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THE PREVALENCE OF INSOMNIA IN PERIMENOPAUSAL WOMEN TRANSITIONING TO MENOPAUSE

A Dissertation in

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by

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ABSTRACT

Background/Significance: Insomnia in adults contributes to poor health outcomes such as myocardial infarction and obesity. Evidence consistently suggests a predisposition to insomnia in women; yet, there is a paucity of research that addresses insomnia in a high-risk group of women – perimenopausal women transitioning to menopause**.** Perimenopause will affect 500 million women within the next decade. Studies of individual sleep symptoms in perimenopausal women are abundant; few studies, however, address such symptoms from the perspective of diagnosable insomnia in perimenopausal women.

Study Purpose: The primary aim of the study was to describe the prevalence of insomnia in perimenopausal women progressing to menopause. Two secondary aims were also addressed; (1) to examine if there is a difference in self-reported insomnia/insomnia symptoms between perimenopausal stages, and (2) to identify independent predictors of influence on chronic insomnia among perimenopausal women.

Theoretical Framework: The Perimenopausal Insomnia Symptom Management Model (PISMM), an adaptation of the Spielman 3 P Model of Insomnia and the Symptom Management Theory (SMT) was used to guide this study. The SMT and 3 P Model of Insomnia, when combined, address the essence of the subjective and objective experience of sleep symptoms and insomnia among perimenopausal women.

Methods: A secondary analysis of publically-available data from the Study of Women's Health Across the Nation, a multisite, longitudinal study of the natural history of menopause (N=3302) was conducted. The purpose of the Study of Women's Health

Across the Nation was to describe the chronology of the biological and psychological characteristics of the menopausal transition on health and risk factors for age-related chronic illnesses; survey and biophysical data were collected at baseline and 13 annual intervals. For the secondary analysis, survey data (baseline and 10 annual data points) were analyzed. Self-reported sleep symptoms survey data were used to examine the prevalence of insomnia as defined by American Academy of Sleep Medicine insomnia criteria. The primary outcome variables were four insomnia symptoms: difficulty falling asleep, sleep latency, awakenings from sleep, wake after sleep onset, and sleep quality. Descriptive analysis of all variables for each study interval was completed. Repeated measures logistic regression was used to identify if insomnia symptoms change over time by perimenopausal stage. Multivariable logistic regression models were used to identify predictors of influence on chronic insomnia defined in this study as the presence of insomnia symptoms for two consecutive data collection points.

Results: The sample (n=3302) were middle aged (45.9 ± 2.69) women with high school or more education at baseline survey. Most of the sample was married (65%), mid-high income (78.1%), and of diverse race/ethnicity. Insomnia was present in at least one third or more of perimenopausal women at any point in the transition period (31%-42%). Awakenings were the most frequently reported insomnia symptom (31%); increased sleep latency was least frequently reported (14%); and wake after sleep onset (15%) was reported half as often as awakenings. Self-reported sleep quality (restless or very restless sleep) did not significantly worsen over the ten year study period. Insomnia symptoms were worse and more prevalent in the late stage of perimenopause compared to early perimenopausal stage ($p<0.0001$). The odds of having any one

symptom of insomnia were 1.3 times greater for those in late stage versus early stage of perimenopause (95% CI [1.2, 1.5]; p<0.001). The odds of developing chronic insomnia were 1.5 times greater for those in perimenopause than pre-perimenopausal status at baseline (95% CI (1.3, 1.8); p<0.001). Other important factors of influence for chronic insomnia among PM were: night sweats (p<0.001), depression (p<0.001), higher body mass index (p<0.001), weekly exercise (p=0.005), and younger age (p=0.001).

Conclusions & Implications: The study addressed the prevalence of insomnia in perimenopausal women transitioning to menopause specifically identifying insomnia as highly prevalent in perimenopausal women, significantly more severe insomnia in late stage perimenopausal women, and risk factors for chronic insomnia in perimenopausal women. Perimenopausal women are at risk for developing chronic insomnia when compared to pre-perimenopausal women. Insomnia in perimenopausal women is under-recognized and under-diagnosed; screening for insomnia symptoms by healthcare providers is a necessity to potentially reduce the burden of insomnia among perimenopausal women. The study findings highlight the importance of continued research addressing insomnia in this population and suggest new clinical implications for symptom management in perimenopausal women. Insights for designing/testing interventions to improve the sleep and long-term health of perimenopausal women are suggested.

Keywords: Perimenopause, Insomnia, Sleep, Mid-life, Women, Surgical menopause, Sleep Latency, Wake After Sleep Onset, Sleep Quality, Awakenings

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Dedication

This dissertation is dedicated to my children, Kaitie, Ryan and Norah. I will forever remember your support throughout this process. I thank you from the bottom of my heart for being so patient and forgiving of all the events I missed and the ones I attended with a bag full of books. You are and always will be my greatest accomplishments, I am so proud to be your mom and love you very much.

Chapter 1: Introduction

Perimenopause will affect 500 million women within the next decade (United States Census Bureau, 2010). Perimenopause is defined as the period of time when women start to experience variations in the menstrual cycle. Early perimenopause is defined as having a menstrual period in the preceding three months and having experienced menstrual irregularity while late perimenopause is defined as menstrual bleeding in the last 12 months but not in the preceding three months (Harlow, Crawford, Sommer, & Greendale, 2000). This stage can last several years and concludes 12 months after the final menstrual period when the woman is then considered menopausal (NIH State-of-the Science Panel, 2005).

Insomnia is the most prevalent sleep disorder among the general population (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008). Insomnia is defined as difficulty in initiating or maintaining sleep and includes inadequate or poor sleep quality that has a negative outcome on daytime functioning with subjective sleep dissatisfaction (American Academy of Sleep Medicine, 2005).Though insomnia is a distinctly defined sleep disorder, the symptom components, such as sleep quality and sleep complaints are often empirically examined in isolation and not necessarily equated with a diagnosable sleep disorder (i.e., insomnia). The term insomnia is categorized as chronic, lasting for at least a month, or acute or transient which can last days to weeks (Schutte-Rodin et al., 2008). Chronic insomnia is associated with poor long term health outcomes in the adult population (Grandner et al., 2014).

Women have a higher risk than men of developing chronic insomnia during their life (Ozminkowski, Wang, & Walsh, 2007) with an incidence rate of 63% among all females (National Sleep Foundation [NSF], 2002). The prevalence and frequency of sleep complaints escalate in women as they enter perimenopause (Cirignotta, Mondini, Zucconi, Lenzi, & Lugaresi, 1985; Ensrud et al., 2012; Freeman et al., 2007). An NIH panel reported a 47% increase in perimenopausal symptoms including sleep disturbances, night sweats and hot flashes during perimenopause (National Institutes of Health State-of-the Science Panel, 2005).

Sleep disturbances in perimenopausal women are common and consistent with the diagnosis of insomnia. Sleep disturbance during perimenopause is a significant problem affecting 38% of women between the ages of 40 and 55 years (Kravitz et al., 2003, p. 22). According to the 2007 Sleep in America Poll, 59% of perimenopausal women reported experiencing any symptom of insomnia at least a few nights a week (National Sleep Foundation [NSF], 2007, p. 3). Studies that sought to identify predictors of sleep quality reported that women who experienced other perimenopausal symptoms were more likely to report sleep problems (Arakane et al., 2011; Blumel et al., 2012; Chang, Jou, Hsiao, & Tsao, 2010; Pien, Sammel, Freeman, Lin, & DeBlasis, 2008). Sleep quality encompasses one's perception of sleep disturbances, sleep duration, sleep latency and subjective aspects of sleep such as depth and restfulness (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and is a significant component of an insomnia diagnosis. Poor sleep quality in midlife women has been associated with perimenopause and other comorbid medical diagnoses, primary sleep disorders, anxiety and depression (Joffe, Massler, & Sharkey, 2010) as well as hypertension

(Vgontzas, Liao, Bixler, Chrousos, & Vela-Bueno, 2009). The hormonal alteration in the natural progression of perimenopause has the potential to increase the risk of developing insomnia related to vasomotor symptoms that disrupt the sleep cycle, coexistent psychological disorders such as anxiety or depression, and the altered central neural control of sleep wake states and thermal threshold.

Surgical menopause changes the natural progression of perimenopause with negative consequences especially in women less than 45 years of age (Hendrix, 2005). These women are at high risk for cardiovascular events, dementia, Parkinson's disease, osteoporosis and an increase in all-cause mortality (McCarthy, Menke, Ouyang, & Visvanathan, 2012; Parker, 2009; Parker, Jacoby, Shoupe, & Rocca, 2009; Shuster, Rhodes, Gostout, Grossardt, & Rocca, 2010). Health-related and general quality of life is negatively impacted by surgically induced menopausal changes such as hormone shifts and can include night sweats and hot flashes contributing to sleep disturbances (Moe, 2004). The sudden and abrupt decrease of androgen and estrogen levels that occur after surgical menopause has been linked to worsening climacteric symptoms (Benshushan et al., 2009; Ozdemir et al., 2009).

Statement of the Problem

Insomnia is associated with an increased burden on society. With chronic sleep loss and sleep disorders affecting nearly 70 million Americans (U.S. National Institutes of Health [NIH], 2005, p. 2), the economic burden is estimated at an annual cost of $16 billion in health care expenses and $50 billion in lost productivity. The cost of insomnia treatment (Ozminkowski et al., 2007; Wade, 2011), coupled with (1) the increased use of health care resources (Simon & VonKorff, 1997; Hatoum, Dong, Darnia, Wong, &

Mendelson, 1998), (2) decreased quality of life (Zammit, Weiner, Damata, Sillup, & Mcmillan, 1999; Katz & McHorney, 2002) and (3) a loss of productivity at work (Leger, Guilleminault, Bader, Levey, & Palliard, 2002; Godet-Cayre et al., 2006) emphasize the need to address insomnia to diminish this large burden. Groups at high risk for insomnia, such as perimenopausal women including those who have undergone surgical menopause, are particularly important populations for focused research to reduce long-term negative health outcomes. In the general population, evidence suggests that the cost of insomnia treatment, loss of productivity at work, and decreased quality of life confer tremendous burden on our society. As insomnia is a common sleep disorder in perimenopausal women, it is critically important to gain insight to the prevalence of insomnia over time in perimenopausal women; this insight will help the field identify intervention opportunities to potentially reduce the burden of insomnia in this high risk population.

Women have significantly more insomnia- related complaints than men (Bixler, Vgontzas, Lin, Vela-Bueno, & Kales, 2002; Cirignotta et al., 1985; Zhang & Wing, 2006). Zhang and Wing (2006) discovered a female predisposition for insomnia in their meta-analysis. Parry and colleagues (2006) report in their review that perimenopausal women have more disturbed sleep, including loss of sleep quality and continuity, than postmenopausal women. In a prospective population based study, Phillips and Mannino (2005) found that women were more likely than men to report difficulty falling asleep, waking repeatedly and waking up exhausted. Research has shown a predisposition to insomnia in women; yet evidence is lacking in terms of the prevalence of insomnia in a particularly high risk group of women – those who have undergone

surgical menopause. Understanding the prevalence of insomnia in all stages of perimenopause women will allow preventative interventions such as cognitive behavioral therapy for insomnia (CBT-I) to be used with this population prior to the development of chronic insomnia which may improve health outcomes.

Insomnia during perimenopause is multifactorial in cause with physiologic, psychological, and social triggers. A gradual decrease of hormones produced by the ovaries is the natural progression of perimenopause which predisposes and possibly precipitates the development of sleep disturbances and insomnia. The ovaries, even after menopause, continue to secrete minimal amounts of androgens which are then converted to estrogen in the body. Sleep disturbance during perimenopause has been shown to be caused by vasomotor symptoms (Feldman, Voda, & Gronseth, 1985), fluctuations in endogenous estrogen levels (Weber, Rubin, & Maki, 2013) and dysfunction in the central nervous system thermoregulation center (Rapkin, 2007) which plays a key role in the sleep-wake cycle (Portas, Bjorvatn, & Ursin, 2000). These causal mechanisms of sleep disturbances in perimenopausal women underlie the incidence of insomnia.

For women aged 40 to 44, hysterectomies are the second most frequent surgical procedure (Whiteman et al., 2008), accounting for 600,000 procedures each year in the United States with nearly 50% of these women having elective bilateral oophorectomies (Wang, Robinson, & Burkman, 2013). Termed surgical menopause, the natural perimenopausal progression is thus altered. Surgical menopause is a physiological cause of early menopause and the emergence of vasomotor symptoms and sleep disturbances (Chubaty, Shandro, Schuurmans, & Yuksel, 2011). Women who have

undergone surgical menopause often report more severe menopausal symptoms than those women who naturally progress to menopause (Bhattacharya & Jha, 2010; Hendrix, 2005; Ozdemir, Celik, Gorkemli, Kiyici, & Kaya, 2009).

Research supports the finding that vasomotor symptoms, such hot flashes and night sweats, are a result of a marked reduction in the hypothalamic thermoregulatory neutral zone in the brain (Freeman, 2005). This marked reduction in the thermoregulatory area in the brain has been linked to an increase in reported vasomotor symptoms resulting from a change in central nervous system (CNS) transmitters (Rapkin, 2007). CNS transmitters such as serotonin, norepinephrine, dopamine and endorphins have been associated with menopausal symptoms that include vasomotor symptoms, mood changes and sleep disturbances (Vilet & Davis, 1991). The physiological link of an alteration in hypothalamic thermoregulation related to a decrease in circulating estrogen in perimenopausal women who have undergone surgical menopause can impact the severity of vasomotor symptoms and sleep disturbances (Rapkin, 2007). These same central nervous system transmitters also in part regulate the sleep-wake system. Insomnia and sleep disturbance are therefore physiologically linked with perimenopause. When the ovaries are surgically removed, it stands to reason that the abrupt cessation of hormones may result in a different trajectory with potentially more severe and frequent sleep disturbances and insomnia. This hypothesis supports the current research.

Insomnia in perimenopausal woman is a significant problem; however, little is known about the insomnia prevalence in perimenopausal women who have undergone surgical menopause. Additionally, the limited research in this area has not been

longitudinal and therefore does not capture the prevalence of chronic insomnia. A paucity of research has examined sleep, and more specifically insomnia, in perimenopausal women or those who have undergone surgical menopause. This line of inquiry is an opportunity to add to the state of the science and gain insight for the design and testing of interventions tailored to perimenopausal women for the prevention and early treatment of chronic insomnia.

Purpose of the Study

The overall purpose of the study was to describe the prevalence of insomnia in all perimenopausal women and to gain a better understanding of the course and severity of insomnia in perimenopausal women, including those who have undergone surgical menopause. A secondary analysis of publically available data from a pre-existing large data set that employed a longitudinal cohort design was done. The study focused on perimenopausal women because so little is known about insomnia in perimenopause and even less when early and late perimenopausal stages are considered. This study also examined insomnia from before surgical menopause through one year after surgical menopause. The specific objectives of the present study were to examine the natural course of insomnia and the report of insomnia symptoms in perimenopausal women who have and have not undergone surgical menopause. The study results also identified insomnia risk factors, sleep complaints, persistence and remission of sleep disturbances and described the prevalence of insomnia in perimenopausal women before and through one year after surgical menopause to report critical differences in insomnia for these cohorts.

Research Questions

The following research questions were addressed:

1. What is the prevalence of insomnia, measured annually, in all perimenopausal women?

2. What is the prevalence of insomnia by perimenopausal stage in women?

3. What is the prevalence of insomnia in women who have undergone surgical menopause?

4. Is there a difference in reported insomnia symptoms by perimenopausal stage?

5. Is there a significant difference in insomnia symptoms before and after surgical menopause?

6. Is there a difference in insomnia symptoms among perimenopausal women who have progressed naturally through perimenopause compared to women who have undergone surgical menopause?

7. What are the factors of influence among perimenopausal women that develop chronic insomnia defined as insomnia symptoms present for at least two consecutive annual data collection points?

Research Significance

The research examined the prevalence of insomnia in perimenopausal women. This is significant since no prior research has described the course of insomnia in all perimenopausal women, both by stage and natural/surgical status. The research questions addressed this gap in the evidence.

It is not known if women by perimenopausal stage and/or surgical/natural progression to menopause have significantly different symptoms of insomnia. The results for these questions addressed if such differences exist. If insomnia is prevalent in perimenopausal women, it is imperative to understand the factors of influence for insomnia or risk factors in order to begin to develop intervention strategies to reduce the burden of insomnia in perimenopausal women. Collectively, the seven research questions importantly addressed gaps in our current knowledge about insomnia in perimenopausal women and establish a foundation from which intervention approaches can be designed for this high risk population of women.

Conceptual Framework

This study was guided by a combination of theoretical assertions from the Symptom Management Theory and Spielman's 3P Model of Insomnia.

Symptom Management Theory

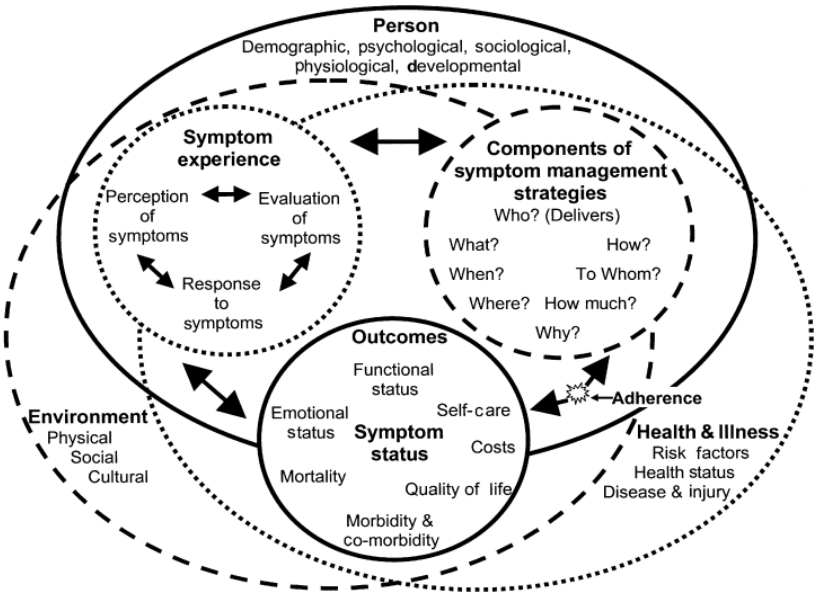
The Symptom Management Theory (SMT), a middle range theory, offers a broad approach to symptom management. The theory's patient-centered focus on the perspective of symptom clusters and management makes it directly applicable to the phenomenon of insomnia in perimenopausal women. The dimensions of person, environment and heath/illness allow this theory to be used across the lifespan. The theory addresses both internal and external factors that are present within the person's life and affect the symptom experience. Sleep and the person's perspective about the quality of their sleep is explored using this theory. In the absence of objectively measured sleep, sleep quality is a subjective concept. The women's symptom experience of sleep as a main concept of this research will be guided by SMT. The use

of SMT in this study is consistent with previous studies of sleep (Hearson, McClement, McMillan, & Harlos, 2011; Humphreys & Lee, 2005; Lee, 2004).

Concepts of the theory

The Symptom Management Theory offers a unique three pronged approach to symptom management. The theory includes three major concepts, symptom experience, symptom management and symptom outcomes, all of which are directly related to each other (Dodd et al., 2001). The relationships among the concepts are further explained by the use of bidirectional arrows, suggesting the inter-relatedness of the concepts (Figure 1.1).

Figure 1.1 The Symptom Management Theory



(Dodd, Janson, et al., 2001). Reprinted with permission from Wiley-Blackwell

The three concepts are framed within the nursing metaparadigm of person, environment, and health/illness (Humphreys et al., 2008). The figure below represents the interrelated concepts of the theory with the central concept of person acknowledged

within a solid circle. The domain of nursing surrounds the symptom experience and is separable. Person according to the model is comprised of different demographic, psychological, sociological, physiological and developmental characteristics. The dotted lines surrounding the environment and health/illness dimensions of the metaparadigm are fluid in nature and change depending on the context and corresponding variables. Environment is comprised of physical, social and cultural differences while health/illness is comprised of risk factors, health status and disease or injury states. These environmental factors are subjective in nature and depend on the perception of the person. The authors operationalize the definition of a symptom as "a subjective experience reflecting changes in the biophysical functioning, sensations, or cognition of an individual" (Dodd et al., 2001, p. 669).

Symptom Experience

The first concept of the SMT is symptom experience. The symptom experience is an individual's subjective perception of the symptom, which is given meaning by the person. Perception of the symptom defines the way that a particular symptom has caused a change in the way a person usually feels. The response to the symptom experience may be physical, psychological, sociocultural or behavioral (Dodd et al., 2001). This is the first step in the model and needs to be understood before being able to move on to the next two steps of management strategies or outcomes.

Although a step process, but yet not linear, the symptom experience can be addressed separately from the other two concepts. Within the symptom experience concept there are the components: 1) perception of symptoms, 2) response to symptoms and 3) evaluation of symptoms. Bi-directional arrows among these

dimensions suggest that an individual's perception of the symptom has a direct impact on how that symptom is managed or, if not bothersome, is not managed. The bi-directional arrows show the relationships between these components of the symptom experience concept.

Symptom Management Strategies

The second concept of the SMT is symptom management strategies. The symptom management strategies are the "what, when, where, why, how much, to whom, and how" symptoms are managed (Dodd et al., 2001). The purpose of symptom management is "to avert or delay a negative outcome through biomedical, professional and self-care strategies" (Dodd et al., 2001, p. 673). These strategies are directed at the individual perception of the symptom experience and are intended to achieve one or multiple outcomes. These strategies, or interventions, are directed toward the individual, family or community (Dodd et al., 2001, Humphreys et al., 2008) experiencing the symptom or cluster of symptoms.

Outcomes

The third concept of the SMT is the outcomes of symptom status or an evaluative process of the theory. In this concept there are factors such as functional and emotional status and self-care, which impact adherence to the symptom management strategy. The eight variables that can affect outcomes are functional status, emotional status, self-care, costs, quality of life, morbidity and co-morbidity and mortality (Dodd et al., 2001). The authors did not place any directional arrows within this concept but have addressed the variables in their written work by stating that "all outcomes can be related to each other as well as to symptom status" (Dodd et al., 2001, p. 674).

