M H E	8 L M H E	9 L M H E	10 L M H E	11 L M H E	12 L M H E
13 L M H E	14 L M H E	15 L M H E	16 L M H E	17 L M H E	18 L M H E	19 L M H E
20 L M H E	21 L M H E	22 L M H E	23 L M H E	24 L M H E	25 L M H E	26 L M H E
27 L M H E	28 L M H E	29 L M H E	30 L M H E			

✈✈✈✈ **PLEASE TURN OVER TO ANSWER QUESTIONS. THANK YOU!!** ☺

Please use the following letters when filling out the calendar:

Menstrual Flow

- Circle date your menstrual flow started.
- Circle letter for describing flow on each day of period.
  - Flow: L Light flow or spotting
    M Medium flow (change sanitary protection about every 3-4 hours)
    H Heavy flow (change sanitary protection about every 1-2 hours)
    E Extreme flow (change sanitary protection **every hour for at least 3 hours**)

Sleep Problems

- Write in code for any sleep problem(s) you experience.
  - Enter the code(s) on the day you woke up:
    - Codes: 1 = Nighttime hot flashes
      2 = Daytime hot flashes
      3 = Insomnia (getting to sleep)
      4 = Insomnia (staying asleep)
      5 = Nightmares/Bad dreams
      6 = Restless sleep

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
 *Please mail after filling out the back.*				**1** L M H E	**2** L M H E	**3** L M H E
4 L M H E	**5** L M H E	**6** L M H E	**7** L M H E	**8** L M H E	**9** L M H E	**10** L M H E
11 L M H E	**12** L M H E	**13** L M H E	**14** L M H E	**15** L M H E	**16** L M H E	**17** L M H E
18 L M H E	**19** L M H E	**20** L M H E	**21** L M H E	**22** L M H E	**23** L M H E	**24** L M H E
25 L M H E	**26** L M H E	**27** L M H E	**28** L M H E	**29** L M H E	**30** L M H E	

Appendix 3: Interview Questionnaire

Measurements:

Weight (without shoes & in light clothing only, to nearest 0.1 kg): _____ kg _____ kg

Measure all girths in nearest 0.5 cm. Neck girth 1:_____ Neck girth 2:_____

Clothed? Circle Yes or No Waist girth 1: _____ Waist girth 2: _____

Clothed? Circle Yes or No Hip girth 1: _____ Hip girth 2: _____

PM Blood Pressure (After 5 minutes of quiet sitting, take 2 readings 2 minutes apart.)

Seated Left Arm 1 _____/_____ Seated Left Arm 2 _____/_____

The first set of questions are about your activities over the past 24 hours.

1. About what time did you fall asleep last night: _____ AM/PM

2. How well did you sleep, was it? _____Better than usual, or
_____As well as usual, or
_____Worse than usual.

3. What time did you wake up today? _____AM/PM

4. Did you take any naps today? _____Yes _____ No

(If yes) What time did you nap: _____How long did you sleep? _____# of minutes

5. How was your day today, was it? _____ A very typical day, or
_____ Less stressful than usual, or
_____ More stressful than usual.

6. Do you have any physical problems or discomforts tonight? _____Yes _____No

(If yes) What is it? _____

7. Have you had any nasal congestion or stuffiness **today or tonight**? _____ None
_____Today
_____Tonight

The next few questions are about any medicines or drugs that you take daily or almost daily.

8. Do you **regularly** take any medicines (including prescription & over the counter drugs)?
_____Yes _____ No

(If yes) Could you tell me the name of each drug you take:

Name of drug Did you take it today?

a. _____Yes _____ No _____

b. _____ Yes _____ No _____

c. _____ Yes _____ No _____

d. _____ Yes _____ No _____

9. Have you taken any other kind of drug today? _____Yes _____ No

(If yes) What was it?_____

Now I'm going to ask you about specific medical problems. I would like you to tell me if you have ever been told by a doctor that you have or have had any of these conditions.

10. Coronary artery disease _____Yes _____ No

(If yes) how many years ago were you told _____ or what year 19_____ _____

What, if any, treatment are you receiving for this now?

_____
_____
_____

11. Atherosclerosis (hardening of the arteries) _____Yes _____No

(If yes) how many years ago were you told _____ or what year 19_____ _____

What, if any, treatment are you receiving for this now?

_____
_____

12. Irregular heartbeat or arrhythmia _____Yes _____No

(If yes) how many years ago were you told _____or what year 19_____

What, if any, treatment are you receiving for this now?

_____ _____
_____
_____

13.Heart attack or infarct _____Yes _____ No

(If yes) how many years ago were you told _____ or what year 19_____

What, if any, treatment are you receiving for this now?

_____
_____

14. Congestive heart failure _____Yes _____No

(If yes) how many years ago were you told _____or what year 19_____

What, if any, treatment are you receiving for this now?

_____
_____

15. Angina _____Yes _____No

(If yes) how many years ago were you told _____ or what year 19_____

What, if any, treatment are you receiving for this now?

_____

16. Have you ever had any of the following procedures? (Show card A)

a. Coronary bypass surgery? _____Yes _____ No

b. Coronary/balloon angioplasty? _____Yes _____ No

c. Insertion of pacemaker/defibrillator? _____Yes _____No

d. Other heart/cardiac surgery? _____ Yes _____No If Yes, what? _____

17. High blood pressure or hypertension? _____ Yes _____ No

(If yes) how many years ago were you told _____ or what year 19_____

What, if any, treatment are you receiving for this now?

_____

18. Stroke? _____Yes _____No

(If yes) how many years ago were you told _____ or what year 19_____

_____What, if any, treatment are you receiving for this now?

_____
_____

19. Diabetes? _____Yes _____ No

(If yes) how many years ago were you told _____ or what year 19_____

What, if any, treatment are you receiving for this now?

_____

20. Asthma? _____ Yes _____ No

(If yes) how many years ago were you told_____ or what year 19_____

What, if any, treatment are you receiving for this now?

_____

21. Emphysema or Obstructive Lung Disease? _____ Yes _____ No

(If yes) how many years ago were you told _____ or what year 19_____

What, if any, treatment are you receiving for this now?

_____
_____

22. Thyroid problem? _____ Yes _____ No

(If yes) how many years ago were you told _____ or what year 19_____

Describe the type of thyroid problem and what, if any, treatment are you receiving for this now?_____

23. Arthritis? _____ Yes _____ No

(If yes) how many years ago were you told _____ or what year 19_____

What, if any, treatment are you receiving for this now?

_____

The next series of questions concern your health since your last sleep study.

24. Since your last study have you developed any chronic joint or back pain?____Yes ____No

(If yes) when did it occur? _____ Month/Year Please describe it:_____

_____

25. Since your last study have you had any major illness or hospitalization? ____ Yes ____ No

(If yes) when did it occur? _____ Month/Year Please describe it:_____

_____

The next few questions are about your typical alcohol use and smoking habits. We realize that most people's habits vary a lot, depending on their weekly social plans and so on, but we hope to get an idea of your "usual" or average.