There is one minor concept, adherence, which emerged during the 2001 revision of the SMT. Adherence has been defined by the authors as "whether the intended recipient of the strategy actually receives or uses the strategy prescribed" (Dodd et al., 2001, p. 674). This is shown pictorially on the theory model by a broken arrow between the concepts of symptom management strategies and outcomes. In the more recent publication, the authors identify the source of nonadherence are those symptom management strategies that are too demanding, are not utilized, or applied with inconsistency (Humphreys et al., 2008).

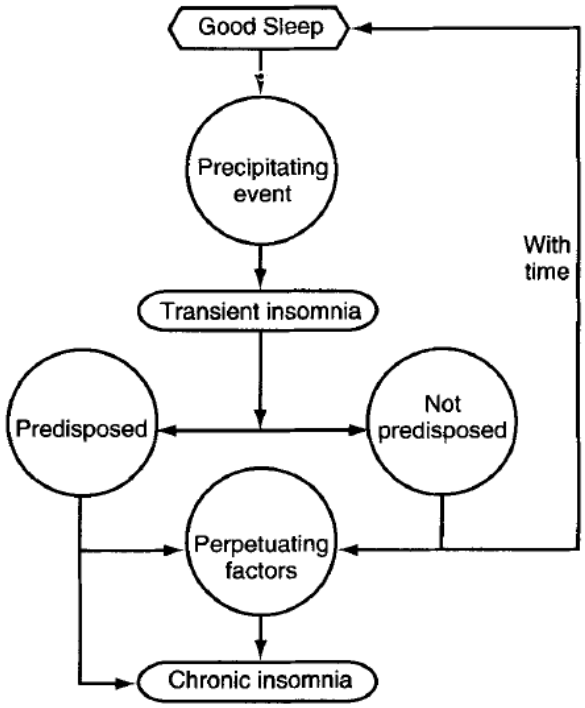
The SMT is a middle range theory with clinical applicability. The concepts, once operationally defined for the phenomenon of insomnia in perimenopausal women that have undergone surgical menopause, are potentially measurable. Sleep-specific variables for empirical application are measured with, for example, (1) qualitative measures, such as interviews; (2) quantitative measures, such as survey tools; and (3) physiologic measurements, such as actigraphy. The SMT, having only three major concepts, lends itself to being readily understood with easy application to different populations. The reader must have a working knowledge of the nursing paradigm to be able to incorporate and apply the theory within practice but it has been extensively tested by its authors (Humphreys, 2003; Humphreys & Lee, 2005; Lee, 2006). The theory is clarified through the visual representation and the simplistic and relevant language.

Spielman's 3 P Model of Insomnia

Spielman's 3 P Model of Insomnia has been used as a framework in the literature that addresses perimenopause and sleep (Joffe et al., 2010; Kravitz & Joffe, 2011).

Spielman's 3 P Model includes three concepts: predisposing, precipitating and perpetuating factors of insomnia (Figure 1.2) (Spielman, Caruso, & Glovinsky, 1987).

Figure 1.2 *Spielman's 3 P Model of Insomnia*



(Spielman, Nunes, & Glovinsky, 1996)

Also called the diathesis-stress model, the 3 P Model has three concepts that explain the development and maintenance of insomnia (Buysse, Germain, Hall, Monk, & Nofzinger, 2011). The 3 P Model is useful in its potential to identify possible causal targets of insomnia for which treatment strategies can address. Although the model can be applied to a variety of psychological and behavioral conditions related to insomnia, this model does not include neurocognitive mechanisms of insomnia and is therefore limited in terms of applicability due to the model's generality (Buysse et al., 2011).

3 P Model Concepts

Predisposing factors are related to biological, psychological or social influences such as hormone changes, stress or environment. Precipitating factors are described as stressful life events such as death, empty nest or role changes. Perpetuating factor examples are behavioral conditioning, poor coping or comorbid health issues (Spielman et al., 1987). Spielman's 3 P Model of Insomnia provides a framework to explain the factors that impact the development and persistence of insomnia over time. The model will be utilized as a framework for the descriptive longitudinal study of the impact of surgical menopause in the trajectory of insomnia among perimenopausal women.

Predisposing Factors

Predisposing factors is the first concept described in the 3P Model of Insomnia. Predisposing factors, as defined in the model, are constant risk factors held by the person that, without intervention, can heighten the risk of developing insomnia, delay improvement in insomnia symptoms and can transform acute or transient insomnia to chronic insomnia (Spielman, Nunes, & Glovinsky, 1996). For example, individuals with a predisposition for worrying about future challenges may plan their lives and activities in anticipation of problems/challenges. However, if their external stressors become increasingly more demanding, their expectations of themselves may produce chronic arousals in the brain and distress leading to insomnia. In this example, maladaptive psychological coping behaviors predispose the individual to developing insomnia. Physiological variables such as arousal levels related to changes in the sleep wake cycle also are considered predisposing factors. Shift work or being a light sleeper are both examples of physiological predisposing factors (Spielman et al., 1996).

Precipitating Factors

Precipitating factors is the second concept in the 3P Model of Insomnia and further explains the trajectory of developing insomnia. Precipitating factors layer on top of the predisposing factors that are already present in the individual. Precipitating factors act as the trigger event for the development of insomnia. The event that precipitated, or came before the development of insomnia, can be categorized as a sudden or gradual event (Spielman et al., 1996). It is essential to understand the precipitating event in order to effectively treat insomnia. Insomnia causal mechanisms are commonly multifactorial; to address this complexity, tailored, or highly individualized approaches, to treatment are often needed. Precipitating factors can be physiological or psychological such as a surgery or loss of a job. Spielman, Nunes and Glovinsky (1996) describe precipitating factors as the circumstances that set the trajectory of insomnia into motion but often these precipitating events take a secondary role as the acute sleep problem becomes a chronic problem.

Perpetuating Factors

Perpetuating factors constitute the final concept of the model and are factors necessary to sustain insomnia. Perpetuating factors can be psychological, such as a conditioned response of worrying about going to bed or trying too hard to initiate or maintain sleep. Physiological perpetuating factors are described as an alteration in the sleep wake cycle as occurs with napping or sleeping late. Such sleep patterns alter the circadian rhythm and ultimately the internal clock of sleep-wake patterns. Perpetuating factors can also be external, such as the use of stimulants like caffeine, and/or depressants such as alcohol and hypnotic drug dependence (Spielman et al., 1996).

One of the most important assumptions of the model is the impact perpetuating factors continues to have long after the precipitating event has subsided (Spielman, Caruso, & Glovinsky, 1987).

Summary of Spielman's 3P Model of Insomnia

Spielman's 3P Model of Insomnia will guide this study with the identification of predisposing, precipitating and perpetuating factors of the insomnia trajectory in perimenopausal women. Perimenopause is a period of change within a woman's life from reproductive to non-reproductive status. This process of change, consisting of psychological and biological shifts, is hypothesized as the constant predisposing factor for the development of insomnia in perimenopausal women. When a precipitating event, such as surgical menopause occurs and changes the progression of this natural process, it has the potential to impact the insomnia trajectory. This particular precipitating event interrupts the natural process of perimenopause with an abrupt cessation of estrogen and androgens produced in the woman's body. This change in hormone levels is then the perpetuating factor that can lead to persistent insomnia in this population. Beyond the exploratory hypothesis addressing surgical menopause as a precipitating event, the 3P Model also guides the study in terms of identifying important factors of influence on insomnia (i.e., predisposing and precipitating factors) and the overall trajectory of insomnia (i.e., precipitating and perpetuating factors) in this target population.

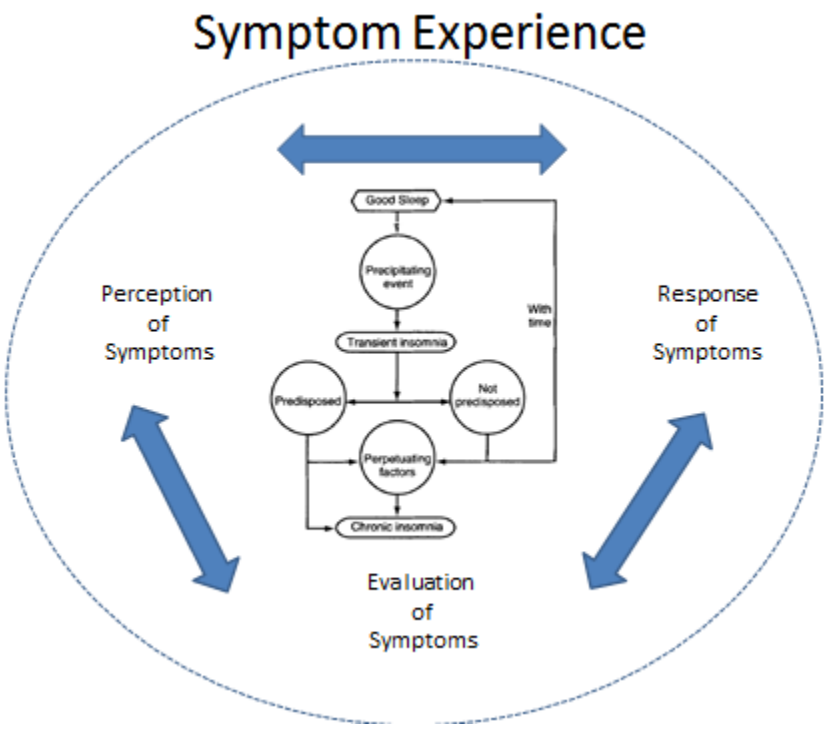
SMT and 3 P Model of Insomnia: A Research Framework

The SMT and 3 P Model of Insomnia, when combined, address the essence of the subjective and objective experience of sleep complaints among perimenopausal

women. The symptom experience concept including the perception, response and evaluation constructs is inclusive of the predisposing, precipitating and perpetuating factors of the 3 P Model of Insomnia. Combining the two models offers an opportunity to further understand not only the symptom experience of insomnia but how this experience changes over time. The SMT does not address time; yet, the 3 P Model is based on the assumption that at baseline, good sleep was present and through a series of events (i.e., precipitating factors), good sleep was altered and insomnia emerged.

The purpose of the study is to describe the insomnia trajectory in perimenopausal women. The primary goal of the study is to gain a better understanding of the course and severity of insomnia in perimenopausal women, including those who have undergone surgical menopause as compared to women who progress naturally to menopause. The aims of the study were: 1) to describe the insomnia trajectory of perimenopausal women; 2) to describe the insomnia trajectory of perimenopausal women who have undergone surgical menopause; 3) to identify if differences exist between the insomnia trajectories in naturally progressing compared to surgical menopause groups and; 4) to identify factors of influence on chronic insomnia among perimenopausal women. By utilizing two models to frame this study, both time and symptomology can be addressed (Figure 1.3).

Figure 1.3 *Perimenopausal Insomnia Symptom Management Model*



Definition of Key Terms

Perimenopause-The period immediately prior to menopause indicated by increasing irregularity of menses with or without skipping periods and ends 12 months after the final menstrual period (Harlow et al., 2012; Soules et al., 2001; McKinlay, Brambilla, & Posner, 1992).

Early Perimenopause- Menstrual period in the past three months and has experienced irregularity of menses schedule (Harlow et al., 2000).

Late Perimenopause- Menstrual bleeding in the last 12 months but not in the preceding three months (Harlow et al., 2000).

Surgical menopause- A surgical procedure that often accompanies a total hysterectomy and is the second most frequent surgical procedure in women aged 40-

44. This procedure, known as a bilateral oophorectomy, includes removing both ovaries (Wild, 2007).

Insomnia- According to the American Academy of Sleep Medicine, insomnia is defined as difficulty initiating sleep, repeated or lengthy awakenings, early awakening, inadequate total sleep time, or poor quality of sleep and presents with evidence of daytime dysfunction such as a change in alertness, energy, cognitive function, behavior or emotional state (American Academy of Sleep Medicine, 2005).

Sleep Latency (SL) - Trouble falling asleep or difficulty with sleep initiation (Kravitz et al., 2008).

Wake after Sleep Onset (WASO) – Waking up several times a night or difficulty with sleep maintenance (Kravitz et al., 2008).

Awakenings (A) - Waking up earlier than planned and unable to return to sleep (Kravitz et al., 2008).

Sleep Quality (SQ) – Sleep quality is the subjective definition defined by tiredness on waking and throughout the day, feeling rested and restored on waking, and the number of awakenings experienced in the night (Harvey, Stinson, Whitaker, Moskovitz,& Kirk, 2008; Kline et al., 2014). For the purposes of this study, SQ was measured based on average restful/restless sleep.

Acute/Transient Insomnia- The presence of insomnia in association with an identifiable stressor, such as psychosocial, physical, or environmental disturbances. Acute/transient insomnia has a short duration (days-weeks) and is expected to resolve when the stressor resolves (Schutte-Rodin et al., 2008).

Chronic Insomnia- Inadequate quantity or quality of sleep characterized by a subjective report of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep that results in some form of daytime impairment and has persisted for at least a month (Raijput & Bromley, 1999) For the purposes of this study, chronic insomnia is operationalized within this study to be presence of insomnia symptoms for two consecutive data collection points.

Assumptions

1. Perimenopausal women experience sleep disturbances.
2. Insomnia symptoms differ between perimenopausal women who have undergone surgical menopause and perimenopausal women who progress naturally to menopause.
3. Surgical menopause negatively impacts sleep.
4. The abrupt cessation of hormones after surgical menopause alters the insomnia prevalence.

Significance of the Study

Sleep disturbances in the perimenopausal period are highly prevalent. Evidence to date has focused on sleep disturbances during the natural progression to menopause. Few studies have specifically addressed surgical menopause and sleep. The perimenopausal population is large and the risk of insomnia is likely high in all perimenopausal women but may be worse in women who have undergone surgical menopause due to the abrupt hormone changes that occur after the surgical procedure. The proposed study will address this gap in the evidence by describing the prevalence of insomnia in all stages of perimenopause and perimenopausal women who have

undergone surgical menopause. This research importantly contributes new knowledge about insomnia and its trajectory in perimenopausal women who have and have not undergone surgical menopause.

Chapter Summary

It is evident that the research on the prevalence of insomnia by stages of perimenopause and in perimenopausal women who have undergone surgical menopause is incomplete. The purpose of the study was to understand the insomnia prevalence in perimenopausal women who have undergone surgical menopause and perimenopausal women who progress naturally to menopause and to identify if differences exist in the prevalence of insomnia in these sub-groups and by perimenopause stages. Risk factors for developing insomnia in perimenopausal women were also described. The study design allowed for analysis of pre-existing longitudinal data to address the current gap in knowledge and address an important problem in an under-researched population. The results of this study provide a foundation for future research that will focus on the design and testing of tailored, or patient-centered, interventions for perimenopausal women who experience insomnia. Efficacious and effective tailored interventions to reduce the insomnia burden has high potential to improve the overall health and quality of life of perimenopausal women as well as decrease the overall societal burden of insomnia. Findings from this study hold strong potential for making important contributions to the scientific literature on perimenopause, surgical menopause and insomnia and will likely help to identify appropriate timing for interventions to improve the sleep and long term health of perimenopausal women.

Chapter 2: Review of the Literature

Sleep disturbances often accompany perimenopause. These disturbances include difficulty maintaining sleep, dissatisfaction with sleep, early morning awakenings and poor sleep quality; all of which are symptoms of insomnia. Insomnia is defined as difficulty in initiating or maintaining sleep and can include inadequate or poor sleep quality that has a negative outcome on daytime functioning with overall sleep dissatisfaction (American Academy of Sleep Medicine, 2005).

Perimenopause is a period of physiologic and psychologic changes within a woman's life that can last for over a decade. This can be a natural process or as a result of a bilateral oophorectomy which is termed surgical menopause. Surgical menopause changes the natural perimenopausal progression and is a physiological trigger of early menopausal symptoms such as vasomotor symptoms and sleep problems (Chubaty, Shandro, Schuurmans, & Yuksel, 2011); among women who have undergone surgical menopause they often report more severe menopausal symptoms than women who progress naturally to menopause (Bhattacharya & Jha, 2010; Hendrix, 2005; Ozdemir, Celik, Gorkemli, Kiyici, & Kaya, 2009). Perimenopausal women who undergo surgical menopause before natural menopause has occurred are at risk for developing sleep disturbances and persistent insomnia yet there is a vast gap in the literature addressing this problem. This review of literature, with a focus on perimenopausal women, sleep disturbances and surgical menopause, will identify strengths and gaps within the scientific literature of this health problem.

The purpose of this review is to analyze the medical, nursing, and psychology literature to examine what is known about perimenopause and insomnia with an

emphasis on the prevalence and course of insomnia and insomnia risk factors. Surgical menopause and its impact on health and quality of life will be critically analyzed and scientific gaps identified. This review begins with an explanation of the pertinent concepts, followed by a summary of the empirical studies, including the methodologies and findings. The findings are organized by key results from the literature.

Review Methodology

The review of literature includes research that was published in peer reviewed journals and focused on the perimenopausal period, surgical menopause and sleep. Relevant articles were identified through searches using the following academic databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Psyc.Articles and PsycInfo via ProQuest and PubMed. Sleep science is a highly interdisciplinary field that predominantly includes nursing, psychology and medicine, which is why the aforementioned databases were selected. The key inclusion criterion was peer reviewed publications. No limitations were placed on publication years. Literature was excluded if it was not available in English or if the content was not relevant to the research topic. Searches were limited to dissertations and peer reviewed journals. Search terms used were perimenopause, women, mid-life women and climacteric, sleep, sleep disturbances in women, sleep quality and insomnia and surgical menopause. A broad key word search was initially used to identify keywords appearing in the title or abstract. Titles were scanned for appropriateness. Articles were reviewed for background and appropriateness and then an advanced search was used to identify key research articles. Additional studies were located from relevant

empirical articles using a reference snowball technique. All accessed articles were then reviewed for relevance to this research study.

Review of Concepts

The literature search revealed a variety of definitions and terms relating to perimenopause. Perimenopause means "about or around the menopause" (Soules et al., 2001, p. 877). Perimenopause was most often defined as the period of time when the first signs of menopause are detected until 12 months of permanent amenorrhea (Polo-Kantola, 2008). A clinical definition of perimenopause has been defined by the Stages of Reproductive Aging Workshop (STRAW):

> The menopausal transition begins with variations in the menstrual cycle length and a monotropic rise in follicle-stimulating hormone (FSH) with no associated increase in luteinizing hormone (LH) and ends with a final menstrual period that is only confirmed after 12 months of amenorrhea (Soules et al., 2001, p. 877).

Some of the more popular terms seen in the literature are perimenopause, menopause, the climacteric, and the change of life (McCloskey, 2012).

Insomnia is easily defined yet includes many facets of sleep complaint descriptors such as sleep quality, sleep disturbances and sleep dissatisfaction. Insomnia is defined as difficulty initiating or maintaining sleep and/or poor sleep quality despite adequate opportunities occasions for sleep, resulting in impaired daytime functioning (American Academy of Sleep Medicine, 2005). The International Classification of Sleep Disorders-2 (2005) offers additional criteria for insomnia, such as waking up too early, non-restorative sleep and daytime impairment of one of the following: fatigue, attention or concentration impairment, social dysfunction, poor school

performance, mood disturbance, daytime sleepiness, energy reduction, accidents at work or while driving, tension, physical symptoms such as headaches and gastrointestinal complaints, and worrying about sleep. A variety of concepts have been studied and reported in the literature in regard to perimenopausal women and sleep, including: poor sleep quality, sleep disturbances, insomnia, insomnia related symptoms, menopausal related insomnia, and impaired sleep. Although a fair amount of research literature was identified on perimenopause and sleep, no literature was found that focused on surgical menopause and sleep.

Surgical menopause is defined as removal of the ovaries; bilateral oophorectomy, before natural menopause or the natural cessation of menses occurs (Wild, 2007). Some estimates suggest approximately 300,000 US women will have prophylactic bilateral oophorectomies each year simultaneously with hysterectomies. According to the CDC, 55% of women who had a hysterectomy had a bilateral oophorectomy and the percentage, 75%, was highest for women aged 45-54 years (Keshavarz, Hillis, Kieke, & Marchbanks, 2002, p. 5). This group of women represents the perimenopausal population: A group of women with a predisposition for developing insomnia precipitated by the abrupt decline in ovarian estrogens and androgens, including testosterone and progesterone, secondary to surgical menopause.

Overview of Perimenopause and Associated Symptom Clusters

Several reviews have focused on sleep in perimenopause over the last 15 years (Joffe, Massler, & Sharkey, 2010; Kravitz & Joffe, 2011; Krystal, Edinger, Wohlgemuth, & Marsh, 1998; Polo-Kantola, 2008; Soares & Murray, 2006; Woods & Mitchell, 2005). The terms used to refer to this period in a woman's life have been diverse, such as

perimenopause, climacteric, mid-life and menopause transition. Few reviews have given a consistent definition of these terms, if defined at all. Sleep-related symptom definitions have also been diverse and vague at times. The terms seen in the literature have included sleep disturbance, sleep complaints, insomnia and insomnia symptoms. Regardless of the applied definition, findings consistently indicate that sleep disturbances increase in women during the natural progression of perimenopause (Joffe et al., 2010; Krystal et al., 1998; Soares & Murray, 2006; Woods & Mitchell, 2005). What has not been examined is insomnia in women who have experienced surgical menopause during this already-troubling life stage.

A recurrent topic noted within several reviews is the occurrence of sleep disturbances related to life-stage changes (Krystal et al., 1998), also referred to as perimenopausal sleep disorder and vasomotor initiated insomnia (Kravitz & Joffe, 2011). Joffe, Massler and Sharkey (2010) reported that the likelihood of documenting insomnia in perimenopausal and early postmenopausal women is 26% higher than in older women.

The prevalence and frequency of symptoms during perimenopause was the focus of several studies. Vasomotor symptoms that included hot flashes and hot flushes, depressed mood, sleep complaints and sexual symptoms were equally mentioned in the literature. These symptoms take on a distinct pattern perceived as clusters related to perimenopause (Joffe et al., 2010; Kravitz & Joffe, 2011; Soares & Murray, 2006; Woods & Mitchell, 2005).

Quality of life and mental well-being were persistent topics that emerged in the literature. Reports of uncertainty, emotional changes, anxiety and depression

associated with perimenopause were commonly reported (Kravitz & Joffe, 2011; Krystal et al., 1998; Soares & Murray, 2006, Woods & Mitchell, 2005). Joffe, Massler and Sharkey (2010) found that sleep disruptions often co-occur with anxiety and depression but with inconsistency. It is therefore difficult to discern the contributions of each of these complaints as potential contributors to disrupted sleep.

Common Perceptions of Perimenopause Derived from Qualitative Studies

The menopause transition has been called many different names; menopause, perimenopause, change of life, and the climacteric. Women often experience many other stressors at this point in their lives such as caring for aging parents, raising children and remaining productive in challenging workplaces while transitioning to post-reproductive age. How women describe this stage of life is the subject of many qualitative studies. This period of time in a woman's life is the focus of this section and begins by focusing on the common themes surrounding this experience as perceived by the women participants; also included is a summary of the qualitative study results that examined the experience of sleep among women dealing with menopausal symptoms.

The Journey

The perimenopausal journey is unique to each woman; however, the common thread is that this biological change is inevitable. Qualitative studies describing the women's perspective of the journey have been conducted over the past decade. George (2002) completed a phenomenological study to understand the experience of menopause in American women and concluded that three major themes evolved from the interviews: expectations and realization; sorting things out; and a new life phase. George (2002) reported that women are confused during this transitional time and are

unsure whether they are experiencing menopause or not which is sometimes due to the subtle and slow onset of menopause. Women described being confused with inconsistent symptoms such as irregular periods and hot flashes. Hot flashes were reported as interfering with sleep in the 15 women participants in George's study (2002). Women reported emotional changes and were quoted as "being on an emotional roller coaster" (George, 2002, p. 82). Similarly, mood swings were reported in a grounded theory study to examine the changing focus of women on the perimenopausal journey (McCloskey, 2012). Similar to the George (2002) study, McCloskey (2012) reported that women needed to determine normalcy by discussing their experiences with other women. Confusion related to menopausal symptoms dominated the interviews. Symptoms experienced by the women and symptom treatment options were the focus of the narratives. Women reported seeking out other women's wisdom to gain an understanding of the journey (McCloskey, 2012).

Morgan, Merrell, Rentschler and Chadderton (2011), using a hermeneutic phenomenology approach, concluded that perimenopause is a time of health uncertainty; with the experience of inconsistent symptoms adding to the knowledge deficit. Women reported feeling that these changes must be something other than perimenopause and sought answers to their questions, but found few credible sources of information (Morgan, Merrell, Rentschler, & Chadderton, 2011). Qualitative studies commonly reported participants lacked knowledge (George, 2002; McCloskey, 2012; Nosek, Kennedy, & Gudmundsdottir, 2012), which supports the need for further education about perimenopause in this large population.

Symptom Experience

Distress was common among perimenopausal women. Symptom experience was the focus of a narrative study that involved collection of the stories of 15 women within the menopause transition (Nosek et al., 2012). This study, conducted at the University of California, San Francisco utilized Symptom Management Theory as its framework. Women reported the distressful symptoms that they were experiencing and how the symptoms affected all aspects of their lives, including work and partner and family relationships. Some of the distressful symptoms were hot flashes, night sweats, mood changes, sexual symptoms, sleep disruption and an overall decrease in quality of life. These distressing symptoms and negative perspectives are consistent with other findings (George, 2002). Interestingly, McCloskey (2012) portrayed the experiences of study participants in a positive light, using terms such as seeking wisdom, monitoring the voice from within, nourishing the woman within, and becoming a wise woman. These contrasting perspectives on the perimenopausal symptom experience highlight the uniqueness of the perimenopausal experience described by some as “a web of symptoms.”

Hsu, Chen, Jou, An, and Tsao (2009) used a grounded theory approach to describe the experiences of sleep disturbance among perimenopausal women in Taiwan. Five categories of themes emerged from the data: worsening health status, living with lonely nights, a search for resources, vicious cycle, and acceptance of insomnia. The participants reported disturbed sleep as the cause of their sleep issues. Disturbed sleep was characterized by easy awakening, difficulty falling asleep, inner worries, and physical discomfort related to vasomotor symptoms and back pain. The

core desire of women in this study was “getting back to a good night’s sleep” (Hsu et al., 2009, p. 2121). Vigeta, Hachul Tuflik and Menicucci (2012) utilized Spielman’s 3 P Model of Insomnia (Speilman, Caruso, & Glovinsky, 1987) as a framework in their study of 22 postmenopausal women. The purpose of this study was to identify factors that influence the perception of sleep quality. Similar themes emerged as previously reported. Women reported sleep difficulties and sleep that worsened during the perimenopausal period. This period of time included dealing with the consequences of poor sleep, such as fatigue and poor work productivity (Vigeta, Hachul, Tuflik, & Menicucci de Oliveira, 2011). The investigators concluded that poor sleep hygiene and lack of knowledge related to sleep hygiene impacted the women’s sleep opportunities (Vigeta et al., 2011). Women experiencing sleep disturbances in the perimenopausal period lacked knowledge of the symptoms and potential opportunities to improve sleep symptoms. Additional studies are needed to gain further insight into the treatment options for women experiencing sleep difficulties during perimenopause.

Summary

Qualitative studies describe the essence of women’s experiences of perimenopause and the women’s perceptions of symptoms. Perimenopause is a time of change, marked by physical and psychological stressors that are further impacted by the increased risk for sleep disturbances and poor sleep quality. These symptoms can potentially progress to a diagnosis of insomnia. While the qualitative research is diverse in design and thereby gives rise to varied perspectives of perimenopause as a journey or a symptom cluster, there are relatively few such studies. Women described this period of life as emotionally and physically distressful. Poor quality-of-life, knowledge

deficit and information-seeking, worsening health status and inconsistent physical changes were common themes described in the literature. Quantitative studies far out-numbered qualitative studies in this population, most likely due to the medical approach often used in the treatment of insomnia and management of sleep disturbances. Quantitative studies are reviewed in the following section.

Burden and Symptoms of Perimenopause Derived from Quantitative Studies

Quantitative studies related to perimenopause are abundant yet gaps remain. Women experiencing perimenopausal symptoms have been the focus of randomized controlled trials, as well as quasi experimental, correlational and longitudinal cohort design studies over the last two decades. Researchers have not yet been able to frame the symptom experience of perimenopause in its entirety and continue to focus on single symptoms rather than symptom clusters which may be more amenable for treatment options. The next section focuses on the quantitative studies that offer findings that support the burden and symptoms of perimenopause and the relationship with sleep complaints in this population.

Perimenopause and Burden

Perimenopause is a unique process for each woman and the insomnia symptoms and negative outcomes can place a considerable burden not only on the women who are directly affected, but also on society (Bolge, Balkrishnan, Kannan, Seal, & Drake, 2010) through health-care expenditures (Chilcott & Shapiro, 1996; Walsh, 2004), higher rates of absenteeism in the workplace (Leger & Massuel, 2006), decreased productivity (Linton & Bryngelsson, 2000; Schweitzer, Engelhardt, Hilliker, Muehlbach, & Walsh, 1992), and increased risk of work related accidents (Walsh, 2004)

compared to the general population. In a study that measured direct and indirect costs of untreated insomnia in adults in the United States, it was found that younger adults (i.e. aged 18-65) with insomnia had insomnia related costs; about $1253 per year greater than patients without insomnia (Ozminkowski et al., 2007). A cross-sectional study by Whiteley et al. (2013) using the 2010 US National Health and Wellness Survey was performed to describe health-related quality-of-life, work productivity and resource use among postmenopausal women by severity of vasomotor symptoms. Researchers found that severity of vasomotor symptoms was significantly and directly associated with use of healthcare resources and inversely related to health status and work productivity.

The burden associated with chronic sleep maintenance insomnia characterized by nighttime awakenings (CINA) among women with menopausal symptoms was studied to determine if there was a relationship between CINA and health care costs, indirect costs at work, activity impairment and health related quality of life (Bolge et al., 2010). A secondary analysis was completed using data from a sample of 1,446 women enrolled in the 2006 US National Health and Wellness Survey; approximately 10% (n=141) met the inclusion criteria for insomnia with 90% (n=1305) meeting the criteria for no insomnia. Women experiencing CINA were significantly younger than the women who were not experiencing CINA, with an average age of 51 and of 53 years, respectively ($p=0.026$). Women with CINA experienced a significantly greater number of physical conditions and were more likely to experience a psychiatric condition ($p< 0.001$) (Bolge et al., 2010). The researchers also noted that women with menopausal symptoms with CINA had significantly greater healthcare resource utilization with more

emergency department visits ($p<0.001$) than the no insomnia group (Bolge et al., 2010). The investigators concluded that insomnia characterized by nighttime awakenings was associated with diminished health-related quality-of-life and work productivity, and increased absenteeism and health care resource utilization (Bolge et al., 2010).

Perimenopause is also associated with an increased burden on society. Taken together, the cost of insomnia treatment, increased use of health related resources, decreased quality of life and decreased work productivity emphasize the need to examine the association between perimenopause and insomnia.

Perimenopausal Symptoms

Symptoms have been studied extensively in women during the transition to menopause. Symptoms during natural progression to menopause are gradual and typically resolve within six months to two years (Freeman et al., 2007; Woods & Mitchell, 2005). Yet, this is not the case in surgical menopause when these symptoms appear abruptly and with increased severity (Benshushan et al., 2009). Kronenberg (1990) reported that menopausal vasomotor symptoms during the natural progression almost always resolve within one year but in some individuals, menopausal vasomotor symptoms may persist for 30 years which potentially extends the risk for chronic insomnia. Kronenberg (1990) reported that although the total time of experiencing hot flashes ranged from a few months to more than 20 years, 60% of the women had experienced hot flashes for greater than seven years while 19% had never experienced hot flashes. Feldman, Voda and Groneth (1985) reported that 88% of women in their study (n=594) reported hot flashes. The largest group that experienced hot flashes was the surgical menopause group with 91.5% experiencing hot flashes (Feldman, Voda, &

Gronseth, 1985). Berg, Larson and Pasvogel (2008) recruited 110 Caucasian women, aged 43 to 55 years old, for a cross-sectional descriptive study of menopausal symptoms and symptom severity. The researchers reported sleep difficulties as the most frequently experienced symptom (94.5%), along with forgetfulness (91.8%), irritability (87.3%), night sweats (85.5%), hot flashes (82.7%) and mood swings (74.5%) (Berg, Larson, & Pasvogel, 2008).

In a nine- year longitudinal cohort study, 404 African American and Caucasian women aged 39 to 59, reported that hot flushes, aches, joint pain and stiffness as well as depressed mood increased in the menopausal transition (Freeman et al., 2007). Poor sleep and sexual changes were not found to be associated with menopausal stages (Freeman et al., 2007). The investigators concluded that lower levels of inhibin b, a hormone present during the latter reproductive years, were associated with poor sleep. Freeman et al. concluded that the prevalence of poor sleep in their sample ranged from 43% to 53% however sleep quality was not significantly related to menopausal stages (Freeman et al., 2007).

Significant relationships have been found between vasomotor symptoms and lower levels of estrogen that occur during perimenopause. Not surprisingly, vasomotor symptoms have been treated with hormone replacement therapy (Gambacciani et al., 2005; Shanafelt, Barton, Adjei, & Loprinzi, 2002; Sikon & Thacker, 2004). Emerging research supports the finding that hot flashes are a result of a marked reduction in the hypothalamic thermoregulatory neutral zone in the brain (Freeman, 2005). This marked thermoregulatory area of the brain has been connected to an increase in vasomotor symptoms such as hot flashes and night sweats resulting from the change in the central

nervous system transmitters (Rapkin, 2007). Central nervous system transmitters such as serotonin, norepinephrine, dopamine and endorphins contribute to troubling symptoms that include vasomotor symptoms, mood changes and sleep disturbances.

Sleep difficulties are among the most frequently reported symptoms reported by perimenopausal women (Berg et al., 2008), although sleep difficulties are not always associated with specific menopausal stages (Freeman et al., 2007). Vasomotor symptoms are related to the decrease in estrogen that is consistent with perimenopause (Gambacciani et al., 2005). This hormone shift is contributory to the sleep complaints, in part influenced by hot flushes and sweating in perimenopausal women.

Vasomotor Symptoms and Sleep Complaints

Sleep complaints increase with age and women report more sleep difficulties than men (Zhang & Wing, 2006). Sixty-three healthy postmenopausal women were the focus of a study to evaluate the association between climacteric vasomotor symptoms and sleep quality which was measured by self-report and polysomnography (Polo-Kantola et al., 1999). Vasomotor symptoms were defined as hot flushes and sweating. A significant positive relationship was identified between subjective reports of impaired sleep and vasomotor symptoms ($p<0.001$). No significant relationship was found between any sleep variables measured by polysomnography and vasomotor symptoms ($p \geq 0.337$). However, high body mass index predicted longer sleep latency measured by polysomnography ($r=0.27$, $p=0.031$) (Polo-Kantola et al., 1999).

Ohayon (2006) reported that in a sample of 982 women who were categorized as premenopausal (57.2%), perimenopausal (22.3%) and postmenopausal (20.5%), severe hot flashes were strongly associated with chronic insomnia in midlife ($p<0.001$).

Hot flashes were present in 79% of perimenopausal women and the prevalence of chronic insomnia in this subgroup was 56.6% (Ohayon, 2006).

Vasomotor symptoms are not the only connection to insomnia and sleep disturbances during the menopausal transition. In a cross-sectional study, 340 women, ages 40 to 59 years, completed the Insomnia Severity Index (ISI) and Menopausal Rating Scale (Arakane et al., 2011). Findings indicated that more severe hot flushes were positively related to increased ISI scores ($p<0.001$), however no significant relationships were found between ISI scores with either female age or menopausal status. The researchers also found that the ISI scores were related to hot flushes ($p<0.001$), psychotropic drug use ($p=0.001$) and sedentary lifestyle ($p=0.01$). They concluded that future research might examine links between comorbid disorders and potential risk factors, as well as investigate sleep disturbances (Arakane et al., 2011). Terauchi, Obaryashi, Akiyoshi, Kato, Matsushima and Kubota (2010) completed a retrospective analysis of the medical records of 1,451 peri- (27.8%) and postmenopausal (72.2%) women to determine the prevalence of insomnia (50.8%) and the relationship with health-related quality of life (Terauchi et al., 2010) An inverse relationship was found between insomnia and health-related quality of life ($p<0.0001$). The researchers also reported that insomnia was positively correlated with every other symptom score ($p< 0.0001$) (Terauchi et al., 2010).

Finally, a cross-sectional study of 237 perimenopausal and postmenopausal women in Tokyo examined the prevalence of insomnia and reported that insomnia was present in 30.8% of the perimenopausal women (Terauchi et al., 2012). Difficulty in initiating sleep and non-restorative sleep was found to have a positive association with

psychological symptoms, depression and anxiety ($p < 0.001$), while not with hot flushes ($p=0.068$) or menopausal status ($p=0.151$). The researchers further reported that difficulty initiating sleep was correlated with anxiety ($p=0.006$) while non-restorative sleep had a positive relationship with depression ($p =0.016$). Overall, insomnia was more closely related to psychological than somatic symptoms using Spearman's rank coefficient (Terauchi et al., 2012). This study further explored the long-term mental health consequences of menopause-related insomnia. Depression as reflected in the symptoms of "loss of interest in things", "lack of enjoyment", "low energy", and "depressed mood" was correlated with non-restorative sleep and difficulty initiating sleep for most of the psychological variables (Terauchi et al., 2012). Terauchi et al. report findings consistent with others reporting a lower rate of menopausal and vasomotor complaints in Asian populations (Avis et al., 2001; Gold et al., 2006; Loh, Khin, Saw, Lee, & Gu, 2005) further supporting the concept that the occurrence of vasomotor symptoms is impacted by multiple factors such as ethnicity and culture.

In order to better understand the role of sleep in perimenopause, it is imperative to further investigate all aspects of sleep occurring in perimenopause. The following section explores literature relevant to sleep disorders, sleep quality and sleep data among peri- and postmenopausal women.

Sleep Disturbances and Quality of Sleep

Shaver, Giblin, Lentz and Lee (1988) completed one of the first studies of the sleep patterns of women during perimenopause. Their descriptive correlational study of 76 healthy women ages 40-59 years used objective and subjective sleep data. Objective sleep data was measured by in-laboratory polysomnography over a two,

consecutive night data collection period. Poorest sleep efficiency was found in perimenopausal women and sleep efficiency was associated with hot flashes (Shaver, Giblin, Lentz, & Lee, 1988). The researchers concluded that although the sleep patterns of perimenopausal women did not differ significantly from premenopausal and postmenopausal women, sleep efficiency might be affected by menopausal status and vasomotor symptoms. Therefore, future studies involving hormone levels and sleep in this population was suggested (Shaver et al., 1988).

The Study of Women's Health Across the Nation (SWAN), a multiethnic community-based cross-sectional study conducted at seven sites in the United States compared age-adjusted and ethnic differences in prevalence of sleep difficulty at various stages of the menopause transition. The aim of the parent study was to determine the relative contribution of vasomotor symptoms, sociodemographic, and psychological and physical health factors, to self-reported sleep difficulty in mid-life women (Kravitz et al., 2003). A sample of 12,603 women, aged 40 to 55, was recruited to compare age-related, self-reported sleep difficulties among women at various stages of the menopausal transition who were either using or not using hormone replacement therapy. The objective of the research was to examine if menopausal status, independent of other potentially influential variables, was associated with sleep difficulty (Kravitz et al., 2003). Difficulty sleeping was highest in the perimenopausal group (45.4%) while 38% of the entire sample reported difficulty sleeping (Kravitz et al., 2003). Menopausal status was positively correlated with difficulty sleeping as well for women who had surgical menopause and were not treated with hormone-related therapy (Kravitz et al., 2003).

The Penn Ovarian Aging Study, a longitudinal study of ovarian aging in a population-based cohort from the Philadelphia area, sought to identify predictors of poor sleep quality in women in the menopausal transition. The cohort consisted of 218 African American and 218 Caucasian women aged 35 to 47 years at enrollment. Worse sleep quality was predicted by lower inhibin B levels, hot flashes and more depressive symptoms (Pien et al., 2008). This secondary analysis of data from the Penn Ovarian Study also reported no significant relationship between menopausal status, age or race with sleep quality. A significant limitation of this study was the self-reported measurement of menopausal status and also the lack of racial diversity in the study. However, the results of sleep quality associated with hot flashes are consistent with studies previously discussed (Freeman et al., 2007; Shaver et al., 1988).

Hollander and colleagues (2001) completed a secondary analysis of the Penn Ovarian study and found that 17% of women complained of poor sleep at each of the three assessment periods (approximately every eight months after the baseline assessment). Increased hot flashes were found to predict poor sleep while diminishing estradiol levels (E2) associated with age (45-49) were related to poor sleep quality. Diminishing E2 levels were seen more often in perimenopausal women than in postmenopausal women (OR 0.53; 95% CI 0.34-0.84, p=0.006), suggesting that treatment for sleep-related complaints may need to be initiated earlier in the transition period than originally thought (Hollander et al., 2001). According to this study, E2 levels may have greater importance for younger women who report poor sleep quality than shown in previous studies.

Studies from around the world support the fact that approximately 50% of middle-aged women suffer from sleep disturbances. A cross-sectional study was performed in 11 Latin American countries with a total sample of 6079 women with a mean age of 49.8 and an educational level of 10.8 years (Blumel et al., 2012). The instruments used to measure sleep complaints were the Athens Insomnia Scale and the Pittsburgh Sleep Quality Index. Overall, 56.6% of the women suffered some sleep difficulties (e.g. insomnia or poor sleep quality). The prevalence of sleep difficulties increased with age and menopausal status (Blumel et al., 2012). A significant positive relationship was also identified between sleep disturbances and vasomotor symptoms, as well as with depressive mood and anxiety. These findings are consistent with previous studies (Arakane et al., 2011; Shaver et al., 1988; Terauchi et al., 2012).

Finally, Xu, Belanger, Ivers, Guay, Zhang and Morin (2011) presented findings from a descriptive correlational design comparing subjective and objective sleep quality in menopausal and non-menopausal women with insomnia. Seventy-four women with a diagnosis of insomnia were evaluated to examine the relationship of sleep quality and insomnia and the impact that hormone therapy had on their reports of sleep quality. The mean age of the sample was 50.3 years with 41 being identified as peri- or postmenopausal. Analysis of the objective sleep data by polysomnography confirmed the hypothesis that menopausal women had lower sleep efficiency and less total sleep time than premenopausal women. None of the subjective sleep variables (i.e. sleep diaries, Insomnia Severity Index (ISI) scores, as well as other psychological and insomnia questionnaires), were significantly related to insomnia severity (Xu et al., 2011). The use of both objective and subjective sleep measures clearly linked sleep

complaints and perimenopausal status. However women using hormone replacement therapy did not show significantly better sleep quality when compared to those not using hormone replacement therapy. Future studies with large samples, using both subjective and objective sleep data along with hormone levels, are needed to build on this research and to potentially offer insights for the design of appropriate insomnia interventions for women entering perimenopause.

Surgical Menopause

According to statistics from the National Center for Chronic Disease Prevention and Health Promotion 1988-1993, among 45 to 54 year old women who have had a hysterectomy, 76% also had their ovaries removed (Lepine et al., 1997). This supports a safe estimate that more than half of the oophorectomies performed in the United States will be completed before the median age (51 years) of natural menopause (Wild, 2007). Surgical menopause, defined as the removal of both ovaries prior to menopause, has been associated with a rapid decrease in gonadal hormones (Chubaty et al., 2011) leading to menopausal symptoms including hot flashes and trouble sleeping (Wild, 2007). The sudden shift in hormones with surgical menopause has a detrimental effect on the physiologic and psychological health of perimenopausal women (Bhattacharya & Jha, 2010; Collaris, Sidhu, & Chan, 2010; McCarthy et al., 2012). As previously discussed, perimenopause is marked by a gradual decline in reproductive hormones and androgens that result in an increase in sleep complaints. In surgical menopause, the natural progression of diminishing estrogen and androgens is abruptly halted and poses great risks for increased sleep disturbances (Chubaty et al., 2011), vasomotor symptoms (Hendrix, 2005) and a loss of quality of life (Bhattacharya

& Jha, 2010). It is yet unclear, due to a lack of evidence, if there is a difference in the severity of menopausal symptoms and if the symptoms last longer in women who have undergone surgical menopause when compared with women who experience natural menopause.