26. About how many: a. cans/ bottles of beer might you have per week? ____ b. glasses of wine per week? _____
c. mixed drinks or shots might you have per week? _____
_____NONDRINKER? _____ (skip to question 29)____

27. How many nights, during a typical week, might you have an alcoholic drink just before bed? _____ # of nights

28. Have you had any alcoholic beverage within the last 24 hours? _____ Yes _____ No

(If yes) At about what time was that? _____ pm **OR** _____ am

How much did you drink? _____ # of drinks

29. Have you ever smoked tobacco regularly? _____Yes _____ No (if no go to #31)

30. Do you currently smoke? _____Yes _____ No

(If no) When did you quit? _____ Year

How much do you smoke now, OR if you quit smoking, how much did you smoke in the past?

_____ Cigarettes a day **OR** _____ packs a week

The next series of questions concern how you generally feel.

31. Do you usually feel tired or fatigued at times **during a typical day**? _____Yes _____ No

(If yes) Does the tiredness interfere with your (Show card B/check all that apply):

_____ _____ Work
_____ _____ Mood
_____ _____ Relationships with people
_____ _____ Enjoyment of life
_____ _____ Ability to concentrate
_____ _____ Motivation
_____ Housework
_____ None of the above, tiredness does not interfere with my activities

32. Many people have periods of low energy or fatigue, but, **during a typical day** do you experience excessive sleepiness when it is difficult to fight an **uncontrollable urge to fall asleep**? _____ Yes _____ No
(If yes) Does your sleepiness interfere with your (Show card B/check all that apply):

_____ _____Work
_____ _____ Mood
_____ _____ Relationships with people
_____ _____ Enjoyment of life
_____ _____ Ability to concentrate

_____ _____ Motivation
_____ _____ Housework
_____ None of the above, sleepiness does not interfere with my activities

Do you know why you have periods of sleepiness? _____Yes _____ No

(If yes) What is the reason(s)? _____

33. How often, on the average, do you take a nap during the day or evening?
(Show card C/check one)

_____ _____ Never, or less than once a month

_____ _____ On a few days per month

_____ _____ Irregularly, but at least once a week

_____ _____ Every day or almost every day

The following questions concern your sleep habits over the last 6 months.

34. According to what others have told you and to your own awareness, how often do you snore? (Show card D/check one)

_____ Never or rarely - only once or a few times ever.

_____ Sometimes - a few nights per month; under special circumstances.

_____ At least once a week, but pattern may be irregular.

_____ Several (3 to 5) nights per week.

_____ Every night or almost every night (6 to 7 nights per week).

_____ Do not know.

35. How loud do you think or have others said your snoring is? (Show card E/check one)

_____ Only slightly louder than heavy breathing.

_____ About as loud as mumbling or talking.

_____ Louder than talking.

_____ Extremely loud, can be heard through a closed door.

_____ Do not know.

_____ Does not apply.

36. According to what others have told you, how often, if ever, do you gasp, choke, or make snorting sounds during sleep? (Show card D/check one)

_____ Never or rarely - only once or a few times ever.

_____ Sometimes - a few nights per month; under special circumstances.

_____ At least once a week, but pattern may be irregular.

_____ Several (3 to 5) nights per week.

_____ Every night or almost every night (6 to 7 nights per week).

_____ Do not know.

37. How often, if ever, have you awakened suddenly with the feeling of gasping or choking?
(Show card D/check one)

_____ Never or rarely - only once or a few times ever.

_____ Sometimes - a few nights per month; under special circumstances.

_____ At least once a week, but pattern may be irregular.

_____ Several (3 to 5) nights per week.

_____ Every night or almost every night (6 to 7 nights per week).

_____ Do not know.

38. According to what others have told you, or to your own awareness, how often, if ever, do you have momentary periods during sleep when you stop breathing or you breathe abnormally?

(Show card D/check one)

_____ Never or rarely - only once or a few times ever.

_____ Sometimes - a few nights per month; under special circumstances.

_____ At least once a week, but pattern may be irregular.

_____ Several (3 to 5) nights per week.

_____ Every night or almost every night (6 to 7 nights per week).

_____ Do not know.

39. Now I'm going to ask you about different sleep problems. I'd like you to look at this list and tell me how often you have these problems.(Show card F/enter a number for each item: 0=Never 1=Rarely: once/month 2=Sometimes: 2-4/month 3=Often: 5-15/month 4=Almost always:16-30/month)

_____a.Do you have difficulty getting to sleep?

_____b.Do you wake up during the night and have a hard time getting back to sleep?

_____c.Do you wake up repeatedly during the night?

_____d.Do you wake up too early in the morning and can't get back to sleep?

_____e.Do you not feel rested during the day no matter how many hrs of sleep you had?

_____f.Do you find it very difficult to wake up in the morning?

_____g. Do you have nightmares or disturbing dreams?

_____h.Do you have feelings of excessive daytime sleepiness?

40. About how many minutes does it usually take you to fall asleep at night? _____ #min.

41. How many hours of sleep do you usually get during:

a. a workday night? _____ # of hours

b. a weekend or nonwork night? _____ # of hours

c. a typical week from daytime or evening **naps**? _____ # of hours (enter 0 if none)

The next set of questions are about getting medical care for any sleep problem.

42. Have you ever gone to a doctor specifically for any sleep problem? _____Yes _____No

(If yes) When was this _____ (Month/Year) and:

What was the sleep problem(s) you were trying to get help for? _____

_____

What kind of doctor (general, family doctor, sleep medicine doctor, etc) examined you?

_____

_____What tests, if any, were done? _____

_____ What was the diagnosis? _____

Did you go to a doctor because of the results of your last study in our lab?

_____ Yes _____No

43. Have you ever been told by a doctor that you have Sleep Apnea? _____Yes _____No

(If yes) When was this?_____ Month/Year and:

What tests, if any, were done? _____

_____Were you told you needed treatment? _____Yes _____No

(If yes) What treatment was recommended? _____ _____

_____Did you have the treatment? _____Yes _____No

(If yes) when did you first have the treatment? _____Month/Year

Did the treatment help? _____Not at all

_____ _____ Helped a little
_____ _____ Helped moderately
_____ _____ Helped a lot

Comments:

If the treatment was CPAP or BiPAP (air pressure machine connected to a nose mask), please answer the following questions:

If you **are not using** the recommended CPAP/BiPAP, please explain why.

If you **are using** the recommended CPAP/BiPAP, please indicate:

a. How many nights per week do you use it? _____
b. How many hours per night do you use it? _____

Describe the problems, if any, you have with the CPAP/BiPAP: _____

The final section concerns your general health and the quality of your sleep.

44. Are you satisfied with your **usual** night's sleep? (Show card G/check one)

_____ Most of the time
_____ Some of the time
_____ Not usually
_____ Never

Are there any comments you would like to make about the quality of your sleep, or getting to sleep, staying asleep, or waking up?

45. In general, would you say your health is: (Show card I/check one)

_____ Excellent
_____ Very good
_____ Good
_____ Fair
_____ Poor

Tech: _____

Date: _____

Appendix 4: Methods for Handling Missing Menopause Data

Menopausal status was missing at 379 observations, nearly a fifth of the entire sample. Missingness was primarily a result of an unknown date for the start of postmenopause. In Chapter 6 and Chapter 7, missingness was handled by creating a category of menopausal status for subjects who were in undetermined peri-postmenopause as a result of missing postmenopause date. In Chapter 8, date of postmenopause was imputed using the mean of the sample for which complete data were available. In addition to these approaches, three other methods were also attempted to handle missing menopausal status: hot deck imputation using the cell adjustment technique, hot deck imputation using a distance technique, and multiple imputation.