Surgical menopause changes the normal progression of menopause which has been found to result in a sudden drop in circulating hormones as early as 24 hours after surgery (Bachmann, 2001). Women that have undergone surgical menopause have reported more severe climacteric symptoms than women progressing naturally through menopause (Benshushan et al., 2009; Chubaty et al., 2011). Relatively little research focusing on sleep disturbances has been completed in perimenopausal women who have undergone surgical menopause. This lack of research affords an opportunity to add to the state of the science and more importantly develop interventions for perimenopausal women who undergo surgical menopause and experience sleep disturbances. The following section will discuss the evidence related to surgical menopause in women who have not yet entered natural menopause with an emphasis on health outcomes and risk factors.

Physiologic Aspects of Surgical Menopause

Preliminary work on surgical menopause was undertaken by Richards (1951). Ninety-eight percent of women who underwent bilateral oophorectomy developed menopausal symptoms either immediately or within several weeks of the operation. The menopausal symptoms were more severe in women who underwent bilateral oophorectomy than in cases where ovarian tissue was preserved. Menopausal symptoms experienced by naturally and surgically menopausal women differ. Studies

have reported more severe symptoms in women who have undergone surgical menopause than natural menopause due to the abrupt decline in estradiol (Thompson, Hart, & Durno, 1973; McKinlay, McKinlay, & Brambilla, 1987; Wild, 2007). Examples of severe symptoms include hot flashes (Guzick & Hoeger, 2000), depression (Sherwin & Gelfand, 1987; Dennerstein, Guthrie, Clark, Lehert, & Henderson, 2004) and cardiac symptoms (Riedel, Lehmann-Willenbrock, & Semm, 1986). For the majority of these women, hormone replacement therapy (HRT) is necessary for symptom relief (McKinlay et al., 1987; Luborsky, Meyer, Sowers, Gold, & Santoro, 2003; Wild, 2007). Women who have undergone surgical menopause will need to stop HRT sometime in their lives; at that time, women are often faced with the recurrence of severe symptoms, including hot flashes, night sweats and insomnia (Hendrix, 2005; Wild, 2007). Research remains limited on the best approach to care for the multitude of symptoms experienced by perimenopausal women who have undergone surgical menopause.

Surgical menopause and menopausal symptoms

During the past 35 years, much more information has become available on the effects of surgical menopause. A number of studies have found that menopausal symptoms were more severe in women who had undergone surgical menopause than those in natural menopause (Benshushan et al., 2009; Chakravarti, Collins, Newton, Oram, & Studd, 1977; Haines, Chung, & Leung, 1994; Ozdemir et al., 2009). Collaris, Sidhu and Chan (2010) reported contrary results in their prospective study. The researchers reported that vasomotor symptoms remained unchanged while other symptoms such as anxiety, depression and somatic symptoms improved following surgery among women who had a total abdominal hysterectomy with bilateral

oophorectomy when compared to women who had a total abdominal hysterectomy with ovarian preservation (Collaris et al., 2010). Bhattcharya and Jha (2010) completed a cross-sectional study to investigate health-related quality of life after natural and surgical menopause. Although limited by a small sample size (n=64), the use of the menopausal rating scale (MRS-II), was a strength of the study. The results of this study identified differences in symptoms between the two groups. The total MRS-II scores were higher for the surgical menopause group compared with natural menopause group (mean 29.4, [SD=6.7] and 20.7, [SD=6.5], respectively, $p<0.0001$) supporting the hypothesis that surgical menopause negatively influences health-related quality of life (Bhattacharya & Jha, 2010). Chubaty, Shandro ,Schuurmans and Yuksel (2011) interviewed 70 women to determine practice patterns with hormone replacement therapy (HRT) after surgical menopause. It was found that 40% of women (28/70) were started on HRT after surgical menopause. Women not taking HRT were more likely to report daily hot flashes when compared to women taking HRT (74% versus 30%). Night sweats and sleep complaints did not differ between groups (Chubaty et al., 2011).

Several studies have examined the relationship between surgical menopause and sexuality and sexual functions (Aziz, Bergquist, & Silfverstolpe, 2005; Topatan & Yildiz, 2012). Aziz, Bergquist and Silfverstolpe (2005) carried out a prospective observational study comparing women with total abdominal hysterectomies (n=217) to women with total abdominal hysterectomies and bilateral oophorectomies (n=106) to determine if oophorectomy during perimenopause negatively influenced sexual function and psychological well-being. The results showed no significant difference in sexuality between the two groups and an improvement in psychological well-being one year after

surgery in both groups. The researchers concluded that hormonal changes alone do not impact on sexuality or psychological well-being after surgical menopause (Aziz et al., 2005).

Conversely, Topatan and Yildiz, (2012) reported a significant negative relationship among the severity of symptoms with sexual functions in women who have undergone surgical menopause. In a descriptive cross-sectional study of 200 women that had undergone surgical menopause and 250 women who had entered into natural menopause, the researchers studied the symptoms experienced by menopausal type and the impact of these symptoms on sexual functions (Topatan & Yildiz, 2012). Utilizing the Menopausal Rating Scale (MRS) and the Golumbok Rust Inventory of Sexual Satisfaction (GRISS), the women experienced varying degrees of menopausal symptoms. Reported most frequently as significant among all participants were hot flushes and sweating ($p< 0.001$) and heart discomfort ($p<.002$) followed by sleep problems ($p < 0.006$) and sexual problems ($p< 0.004$) (Topatan & Yildiz, 2012). The researchers also reported that women define menopause differently with women entering natural menopause seeing it as a natural process and women in the surgical menopause group seeing it as the end of womanhood, fertility, and sexuality (Topatan & Yildiz, 2012). This previously unreported finding further supports the multifactorial influences on symptom perception and experiences during perimenopause.

Overall, evidence suggests that surgical menopause negatively impacts women who undergo this procedure prior to natural menopause. Vasomotor symptoms (Benshushan et al., 2009), depression (Rocca et al., 2009), anxiety (Rocca et al., 2009), sexual dysfunction and sleep disturbances (Topatan & Yildiz, 2012) were some of the

problems identified by the studies especially in women undergoing surgical menopause before the age of 45. Perimenopausal women who have undergone surgical menopause require support to effectively manage the menopausal symptoms. Key information related to the symptom experience of sleep disturbances is largely absent from the literature and is needed to care for this large group of women.

Long term health after surgical menopause

Several review articles focusing on the long term health outcomes of surgical menopause in premenopausal women have been published (Parker, 2009; Parker et al., 2009; Shuster, Gostout, Grossardt, & Rocca, 2008; Shuster et al., 2010). There is an overwhelming amount of evidence that suggests bilateral oophorectomy before the age of 45 is associated with increased cardiovascular risk and premature death in women (Lobo, 2007; Lokkegaard et al., 2006). In the Nurses' Health Study, oophorectomy in women that never used estrogen doubled the risk for myocardial infarction (MI; RR 2.2; 95% CI: 1.2-4.2) when compared to age-matched premenopausal women (Colditz, Manson, & Hankinson, 1997). Additionally, the Nurse Health Study data through 2002 showed that oophorectomy was associated with an increased risk of coronary artery disease for all women (HR 1.17; 95% CI 1.02-1.35). This risk was higher for women undergoing surgical menopause prior to age 45 years (HR 1.26; 95% CI 1.04-1.54) (Rocca, Grossardt, De Andrade, Malkasian, & Melton, 2006). In a meta-analysis of observational studies, it was found that oophorectomy doubled the risk of cardiovascular disease (RR 2.62; 95% CI: 2.05-3.35) (Atsma, Bartelink, Grobbee, & Van der Schouw, 2006). There are, however, several studies that suggest oophorectomies do not increase the risk of cardiovascular disease (Howard et

al., 2005; Palmer, Rosenberg, & Shapiro, 1992). Overall, there is more evidence supporting increased cardiovascular risks among women who have undergone oophorectomies, especially if it occurs prior to natural menopause, than those women who retain ovarian tissue. According to Howard et al. (2005) women who have had an oophorectomy have slightly worse health characteristics than those that retain their ovaries. There are few studies that have focused on hormone therapy in younger women which may offer insight into the beneficial properties of estrogen in cardiovascular health (Bushnell et al., 2006).

A number of studies have examined the psychological impact of surgical menopause (Farrag, Khedr, Abdel-Aleem, & Rageh, 2002; Henderson & Sherwin, 2007; Phillips & Sherwin, 1992; Rocca et al., 2007). In the Mayo Clinic Cohort Study of Oophorectomy and Aging, the risk of cognitive impairment increased with younger age at oophorectomy with women under age 43 years having the greatest risk (HR 1.74; 95% CI 0.97-3.14; p=0.06). The trend of elevated risk among younger women to develop cognitive impairment when not treated with estrogen at the time of oophorectomy was reported as significant (p=0.01) (Rocca et al., 2007). Farreg et al. (2002) reported that surgically menopausal women had significant decreases in global cognitive functioning, measured by MMSE ($p < 0.05$) at six months after oophorectomy when compared to women progressing naturally through perimenopause. Phillips and Sherwin (1992) investigated the effect of estradiol versus placebo on neuropsychological outcomes. The researchers found that women randomized to estradiol following oophorectomy performed significantly better ($p<0.05$) on verbal memory than women who were given a placebo (Phillips & Sherwin, 1992). Evidence

has suggested that estrogen may have a neuroprotective effect on the brain and that the effect may depend on age. It is important for women undergoing surgical menopause prior to the age of natural menopause to be educated on the importance of estrogen for neuroprotection (Henderson & Sherwin, 2007).

Similar to the protective nature of estrogen on brain health, estrogen also plays an important part in bone health (Raisz et al., 1996). Oophorectomy is an important risk factor for the development of osteoporosis (Kreiger, Kelsey, Holford, & O'Connor, 1982; Gallagher, 2007). Gallagher (2007) reported that oophorectomy before the age of 45 is a risk for osteoporosis and the earlier the surgical menopause occurs, the lower the bone density in later life. Estrogen therapy does prevent bone loss (Lindsay, Hart, Forrest, & Baird, 1980; MacLean et al., 2008); Long- term use of hormone therapy, however, has declined after the results of the Women's Health Initiative clinical trials were published (Rocca et al., 2009).

Collectively, these studies provide convincing evidence that surgical menopause prior to natural menopause has many negative effects on a woman's life. Surgical menopause in perimenopausal women triggers a sudden loss of estrogen manifesting itself in severe symptoms of hot flashes, mood changes, sleep disturbances, headaches and a decline in well-being (Nathorst-Boos, Von Schoultz, & Carlstrom, 1993; Nieman, 2003). In perimenopausal women, immediate effects of oophorectomy on cognitive outcomes, energy level, mood and feelings of well-being have been identified within a few weeks of surgery when compared with women undergoing total abdominal hysterectomy alone (Sherwin, 1988; Farrag et al., 2002). Several studies have also identified an increase in overall mortality (Rocca et al., 2006; Parker et al., 2009). In the

Nurses' Health Study, it was reported that all-cause mortality was increased by oophorectomy (HR 1.12: 95% CI 1.03-1.21) and at no age did oophorectomy provide a survival benefit (Parker et al., 2009). Similarly the Mayo Clinic Cohort Study of Oophorectomy and Aging reported all-cause mortality to be significantly higher in women who had prophylactic bilateral oophorectomy before the age of 45 when compared to referent women (HR 1.67: 95% CI 1.16-2.40); this evidence further supports that there are important negative outcomes of surgical menopause (Rocca et al., 2006).

In conclusion, surgical menopause increases the risk of a multitude of long term health problems including but not limited to heart health, neurocognitive problems, sexual dysfunction, all-cause mortality, and severity of menopausal symptoms including vasomotor symptoms and anxiety as well as sleep disturbances. Evidence is lacking in the area of insomnia and surgical menopause despite its importance related to long term health, productivity and quality of life.

State of the Science

Sleep difficulties in the perimenopausal period are highly prevalent. Evidence to date has focused on natural menopause. Few studies have specifically addressed surgical menopause and sleep. The extant literature has also not systematically examined commonly measured "sleep disturbances" as diagnosable insomnia. A few studies have used insomnia measures but have examined symptoms only without any intention/ability to equate symptoms to an insomnia definition (Kravitz et al., 2003; Kravitz et al., 2008; Pien et al., 2008). The perimenopausal population is large and the risk of insomnia is likely great in this population due to the hormone changes, including

abrupt hormone changes related to the surgical procedure of bilateral oophorectomy. The study addresses an important gap in the scientific research and describes the insomnia prevalence in perimenopausal women, including those who have undergone surgical menopause. This research will contribute new knowledge about perimenopausal women who have undergone surgical menopause.

Conclusion

A review of the surgical menopause literature did not reveal any studies that specifically examined the relationship between surgical menopause in perimenopausal women and insomnia. However, several studies included sleep disturbances in perimenopausal women (Hollander et al., 2001; Kravitz et al., 2003; Pien et al., 2008; Shaver et al., 1988; Xu et al., 2011) and consistently found that perimenopausal women are at greater risk for sleep disturbances than postmenopausal women. It is surprising then that sleep disturbances are overlooked in the literature addressing surgical menopause.

Surgical menopause is an intervention that results in a change to the normal progression of menopause. This is manifested by a sudden drop in circulating estrogen and androgens resulting in a vast multitude of symptoms and health related challenges. Women who have undergone surgical menopause report more severe menopausal symptoms than women progressing naturally through menopause (Benshushan et al., 2009; Chubaty et al., 2011; Topatan & Yildiz, 2012).

Although some evidence demonstrates that perimenopausal women who have undergone surgical menopause experience more sleep disturbances and have a greater risk of developing insomnia than other perimenopausal women, the evidence is

far from definitive and no studies, identified to date, address this relationship. This study used the concept of surgical menopause in perimenopausal women to further explore the prevalence of insomnia in a large sample of perimenopausal women. The study period included data from at least one year before surgical menopause through one year after surgical menopause in order to describe the relationship of surgical menopause and insomnia. This research will serve as a foundation to support future development of tailored interventions to address sleep disturbances and insomnia for perimenopausal women.

Chapter 3: Methods

Empiric studies consistently suggest women experience insomnia more frequently and with a higher prevalence than men (Bixler, Vgontzas, Lin, Vela-Bueno, & Kales, 2002; Cirignotta et al., 1985; Zhang & Wing, 2006). Phillips and Mannino (2005) reported in their prospective population- based study that women were more likely than men to report difficulty falling asleep, waking repeatedly from sleep and waking up exhausted. Zhang and Wing (2006) reported discovering a female predisposition for insomnia in their meta-analysis. Among middle-aged women, perimenopausal women have more disturbed sleep, including loss of sleep quality and continuity, than postmenopausal women (Berg et. al., 2007; Parry et al., 2006; Shaver et al., 1988). Research has shown a predisposition to insomnia in women yet there is a paucity of evidence that addresses the trajectory of insomnia in a particularly high risk group of women – those who have undergone surgical menopause.

Few studies have focused on sleep in women who have undergone surgical menopause. Kim and Lee (2006) examined sleep and fatigue before and after hysterectomy using objective and subjective measures of sleep; self-reported sleep disturbance increased three weeks after surgery compared with baseline. This study was limited by the short study duration during the post-operative recovery period and a small sample size (n=25). Benshushan, Rojansky, Chaviv, Arbel-alon, Imbar and Brzezinskis' (2009) retrospective study identified that risk-reducing elective bilateral oophorectomy is associated with more climacteric symptoms including difficulty sleeping than naturally occurring menopause. Chakravarti et al. (1977) studied the symptoms present after bilateral oophorectomy and reported insomnia in nearly 50% of the

participants (n=48). Finally, in a large cross sectional community survey (n=12,603) conducted from November 1995 to October 1997, it was reported that 38% of mid-life women reported difficulty sleeping with the highest rates in the late perimenopause and surgical postmenopausal groups (45.4%, 47.6%, respectively) with a significant relationship between menopausal status, vasomotor symptoms and difficulty sleeping (Kravitz et al., 2003). These findings reinforce the necessity for systematically examining insomnia in mid-life women.

There is a lack of empirical longitudinal studies examining the impact of surgical menopause on the development of insomnia. There is but one study that reported an increased likelihood for trouble falling asleep (sleep latency) and waking up several times per night (awakenings) among surgical menopausal women who were not taking hormone replacement therapy (Kravitz et al., 2008). This study examined age-adjusted odds for sleep disturbances and racial/ethnic differences in sleep disturbance as women progress through the menopausal transition. Kravitz and colleagues (2008) examined three categories of characteristics; symptoms, endogenous hormones, and bleeding patterns in relation to sleep disturbance. No studies to date, to our knowledge, have examined insomnia symptoms over time and the association of sleep-specific symptoms with perimenopausal stage or surgical menopause.

The purpose of the study was to describe the prevalence of insomnia in all perimenopausal women. The primary goal of the study was to gain a better understanding of the course and severity of insomnia in perimenopausal women who have undergone surgical menopause as compared to women who progress naturally to menopause. The aims of the study were: 1) to describe the prevalence of insomnia in

all perimenopausal women; 2) to describe the insomnia prevalence in perimenopausal women who have undergone surgical menopause; 3) to identify if differences exist between the insomnia prevalence in naturally progressing menopause group compared to the insomnia prevalence in surgical menopause groups and; 4) to identify factors of influence on chronic insomnia among perimenopausal women.

A secondary analysis of a pre-existing large data set from an epidemiological parent study that employed a longitudinal cohort design was used for the research. The objectives of the present study were to examine the course of insomnia and the report of insomnia symptoms in perimenopausal women who have and have not undergone surgical menopause. This study only focused on perimenopausal women, because there is little known about insomnia in perimenopause. Perimenopause was stratified as early perimenopause and late perimenopause in congruence with the parent study. The study used data for early and late perimenopause from the entire sample; among the surgical group, data was used through one year after surgical menopause as this period of time is defined as late perimenopausal; one year status-post surgical menopause is considered menopause and not the focus of this study. The study described the trajectory of insomnia in all perimenopausal women. Perimenopausal women who have undergone surgical menopause were compared to perimenopausal women who progress naturally to menopause to discover critical differences in insomnia for these cohorts. The study also identified predictors of chronic insomnia in all perimenopausal women with chronic insomnia.

Research Questions

The following research questions were addressed:

1. What is the prevalence of insomnia, measured annually, in all perimenopausal women?

2. What is the prevalence of insomnia by perimenopausal stage in women?

3. What is the prevalence of insomnia in women who have undergone surgical menopause?

4. Is there a difference in reported insomnia symptoms by perimenopausal stage?

5. Is there a significant difference in insomnia symptoms before and after surgical menopause?

6. Is there a difference in insomnia symptoms among perimenopausal women who have progressed naturally through perimenopause compared to women who have undergone surgical menopause?

7. What are the factors of influence among perimenopausal women that develop chronic insomnia defined as insomnia symptoms present for at least two consecutive data collection points?

Study Design

This study was a secondary analysis of publically-available data from the Study of Women's Health Across the Nation (SWAN), a multisite, longitudinal study of the natural history of menopause, funded by the National Institute on Aging, the National Institute of Nursing Research, and the Office of Research on Women's Health. The original goal of the SWAN was to describe the chronology of the biological and psychological characteristics of the menopausal transition on health and risk factors for age-related chronic illnesses (Sowers et al., 2000). This chapter will first describe the

SWAN study (parent study), followed by a detailed discussion of the methods for the current study including the sample, data access, variables, data management, protection of human subjects, analysis plan and study limitations.

The SWAN Study

The SWAN study was organized as a prospective, multicenter, multiethnic, multidisciplinary study of the natural history of the menopausal transition. The study has both a cross-sectional and longitudinal component with an emphasis on including minority populations. The study included seven sites; Boston (45% African American, 55% Caucasian), Chicago (55% African American, 45% Caucasian), Detroit (66% African American, 33% Caucasian), Los Angeles (55% Japanese, 45% Caucasian), Newark (66% Hispanic, 33% Caucasian), Oakland (55% Chinese, 45% Caucasian), and Pittsburgh (33% African American, 66% Caucasian). The SWAN study sought to describe the sociocultural, lifestyle, psychological and biological characteristics of racially and ethnically diverse women in relation to the menopause transition. The study objectives were: 1) to characterize the symptomatology, hormonal, and bleeding pattern characteristics related to the menopausal transition; 2) to investigate the hormonal and menstrual bleeding characteristics related to change in bone mineral density, cardiovascular status markers, measures of carbohydrate metabolism, and body composition during the menopausal transition; 3) to examine the relationships among psychological factors, personality characteristics, and behaviors, including lifestyle behaviors, as they may relate to age at onset, symptoms, and physiological changes of the menstrual transition; 4) to discern what changes observed over time are related to the menopausal transition as compared to age-related changes, including those

changes that appear to accelerate the aging process; and 5) to describe and quantify cultural and ethnic differences among women with respect to midlife aging and the menopausal transition among the four race/ethnic groups of the cohort, in addition to non-Hispanic Caucasians (Sowers et al., 2000).

SWAN Cross-sectional Study

The SWAN cross-sectional study had two main purposes which were to 1) identify women eligible for the longitudinal study and 2) assess cross-sectionally, factors associated with the age at natural menopause, the prevalence of surgical menopause, symptoms of menopause, health status, and health care utilization taking into account the use of medical services and medications. The SWAN cross-sectional study was conducted between November 1995 and October 1997 in preparation for enrollment into a multi-ethnic longitudinal cohort study of perimenopause. The cross-sectional survey consisted of a 15 to 20 minute telephone interview or face-to-face interview if no telephone number could be correctly identified for the sampled participant. The interview survey was developed with the use of focus groups to inform the development of the survey items and research protocol for relevance and appropriateness. All sites were required to use a standardized interview procedure, supported by a written manual of operations and standardized training of research staff. The Detroit area census information was unable to provide telephone numbers for a large proportion of the population so these interviews were all conducted face-to-face.

Sampling Strategies

Sampling procedures varied across the seven sites including conducting a census, implementing probability sampling, as well as identifying networks with

snowballing. The recruitment goal for each of the seven sites was to obtain representative samples of at least 450 women, including non-Hispanic Caucasian women and one designated minority group (African-American, Chinese, Hispanic, and Japanese) in a specific proportion designated for each site. A probability proportional stratified sampling design was developed at each site that would fulfill the sampling plan. For this reason, sites had different sampling frames and recruitment approaches that are described in the next section.

Sampling Frames

Sampling strategy procedures varied across the sites and have been discussed in detail elsewhere (Sowers et al., 2000). The cross-sectional study recruitment process had to meet three requirements in order to identify a population cohort for the study sample. Sites had to successfully; 1) identify populations representative of *a priori* defined diverse communities; 2) recruit women from a specified race/ethnic minority group in a proportion significantly larger than the groups' representation in the general United States population; and 3) implement recruitment in a geographic area in which an intense longitudinal protocol could be efficiently completed. In order to meet these requirements, the seven sites utilized a variety of sampling frames. Generally the sampling frames included telephone numbers generated randomly from random digit dialing (RDD) lists and list-based frames such as city census, electrical utility customer lists, HMO enrollment lists and an enrollment list from an earlier study.

Random Digit Dialing (RDD) based frames utilized random telephone numbers as a sampling frame. The only information available from the RDD frames were the telephone numbers and the geographic location associated with the exchange. RDD

was used as the major sampling frame at three sites (Newark, Pittsburgh and Los Angeles). Newark and Los Angeles used only RDD-based sampling and Pittsburgh also used voter registration lists as a secondary frame. The following steps were implemented with RDD sampling:

1. Each telephone number was screened to determine if it represented a household.
2. The household was then screened to verify that the household was in the target geographic area and to determine if any age-eligible woman resided at the residence.
3. Interviewers then determined whether the household included at least one eligible woman who was non-Hispanic Caucasian or was from the site's designated racial/ethnic minority group during a screening interview.

These three sites also supplemented RDD sampling with list-based or snowball sampling frames. Snowball sampling was achieved with participant referrals of acquaintances to the study.

List-based frames were utilized as the primary sampling frames for recruitment by four sites (Detroit, Boston, Chicago and Oakland). The list-based frames included a state-mandated census in Boston, an electrical utility customer list in Detroit, a census from a previous study in Chicago and a health maintenance organization (HMO) enrollment list in Oakland, California.

Sampling was completed by organizing the contacts with the sampling units into batches and each batch was a random sample from the overall site population. This minimized selection bias such as seasonal variation or systematic error. In households

with more than one eligible woman, a single eligible woman was sampled by one of two procedures. Five sites sampled by choosing the woman in the household with the most recent birthday (month and day) which was called the birthday method. Newark and Los Angeles sampled the first woman contacted who was willing to offer information. Only one household member was sampled to avoid clustering of women within households.

Cross-sectional Study Response Rates

A total of 202,985 sampling units were screened for potential participation in the SWAN cross-sectional study resulting in 34,446 eligible women. The screening interviews were completed during the period between November 1995 and October 1997 with 16,065 women completing screening interviews. Key screening variables are described in Table 3-1. There was an overall response rate of 46.6% for the SWAN cross-sectional Study (Sowers et al., 2000).

Cross-sectional Inclusion Criteria

The following inclusion criteria were used for the cross-sectional study:

1. Primary residence in designated geographic area
2. Ability to speak English or designated other language – Spanish, Cantonese, or Japanese
3. Age 40-55 years at time of contact
4. Cognitive ability to provide verbal informed consent
5. Membership in the site's targeted ethnic groups

Table 3.1 describes the SWAN Cross-sectional participants. Although one of the main functions of the cross-sectional study was to determine a pool of participants to

include in a longitudinal study, the cross- sectional study supported empiric findings for the following: 1) factors associated with age at natural menopause (Harlow et al., 2000); 2) prevalence of surgical menopause and vasomotor symptoms related to menopausal status (Avis et al., 2001); 3) medical conditions and health status among mid-life women (Avis et al., 2004); 4) physical functioning and menopause (Matthews et al., 2001; Sowers et al., 2001); 5) women's attitudes toward menopause and aging (Sommer et al., 1999); and 6) socioeconomic status among mid-life women transitioning to menopause (Gold et al., 2001).

To date, there is but one study that used the cross-sectional data to examine sleep disturbances in women transitioning to menopause. Kravitz, Ganz, Bromberger, Powell, Sutton-Tyrrell and Meyer (2003) compared ethnic differences in the prevalence of sleep difficulty in women (n=12,603) at different stages of the menopause transition. The authors found that difficulty sleeping was reported by 38% of the women surveyed with rates ranging from 28% in Japanese women to 40% in Caucasian women (Kravitz et al., 2003). However significant additional empiric studies are needed to understand sleep disturbances in mid-life women. The increased prevalence and course of sleep disturbances in women traversing the menopause transition is not well understood. The proposed study will, in part, address this gap by examining the trajectory of insomnia in middle-aged women progressing through perimenopause.

SWAN Longitudinal Study

A longitudinal cohort from the SWAN cross-sectional study was developed to examine the natural progression of the menopausal transition in a prospective, multi-ethnic, multi-site study of pre- and perimenopausal American women.

Of the cross-sectional participants, 6521 woman were eligible for the SWAN longitudinal study and were asked to participate. A total of 3306 women were included in the longitudinal study (Table 3.2) resulting in an overall response rate of 50.7% (Sowers et al., 2000). Each participant provided written informed consent. The inclusion criteria for the SWAN longitudinal study were:

1. Aged 42-52 years
2. No surgical removal of the uterus and/or both ovaries prior to study enrollment
3. Not currently using exogenous hormone preparations affecting ovarian functions
4. At least one menstrual period in the past 3 months
5. Self-identification with one of each site's designated race/ethnic group

Women meeting the inclusion criteria of the SWAN longitudinal cohort completed annual research visits from 1995 to 2013. This included the baseline interview from the cross-sectional study and 13 follow-up visits for the longitudinal study (Figure 3.1). The research visits included self-administered questionnaires, blood and urine specimen collection, and physical measures (Table 3.3). Annual research visits were scheduled for 2-5 days after menstrual bleeding ceased in order to standardize serum hormone measures to the early phase of the menstrual cycle across visits. The SWAN coordinating center trained all interviewers and certified each based on recorded and/or monitored test interviews with naïve interviewees. Interviewer performance was periodically monitored by the SWAN coordinating center or specific site senior staff. All interviewers used standard scripts with additional computer assisted automatic checks of data ranges at time of collection (Matthews et al., 2001).

In addition to the primary aims of the SWAN longitudinal study, a Daily Hormone Study (DHS) was conducted to provide descriptions of the hormone changes at important points within the menstrual transition and prior to the final menstrual period (FMP). A subsample of 900 women were followed with monthly blood and daily urine specimen collection as well as daily symptom diaries for one complete menstrual cycle per year throughout the study period. This data was collected to gain a more complete understanding of hormone variations throughout menstrual cycles of the perimenopausal transition and changes in the nature and frequency of within-cycle events such as ovulation.

Bleeding patterns during the menopausal transition were also studied in a subgroup of the SWAN longitudinal cohort. A total of 1320 midlife women from three participating sites in the SWAN longitudinal study were included in the Menstrual Calendar Sub study. The participants included African-American, Caucasian, Chinese and Japanese women. This group of participants self-administered daily menstrual calendars that began in 1996 and continued through to 2006. The objective of this sub-study was to identify the frequency of and risk factors for prolonged bleeding patterns during the menopausal transition in an ethnically diverse population.

Summary of SWAN Parent Studies: Cross-sectional and Longitudinal

The SWAN longitudinal and cross-sectional studies have been the focus of over 350 published manuscripts and have had an extraordinary impact on generating and extending the field's knowledge of the health of mid-life women. The longitudinal study variables were selected based on multiple theoretical and research hypotheses. The goal was to gain a holistic understanding of the transition to menopause. The

biological hypotheses were informed by menopausal alterations in metabolism and endocrine status. The psychological and psychosocial hypotheses were informed by the importance of stressors related to symptoms. The sociocultural and environmental differences that impact mid-life women were hypothesized to be impacted by cultural constructs and lifestyle factors. Finally based on feminist theory, the menopause transition is hypothesized to be a normal stage of development women go through with unique challenges. The SWAN study methodologies allowed for an inclusive approach for understanding the characteristics of the menopause transition from multiple theoretical perspectives.

Current Study

Study sample

The study utilized secondary data analysis to examine differences in the insomnia prevalence between perimenopausal women who have undergone surgical menopause and perimenopausal women who have not undergone surgical menopause. This study focused on perimenopausal stages, further categorized as early and late, because there is little known about insomnia by perimenopause stage. Data from perimenopause through one year after surgical menopause were used to examine the differences in the insomnia prevalence between the groups. Participants were included if they had complete data for menopausal status and all sleep variables. Surgical menopause was defined as a surgical procedure removing both ovaries that often accompanies a total hysterectomy and is the second most frequent surgical procedure in women aged 40-44. This procedure, known as a bilateral oophorectomy, includes removing both ovaries (Wild, 2007). Women who reported one ovary removed or

hysterectomy were assigned to the non-surgical group as is consistent with the definition of surgical menopause.

A basic *a priori* power analysis was conducted to estimate the required sample size for the repeated measures logistic regression model with a significance level of 0.05, an odds ratio of 1.6 from a previous study (Kravitz, 2008) and a beta of 0.10. A decrease in yearly participants of 1.5% was accounted for by approximating the attrition rate from the first four years of publically available data. To address the central objective of the proposed research, a sample size of 2,338 was required, inclusive of 2,078 natural perimenopausal women and 260 surgical menopausal women (Table 3.4).

Data Access

SWAN data access application was submitted to the SWAN data coordinating center for data access permission. Initially, the primary investigator completed an inquiry/checklist form available from the SWAN web site to confirm availability of the requested materials. Based on this checklist, the SWAN repository staff provides a sample size estimate to the research applicant. The SWAN data access application was completed (Appendix A) and submitted along with a curriculum vitae and letter of support from the dissertation chair. A research proposal was submitted to the SWAN repository that included: 1) introduction; 2) specific aims and hypotheses; 3) background and significance; 4) preliminary studies; and 5) methods and materials. The submitted application was reviewed by the SWAN coordinating center for approval. If approved a SWAN mentor is then assigned to the project. The following forms are required prior to data access: 1) Material Transfer Agreement (MTA); Data Transfer Agreement (DTA); and Concept Sheet for new SWAN Publications (CSAP); (Appendix B).

The SWAN data application was submitted to the coordination center. Access to the data was denied due to similar questions under study by the SWAN researchers; and “duplication of research” was stated as the reason for denial. SWAN then released 10 years of data to a public repository. The public repository is The Inter-university Consortium for Political and Social Research (ICPSR) which is a unit within the Institute for Social Research at the University of Michigan. Prior to pursuing the publically available SWAN data, in light of possible ethical and legal concern, an ethics consultation was completed with the Penn State Department of Humanities in the College of Medicine. After the ethics consultation was completed it was determined that there were no ethical concerns moving forward with the study (Appendix C). SWAN publically available data was used for the study.

Variables and Measures

Dependent Variables

The primary outcome variables used were self-reported sleep complaints addressed by the following survey items: 1) did you have trouble falling asleep; 2) did you wake up several times a night; 3) did you wake up earlier than you had planned to, and were you unable to fall asleep again; and 4) average sleep quality. The first three survey items were on a five point Likert scale; 1) no, not in the past 2 weeks; 2) yes, less than once a week; 3) yes, 1 or 2 times per week; 4) yes, 3-4 times per week; and 5) yes, 5 or more times a week. Participants were asked to respond to these items by reflecting on the past two weeks. The last survey item, sleep quality (SQ) was assessed using a different scale. Sleep quality (SQ) was assessed on a four point Likert scale; 1) restful; 2) average quality; 3) restless; and 4) very restless.

Trouble falling asleep (Sleep latency, SL), waking up several times a night (wake after sleep onset, WASO), waking up earlier than planned and unable to fall asleep again (awakenings, A) and sleep quality (SQ) are the dependent variables self-reported at baseline and at each annual assessment. These four questions were adapted from the 5-item Women's Health Initiative Insomnia Rating Scale that resulted from the Women's Health Initiative project (Troxel, Buyesse, & Hall, 2009). The Women's Health Initiative (WHI), a 15 year project sponsored by the NIH that began in 1993 included a randomized clinical trial, an observational study and a community prevention program, had several aims including sleep disturbance in postmenopausal women. Sleep disturbance was examined using 10 items designed by sleep research consultants (Matthews et. al, 1997). As part of the WHI Study, the five item Women's Health Initiative Insomnia Rating Scale was developed to be used as a short, reliable and valid measure of sleep disorders (Levine et al., 2003). Levine, Lewis, Bowen, Kripke, Kaplan, Naughton and Shumaker (2003) demonstrated reliability of the Women's Health Initiative Insomnia Rating Scale (WHIIRS) with a resampling approach; the Cronbach's alpha was .78. Test-retest reliability coefficients were .96 for the same day administration and .66 after a year or more. In an additional study with a sample of 459 women, the WHIIRS was compared with objective indicators of sleep quality measured by actigraphy including trouble falling asleep, awakenings, wake after sleep onset and sleep duration. The results showed that differences in the sleep quality objective variables could be detected by the instrument further supporting construct validity (Levine et al., 2003). These studies provide evidence of the validity, internal

consistency, and reliability of the WHIIRS and support the employ of the specific items in the SWAN longitudinal study and the current study.

Independent Variables

Menopausal status is the independent variable in the proposed study. Irregular menstrual bleeding was used to distinguish between categories of menopause including postmenopausal, late perimenopausal, early perimenopausal and premenopausal. Postmenopausal was defined as no menses for 12 months. Late perimenopausal was defined as no menses for three to 12 months. Early perimenopausal was defined as menses had occurred in the last three months but was less predictable. Premenopausal was defined as menses occurring in the last three months with no decrease in predictability of menstruation (Harlow, Crawford, Sommer, & Greendale, 2000). In addition to the above categories, surgical menopause was defined as undergoing a bilateral oophorectomy within the previous 12 months. If 12 months have elapsed since surgical menopause occurred, the participant was included in the postmenopausal group and excluded from further analyses.

Covariates

Covariates were selected based on prior studies that have consistently identified influential variables on insomnia in the general adult population. Covariates included sociodemographic characteristics including education level and household income (Grandner et al, 2010; Walsh et al., 2011), age (Sanford et al., 2006; Walsh et al., 2011) smoking (Mehari et al., 2014), presence of shift work (Jarnefelt et al., 2012; Yazdi et al., 2014), marital status (Troxel, Buyesse & Hall, 2009), race/ethnicity (Gold et al.; 2001, 2006; Grandner et al., 2010), self-reported health problems (Loh et al., 2005;

Lokkegaard et al., 2006), menopausal status (Ohayon, 2006; Ozdemir et al., 2009; Shaver et al., 1988), vasomotor symptoms (Whiteley et al., 2013; Ohayon, 2006; Moe, 2004; Sikon & Thacker, 2004; Shanafelt et al., 2002; Polo-Kantola et al., 1999), BMI (McCarthy et al., 2012), alcohol use (Seib, Anderson & Lee, 2014), psychological disorders (Rocca et al., 2008; Serrano et al., 2007; Taylor et al., 2005), and exercise (Kline et al., 2013). Table 3.5 outlines each of the covariates included in the analysis.

Vasomotor symptoms (VMS) were included as covariates as their impact on sleep disturbance during the menopausal transition is important. In a study examining the impact of vasomotor symptoms among women aged 42-52, it was reported that women who reported more frequent VMS had higher odds ratios for disturbed sleep (Kravitz et al., 2008). In the proposed study, vasomotor symptoms included hot flashes/flushes, cold sweats and night sweats from the annual self-administered questionnaire, part A. For each of the vasomotor symptoms, women were asked to check one of the following on a five point scale: none, 1-5 days, 6-8 days 9-13 days or every day in the past two weeks.

The SWAN survey utilized the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item depression symptom scale and four additional questions assessing anxiety annually. The menopause transition has been shown to increase a women's risk of developing depression by two-fold (Cohen et al., 2006). Additional risk factors include vasomotor symptoms, stress and poor sleep which can also impact the development of depression (Serrano & Wamaock, 2007). Depression was considered as a covariate in the present study with CES-D scores derived from question C10 on the

interview administered questionnaire. The CES-D is a valid and reliable instrument being utilized for over four decades in empirical studies (Radloff, 1977).

Health care conditions were assessed by listing 13 separate diagnoses on the Follow-Up Visit Interview Administered Questionnaire with a yes/no answer. Self-reported health problems were selected to be included in the study analysis based on empiric evidence suggesting association between cardiometabolic consequences of insomnia. Grandner, Jackson, Pak and Gehrman (2012) reported a significant risk factor for obesity, diabetes, myocardial infarction and coronary artery disease among adults reporting sleep disturbance. Van Cauter (2011) reported overwhelming evidence that sleep disturbance in adults is associated with insulin resistance including diagnoses of obesity, polycystic ovary syndrome and diabetes. Hypertension in women has been associated with decreased sleep duration and less efficient sleep (Gottlieb et al., 2006; Matthews et al., 2014). The following health care conditions were included in the analysis based on the extant evidence; 1) diabetes, 2) hypertension, 3) stroke, 4) heart attack (myocardial infarction) and 5) angina.

Alcohol use has been shown to impact insomnia (Canham et al., 2014; Chakravorty et al., 2014; Chaput et.al, 2012). Alcohol use was included at each of the data collection interviews within the SWAN study. Specifically alcohol use was assessed using three separate questions about frequency of having a glass of beer, wine or liquor with the following possible responses; none or less than one drink per month, 1-3 drinks per month, 1 drink per week, 2-4 drinks per week, 5-6 drinks per week, 1 drink per day, 2-3 drinks per day, 4 drinks per day and 5 drinks or more per day. This variable was collapsed to translate to alcohol use (yes/no) with a cut point of

7 drinks or less per week versus 8 drinks or more per week (Table 3.6). This cut point has been demonstrated as valid in the scientific literature (Canham et al. 2014). Canham et al. (2014) reported overall greater odds of insomnia in participants that engaged in alcohol use when compared to non-drinkers. Greater than eight drinks per week (binge drinkers) was associated with 64% greater odds of insomnia than non-binge drinkers (Canham, Kaufman, Mauro, Mojtabai, & Spira, 2014).

Protection of human subjects

This study was eligible for exemption under the DHHS human subject regulations. Exemption 4 applies because it pertains to the use of previously collected data available to the researcher without knowledge of identifying information. The publically-available SWAN longitudinal study data is stored as de-identified data. This study was reviewed and approved by the Institutional Review Board of the Pennsylvania State University (Appendix D).

Data Management

The initial step in data management is becoming familiar with the dataset in order to design, develop and construct an analysis plan. Initial reviews of previous studies using the SWAN cross-sectional and longitudinal data supported a preliminary design and analysis plan. Access to the codebooks and review of actual de-identified data from the cross-sectional baseline interviews, longitudinal baseline interview and year 1 follow up data were accessed from the ICPSR website (http://www.icpsr.umich.edu/icpsrweb/ICPSR/index.jsp) and permitted familiarity with the design of the database including the data and variable labels. Review of the dependent and independent variable data pertinent to this study is required in

secondary analysis to confirm the quality and completeness of the data. Missing data for the dependent variable at a 25% level was determined as tolerable for the planned analysis. According to the *a priori* power analysis that was completed, 25% missing data will result in a sample (n=2480) which is ample power for the proposed study; the actual data missing was found to be 5.4% (Table 3.7). Validity of the data in its ability to address the research questions of this study has been confirmed by the principal investigator.

Data analysis

Descriptive procedures were used to determine the distribution of all study variables (e.g. frequencies, means, and standard deviations) for baseline and annual data. Diagnostic tests for skewness and kurtosis were conducted. Although distribution is expected to approximate normal distribution with the large sample size, graphical tests (boxplots, stem and leaf, histograms) were examined to confirm these assumptions. Data transformation, if necessary for marked skewness or heterogeneous variances, was applied. Significance level for this study was identified at $p < 0.05$ for all analyses.

1. **What is the prevalence of insomnia, measured annually, in all perimenopausal women?**

The four questionnaire items that address frequency of insomnia symptoms were analyzed as interval data. Frequency of symptoms was reported on a Likert scale, 1-5 scale range for the first three insomnia symptoms; (SL, WASO, A) and on a four point Likert scale for SQ, the last dependent variable. Descriptive analysis with frequencies (n [%]) was reported for each symptom for the entire perimenopausal sample.

Descriptive analysis included mean, standard deviation, median and interquartile range for each symptom (SL, WASO, A, SQ). Graphical presentation of the results such as histograms, box plots and stem and leaf graphs were examined.

Secondly, the frequency of the first three insomnia symptoms (SL, WASO, A) was dichotomized as "no" (< 3 times per week) for the first three levels and "yes" (≥3 times per week) for the latter two levels which is consistent with the definition of insomnia (American Academy of Sleep Medicine [AASM], 2005). The fourth dependent variable, SQ, was collapsed and dichotomized as "overall good" sleep quality (restful, average quality) and "overall poor" sleep quality (restless, very restless). The overall directionality of the item responses, two positive and two negative, supported the dichotomization of this variable. Frequency tables were used to examine the overall rate of insomnia in the entire sample of perimenopausal women. Frequencies were examined by study interval (Y0-Y1, Y1-Y2, Y2-3; etc.) and across all intervals to describe the overall rate of insomnia in perimenopausal women. Menopausal women were excluded from the sample since the primary focus of the study was perimenopausal women. This analysis resulted in an overall description of insomnia symptoms for the entire sample of perimenopausal women.