Hot Deck imputation[102] was attempted two ways. First, adjustment cells were created using age at early perimenopause (dichotomized as before or after 45), age at late perimenopause (dichotomized as before or after 50), and birth year (dichotomized as before or after 1950). The method then calls for imputing each subject's missing age at postmenopause by taking a random draw from among observed values on subjects with matching values of these categorical variables. This method is appealing because it is nonparametric and makes no assumptions about the distribution of age at postmenopause. However, sample size did not allow this step to be completed (see Table A-2, p. 152).

A second method of Hot Deck imputation was also attempted, using the distance metric developed by Siddique et. al., implemented with the MIDAS macro.[117] This method is also nonparametric. The probability that an observed value of age at postmenopause would be sampled to impute a missing value was proportional to the distance metric, which was estimated based on continuous versions of the same variables used to create the adjustment cells described above. Five imputations were run.

However this method has an important limitation in the context of this particular project. It does not offer a way to draw values conditional on other values. In this case that meant that it was possible for a given subject to draw a value of age at postmenopause that was *earlier* than the observed age at late perimenopause. Thus while age at postmenopause might be statistically valid in itself, using it to calculate menopausal status introduces a differential misclassification: subjects with missing dates at postmenopause had a nonzero chance of having observations at which they were observed to be in perimenopause misclassified as postmenopause.

Multiple imputation was also used to impute age at postmenopause, using the same criteria based on birth year and age at other menopausal stages. PROC MI was used, with a Markov chain Monte Carlo method, as this made the fewest assumptions about the pattern of missing data. A normal distribution of age at postmenopause was assumed, and five imputations were run. The same problem arises using this method of imputing postmenopause ages earlier than observed late perimenopause ages.

The distribution of AHI among observations at which subjects' menopausal status could not be determined was unremarkable, roughly normal, and similar in range to nonmissing (Figure A-1, p. 150). Age at postmenopause was normally distributed, making it a suitable choice for multiple imputation (Figure A-2, p. 150).

Neither multiple imputation nor either hot deck imputation method succeeded. Both multiple imputation, and hot deck imputation using a distance metric, produced imputed values of age at postmenopause that led to substantial misclassification of observed values of postmenopause (Table A-1, p. 151). Out of all observed values of menopausal status, 32% were misclassified using multiple imputation, and 30% were misclassified using hot deck imputation with the distance metric. There was insufficient sample size in adjustment cells to allow hot deck imputation using this technique; in some cells there were more missing values than observed (Table A-2, p. 152). In summary none of the three methods had sufficient face validity to allow them to be used to impute missing menopausal status.

Figure A-1. Distribution of AHI by missingness of menopausal status

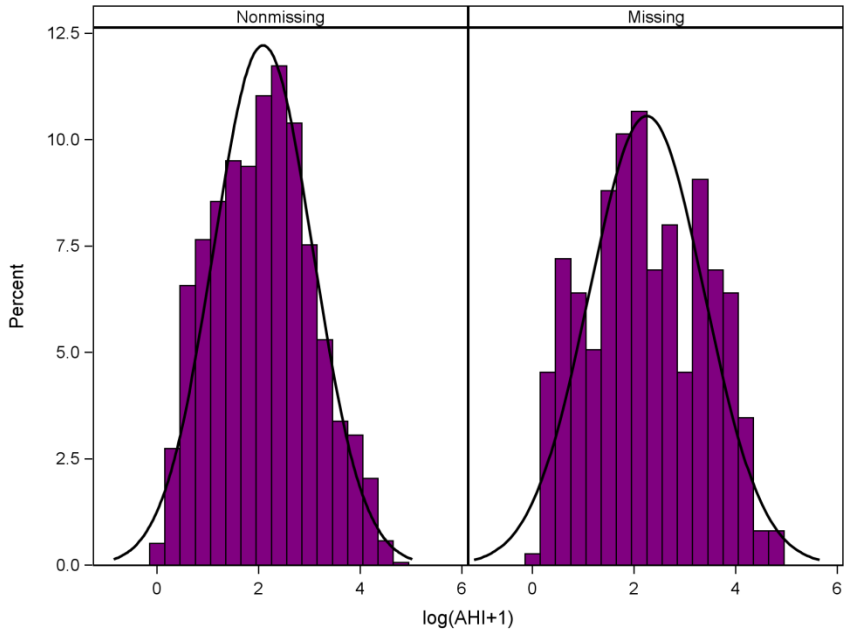

Figure A-2. Distribution of age at postmenopause over all subjects whose date of start of perimenopause was known.

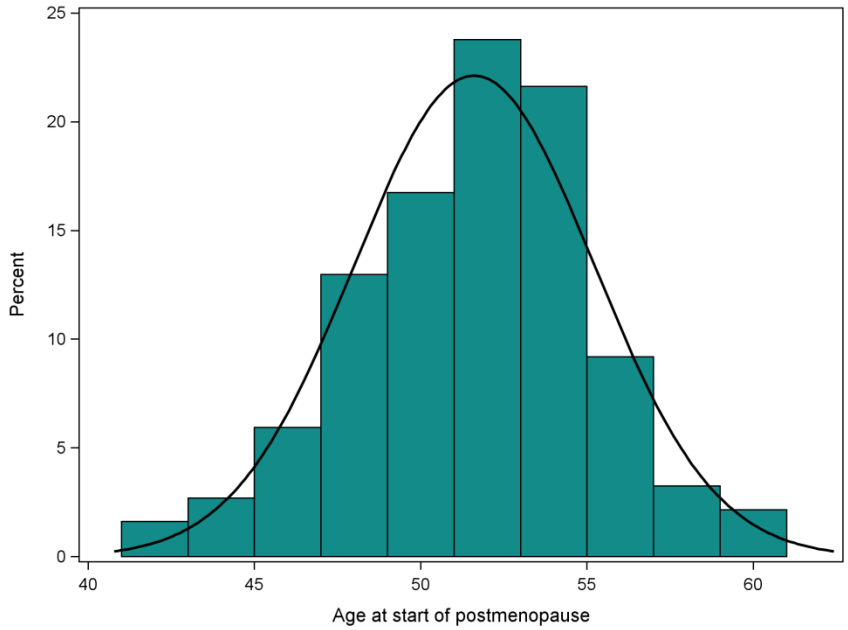

Table A-1. Misclassification of observed menopausal status using five Multiple Imputations or five Hot Deck Imputations to impute age at postmenopause.

	Observed							
	Missing		Premenopause		Perimenopause		Postmenopause	
	N	(%)	N	(%)	N	(%)	N	(%)
Multiple Imputation								
Premenopause	887	(47%)	140	(56%)	417	(16%)	247	(5%)
Perimenopause	593	(31%)	81	(32%)	918	(36%)	508	(10%)
Postmenopause	415	(22%)	29	(12%)	1245	(48%)	4325	(85%)
Hot Deck Imputation								
Premenopause	650	(34%)	110	(44%)	310	(12%)	185	(4%)
Perimenopause	861	(45%)	111	(44%)	1096	(42%)	590	(12%)
Postmenopause	384	(20%)	29	(12%)	1174	(46%)	4305	(85%)

Table A-2. Adjustment cells created for Hot Deck imputation

			Age at start of postmenopause	
			Nonmissing	Missing
Birth year	Age at early perimenopause	Age at late perimenopause		
≤1950	Missing	Missing	2	0
		≤50	14	0
		>50	14	0
	≤45	≤50	2	0
		>50	1	0
	>45	Missing	1	0
		≤50	13	1
		>50	67	2
>1950	Missing	Missing	1	0
		≤50	8	0
		>50	1	0
	≤45	Missing	0	18
		≤50	24	7
		>50	1	1
	>45	Missing	0	11
		≤50	14	5
		>50	9	10
Total			172	55

Appendix 5: Including In-Laboratory Observations from the Wisconsin Sleep Cohort Study

While the Sleep in Midlife Women Study was in progress, subjects were also participating in the parent study, and coming to the sleep laboratory every four years on average for overnight studies. Since menopausal status and HT use were known during whatever period of time subjects completed diaries, those laboratory observations could also be used for the analyses of menopausal status and SDB, and of HT on SDB. Complete data on all covariates was available at 351 laboratory visits.

5.1 Measurement

The equipment used for sleep studies in the laboratory was different from the in-home equipment. In the laboratory, 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).

5.2 Descriptive Results

Figure A-3 (p. 154) shows a comparison between AHI measured in the sleep laboratory for the Wisconsin Sleep Cohort study, and AHI measured at the home visit closest in time to that laboratory visit. The in-home equipment systematically measured higher AHI. On the log scale there was a roughly linear relationship between AHI measured at home and in the laboratory.

This relationship suggests that combining data from laboratory visits with data from home visits is reasonable, provided regression models adjust for the venue at which AHI was measured. Table A-3 and Table A-4 (p. 154-155) show descriptive characteristics of the sample by menopausal stage. Table A-5 and Table A-6 (p. 157-158) show descriptive characteristics of the sample by HT use before and after July 2002 when lab visits are included. Patterns are similar to those observed without lab visits included.

Figure A-3. Linear relationship between log(AHI+1) measured in laboratory and log(AHI+1) measured at the home visit closest in time. Dashed line represents the line of unity. Regression line is equal to y = 0.65x + 0.23.

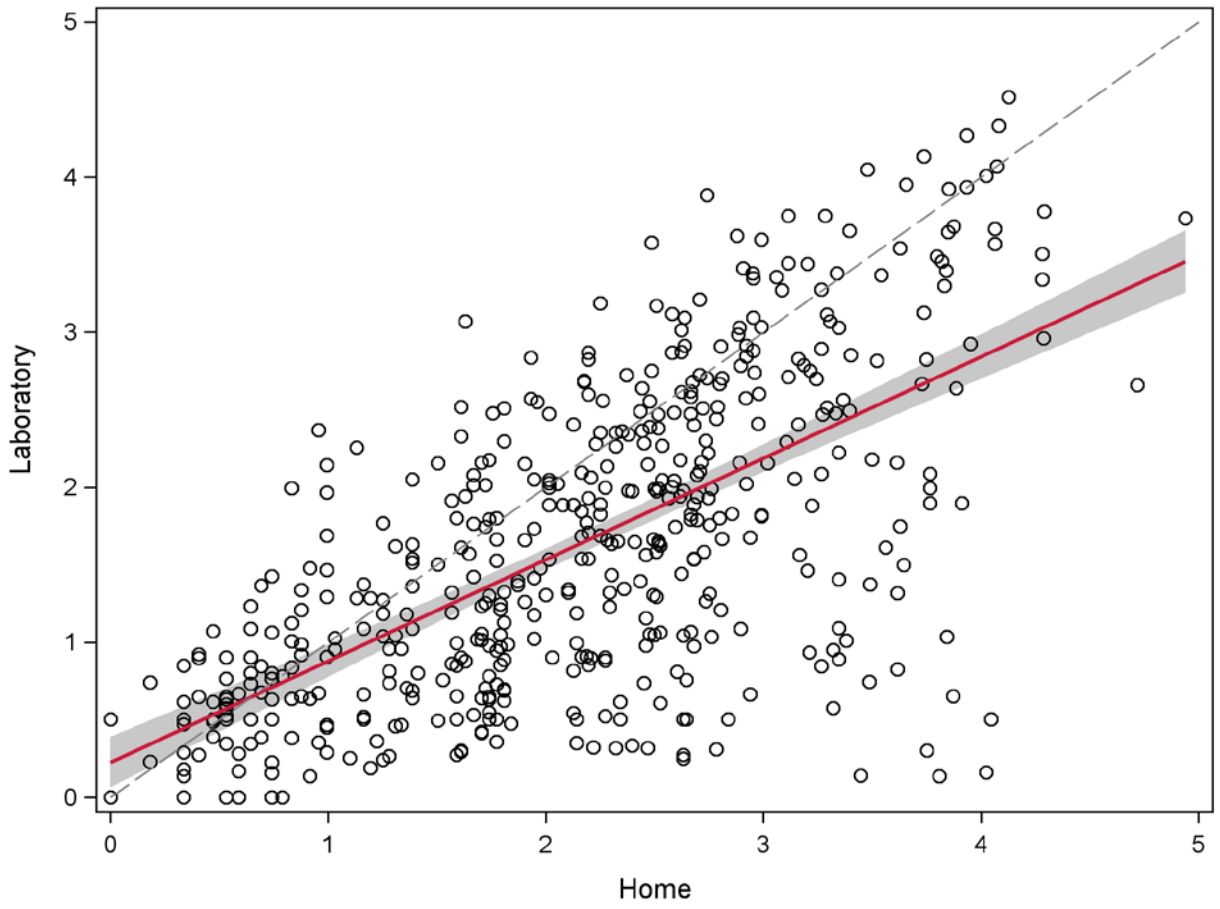

Table A-3. Participant characteristics over all home and lab visits, continuous variables. Means are calculated as the mean of each individual subject's mean. Standard deviations are across subjects.

	Premenopause		Perimenopause		Postmenopause		Peri-Postmenopause (undetermined)		All	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Apnea-Hypopnea Index (AHI)	4.2	(5.5)	9.9	(13.3)	11.6	(12.3)	10.8	(12.1)	10.2	(12.2)
Age (years)	40.9	(5.3)	50.7	(3.1)	54.7	(3.6)	48.3	(3.6)	51.0	(5.7)
BMI	29.9	(6.2)	31.4	(8.2)	31.8	(8.8)	32.2	(6.7)	31.5	(8.1)
Neck circumference (cm)	35.3	(3.2)	35.4	(3.4)	35.6	(3.5)	35.9	(3.2)	35.5	(3.4)
Waist circumference (cm)	90.0	(13.8)	93.9	(18.3)	95.0	(17.8)	95.4	(14.9)	94.2	(17.2)
Alcoholic drinks per week	2.6	(3.5)	2.1	(3.0)	2.3	(3.0)	2.6	(3.4)	2.3	(3.1)

Table A-4. Subject characteristics over all home and lab visits, categorical variables.