2. What is the prevalence of insomnia by perimenopausal stage in women?

The second question examined the entire sample and described the prevalence of insomnia by perimenopausal stage. Descriptive procedures were used to examine the frequency of insomnia symptoms and severity of symptoms by perimenopausal stage, early or late. Early perimenopause was defined as having a menstrual period in the preceding three months and having experienced menstrual irregularity while late

perimenopause was defined as menstrual bleeding in the last 12 months but not in the preceding three months (Harlow, Crawford, Sommer, & Greendale, 2000). For study intervals (Y0-1, Y1-2, Y2-3, etc.), subjects were sorted by perimenopausal stage prior to the analysis. Insomnia as a dichotomized outcome (yes/no) for each interval was described as present by perimenopausal stage (early or late). Frequency of symptoms was reported on a Likert scale, 1-5 scale range for the first three insomnia symptoms; (SL, WASO, A) and on a four point Likert scale for SQ, the last dependent variable. The frequency of sleep problems was dichotomized as "no" (< 3 times per week) for the first three levels and "yes" (≥3 times per week) for the latter two levels which is consistent with the definition of insomnia (American Academy of Sleep Medicine [AASM], 2005). The fourth dependent variable, SQ, was collapsed and dichotomized as "overall good" sleep quality (restful, average quality) and "overall poor" sleep quality (restless, very restless). Insomnia frequencies (n [%]) for early and late perimenopausal groups were reported. Insomnia symptoms (yes/no) within groups (early or late) were reported using frequency tables.

The four questions that addressed insomnia symptoms (SL, WASO, A, SQ) were individually analyzed as interval data. Symptoms were reported on a Likert scale, 1-5 scale range. Frequencies (n [%]) were examined for each symptom per perimenopausal group (early and late) for each study interval. The mean, standard deviation, median and interquartile range were reported for each symptom (SL, WASO, A, SQ). Graphical presentation of the results including histograms and box plots were included. Menopausal women were excluded from the sample since the primary focus of the study was perimenopausal women. This analysis resulted in a description of the

presence of insomnia symptoms (yes/no) and the specific symptom frequencies during early and late perimenopause.

3. **What is the prevalence of insomnia in women who have undergone surgical menopause?**

This question described the prevalence of insomnia measured annually from baseline until one year after the occurrence of surgical menopause among perimenopausal women who have undergone surgical menopause; surgical menopause was identified as a bilateral oophorectomy. Data for the analysis included only the sub-sample of women who have had surgical menopause, inclusive of intervals from baseline to one year post surgery. The dependent variable, insomnia symptoms, was analyzed at each measurement interval with the following questions: 1) did you have trouble falling asleep (SL); 2) did you wake up several times a night (WASO); 3) did you wake up earlier than you had planned to, and were you unable to fall asleep again (A); and 4) average sleep quality in the past two weeks (SQ). The frequency of sleep problems in the past two weeks was assessed on a Likert scale as: 1) none, 2) less than once a week, 3) one or two times per week, 4) three or four times per week and 5) five or more times per week. Frequency of symptoms was reported on a Likert scale, 1-5 scale range for the first three insomnia symptoms; (SL, WASO, A) and on a four point Likert scale for SQ, the last dependent variable. The frequency of SL, WASO and awakenings (A) was dichotomized as "no" (< 3 times per week) for the first three levels and "yes" ($\geq$3 times per week) for the latter two levels which is consistent with the definition of insomnia (American Academy of Sleep Medicine [AASM], 2005). The fourth dependent variable, SQ, was collapsed and dichotomized as "overall good" sleep

quality (restful, average quality) and “overall poor” sleep quality (restless, very restless). Insomnia frequency tables were used to examine the overall rate of insomnia in the subjects who have undergone surgical menopause. Frequencies were examined by interval (Y0-1, Y1-2, Y2-3; etc.) and reported until one year after surgical menopause. Menopausal women were excluded from the sample. This analysis resulted in an overall description of insomnia symptoms for subjects that underwent surgical menopause.

Secondly, the four questions that addressed insomnia symptoms were analyzed as interval data using the reported frequencies. Frequency of symptoms was reported on a Likert scale, 1-5 scale range for the first three insomnia symptoms; (SL, WASO, A) and on a four point Likert scale for SQ, the last dependent variable. Descriptive analysis including frequencies (n [%]) was reported for each symptom for the subset that have undergone surgical menopause. Menopausal women were excluded from the sample. Descriptive analysis included mean, standard deviation, median and interquartile range for each symptom (SL, WASO, A, SQ). Prior to the analysis, the sample was sorted to include only women who underwent surgical menopause. Next, the interval that the surgery was completed was identified for each subject by perimenopausal status, information acquired at each annual study interview and the analysis was conducted considering time frame from baseline to one year post surgery. This controlled for timing of surgery in order to answer the question and diminish both Type I and Type II error. The limitation of the exact timing of the surgery that corresponded with the related to the collection of the annual data remains a limitation of the study.

4. Is there a difference in reported insomnia symptoms by perimenopausal stage?

This question suggests that there is a period of time when perimenopausal women start to experience insomnia symptoms or an onset of sleep problems and that this onset or change of symptoms may be associated with perimenopausal stage. Menopausal stage is hypothesized to influence insomnia. In order to test for this change, the variables of menopausal status (early/late) and insomnia symptoms; SL, WASO, A, SQ; (yes/no) were analyzed annually (Table 3.4).

Repeated measures logistic regression was used to identify if insomnia symptoms (SL, WASO, A, SQ) change over time by perimenopausal stage. Subjects reaching menopause were excluded from the analysis as the focus of the research is on perimenopausal women. Change was analyzed annually from baseline until the participant was considered menopausal taking into account the menopausal stage (early or late perimenopause). If the repeated measures logistic regression demonstrated that there was a significant difference between stages at $p< 0.05$, further analyses were conducted to identify which rates were significantly different and to identify relationships among variables that were not identified *a priori*. The four insomnia symptoms were also evaluated on their original ordinal scale in repeated measures mixed effects models. From these mixed effects models, the average scores at each stage were estimated, and compared between stages using repeated measures logistic regression analysis.

5. Is there a significant difference in insomnia symptoms before and after surgical menopause?

The outcome variable, insomnia symptoms (yes/no), was examined for the assessment intervals one year before and one year after surgical menopause was reported. Change was analyzed at only two interval points, year before and year after occurrence of surgical menopause. The change was the presence of insomnia symptoms self-reported by the participant ("yes" for any one of the dichotomized sleep variables or absence of all insomnia symptoms "no"). McNemar's Test was used to identify if insomnia (yes/no) changed pre-post the occurrence of surgical menopause.

In the absence of experimental or quasi-experimental study data, the effect of surgical menopause on insomnia symptoms was further explored using repeated measures logistic regression for the dichotomized insomnia symptoms, and repeated measures mixed regression for the symptoms on the ordinal scale. Repeated measures logistic regression was used to examine change over time for the entire interval of measures of insomnia.

6. Is there a difference in insomnia symptoms among perimenopausal women who have progressed naturally through perimenopause compared to women who have undergone surgical menopause?

This research question compared three independent groups over time; natural early perimenopause, natural late perimenopause and surgical menopause. The natural group was further subdivided into two groups, early perimenopause and late perimenopause. The first statistical test to address this question was a two-way between groups repeated measures logistic regression. A two-way repeated measures

logistic regression was used with three independent variables (natural early, natural late and surgical menopause) with one within-subjects factor (time), annual collection points. The comparison groups for this analysis were natural perimenopause; early and late, and surgical menopause. The dependent variable for this analysis was the dichotomized insomnia variable (yes/no) according to the AASM definition. This analysis addressed the question by demonstrating differences in insomnia symptoms between the two independent groups (naturally perimenopausal and surgical menopause).

Repeated Measures logistic regression analysis was completed to examine if there were significant differences with respect to the combined dependent variables across time intervals. The four categories of dependent variables; SL, WASO, A, SQ; will be examined among the cohorts; natural menopause group subdivided into; early and late perimenopause compared to those women who had undergone surgical menopause. If an interaction was present in the analysis between independent variables, a series of one-way repeated measures logistic regression models was examined to discern the impact of the second variable.

7. What are the factors of influence among perimenopausal women that develop chronic insomnia defined as insomnia symptoms present for at least two consecutive data collection points?

The final research question identified the factors of influence for developing chronic insomnia among perimenopausal women. A multivariable logistic regression framework was used for the categorical insomnia outcome (yes/no), and multivariable logistic regression for interval level insomnia outcomes (Likert scale). Multivariable

regression allowed for relationships between independent predictor variables and the dependent variable to be examined.

The sample for this analysis included only perimenopausal women who developed and maintained insomnia symptoms for at least two consecutive data collection points which is operationalized as chronic insomnia for this study. The analysis examined data from the interval immediately preceding the first year of chronic insomnia. This approach controlled for those individuals that have transient or acute insomnia which was beyond the scope of this study.

The analysis approach assessed what factors were influential in the development of chronic insomnia among subjects that develop chronic insomnia during perimenopause. Collinearity was analyzed for all models using the variance inflation factor (VIF) and variables that were found to be highly collinear were excluded. A VIF score of 5 translates to an inflated standard error. Collinearity was corrected by removing the most inter-correlated variables from the analysis.

Logistic regression with simultaneous loading was used to examine influential factors on the categorical dependent variable insomnia (yes, no), as follows: vasomotor symptoms, menopausal status, depression, BMI and rotating work shifts (model 1). Model two with stepwise forward loading carried through significant independent predictors from Model 1 and add the following predictors: age (5 year bins), race/ethnicity, income level and education level. Model three carried through significant independent predictors from Model 2 and add diabetes, hypertension, hormone therapy use, alcohol use and marital status. Model four carried forward significant independent predictors from Model 3 and added myocardial infarction, angina, stroke, health status,

exercise and smoking. The final model included all independent significant predictors ($p < 0.10$) simultaneously loaded to define significant independent predictors of chronic insomnia in perimenopausal women. Applying logistic regression analysis permitted the identification of factors of influence for developing chronic insomnia in perimenopausal women. Table 3-9 outlines the analysis strategy for each of the factors of influence.

Limitations

The main study limitations are related to the secondary analysis study design. The SWAN data was not designed or collected explicitly for the research questions outlined in this study. A limitation included the inability to control for variables such as sleep aids, complementary medicine for sleep disturbances and timing of exercise which could have had influence on the study outcomes. Yet, the longitudinal nature of the parent study that collected a voluminous data set permitted secondary analysis of a broad range of research questions. As the parent study included measures of the variable pertinent to the proposed research questions, the research was feasible. Another limitation acknowledged is with the participant sample. The design of the longitudinal study allowed for participants to enter the study at different stages of perimenopause. Perimenopause can continue for decades with symptoms that wax and wane. It is difficult to ascertain how long a woman has been experiencing the symptoms prior to entering the study. This limitation is acknowledged and through a well-designed secondary analysis that considers this, has been minimized.

With regard to the questionnaires used to measure the sleep variables, the measures are simplistic screening tools with single items extracted from a larger sleep instrument and are therefore specific to individual symptoms that are characteristic of

insomnia. The four selected items for this study measure the domains of importance of insomnia; sleep latency, wake after sleep onset, early morning awakenings and sleep quality. By employing an operational definition of insomnia based on established criteria in this study (AASM), the limited item set permitted an analysis that addressed this study's research questions. Objective sleep data were not available from the SWAN parent study. Objective sleep data would have further strengthened the results of this study.

The self-report nature of the primary variable of insomnia symptoms is a limitation. Recall bias is the most prominent limitation of self-reported measures. As the instructions for completing the study questionnaires asked participants to reflect on the past two weeks, recall bias is minimized. Furthermore, the gold standard of self-reported sleep disturbances can be measured using such instruments as the Pittsburgh Sleep Quality Index or the Insomnia Severity Index however, the four sleep items used in the parent study are concise and mirror the longer gold standard sleep instruments frequently used in the extant literature that addresses insomnia.

The SWAN longitudinal study gathered the majority of its data through the use of self-report methods and repeated data collection. Self-report is a method that favors directness and versatility as well as efficiency in gathering large amounts of information. In the SWAN longitudinal study the use of self-report is supported since the participants cannot be observed doing the behaviors and so retrospective data about participants' activities, experiences and health practices during the menopausal transition can be collected using this method. Although an advantage, self-report has several limitations that must be acknowledged. The most serious are the validity and accuracy of the

information obtained (Polit & Beck, 2004). Researchers need to assume that participants have been truthful in their responses but this limitation needs to be recognized and taken into consideration when interpreting the results.

Analyses of data from large sample sizes can lead to associations that are highly significant but are not clinically meaningful (Smith et al., 2011). However as an expert in women's health and insomnia, the principal investigator is well prepared to outline clinically relevant results. The SWAN longitudinal data set is very large with over 3000 participants which allow multiple applications of different analyses to examine the data. Multiple testing risks false positives. Therefore there is a risk of Type I error. Control with post hoc correction procedures was utilized for multiple testing which minimizes the risk of Type 1 errors.

Repeated measures increase the risk of response bias which is also a limitation. Participants may become bored with the same questions being asked year after year resulting in response bias and risk of practice effects. Although this is a limitation, the use of repeated measures in a longitudinal cohort allows for sensitivity which enables the detection of small effects of the independent variable on the outcome variable. Practice effects can be reduced through randomizing order presentation of items at the time of data collection. There were no reported strategies to reduce practice effects in the parent study.

It is known that missing data is a consideration in all research. This is of particular concern in secondary analysis. Data contained in large datasets can contain missing data coded as "don't know" or "not sure" (Magee et al., 2006). The SWAN data is coded both with "do not know", "refused", "not applicable" and "missing". As the

analysis is performed it is important to note the amount of data coded as such. This could be a potential limitation if existing data of important variables is not available for analysis. Missing data of the dependent variables at a 5.4% level was tolerated for the analysis. The primary investigator is confident that these limitations will not minimize the value of this study in the area of perimenopausal women and the insomnia trajectory.

Table 3.1

Study of Women's Health across the Nation Cross Sectional Participant Screening Variables

Variable	**Operationalized Definition**
Age	Rounded to the nearest year
Months since last menstrual period	Calculated from month, day, year of LMP
Menopausal status	Categorized Bleeding Patterns
	Surgical menopause
	Postmenopausal
	Late perimenopausal
	Early perimenopausal
	Premenopausal
	Undetermined
Use of reproductive hormones	Ever
	Less than 1 year
	At least 1 but less than 3 years
	3-5 years
	More than 5 years

Smoking	Never Past smoker Current smoker
Education level	Less than high school High school only Some college College degree Post-college
Perceived stress	Scores derived from 4 Likert based questions Scores ranged 4-20 Perceived stress – maximum score of 20
Body mass index	Metric height and weight measures – self report
Reported age of hysterectomy	Reported year of birth minus the reported year of hysterectomy
Reported age of oophorectomy	Reported year of birth minus the reported year of oophorectomy
Reported age of last menopausal period	Reported year of birth minus the reported year of last menopausal period

Marital group	Single, never married
	Currently married or living as married
	Separated
	Widowed
	Divorced
Interview language	English
	Spanish
	Cantonese
	Chinese
Diagnosis groups/medications	High blood pressure
	Diabetes
	Heart attack or angina
	Arthritis
	Osteoporosis
	Benign growths of the uterus
	Cancer other than skin
Common problems experienced over	Difficulty sleeping

the last 2 weeks Categorized • No • Yes • Don't know • Refused	Night sweats Stiff joints Headaches Hot flushes or flashes Forgetfulness Feeling tense or nervous Feeling blue or depressed Vaginal dryness Irritability or grouchiness Heart pounding or racing Leaking urine
Quality of life	Numeric value ranged 0 worst to 10 best quality of life
Paying for very basics: • Food • Housing • Medical care • Heating	Very hard Somewhat hard Not very hard at all Don't know Refused

Table 3.2

Study of Women's Health Across the Nation Cross Sectional Participant Socio-demographic Factors

Characteristic	N (%)
Race/Ethnicity	
African American	4352 (27.9)
Caucasian	7805 (50.1)
Japanese	855 (5.5)
Chinese	652 (4.2)
Hispanic	1911 (12.3)
Age [Mean (SD)]	47.09 (4.34)
Education	
Less than high school	1601 (10.0)
High School Graduate	4219 (26.3)
Some College/Technical School	5044 (31.4)
College Graduate	2651 (16.4)
Post Graduate Education	2540 (15.8)
Marital Status	

Never Married	2043 (12.7)
Currently Married/Partnered	10104 (63.0)
Separated	786 (4.9)
Widowed	594 (3.7)
Divorced	2519 (15.7)
Employed	
No	3975 (24.7)
Yes	12100 (75.3)
Difficulty paying for basics	
Very difficult	1910 (11.9)
Somewhat difficult	5242 (32.7)
Not very difficult	8899 (55.4)
Smoking	
Never	8386 (52.4)
Former	3962 (24.8)
Current	3646 (22.8)
Body Mass Index [Mean (SD)]	27.15 (6.48)
History of high blood pressure	

No	12066 (75.1)
Yes	4011 (24.9)
History of diabetes	
No	15018 (93.4)
Yes	1060 (6.6)
History of heart disease	
No	15612 (97.1)
Yes	467 (2.9)
Menopausal Status	
Surgical Post	3217 (20.6)
Natural Post	2293 (14.7)
Late Perimenopausal	637 (4.1)
Early Perimenopausal	3660 (22.7)
Premenopausal	4653 (29.7)
Undetermined	1185 (7.6)

Table 3.3

Study of Women's Health Across the Nation Longitudinal Participant Socio-demographic Factors

Characteristic	N (%)
Race/Ethnicity	
African American	935 (28.3)
Caucasian	1550 (46.9)
Japanese	281 (8.5)
Chinese	250 (7.6)
Hispanic	286 (8.7)
Age [Mean (SD)]	45.9 (2.69)
Education	
Less than high school	238 (7.3)
High School Graduate	581 (17.8)
Some College/Technical School	1051 (32.1)
College Graduate	661 (20.2)
Post Graduate Education	739 (22.6)
Marital Status	

Never Married	440 (13.6)
Currently Married/Partnered	2148 (66.1)
Separated	157 (4.8)
Widowed	66 (2.0)
Divorced	437(13.5)
Employed	
No	645 (19.6)
Yes	2643 (80.4)
Difficulty paying for basics	
Very difficult	306 (9.3)
Somewhat difficult	1006 (30.7)
Not very difficult	1968 (60.0)
Smoking	
Never	1876 (56.9)
Former	1397 (42.4)
Current	569 (17.2)
Body Mass Index [Mean (SD)]	28.27 (7.22)

Currently taking high blood pressure medication	
No	2902 (87.9)
Yes	389 (11.8)
Currently taking Insulin	
No	3191 (96.6)
Yes	100 (3.0)
Currently taking heart medication	
No	3229 (97.8)
Yes	61 (1.8)
Menopausal status	
Early Perimenopausal	1498 (46.4)
Pre-menopausal	1727 (52.3)

Table 3.4

SWAN Longitudinal Measures

Construct	Contributing Variables	Measurement	Frequency
Acculturation	Language used, cultural and religious practices, dietary practices	Questionnaire	Annual
Body Size History	Weight changes associated with each pregnancy, weight cycling	Clinic Measurements	Annual at 5 sites
Contraception	Use of contraceptive methodologies	Questionnaire	Annual
Hormone Use Practices	Use of hormone preparations, past use of oral contraceptives, and current contraception methodology	Questionnaire	Annual
Lifestyle Behaviors	Smoking history and current passive smoke exposure; current caffeine and alcohol consumption; diet and dietary practices, including use of supplements; amount and frequency of physical activity practices, including planned exercise	Questionnaire	Annual
Menstrual Status	Current menstrual bleeding characteristics and their variation according to timing, duration, and intensity; usual premenstrual symptoms, if any	Questionnaire	Annual
Psychological Status	Depression, hostility, and stress	Questionnaire	Annual
Recent Medical Care Utilization	Frequency of prevention behaviors, including Pap smear, physical breast exam, and physician visit for health problem or routine check-up; use of	Questionnaire	Annual

	complementary and alternative health approaches; health insurance		
Relationships	Number, nature, and satisfaction with relationships; life satisfaction	Questionnaire	Annual
Reproductive History	Age at menarche, gravidity, parity, pregnancy losses, infertility, lactation practices	Questionnaire	Annual
Self-perception	Quality of life, health status, degree of physical activity	Questionnaire	Annual
Sexuality	Types of practices, satisfaction, and attitudes toward sex	Questionnaire	Annual
Significant Life Events	Marriage, divorce, death or birth in family, change in or loss of job, illness, social support, occupational stress (autonomy)	Questionnaire	Annual
Significant Medical History	Diagnosis by a physician of hypertension, cardiovascular disease, malignancies, or thyroid disease; fractures, pelvic surgery, urinary incontinence, current medications, family history of health events	Questionnaire	Annual
Sociodemographic Status	Age, birth date, birthplace, marital status, level of education, income of household, occupation and the physicality of one's work, household composition	Questionnaire	Annual
Social Environment	Discrimination, religiosity, and spirituality	Questionnaire	Annual
Blood Pressure	Resting systolic and diastolic blood pressure, resting heart rate	Blood Pressure, heart rate	Annual

Body Composition and body topology	Weight, height, waist and hip circumference, body composition (the later from five sites with bone densitometry facilities)	Clinical measurements	Annual
Bone Status and its turnover	Bone mineral density of the femoral head, lumbar spine, and total body (from five sites with bone densitometry facilities); biochemical measures of bone formation and resorption	Clinical measurements	Annual
Carbohydrate and energy metabolism	Glucose, insulin and thyroid-stimulating hormone concentrations (the latter at base line)	Clinical measurements	Annual
Clotting factors	Fibrinogen, factor VIIc, plasminogen activator inhibitor-1, tissue plasminogen activator antigen	Clinical measurements	Annual
Lipid metabolism	Total cholesterol, triglycerides, high and low density lipoprotein cholesterol subfractions, lipoprotein	Clinical measurements	Annual
Reproductive hormones	Estradiol, follicle-stimulating hormone, sex hormone binding globulin (SHBG), progesterone, and testosterone	Clinical measurements- 2-5 days after bleeding commences to standardize serum hormones measures to the early phase of the menstrual cycle	Annual
Monthly Menstrual Cycle Calendars	Record of changing characteristics of menstrual bleeding from month to month, record of the use of oral contraceptives or other hormones,	Diaries	Monthly

	symptoms, and the occurrence of any gynecological surgery or procedures. Three clinical sites to included lifestyle factors including dieting, shift work, exercise practice, and smoking behavior, as well as stress		
Daily Hormone Study (DHS)	Gonadotropins, luteinizing hormone, and follicle stimulating hormone, estrone conjugate and pregnanediol glucuronide,	Subsample of 900 Blood and urine samples Daily urine samples Daily diaries to characterize symptoms and social dimensions of each day during the daily urine collection	One cycle annually