	Premenopause		Perimenopause		Postmenopause		Peri-Postmenopause (undetermined)		All	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Apnea-Hypopnea Index										
< 15	96	(100%)	474	(93%)	785	(73%)	329	(98%)	1684	(83%)
≥ 15	0	(0%)	35	(7%)	293	(27%)	6	(2%)	334	(17%)
Menopausal Hormone Therapy										
No	54	(56%)	266	(52%)	581	(54%)	173	(52%)	1074	(53%)
Yes	32	(33%)	145	(28%)	382	(35%)	130	(39%)	689	(34%)
Smoking history										
Never	10	(10%)	98	(19%)	115	(11%)	32	(10%)	255	(13%)
Past	25	(26%)	481	(94%)	885	(82%)	276	(82%)	1667	(83%)
Current	71	(74%)	28	(6%)	193	(18%)	59	(18%)	351	(17%)
Total subjects[a]	44		108		170		24		226	
Total Observations	96		509		1078		335		2018	

[a]Subjects may contribute observations to more than one category of menopausal status

Table A-5. Subject characteristics over all observations, including laboratory observations, by HT status and period, continuous variables

	Before July 2002				After July 2002				All	
	No HT		HT		No HT		HT			
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
AHI	9.7	(12.6)	9.0	(9.7)	11.2	(11.9)	12.1	(11.7)	10.5	(11.9)
Age (years)	49.6	(6.6)	53.5	(3.9)	53.7	(5.1)	54.0	(3.6)	52.3	(5.7)
BMI	31.3	(8.2)	30.5	(8.3)	32.2	(8.5)	32.1	(8.5)	31.7	(8.4)
Neck girth (cm)	35.6	(3.7)	35.3	(3.4)	35.8	(3.4)	35.7	(3.3)	35.6	(3.5)
Waist girth (cm)	94.4	(18.2)	93.4	(17.2)	95.3	(17.4)	95.5	(18.9)	94.8	(17.8)
Alcoholic drinks per week	2.5	(3.3)	2.1	(2.6)	2.3	(3.1)	2.3	(3.3)	2.3	(3.1)

Table A-6. Subject characteristics over all observations, including laboratory observations, by HT status and period, categorical variables.

	Before July 2002				After July 2002				All	
	No HT		HT		No HT		HT			
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
AHI										
<15	499	(78%)	188	(83%)	810	(78%)	82	(77%)	1579	(78%)
≥15	140	(22%)	39	(17%)	235	(22%)	25	(23%)	439	(22%)
Menopausal stage										
Premenopause	86	(13%)	0	(0%)	10	(1%)	0	(0%)	96	(5%)
Perimenopause	277	(43%)	22	(10%)	197	(19%)	13	(12%)	509	(25%)
Postmenopause	191	(30%)	203	(89%)	594	(57%)	90	(84%)	1078	(53%)
Peri-Postmenopause (undetermined)	85	(13%)	2	(1%)	244	(23%)	4	(4%)	335	(17%)
Smoking history										
Never	313	(49%)	128	(56%)	567	(54%)	66	(62%)	1074	(53%)
Past	230	(36%)	80	(35%)	350	(33%)	29	(27%)	689	(34%)
Current	96	(15%)	19	(8%)	128	(12%)	12	(11%)	255	(13%)
Venue										
Home	512	(80%)	204	(90%)	863	(83%)	88	(82%)	1667	(83%)
Laboratory	127	(20%)	23	(10%)	182	(17%)	19	(18%)	351	(17%)
Total subjects[a]	155		61		205		49		226	
Total observations	639		227		1045		107		2018	

[a]Subjects may contribute observations to more than one category

5.3 Regression Results with laboratory values included

Regression results with laboratory observations included show similar relationships to those observed with home visits only. As expected, including lab visits increased power, but did not substantially change the estimated association, suggesting that adjusting for venue was sufficient to remove potential sources of bias. With this increased power, all confidence intervals on menopausal status excluded one (Table A-7 and Table A-8, p. 160-161). With increased power, the confidence interval on HT use before 2002 also excluded one (Table A-9, p. 162). These findings do not change the conclusions of earlier chapters, but are provided here in part to demonstrate the increase in precision, which may be important given the continuing cultural emphasis on so-called “statistical significance.”

Table A-7. Results of multivariable linear regression of log(AHI+1) on menopausal status, with laboratory values included. N=2,018

	AHI Ratio (95% CI)
Menopausal stage	
Premenopause	1.00
Perimenopause	1.22 (1.02, 1.46)
Postmenopause	1.30 (1.07, 1.58)
Peri- to Postmenopause (undetermined)	1.34 (1.11, 1.63)
Overall *F* test	*P* = 0.02
Test for trend[a]	*P* = 0.01
Age (years)	1.04 (1.03, 1.05)
BMI	1.02 (1.00, 1.05)
Neck circumference (cm)	1.02 (1.00, 1.04)
Waist circumference (cm)	1.02 (1.01, 1.03)
Menopausal Hormone Therapy	
No	1.00
Yes	0.95 (0.85, 1.06)
Alcoholic drinks per week	1.01 (0.99, 1.02)
Smoking history	
Never	1.00
Past	0.98 (0.83, 1.17)
Current	1.09 (0.90, 1.32)

Table A-8. Results of multivariable regressions of log(AHI+1) on years in menopause, with laboratory visits included. Observations on subjects in premenopause were excluded. N=1,638.

	AHI Ratio (95% CI)
Years since start of perimenopause	1.04 (1.01, 1.06)
Age (years)	1.03 (1.01, 1.05)
BMI	1.02 (0.99, 1.04)
Waist circumference (cm)	1.03 (1.01, 1.05)
Neck circumference (cm)	1.02 (1.01, 1.03)
Menopausal Hormone Therapy	
No	1.00
Yes	0.95 (0.85, 1.06)
Alcoholic drinks per week	1.00 (0.99, 1.02)
Smoking history	
Never smoker	1.00
Past smoker	0.88 (0.73, 1.06)
Current smoker	0.96 (0.77, 1.19)
Venue	
Home	1.00
Laboratory	1.49 (1.39, 1.60)

Table A-9. Results of linear regression of AHI on menopausal hormone therapy interacted with a pre/post-July 2002 indicator, including laboratory values. N=2,018

	AHI Ratio (95% CI)
HT Use Pre/Post	
No HT Before	1.00
HT Before	0.85 (0.74, 0.99)
No HT After	0.97 (0.90, 1.05)
HT After	1.01 (0.89, 1.14)
Overall *F* test	*P* = 0.02
HT After vs. No HT After	1.04 (0.93, 1.15)
Menopausal stage	
Premenopause or Early Perimenopause	1.00
Late Perimenopause	0.95 (0.80, 1.14)
Postmenopause	1.04 (0.85, 1.27)
Peri-Postmenopause (undetermined)	1.05 (0.87, 1.28)
Age (years)	1.05 (1.04, 1.06)
BMI	1.02 (1.00, 1.05)
Neck girth (cm)	1.04 (1.02, 1.06)
Waist Girth (mean cm)	1.02 (1.01, 1.02)
Alcoholic drinks per week	1.00 (0.99, 1.02)
Smoking history	
Never	1.00
Past	0.90 (0.76, 1.05)
Current	0.96 (0.79, 1.15)
Venue	
Home	1.00
Laboratory	1.44 (1.35, 1.54)

The source of the difference between the types of equipment is not known, and one is not necessarily more correct than the other, but the laboratory measures are more standard.

Appendix 6: Modeling the relationship of continuous AHI to insomnia outcomes

In addition to the models presented in Chapter 8, which used AHI category as a predictor in various models of insomnia outcomes, several models were run using continuous AHI as the predictor variable. Because of the left-skewed distribution of AHI (Figure 5-2, p. 34), it was necessary to log AHI to prevent outliers becoming unduly influential. Models using continuous AHI were consistent with models using categorical AHI. The association of continuous AHI with symptom days of trouble getting to sleep was meaningfully large, and the confidence interval nearly excluded zero. The negative association between AHI and sleep latency also nearly excluded zero. Given that the models that showed the best evidence of an association between categorical AHI and insomnia did so primarily in the most severe category, it is reasonable to wonder whether a nonlinear model might fit the data better. The addition of a quadratic term was considered. However such a model becomes difficult to interpret, as it involves translating the quadratic term of a logged variable into some kind of real-world relationship without any literature to support a biological association with that shape. The categorical variable seemed a simpler and more assumption-free way of describing that higher risk of insomnia in subjects with the worst AHI.

Table A-10. Poisson regressions of diary-reported insomnia outcomes on log(AHI+1)

	Trouble getting to sleep	Trouble staying asleep	Either
	Rate Ratio (95% CI)	Rate Ratio (95% CI)	Rate Ratio (95% CI)
log(AHI+1)	1.20 (0.98, 1.48)	0.98 (0.81, 1.18)	1.06 (0.89, 1.25)
Menopausal stage			
Premenopause or Early Perimenopause	1.00	1.00	1.00
Late Perimenopause	1.27 (0.81, 1.98)	2.09 (1.16, 3.76)	1.76 (1.06, 2.93)
Postmenopause	1.67 (1.03, 2.71)	2.62 (1.23, 5.58)	2.29 (1.20, 4.36)
Age (years)	1.03 (1.01, 1.05)	1.01 (0.98, 1.05)	1.02 (0.99, 1.05)
Zung Score (modified)	0.98 (0.93, 1.03)	1.01 (0.95, 1.07)	1.00 (0.95, 1.05)
BMI	0.99 (0.96, 1.02)	0.99 (0.96, 1.02)	0.99 (0.96, 1.02)
Menopausal Hormone Therapy			
No	1.00	1.00	1.00
Yes	0.69 (0.46, 1.02)	0.80 (0.51, 1.26)	0.77 (0.53, 1.13)
Alcoholic drinks per week	0.98 (0.89, 1.08)	1.03 (0.97, 1.11)	1.02 (0.96, 1.09)
Smoking history			
Never	1.00	1.00	1.00
Past	0.98 (0.58, 1.66)	1.65 (0.94, 2.88)	1.36 (0.84, 2.2)
Current	0.84 (0.47, 1.51)	2.36 (1.19, 4.7)	1.69 (0.96, 2.97)

Table A-11. Results of multivariable logistic regressions of diary-reported outcomes for 3 nights per month for 3 months on log(AHI+1). N=1,299

	Trouble getting to sleep	Trouble staying asleep	Either
	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
log(AHI+1)	1.06 (0.79, 1.43)	0.97 (0.79, 1.19)	1.15 (0.96, 1.38)
Menopausal stage			
Premenopause or Early Perimenopause	1.00	1.00	1.00
Late Perimenopause	1.40 (0.80, 2.47)	1.72 (0.94, 3.13)	1.46 (0.87, 2.42)
Postmenopause	1.93 (1.09, 3.42)	1.70 (0.89, 3.24)	1.51 (0.88, 2.61)
Age (years)	1.07 (1.00, 1.14)	1.02 (0.97, 1.08)	1.04 (0.99, 1.10)
Zung Score (modified)	1.06 (1.03, 1.09)	1.00 (0.98, 1.03)	1.02 (1.00, 1.04)
BMI	0.99 (0.96, 1.03)	0.99 (0.96, 1.02)	0.98 (0.94, 1.01)
Menopausal Hormone Therapy			
No	1.00	1.00	1.00
Yes	0.56 (0.36, 0.87)	1.17 (0.80, 1.70)	0.87 (0.60, 1.27)
Alcoholic drinks per week	0.97 (0.91, 1.03)	1.01 (0.96, 1.07)	1.02 (0.97, 1.07)
Smoking history			
Never	1.00	1.00	1.00
Past	1.31 (0.64, 2.66)	1.66 (0.96, 2.88)	1.35 (0.80, 2.28)
Current	1.25 (0.65, 2.40)	2.10 (1.12, 3.96)	1.42 (0.84, 2.41)

Table A-12. Results of multivariable logistic regressions of interview-reported insomnia outcomes on log(AHI+1).

	Short total sleep time + dissatisfaction	Short total sleep time + Fatigue Affecting Life	Long sleep latency
	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
N	1,430	1,461	1,491
log(AHI+1)	0.96 (0.62, 1.47)	1.22 (0.87, 1.70)	0.57 (0.32, 1.03)
Menopausal stage			
Premenopause or Early Perimenopause	1.00	1.00	1.00
Late Perimenopause	2.23 (1.08, 4.58)	1.55 (0.82, 2.91)	1.65 (0.71, 3.81)
Postmenopause	2.28 (1.01, 5.11)	1.47 (0.72, 3.02)	1.42 (0.42, 4.86)
Age (years)	0.93 (0.83, 1.04)	0.95 (0.88, 1.03)	1.04 (0.86, 1.26)
Zung Score (modified)	1.09 (1.05, 1.14)	1.07 (1.04, 1.11)	1.04 (0.99, 1.09)
BMI	0.96 (0.90, 1.03)	1.00 (0.97, 1.03)	1.05 (0.98, 1.12)
Menopausal Hormone Therapy			
No	1.00	1.00	1.00
Yes	0.85 (0.38, 1.87)	0.88 (0.48, 1.59)	0.95 (0.42, 2.19)
Alcoholic drinks per week	1.08 (0.99, 1.17)	1.02 (0.94, 1.11)	0.93 (0.77, 1.13)
Smoking history			
Never	1.00	1.00	1.00
Past	2.45 (0.97, 6.19)	2.12 (1.13, 4.00)	1.64 (0.44, 6.07)
Current	1.39 (0.43, 4.43)	0.70 (0.28, 1.79)	3.23 (1.12, 9.35)

Appendix 7. Modeling total sleep time as an outcome.

Insomnia was also assessed using interview data, to create three binary outcomes: short total sleep with dissatisfaction, short total sleep with fatigue, and long sleep latency. On the day of their sleep studies, subjects were asked, “How many hours of sleep do you usually get?” (Appendix 3, Question 41) Total sleep time was calculated as a weighted average of subjects’ responses for work nights, nonwork nights, and naps, assuming two nonwork nights per week.

To distinguish insomniacs from natural or intentional short sleepers, this information was coupled with responses to two other questions pertaining to fatigue and satisfaction with sleep. Subjects were asked, “Do you usually feel tired or fatigued at times during a typical day?” (Appendix 3, Question 31). Subjects were classified as having fatigue if they reported that their fatigue interfered with work, mood, relationships, enjoyment of life, ability to concentrate, motivation, or housework. Subjects were also asked, “Are you satisfied with your usual night's sleep?” (Appendix 3, Question 44). Responses were classified as dissatisfied if subjects chose “Not usually” or “Never.”

There was a good deal of overlap between the two definitions of insomnia based on self-reported total sleep time (Table A-13, p. 168), but there were 68 studies that fell into different categories depending on whether fatigue or dissatisfaction with sleep was used. Therefore both definitions were used.

There was little evidence to suggest an association between AHI and short total sleep time. Prevalence of co-occuring SDB and short total sleep time was low (Table A-14, p. 169), and regression models showed no relationship (Tables A-15-A16, p. 169-171).