Table 3.5

Description of study variables

Variable	Instrument	Type of Variable	Description
Independent Variable Menopausal Status	Annual Follow-Up Interview Questionnaire, B33, C1-C5	Nominal	Menopausal Status Early perimenopause Late perimenopause Postmenopause Premenopausal Surgical Menopause – both ovaries removed
Dependent Variable Symptoms of Insomnia in the past 2 weeks	Follow-Up Visit Self-Administered Questionnaire, Part A Questions D2, a-c	Ordinal	Not in the past 2 weeks Yes, less than once per week Yes, 1-2 times per week Yes, 3-4 times per week Yes, 5 or more times per week

Sleep Quality	Follow-Up Visit Self-Administered Questionnaire, Part A Questions D2, d	Ordinal	Very Restful Average Quality Restless Very Restless
Covariates			
Age	Annual Follow-Up Interview Questionnaire	Continuous	Calculated from date of birth and when the form was completed, and is rounded down to the next lowest integer
Marital Status	Annual Follow-Up Interview Questionnaire	Dichotomous	Unmarried Married
Race/ethnicity	SWAN Individual Screener Part 1 Questionnaire	Nominal	African American Hispanic Japanese Chinese Caucasian
Household	Annual Follow-Up Interview	Ordinal	Less than $19,999

Income	Questionnaire		$20,000 to $49,999 $50,000 to $99,999 $100,000 or more Refused Don't know
Education Level	SWAN Individual Screener Part 1 Questionnaire	Ordinal	Less than High School High School Graduate Some College/Technical School College Graduate Post Graduate Education
Prescribed Hormone replacement medications	Follow-Up Visit Interview Administered Questionnaire, B12-B15	Dichotomous	No Yes -Estrogen pills -Estrogen by injection or patch

			-Combination Estrogen/progestin -Progestin pills
Health Care Conditions	Follow-Up Visit Interview Administered Questionnaire, B26a-m	Dichotomous	No Yes Diabetes Hypertension Stroke Heart attack Angina
Health Status	Follow-Up Visit Self-Administered Questionnaire, Part A Questions B1 "In general would you say your health is …"	Ordinal	Likert scale 1-5 Excellent – 1 Very good – 2 Good – 3 Fair - 4 Poor - 5
Rotating Alternating	Follow-Up Visit Interview Administered Questionnaire, D3	Dichotomous	No Yes

Shifts			
Smoking	Follow-Up Visit Self-Administered Questionnaire, Part A Questions B8	Dichotomous	No Yes
Alcohol Use	Follow-Up Visit Self-Administered Questionnaire, Part A Questions B10	Dichotomous	No Yes
Glasses of beer (12 oz)	Follow-Up Visit Self-Administered Questionnaire, Part A Questions B11	Ordinal	None or less than one per month 1-3 per month 1 per week 2-4 per week 5-6 per week 1 per day 2-3 per day 4 per day 5 or more per day

Glasses of wine or wine coolers (4-6 oz)	Follow-Up Visit Self-Administered Questionnaire, Part A Questions B12	Ordinal	Same scale as above question
Glasses or liquor (one shot)	Follow-Up Visit Self-Administered Questionnaire, Part A Questions B12	Ordinal	Same scale as above
Over the past 2 weeks how often did you experience the following problems (VMS)	Follow-Up Visit Self-Administered Questionnaire, Part A Questions D1 c, d, o	Ordinal	Not at all 1-5 days 6-8 days 9-13 days Every day
Depression	Follow-Up Visit Self-Administered Questionnaire, Part A Question C10	CES-D Score Continuous	Total score above 16 will be cutoff for depression symptoms
BMI	Follow-Up Visit Physical Measures B7, B8	Continuous	Utilize B7 and B8 to calculate BMI

Exercise	Follow-Up Visit Self-Administered Questionnaire, Part A Questions C5	Ordinal	Once a month 2-3 times per month Once a week More than once a week

Table 3.6

Alcohol Use Variable

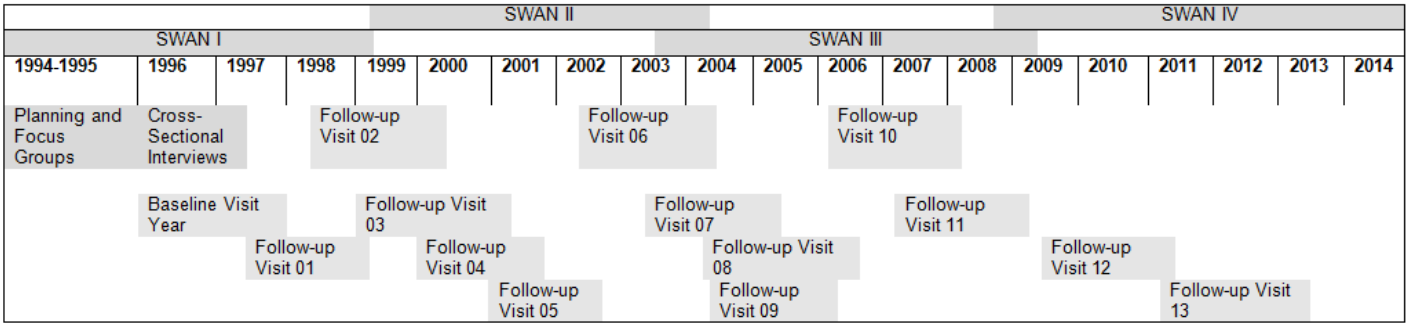
Alcohol Use	Follow-Up Visit Self-Administered Questionnaire, Part A Questions B10	Dichotomous	No Yes
If yes	Follow-Up Visit Self-Administered Questionnaire, Part A Questions B11	Interval	7 drinks or less per week= no influence 8 drinks or more per week= positive influence

Table 3.7

Sample Size Estimation

Outcome							
Primary: Insomnia							
Secondary:	% of sample surgical	Alpha	Group	Sample Size	Event rate*	OR	Power
SL, WASO, Early Awakenings, Sleep Quality							
	11%	0.05	Natural	2078	25%	1.6	90%
			Surgical	260	35%		
	11%	0.0125 for each	Natural	2078	15-35%	1.6-1.8	85%
			Surgical	260	20-50%		

Figure 3-1 *SWAN Visits and Associated Date Ranges*



Chapter 4: Results

Insomnia in perimenopausal women is a significant problem; however, little is known about the insomnia prevalence in perimenopausal women who have undergone surgical menopause. Additionally, the limited research that addresses insomnia or sleep complaints in perimenopausal women has not, to date, included longitudinal studies and therefore does not capture the prevalence of insomnia over time in this high risk population. The results of this study provide an opportunity to add to the state of the science. The findings provide insight for the design of interventions tailored to symptom management needs in perimenopausal women for the prevention and early treatment of chronic insomnia.

A secondary analysis of publically available data from a pre-existing large data set that employed a longitudinal cohort design was conducted. The overall purpose of the secondary analysis was to describe the prevalence of insomnia in all perimenopausal women. A primary aim of the study was to gain a better understanding of the course and severity of insomnia in perimenopausal women who have undergone surgical menopause and discern if differences in insomnia symptoms exist between stages of perimenopause, including early and late. Early perimenopause is defined as having a menstrual period in the preceding three months and having experienced menstrual irregularity. Late perimenopause is defined as menstrual bleeding in the last 12 months but not in the preceding three months (Harlow, Crawford, Sommer, & Greendale, 2000). A secondary aim of the study was to identify risk factors for chronic insomnia in perimenopausal women.

Sample Description

At baseline, the study sample (N=3302) included predominantly white (47%), early perimenopausal (45%) and pre-menopausal (52%), married (65%) women (Table 4.1). The majority of the sample completed some college (74%) and was employed outside of the home (80%). The combined family income was reported as more than $50,000 in nearly half of the sample (49.5%). Fifty-six percent of participants reported less than one day of feeling depressed at baseline, were sedentary (72.2%) and overweight (BMI 28.27 kg/m^2 $\pm$ 7.2). The study sample was categorized as early perimenopausal or late perimenopausal. In year one the early perimenopausal group included the majority of the sample (n=1721) compared to the late perimenopausal group (n=124). Throughout the study period analyzed, spanning 10 years, participants transitioned to menopause and were excluded from the sample; in year 10 the early and late perimenopausal groups were similar in size (n=155, n=128 respectively). In year ten versus year one the surgical menopausal group was nearly five times the size (n=187, n=32 respectively).

Research Question 1; What is the prevalence of insomnia, measured annually, in all perimenopausal women?

Description of insomnia in all perimenopausal women.

Thirty one to 42% of the sample (N=3302) of perimenopausal women (m age 45.9 yrs ± 2.69) self-reported at least one symptom of insomnia at a frequency of ≥ three times per week over a two week measurement interval across the ten year survey (Table 4.2). Insomnia is defined as difficulty initiating sleep, repeated or lengthy

awakenings, early awakening(s), inadequate sleep time, or poor sleep quality and presents with evidence of daytime dysfunction (AASM, 2005). The frequency of insomnia symptoms, categorized as greater than three times per week, self-reported by the participants is equivalent to an insomnia diagnosis, according to the AASM. From year one to year 10, participants who self-reported any one symptom of insomnia less than three times per week over the two week measurement interval reported a lower frequency of insomnia symptoms across the perimenopausal period (69% at Yr 1; 50% at Yr 10; Figure 4.1).

Description of insomnia symptoms.

Sleep latency (SL).

Sleep latency is defined as the time to sleep initiation from intention to initiate sleep; sleep latency in this study is referred to as trouble falling asleep or difficulty with sleep initiation (Kravitz et al., 2008). There was a trend for increased frequency of self-reported difficulty falling asleep (↑SL) from Year 1 to Year 10 (5.6% Yr 1; 6% Yr 10). The percentage of participants self-reporting no difficulty falling asleep in year one diminished across the 10-year study period (Yr1 56%; Yr10 49%). Participants reporting having difficulty falling asleep (↑SL) five or more times per week ranged from 5.6% to 6% over the ten year study period (Table 3). When the variable, SL, was dichotomized according to AASM criteria, women reporting no difficulty falling asleep ranged from 87% in year 1 to 76% in year 10 whereas women reporting difficulty falling asleep (i.e., yes) at year one was 12%, and in year ten was 15% (Table 4.4). Over time, the frequency of difficulty falling asleep was increasingly reported by the perimenopausal participants (Figure 4.2).

Wake after sleep onset (WASO).

Wake after sleep onset is defined as waking up several times a night or difficulty with sleep maintenance (Kravitz et al., 2008). When asked if participants woke up several times a night (WASO) using the AASM criteria (i.e., ≥3 times per week or <3 times per week), participants self-reported WASO increased in frequency over the ten year period, from 26% in year one to 36% in year 10. Participants who self-reported waking up several times a night was not a problem decreased in frequency from 73% in year one to 56% in year 10 (Table 4.5). Thirteen percent of participants self-reported waking up after going to sleep ≥5 times per week in year one; this frequency increased over the ten year study period (21% in Yr10). Thirty-five percent of participants reported no problem with waking up during the night (WASO) in year one with decreasing frequency in year 10 (22%; Table 4.6). Over time, WASO was self-reported as increasing in frequency by participants over the entire 10 year study interval (Figure 4.3).

Awakenings (A).

Awakenings are defined as waking up earlier than planned and unable to return to sleep (Kravitz et al., 2008). A higher percentage of participants self-reported more early morning awakenings (A) in year ten than in year one (16% versus 13%, respectively, using the dichotomized AASM criteria <3/≥ 3). There was a downward trend in the percentage of participants self-reporting less than three awakenings per week at year one versus year ten, 86% versus 75%, respectively, using the dichotomized AASM criteria (Table 4.7, Figure 4.4). The percentage of participants self-

reporting no awakenings decreased over the ten year study period as they transitioned to menopause (50% Yr1; 41% Yr10, Table 4.8).

Sleep quality (SQ).

Sleep quality was rated on a scale of restful, average quality, restless and very restless in this study and has been defined as the subjective report of tiredness on waking and throughout the day and feeling rested and restored on waking in the scientific literature (Harvey et al., 2008). Thirty-six percent of participants reported restful sleep in year one; at year 10, only 22% of participants reported restful sleep. Participants reporting very restless sleep increased from year one (4%) to year ten (5%) (Table 4.9; Figure 4.5). Sleep quality was also examined as a dichotomized variable; good versus poor sleep quality (restful/average; restless/very restless). At any given point across the ten year period, at least 17% of perimenopausal participants self-reported poor sleep quality (Table 4.10, Figure 4.6).

Research Question 2; What is the prevalence of insomnia by perimenopausal stage in women?

Perimenopausal women were categorized as early perimenopausal and late perimenopausal in this study. Early perimenopause is defined as having a menstrual period in the preceding three months and having experienced menstrual irregularity. Late perimenopause is defined as having experienced menstrual bleeding in the last 12 months but not in the preceding three months (Harlow, Crawford, Sommer, & Greendale, 2000). Women self-reported as early perimenopausal at visit 1(n=1723) and visit 10 (n= 155) and late perimenopausal at visit one (n=124) and at visit 10 (n=128) were included in the study.

Early menopausal group.

Description of insomnia.

Thirty-one to 38% of early perimenopausal women self-reported any one symptom of insomnia at a frequency of ≥ 3 times per week over a two week measurement interval over the ten year survey period (Table 4.11). This frequency of self-reported insomnia symptoms meets the AASM criteria for an insomnia diagnosis. Early perimenopausal participants who self-reported any one symptom of insomnia < 3 times per week over the two week measurement interval decreased in frequency over the 10 year survey period (70% at Yr1; 61% at Yr10; Figure 4.7).

Description of insomnia symptoms.

Sleep latency (SL).

Participants in the early menopause group self-reported difficulty falling asleep more frequently at year one than at year 10 using the dichotomized variable and the AASM criteria (12%; 10%, respectively). Eighty-eight percent of early perimenopausal participants reported difficulty falling asleep at a frequency of < 3 nights per week over a two week measurement interval (Table 4.12). Early perimenopausal women self-reporting having difficulty falling asleep (↑SL) five or more times a week ranged from 5.4% in year one to 3.9% in year 10 over the ten year study period. Early perimenopausal women self-reporting no difficulty falling asleep in the past 2 weeks ranged from 56%, in year one, to 57.4%, in year 10, over the ten year study period. Difficulty initiating sleep in the early perimenopausal group did not increase in frequency over the ten year study period (Table 4.13).

Wake after sleep onset (WASO).

When asked if participants in the early perimenopausal group woke up several times a night using the AASM criteria (≥3 times per week or < 3 times per week), the range equal to or greater than three times a week was 26% (Yr1) to 32% (Yr10). Seventy-four percent of the group reported waking up from sleep less than three nights per week in a two week interval (WASO) in year one with a decrease in the frequency over the ten year study period to 68% using the dichotomized AASM criteria (<3/≥3; Table 4.14). Thirteen percent of the early perimenopausal participants reported wake after sleep onset ≥ five times per week in year one; this frequency increased over the ten year study period to 16% in year 10. Thirty-five percent of early perimenopausal women reported no WASO in year one; 30% reported no WASO in year 10 (Table 4.15).

Awakenings (A).

A higher percentage of early perimenopausal women self-reported more early morning awakenings in year ten than in year one; (17.4% versus 13% respectively, using the dichotomized AASM criteria for insomnia). There was a downward trend in the percentage of early perimenopausal participants self-reporting less than three awakenings per week at year one versus year ten, 87% versus 82.6%, respectively (Table 4.16). Approximately 51% of early perimenopausal women self-reported no early morning awakenings in year one with minimal change over the ten year study period; (47% at Yr10). Early perimenopausal women self-reporting ≥ five early morning awakenings per week across the ten year study interval remained stable at 5.8% (Table 4.17).

Sleep quality (SQ).

Sleep quality was assessed on a four point response scale including restful, average quality, restless and very restless. Thirty-six percent of early perimenopausal women self-reported restful sleep in year one; at year 10, 28% of the participants self-reported restful sleep. Very restless sleep remained stable during the ten year study period at 4% (Table 4.18). Sleep quality was also examined as a dichotomized variable, good (restful/average) and poor (restless/very restless). At any given point across the ten year study period, at least 16% of early perimenopausal participants self-reported poor sleep quality (Table 4.19).

Late perimenopausal group.

Description of insomnia.

Thirty-one to 48% of late perimenopausal women self-reported any one symptom of insomnia at a frequency ≥ 3 times per week over a two week measurement interval over the ten year survey period (Table 4.20). This frequency of self-reported insomnia symptoms meets the AASM criteria for a diagnosis of insomnia. From year one to year 10, late perimenopausal participants who self-reported any one symptom of insomnia < 3 times per week over the two week measurement interval ranged from 69% in year one to 52% in year 10 (Figure 4.8).

Description of insomnia symptoms.

Sleep latency (SL).

Participants in the late perimenopause group self-reported difficulty falling asleep more frequently at year 10 than at year one (21% vs. 15%, respectively) using the dichotomized variable per AASM criteria. Eighty-six percent of late perimenopausal

women reported < three nights per week of difficulty initiating sleep in year one; 79% of late perimenopausal women reported < three nights per week of difficulty initiating sleep in year 10 (Table 4.21). Late perimenopausal women self-reporting difficulty falling asleep (↑SL) ≥ than five times a week was 6.5% in year one and in year 10 was 8.6%. Late perimenopausal women self-reporting no difficulty falling asleep in the past two weeks was 60% in year one and 51% in year 10. Difficulty initiating sleep in the late perimenopausal group increased in frequency over the ten year study period (Table 4.22).

Wake after sleep onset (WASO).

When asked if participants in the late perimenopausal group woke up several times a night using the AASM criteria (≥3 times per week or < 3 times per week), 27% reported yes in year one versus 39% in year 10. Seventy-three percent of the group reported less than three nights in a two week interval that they had nighttime arousals (WASO) in year one with a decrease over the ten year study period to 61% using the dichotomized AASM criteria (Table.4.23). Nineteen percent of the late perimenopausal participants reported wake after sleep onset (WASO) ≥ five times per week in year one; this frequency increased over the ten year study period to 25% in year 10. Thirty-three percent of late perimenopausal women reported no WASO in year one; 23% reported no WASO in year 10 (Table 4.24).

Awakenings (A).

A higher percentage of late perimenopausal women self-reported more early morning awakenings in year ten than in year one; (16% versus 13% respectively, using the dichotomized AASM criteria). There was a downward trend in the percentage of

late perimenopausal participants self-reporting less than three awakenings per week at year one versus year ten, 87% versus 84% respectively (Table 4.25). Approximately 52% of late perimenopausal women self-reported no early morning awakenings in year one, with a decrease in frequency over the ten year study period (46% at Yr10). Late perimenopausal women self-reporting ≥ five early morning awakenings ranged from 6.5% in year one to 7.8% in year 10 of the ten year study interval (Table 4.26).

Sleep quality (SQ).

Sleep quality was assessed on a four point response scale including restful, average quality, restless and very restless. Thirty-nine percent of late perimenopausal women self-reported very restful sleep in year one; at year 10, only 23% of the participants self-reported restful sleep. Very restless sleep was self-reported by 4% of late perimenopausal women at year one and by 1.5% at year 10 (Table 4.27). Sleep quality was also examined as a dichotomized variable, good (restful/average) and poor (restless/very restless). At any given point across the ten year study period, at least 20% of late perimenopausal participants self-reported poor sleep quality (Table 4.28, Figure 4.9).

Research Question 3; What is the trajectory of insomnia in women who have undergone surgical menopause?

In this study women who reported having undergone bilateral oophorectomy were categorized as surgical menopause. The category of surgical menopause continues until 12 months of amenorrhea when the participant was considered menopausal. Women self-reporting using hormone replacement therapy (HRT) in the

forms of oral or topical preparations were included in the HRT group. Women denying using HRT were included in the non HRT group.

Surgical menopause group.

Description of insomnia.

Forty-four to 51% of the surgical menopause group self-reported any one symptom of insomnia at a frequency of ≥3 times per week over a two week measurement interval of the time over the ten year survey period (Table 4.29). This frequency of self-reported insomnia symptoms meets the AASM criteria for insomnia. From year one to year 10, the surgical menopause participants who self-reported any one symptom of insomnia less than three times per week over the two week measurement interval were 56% at year one and 49% at year ten (Figure 4.10).

Description of insomnia symptoms.

Sleep latency (SL).

Participants in the surgical menopause group self-reported difficulty falling asleep equally at year one and at year 10 (19% using the dichotomized variable and the AASM criteria). The surgical menopause participants reporting < three nights per week of difficulty falling asleep per week over a two week measurement interval remained at 81% for year one and year 10 with small fluctuations over the ten year study interval (Table 4.30). The surgical menopause group self-reporting having difficulty falling asleep (↑SL) five or more times a week ranged from 13% in year one to 8% in year 10 over the ten year study period. The surgical menopause group self-reporting no difficulty falling asleep in the past 2 weeks ranged from 53% in year one to 51% in year

10 over the ten year study period. Difficulty initiating sleep in the surgical menopause group did not increase in frequency over the ten year study period (Table 4.31).

Wake after sleep onset (WASO).

When asked if participants in the surgical menopause group woke up several times a night using the AASM criteria (≥ 3 times per week or < 3 times per week), the participants self-reporting greater than or equal to three times per week WASO included 41% in year one and 46% in year 10. Fifty-nine percent of the group reported less than three nights in a two week interval with awakenings after going to sleep (WASO) in year one with a decrease over the ten year study period to 54% in year 10 using the AASM criteria (Table 4.32). Twenty-five percent of the surgical menopausal participants reported wake after sleep onset (WASO) ≥5 times per week in year one; this frequency increased over the ten year study period to 27% in year 10. Thirty-four percent of surgical menopausal women reported no WASO in year one; 20% reported no WASO in year 10 (Table 4.33).

Awakenings (A).

Women in the surgical menopause group self-reported greater than or equal to three early morning awakenings during a two week period in year one were 22% and 20% in year 10, using the AASM criteria for insomnia. The surgical menopausal participants self-reporting less than three awakenings per week ranged from 78% at year one to 80% at year ten (Table 4.34). Approximately 44% of surgical menopausal women self-reported no early morning awakenings in year one with little change over the ten year study period; 43% at year 10. The surgical menopause group self-

reporting ≥ five early morning awakenings ranged from 16% in year one to 10% in year 10 (Table 4.35).