Table A-13. Overlap between two definitions of short total sleep time

	Short total sleep time + dissatisfaction				All	
	No		Yes			
	N	(%)	N	(%)	N	(%)
Short total sleep time + fatigue affecting life						
No	1749	(94%)	16	(1%)	1765	(95%)
Yes	52	(3%)	43	(2%)	95	(5%)
All	1801	(97%)	59	(3%)	1860	

Table A-14. Co-occurrence, over all sleep studies, of AHI ≥ 15 and diary-reported insomnia (DSM criteria) or interview-reported insomnia

	AHI < 15		AHI ≥ 15		All	
	N	(%)	N	(%)	N	(%)
Short total sleep time + dissatisfaction						
No	1205	(75%)	348	(22%)	1553	(97%)
Yes	45	(3%)	8	(0%)	53	(3%)
Short total sleep time + fatigue						
No	1188	(74%)	333	(21%)	1521	(95%)
Yes	62	(4%)	23	(1%)	85	(5%)
All	1250	(78%)	356	(22%)	1606	

Table A-15. Results of multivariable regressions of three measures of interview-reported insomnia outcomes on AHI category.

	Short total sleep time + dissatisfaction	Short total sleep time + Fatigue Affecting Life	Long sleep latency
	N = 1,293	**N = 1,315**	**N= 1,336**
	Odds Ratio (95% CI)	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
AHI category			
<5	**1.00 (ref.)**	**1.00 (ref.)**	**1.00 (ref.)**
5-<15	**0.92 (0.45, 1.88)**	**0.78 (0.46, 1.32)**	**0.55 (0.23, 1.35)**
15-<30	**1.08 (0.48, 2.44)**	**1.20 (0.59, 2.42)**	**0.18 (0.02, 1.32)**
≥30	**0.75 (0.18, 3.07)**	**0.92 (0.34, 2.51)**	**0.15 (0.02, 1.43)**
Overall *F*-test	***P* = 0.96**	***P* = 0.63**	***P* = 0.26**
Test for trend	***P* = 0.83**	***P* = 0.87**	***P* = 0.06**
Menopausal stage			
Premenopause or Early Perimenopause	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Late Perimenopause	2.23 (1.07, 4.64)	1.58 (0.85, 2.93)	1.72 (0.76, 3.90)
Postmenopause	2.24 (1.00, 5.02)	1.54 (0.75, 3.15)	1.47 (0.45, 4.86)
Age (years)	0.93 (0.83, 1.04)	0.95 (0.88, 1.03)	1.04 (0.86, 1.27)
Zung score(modified)	1.09 (1.05, 1.14)	1.07 (1.04, 1.11)	1.03 (0.98, 1.09)
BMI	0.96 (0.89, 1.04)	1.01 (0.98, 1.04)	1.05 (0.98, 1.12)
Menopausal Hormone Therapy			
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	0.83 (0.37, 1.84)	0.88 (0.49, 1.60)	0.90 (0.43, 1.89)
Alcoholic drinks per week	1.07 (0.98, 1.17)	1.03 (0.95, 1.11)	0.94 (0.78, 1.13)
Smoking history			
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Past	2.40 (0.94, 6.15)	2.07 (1.11, 3.88)	1.69 (0.44, 6.50)
Current	1.40 (0.43, 4.50)	0.72 (0.28, 1.87)	3.37 (1.08, 10.51)

Table A-16. Results of sensitivity analyses excluding subjects who reported using alcohol within 24 hours of their sleep studies from models regressing interview-reported insomnia on AHI category

	Short sleep time + fatigue	**Long sleep latency**
	Odds Ratio (95% CI)	**Odds Ratio (95% CI)**
	N=1,237	**N=1,257**
AHI category		
<5	**1.00 (ref.)**	**1.00 (ref.)**
5-<15	**0.82 (0.46, 1.47)**	**0.40 (0.10, 1.61)**
15-<30	**1.20 (0.50, 2.89)**	**0.30 (0.04, 2.52)**
≥30	**1.15 (0.41, 3.23)**	**0.11 (0.01, 2.04)**
Overall *F*-test	***P* = 0.87**	***P* = 0.53**
Test for trend	***P* = 0.70**	***P* = 0.17**
Menopausal stage		
Premenopause or Early Perimenopause	1.00 (ref.)	1.00 (ref.)
Late Perimenopause	1.38 (0.76, 2.48)	1.27 (0.52, 3.07)
Postmenopause	1.12 (0.54, 2.33)	0.73 (0.24, 2.23)
Age (years)	0.96 (0.87, 1.06)	1.14 (0.94, 1.37)
Zung Score (modified)	1.06 (1.01, 1.10)	1.05 (0.99, 1.11)
BMI	1.01 (0.98, 1.05)	1.06 (0.98, 1.15)
Menopausal Hormone Therapy		
No	1.00 (ref.)	1.00 (ref.)
Yes	0.59 (0.32, 1.08)	0.85 (0.33, 2.14)
Alcoholic drinks per week	1.03 (0.93, 1.13)	0.98 (0.83, 1.16)
Smoking history		
Never	1.00 (ref.)	1.00 (ref.)
Past	2.61 (1.30, 5.25)	1.66 (0.37, 7.51)
Current	0.64 (0.19, 2.23)	3.06 (0.77, 12.21)

Table A-17. Logistic regressions using interview-reported insomnia on AHI category, without adjusting for depression

	Short total sleep time + dissatisfaction	Short total sleep time + Fatigue Affecting Life	Long sleep latency
	N = 1,319	**N = 1,341**	**N = 1,362**
	Odds Ratio (95% CI)	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
AHI category			
<5	**1.00 (ref.)**	**1.00 (ref.)**	**1.00 (ref.)**
5-<15	**0.77 (0.31, 1.91)**	**0.83 (0.47, 1.46)**	**0.35 (0.10, 1.29)**
15-<30	**0.92 (0.25, 3.34)**	**1.23 (0.51, 3.01)**	**0.27 (0.03, 2.27)**
≥30	**0.83 (0.16, 4.44)**	**1.10 (0.35, 3.45)**	**0.11 (0.01, 2.29)**
Overall *F*-test	***P* = 0.95**	***P* = 0.86**	***P* = 0.52**
Test for trend	***P* = 0.73**	***P* = 0.73**	***P* = 0.16**
Menopausal stage			
Premenopause or Early Perimenopause	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Late Perimenopause	2.16 (0.95, 4.89)	1.39 (0.79, 2.44)	1.24 (0.55, 2.82)
Postmenopause	1.54 (0.53, 4.44)	1.23 (0.62, 2.43)	0.92 (0.27, 3.12)
Age (years)	0.95 (0.82, 1.09)	0.95 (0.86, 1.05)	1.10 (0.89, 1.35)
BMI	0.93 (0.84, 1.03)	1.02 (0.98, 1.05)	1.06 (0.96, 1.15)
Menopausal Hormone Therapy			
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	0.15 (0.03, 0.71)	0.52 (0.27, 0.99)	0.75 (0.31, 1.82)
Alcoholic drinks per week	1.07 (0.98, 1.17)	1.00 (0.91, 1.10)	0.98 (0.83, 1.15)
Smoking history			
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Past	4.04 (1.41, 11.59)	2.55 (1.27, 5.12)	1.94 (0.45, 8.38)
Current	2.10 (0.48, 9.29)	0.75 (0.23, 2.52)	3.53 (0.90, 13.90)

Table A-18. Testing for statistical interaction in models of short total sleep time: *P*-values from cross-product terms in models testing interaction between AHI category and menopausal status.

		Logistic Models		
		AHI		
		5-<15	15-<30	≤30
Short total sleep time + fatigue	Postmenopause	0.62	0.02	0.14
	Late Perimenopause	0.09	0.41	0.65

Appendix 8. Modeling hypnotic medication use

Hypnotic drugs present some challenges for which no entirely satisfying solution exists. On one hand, insomnia symptoms may be masked in patients who take these drugs. On the other hand, many classes of drugs that may be used to treat sleepiness can cause apneas.[103] However, since using hypnotic use is a "causal descendent" of insomnia, conditioning on these medications may cause bias. I took the approach of making hypnotic drug use part of the definition of insomnia. It is difficult to interpret results of such a model, however, since hypnotic drug use and insomnia are qualitatively different experiences, and reverse causation is a meaningful concern.

Drug use was measured using monthly diaries (Appendix 1). In the first version of the diary, subjects were asked, "Did you take melatonin this month?", and in the later versions, subjects were asked, "Did you take any sleeping pills or other substance to help you sleep?" Subjects were defined as taking a hypnotic medication if they reported taking the medication for at least three nights for at least three months. Logistic regressions were performed modeling the odds of taking hypnotic medications, and the odds of either having an insomnia outcome or taking hypnotic medications. Subjects who reported taking sedatives on the night of their sleep studies were excluded from these analyses, as these medications can cause apneas.

There were 104 observations at which subjects did not meet the criteria for either diary-reported insomnia definition, but at which they reported taking hypnotic medications for three months (Table A-19, p.175). Complete data including hypnotic use was available for 1,198 observations, of which 120 were excluded because of sedative use on the study day.

In logistic regression models, AHI category was strongly associated with use of hypnotic medications (Table A-20, p. 176). Comparing the models reported in Table 8-6 (p. 101), and Table 8-12 (p. 106) to models including hypnotic drug use in the outcome demonstrates meaningful differences. Associations with all insomnia outcomes were larger and more positive when drug use was included.

AHI was associated with use of hypnotic medications, and including hypnotic use in the definition of insomnia led to some associations. It is difficult to interpret, however, whether that reflects an association between AHI and subsequent insomnia which is treated with hypnotics, or whether regular use of these medications causes SDB.[111] Although these models were restricted to subjects who did not report using sedatives on the day of their sleep studies, that may not be a sufficient washout period. For example the most common prescription sedative reported in diaries was clonazepam, which has a typical elimination half-life of 30-40 hours.[112]

Table A-19. Diary-reported insomnia with and without use of hypnotic medications, over all sleep studies. N= number of monthly diaries.

	No Hypnotics		Hypnotics		All	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**
Trouble getting to sleep						
No	1138	(90%)	165	(70%)	1303	(87%)
Yes	130	(10%)	72	(30%)	202	(13%)
Trouble staying asleep						
No	992	(78%)	145	(61%)	1137	(76%)
Yes	276	(22%)	92	(39%)	368	(24%)
Either						
No	897	(71%)	104	(44%)	1001	(67%)
Yes	371	(29%)	133	(56%)	504	(33%)
All	1268		237		1505	

Table A-20. Regressions of drug use on AHI category: Multivariable logistic regressions of hypnotic drug use, or of either hypnotic use or having insomnia, on AHI category. Studies at which subjects reported using sedatives were excluded.

	Hypnotic Use	Trouble Getting to Sleep or Hypnotic Use	Trouble Staying Asleep or Hypnotic Use
	N=1,285	N=1,285	N=1,285
	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
AHI category			
<5	**1.00 (ref.)**	**1.00 (ref.)**	**1.00 (ref.)**
5-<15	**1.79 (1.11, 2.88)**	**1.57 (1.09, 2.26)**	**1.21 (0.88, 1.67)**
15-<30	**2.82 (1.49, 5.36)**	**1.69 (0.95, 3.01)**	**1.29 (0.83, 1.99)**
≥30	**2.32 (0.95, 5.66)**	**2.56 (1.18, 5.54)**	**1.53 (0.88, 2.69)**
Overall F test	***P* = 0.05**	***P* = 0.05**	***P* = 0.19**
Test for trend	***P* < 0.01**	***P* < 0.01**	***P* = 0.02**
Menopausal stage			
Premenopause or Early Perimenopause	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Late Perimenopause	1.25 (0.82, 1.90)	1.33 (0.87, 2.03)	1.42 (0.91, 2.22)
Postmenopause	1.14 (0.68, 1.92)	1.43 (0.89, 2.30)	1.35 (0.82, 2.22)
Age (years)	1.03 (0.95, 1.11)	1.05 (0.99, 1.12)	1.04 (0.98, 1.11)
Zung score(modified)	1.05 (1.02, 1.08)	1.05 (1.02, 1.08)	1.01 (0.99, 1.04)
BMI	0.97 (0.92, 1.01)	0.97 (0.94, 1.01)	0.97 (0.94, 1.00)
Menopausal HT			
No	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	0.56 (0.32, 0.98)	0.50 (0.32, 0.78)	0.85 (0.54, 1.34)
Alcoholic drinks/ week	1.07 (1.00, 1.14)	1.02 (0.96, 1.09)	1.03 (0.98, 1.09)
Smoking history			
Never	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Past	1.08 (0.52, 2.26)	1.05 (0.56, 1.97)	1.28 (0.74, 2.19)
Current	0.72 (0.29, 1.77)	0.82 (0.43, 1.56)	1.68 (0.89, 3.17)

Appendix 9. Comparison of insomnia prevalence in the Sleep in Midlife Women Study and the Wisconsin Sleep Cohort Study

Insomnia was assessed in the parent Wisconsin Sleep Cohort Study by interview on the night of sleep studies. The prevalence of self-reported insomnia is much higher in the parent study than recorded in the sleep diaries. Given the precision and prospective nature of the diary data, it is possible that subjects overreport their insomnia symptoms on interview. An alternative explanation is that substudy participants had less insomnia.

Table A-21. Comparison of self-reported trouble or difficulty getting to sleep using diary-reported data from the Sleep in Midlife Women Study vs. interview-reported data from the Wisconsin Sleep Cohort Study.

	Women's Study		Parent Study	
	Trouble getting to sleep		Difficulty getting to sleep	
	N (diaries)	*(%)*	N (interviews)	(%)
Never	12807	(75%)	97	(11%)
Once per month	1413	(8%)	338	(37%)
2-4 times per month	1823	(11%)	344	(38%)
5-15 times per month	892	(5%)	97	(11%)
>=16 times per month	75	(0%)	38	(4%)

Table A-22. Comparison of self-reported trouble staying asleep using diary-reported data from the Sleep in Midlife Women Study vs. interview-reported data from the Wisconsin Sleep Cohort Study.

	Women's Study		Parent Study					
	Trouble staying asleep		Difficulty getting back to sleep		Waking up too early		Waking repeatedly	
	N	(%)	N	(%)	N	(%)	N	(%)
Never	11067	(65%)	102	(11%)	198	(22%)	114	(12%)
Once per month	1435	(8%)	309	(34%)	309	(34%)	237	(26%)
2-4 times per month	2520	(15%)	321	(35%)	250	(27%)	223	(24%)
5-15 times per month	1442	(8%)	151	(17%)	121	(13%)	193	(21%)
>=16 times per month	546	(3%)	31	(3%)	36	(4%)	147	(16%)