Sleep quality (SQ).

Sleep quality was assessed on a four point response scale including restful, average quality, restless and very restless. Thirty-eight percent of the surgical menopausal women self-reported restful sleep in year one; at year 10, 22% of the participants self-reported restful sleep. Very restless sleep was self-reported at year one by 3% of respondents and at year 10 by 9% of the surgical menopausal sample (Table 4.36). Sleep quality was also examined as a dichotomized variable, good (restful/average) and poor (restless/very restless). At any given point across the ten year study period, at least 25% of the surgical menopausal participants self-reported poor sleep quality (Figure 4.11, Table 4.37).

Surgical Menopause with HRT.

Description of insomnia.

Thirty-seven to 38% of the surgical menopause group with hormone replacement therapy (HRT) self-reported any one symptom of insomnia at a frequency of ≥ 3 times per week over a two week measurement interval over the ten year survey period. This frequency of self-reported insomnia symptoms meets the AASM criteria for insomnia. From year one to year 10, the surgical menopause with HRT participants who self-reported any one symptom of insomnia < 3 times per week over the two week measurement interval was 63% at year one and 62% at year 10 (Table 4.38).

Description of insomnia symptoms

Sleep latency (SL).

Twenty-one percent of participants in the surgical menopause with HRT group self-reported difficulty falling asleep at year one; at year 10, 10% reported difficulty falling asleep (using the dichotomized variable and the AASM criteria). The surgical menopause with HRT participants reporting < three nights per week of difficulty initiating sleep over a two week measurement interval at year one was 80% and 90% at year 10 (Table 4.39). The surgical menopause with HRT group self-reporting having difficulty falling asleep (↑SL) five or more times a week ranged from 16% at year one to 3.4% at year 10 over the ten year study period. The surgical menopause with HRT group self-reporting no difficulty falling asleep in the past two weeks ranged from 53%, in year one, to 76%, in year 10. Difficulty initiating sleep in the surgical menopause with HRT group did not increase in frequency over the ten year study period (Table 4.40).

Wake after sleep onset (WASO).

When asked if participants in the surgical menopause with HRT group woke up several times a night using the AASM criteria (≥3 times per week or < three times per week), the range for ≥ three times per week was 32% in year one and 35% in year 10. Sixty-eight percent of the group reported < three nights in a two week interval of awakenings after going to sleep (WASO) in year one with a decrease over the ten year study period to 66% using the AASM criteria (Table 4.41). Twenty-one percent of the surgical menopausal with HRT participants reported wake after sleep onset (WASO) ≥ five times per week in year one; this frequency increased over the ten year study period

to 27% in year 10. Forty-two percent of surgical menopausal with HRT participants reported no WASO in year one; 24% reported no WASO in year 10 (Table 4.42).

Awakenings (A).

A higher percentage of surgical menopausal women taking HRT self-reported early morning awakenings at year 10 versus year one (32% versus 14%, respectively) using the AASM criteria for insomnia (Table 4.43). The surgical menopausal with HRT participants self-reporting < three awakenings per week ranged from 68% at year one to 86% at year ten (Figure 4.12). Approximately 47% of surgical menopausal with HRT women self-reported no early morning awakenings in year one with a modest change over the ten year study period; 41% at Yr10. The surgical menopause with HRT group self-reporting ≥ five early morning awakenings ranged from 21% in year one to 10% in year ten (Table 4.44).

Sleep quality (SQ).

Sleep quality was assessed on a four point response scale including restful, average quality, restless and very restless. Forty-two percent of the surgical menopausal women with HRT self-reported restful sleep in year one as compared to 21%at year 10. None of the respondents of the surgical menopause with HRT group self-reported very restless sleep in year one while 4% did report very restless sleep in year 10 (Table 4.45). Sleep quality was also examined as a dichotomized variable, good (restful/average) and poor (restless/very restless). At any given point across the ten year study period, at least 20% of the surgical menopausal participants self-reported poor sleep quality (Table 4.46).

Surgical Menopause without HRT.

Description of insomnia.

A relatively stable percent of the surgical menopause without HRT group self-reported any one symptom of insomnia at a frequency of ≥ 3 times per week over a two week measurement interval over the ten year survey period (54% in Yr1; 53% in Yr10; Figure 4.13). This frequency of self-reported insomnia symptoms meets the AASM criteria for insomnia. From year one to year 10, the surgical menopause without HRT participants who self-reported any one symptom of insomnia < 3 times per week over the two week measurement interval reported a slight increase in prevalence of insomnia symptoms (46% at Yr1; 47% at Yr10; Table 4.47).

Description of insomnia symptoms.

Sleep latency (SL).

Fifteen percent (Yr1) versus 21% (Yr10) of participants in the surgical menopause without HRT group self-reported difficulty falling asleep three or more times per week using the dichotomized variable and the AASM criteria. Eighty-five percent of the surgical menopause without HRT participants reported no difficulty initiating sleep using the dichotomized criteria and frequency of < 3 nights per week over a two week measurement interval and 80% at year 10 (Table 4.48). The surgical menopause without HRT group self-reporting having difficulty falling asleep (↑SL) five or more times a week ranged from 8% in year one to 9% in year ten. The surgical menopause without HRT group self-reporting no difficulty falling asleep in the past 2 weeks ranged from 54%, in year one, to 46%, in year 10. Difficulty initiating sleep in the surgical

menopause without HRT group did not increase in frequency over the ten year study period (Table 4.49).

Wake after sleep onset (WASO).

When asked if participants in the surgical menopause without HRT group woke up several times a night using the AASM criteria (≥3 times per week or < 3 times per week), the range for yes was54% in year one; 48% in Yr10. Forty-six percent of the group reported awakenings after going to sleep (WASO), < 3 nights in a two week interval, in year one with an increase over the ten year study period to 53% in year 10 using the AASM criteria (Table 4.50). Thirty-one percent of the surgical menopausal without HRT participants reported wake after sleep onset (WASO) ≥5 times per week in year one; this frequency decreased over the ten year study period to 27% in year 10. Twenty-three percent of surgical menopausal without HRT participants reported no WASO in year one; 19% reported no WASO in year 10 (Table 4.51).

Awakenings (A).

More surgical menopausal without HRT women self-reported a decreased frequency of early morning awakenings in year one than in year ten; (8% versus 26% respectively, using the AASM criteria for insomnia). The surgical menopausal without HRT participants self-reporting <3 awakenings per week ranged from 92% at year one to 75% at year ten (Table 4.52). Approximately 38% of surgical menopausal without HRT women self-reported no early morning awakenings in year one with an increase over the ten year study period; 43% in year 10. The surgical menopause without HRT group self-reporting ≥ five early morning awakenings ranged from 8% year one to 10% at year 10 of the ten year study interval (Table 4.53).

Sleep quality (SQ).

Sleep quality was assessed on a four point response scale including restful, average quality, restless and very restless. Thirty-one percent of the surgical menopausal women without HRT self-reported restful sleep in year one; at year 10, 22% of the participants self-reported restful sleep. Very restless sleep was self-reported by 8% of the sample at year one and by 10% of the sample at year 10 among the surgical menopause without HRT group (Table 4.54). Sleep quality was also examined as a dichotomized variable, good (restful/average) and poor (restless/very restless). At any given point across the ten year study period, at least 26% of the surgical menopausal participants self-reported poor sleep quality (Table 4.55).

Research Question 4; Is there a difference in reported insomnia symptoms by perimenopausal stage?

Description of Insomnia Symptoms.

Sleep latency (SL).

With adjustment for the sleep latency baseline value, the late perimenopausal group had significantly worse difficulty initiating sleep (↑SL) than the early perimenopausal group (mean 2.03 ± SE 0.03 vs.1.89± 0.02; t=4.12; $p < 0.001$). Using the AASM criteria for insomnia (≥3 times per week) and accounting for baseline sleep latency, late perimenopausal participants had 1.3 higher adjusted odds of self-reporting trouble sleeping when compared to early perimenopausal participants (X^2=12.17, [df2]; 95%CI 1.1, 1.5; $p = 0.0005$).

Wake after sleep onset (WASO).

The late perimenopausal group had worse nighttime awakenings than the early perimenopausal group after accounting for the baseline WASO (mean 2.95 ± SE 0.03 versus 2.71± 0.02; t=5.91; p < 0.0001). Using the AASM criteria for insomnia (≥ 3 times per week) and accounting for the baseline WASO value, the late perimenopausal group had a 1.4 higher odds of self-reporting nighttime awakenings when compared to the early perimenopausal group (X^2=30.57, [df2]; 95% CI 1.2, 1.5; p<0.001).

Awakenings (A).

After adjusting for the baseline value of awakenings, the late perimenopausal group reported more early morning awakenings compared to the early perimenopausal group (mean 2.15 ± SE 0.03 vs. 2.05 ± 0.02; t= 2.64; p = 0.0082). Using the AASM criteria for insomnia (≥3 times per week) and adjusting for the baseline awakenings value, late perimenopausal participants had 1.3 higher odds of self-reporting waking early when compared to the early perimenopausal group (X^2=9.05, [df2]; 95% CI 1.1, 1.5; p= 0.003).

Sleep quality (SQ).

Sleep quality was self-reported on a four point response scale including restful, average, restless and very restless ratings. The late perimenopausal group self-reported significantly worse sleep quality when compared to the early perimenopausal group (mean 2.06 ± SE 0.018 vs. 1.99 ± SE 0.012; t=2.92; p=0.004) with adjustment for the baseline sleep quality value. The adjusted odds of restless sleep was 1.3 times greater for those in late stage versus early stage of perimenopause (X^2=19.83, [df2]; 95% CI (1.2, 1.5), p<0.001).

Description of insomnia.

Overall insomnia symptoms were more prevalent in the late stage of perimenopause. The adjusted odds of having any one symptom of insomnia are 1.3 times greater for those in late stage versus early stage of perimenopause (X^2=26.01, [df1]; 95% CI (1.2, 1.5); p<0.0001).

Research Question 5; Is there a significant difference in insomnia symptoms before and after surgical menopause?

There was not a significant difference for any of the individual sleep symptom variables, or the dichotomized insomnia outcome as defined by the AASM criteria, before versus after surgical menopause. Examining pre-surgical menopause to post-surgical menopause for all individual outcome variables, as well as the insomnia outcome, there were no significant differences identified using McNemar's Test (Table 4.56; Table 4.57). When HRT status was accounted for (yes/no), there were no significant differences identified before and after surgical menopause for the outcome variables of SL, WASO, A, SQ and insomnia (all p>0.05; Table 4.58; Table 4.59). Prior to surgery, 43% of the surgical sample reported at least one symptom of insomnia during the study interval with 45% of the surgical sample reporting any one symptom of insomnia after surgery using the dichotomized AASM insomnia outcome (</≥ 3 nights per week). Perimenopausal stage, early or late, was not separated from the surgical status.

Research Question 6; Is there a difference in insomnia symptoms among perimenopausal women who have progressed naturally through perimenopause compared to women who have undergone surgical menopause?

Difference in insomnia symptoms.

Sleep latency (SL).

With adjustment for the baseline sleep latency value, the surgical menopause group had a higher frequency of self-reported difficulty initiating sleep (mean 2.12 ± SE 0.05) than both the late and the early perimenopausal group (mean 2.03 ± SE 0.03; 1.89± 0.02). The surgical menopause group had significantly more frequency of self-reported difficulty initiating sleep (↑SL) than the early perimenopausal group ($t=4.27$; $p < 0.001$). Using the AASM criteria for insomnia (≥3 times per week), the adjusted odds of surgical menopause participants reporting difficulty falling asleep were 1.1 times greater than for late perimenopausal participants ($X^2=0.26$, [df2]; 95% CI 0.81, 1.43; $p= 0.61$). The odds of surgical menopause participants reporting difficulty falling asleep are 1.4 times greater than the early perimenopausal group when baseline sleep latency is adjusted ($X^2=5.70$, [df2]; 95% CI 1.06, 1.86; $p= 0.0005$). The late perimenopausal participants had 1.3 higher adjusted odds of self-reporting difficulty falling asleep when compared to early perimenopausal participants ($X^2=12.17$, [df2]; 95% CI 1.1, 1.5; $p = 0.0005$).

Wake after sleep onset (WASO).

After adjusting for the baseline wake after sleep onset (WASO), the surgical menopause group had worse self-reported WASO than the late perimenopause group yet this difference was not significant (mean 3.01 ± SE 0.06 vs. 2.95 ± SE 0.03; $t=0.87$;

p=0.38). The late perimenopausal group had worse nighttime awakenings than the early perimenopausal group after accounting for the baseline WASO value (mean 2.95 ± SE 0.03 vs. 2.71± 0.02; t=5.91; p < 0.0001). Using the AASM criteria for insomnia (≥ 3 times per week) and adjusting for baseline WASO, the late perimenopausal group had a 1.4 higher odds of self-reporting nighttime awakenings when compared to the early perimenopausal group (X^2=30.57, [df2]; 95% CI 1.2, 1.5; p<0.001); similarly, the surgical menopause group had 1.3 times the odds of self-reporting more frequent WASO than the early perimenopause group (X^2=7.02, [df2]; 95% CI 1.07, 1.62, p<0.001). No significant differences were identified between the surgical menopause and late perimenopause groups (X^2=0.14, [df2]; 95% CI 0.78, 1.19; p=0.71).

Awakenings (A).

After adjusting for the baseline value of awakenings (A), the late perimenopausal group reported more awakenings (A) compared to the early perimenopausal group (mean 2.15 ± SE 0.03 vs. 2.05 ± 0.02; t=2.64; p = 0.0082) but the surgical menopause group reported the highest frequency of early morning awakenings when compared to the early perimenopausal groups (mean 2.24 ± SE 0.05; t=3.47; p=0.0005). There was not a significant difference between the surgical menopause and late perimenopause groups for self-reported frequency of early morning awakenings (t=1.61; p=0.11). Using the AASM criteria for insomnia (≥3 times per week) and accounting for baseline awakenings, late perimenopausal participants had 1.3 higher odds of self-reporting waking early when compared to the early perimenopausal group (X^2=9.05, [df2]; 95% CI 1.1, 1.5; p= 0.003). Surgical menopause participants had 1.4 times higher adjusted odds of self-reporting waking early than the early perimenopausal participants (X^2=5.46,

[df2]; 95% CI 1.1, 1.8; p=0.02). Surgical menopause participants when compared to late perimenopause participants were not significantly different in the self-reporting of awakenings (X^2=0.29, [df2]; 95% CI -0.2, 0.34; p=0.59).

Sleep quality (SQ).

Sleep quality was self-reported on a four point response scale (restful, average, restless, very restless ratings). The surgical menopause group self-reported similar sleep quality when compared to the late perimenopausal group (mean 2.1 ± SE 0.03 vs. 2.1 ± SE 0.02; t=1.85; p=0.06) with baseline sleep quality adjusted. The late perimenopausal group self-reported significantly worse sleep quality when compared to the early perimenopausal group (mean 2.06 ± SE 0.018 versus 1.99 ± SE 0.012; t=2.92; p=0.004) with adjustment for the baseline value. The adjusted odds of restless sleep are 1.3 times greater for those in late stage versus early stage of perimenopause (X^2=19.83, [df2]; 95% CI 1.2, 1.5, p<0.001). The surgical menopause had 1.3 times greater adjusted odds for self-reporting restless sleep than the early perimenopause group (X^2=5.56, [df2]; 95% CI 1.04, 1.67; p=0.02).

Description of insomnia.

Overall, insomnia symptoms were worse and more prevalent in the late stage of perimenopause. The adjusted odds of having any one symptom of insomnia are 1.3 times greater for those in late stage versus early stage of menopause (X^2=26.01, [df2]; 95% CI (1.2, 1.5); p<0.001). The adjusted odds of having any one symptom of insomnia are 1.3 times greater for those participants in surgical menopause versus early perimenopause (X^2=7.94, [df2]; 95% CI 1.1, 1.6; p=0.0048). There was not a significant difference between the surgical menopause group versus the late

perimenopause group self-reporting any one symptom of insomnia during the ten year study interval (X^2=0, [df2]; 95% CI -0.21, 0.21; p= 0.9994).

7. Among perimenopausal women what are the factors of influence for chronic insomnia defined as insomnia symptoms present for at least two consecutive annual data collection points?

The baseline variables were used as predictors of the dichotomous outcome, chronic insomnia (yes/no) in a logistic regression framework. All variables were evaluated for collinearity (all VIF NS). Twenty-seven percent (n=707) of the total sample with complete evaluable data (N=2582) were categorized as having chronic insomnia. Chronic insomnia was defined as persistence of any insomnia symptoms for at least two consecutive annual data collection points. Utilizing simultaneous loading multivariable logistic regression analysis framework to develop evaluation models, five models were developed with significant covariables carried forward (p<0.10). Model 1 included cold sweats, hot flashes, night sweats, perimenopausal status depression, BMI and rotating shifts which were simultaneously loaded into the model (Table 4.60). The analysis resulted in the following significant individual predictor covariables; night sweats (p=0.0007), perimenopausal status, depression and BMI, (all p<0.001), and were carried forward to Model 2. Model 2 included significant covariables from Model 1 and added: age (5 year bins), race/ethnicity, income level and education level. The following significant covariables were carried forward to Model 3; night sweats (p=0.004), perimenopausal status (p<0.0001), depression (p=0.0001), BMI (p<0.0001) and age (p=0.0013). Model 3 included significant covariables from Model 2 and added the following covariables: diabetes, high blood pressure, HRT use, alcohol use and

marital status. The predictors that were carried forward to Model 4 were night sweats (p=0.0013), perimenopausal status (p=0.0004), depression (p=0.0027), BMI (p=0.0003), age (0.0030) and alcohol use (p=0.4731). The additional predictors added in Model 4 included significant covariables from Model 3 and added : stroke, myocardial infarction/angina, health status, exercise and smoking. The individual predictors that carried forward to the final model were: night sweats (p<0.0001), perimenopausal status (p<0.0001), depression (p<0.0001), BMI (p<0.0001), age (p=0.0002) and exercise (p=0.0394; Table 4.61).

The adjusted odds of chronic insomnia were:

- 1.3 times greater for every one unit increase in night sweats at baseline (95% CI 1.1, 1.4; p<0.001)
- 1.5 times greater for those in perimenopause than pre-perimenopausal status at baseline (95% CI 1.3, 1.8; p<0.001)
- 1.5 times greater for those who were depressed at baseline (95% CI 1.2, 1.9; p<0.001)
- 1.1 times greater for every 5 unit increase in BMI (95% CI, 1.1, 1.2, p<0.001)
- 1.3 times greater for those that exercised more than once a week at baseline (95% CI 1.1, 1.6; p=0.005)
- 0.8 times less with every 5-year increase in age at baseline (95% CI 0.7, 0.9; p=0.001).

Tables

Table 4.1

Sample Description at Baseline (N==3302)

Characteristic	Frequencies (n[%]) or Mean (SD)
Age (yrs)	45.85 (± 2.69)
Menopausal Status	
Early Perimenopausal	1498 (45.4)
Pre-menopausal	1727 (52.3)
Race/Ethnicity	
White	1551 (47%)
Black or African American	933 (28%)
Chinese or Chinese American	246 (7%)
Japanese or Japanese American	281 (9%)
Hispanic	286 (9%)
Marital Status	
Single	439 (13%)
Married/Living as Married	2149 (65%)
Separated	156 (5%)
Widowed	65 (2%)

Divorced	435 (13%)
Education	
Less than high school	238 (7%)
High school	585 (18%)
Some college or technical school	1045 (32%)
College graduate	662 (20%)
Post graduate or more	737 (22%)
Family Income	
Less than $19,999	490 (14.8%)
$20,000 to $49,999	1088 (32.9%)
$50,000 to $99,999	1162 (35.2%)
$100,000 or more	472 (14.3%)
Employed	
Yes	2643 (80%)
No	649 (19.7%)
Rotating Shifts	
Yes	226 (6.8%)
No	2400 (72.7%)
BMI (kg/m^2)	28.27 ($\pm$ 7.2)
Depressed in past week	
<1 Day	1849 (56%)
1-2 Days	891 (27%)

3-4 Days	372 (11.3%)
5-7 Days	185 (5.6%)
Smoking Status	
Yes	569 (17.2%)
No	2728 (77.6%)
Vasomotor Symptoms	
Frequency ranged from not at all to everyday for the next three characteristics	
Hot Flashes	
Yes	878 (26.6%)
No	2407 (72.9%)
Cold Sweats	
Yes	365 (11.1%)
No	2841 (86%)
Night Sweats	
Yes	963 (29.2%)
No	2321 (70.3%)
Exercise 1 hour a week	
Yes	916 (27.7%)
No	2382 (72.2%)

Abbreviations SD, Standard Deviation; Yrs., Years

Table 4.2

*Frequency of **Any** Insomnia Variable by Annual Visit*

Dichotomized SL,WASO, A as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	1299 (68.7)	578 (30.6)	1890
2	1171 (64.0)	628 (34.3)	1829
3	1061 (61.0)	619 (35.6)	1739
4	944 (58.9)	573 (35.7)	1604
5	821 (57.6)	484 (34.0)	1424
6	607 (52.7)	422 (36.7)	1151
7	521 (53.0)	380 (38.7)	983
8	410 (50.9)	336 (41.7)	806
9	321 (49.8)	261 (40.5)	645
10	254 (49.5)	216 (42.1)	513

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.3

Frequency of Sleep Latency Symptom by Annual Visit

Likert Response Scale: Frequency of Symptom in Past 2 Week

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total N *
1	1055 (55.8)	324 (17.1)	268 (14.2)	125 (6.6)	105 (5.6)	1890
2	958 (52.4)	345 (18.7)	250 (13.7)	143 (7.8)	105 (5.7)	1829
3	904 (52.4)	309 (17.8)	258 (14.8)	101 (5.8)	109 (6.3)	1739
4	852 (53.1)	244 (15.2)	211 (13.2)	122 (7.6)	89 (5.6)	1604
5	706 (49.6)	248 (17.4)	200 (14.0)	85 (6.0)	67 (4.7)	1424
6	577 (50.1)	157 (13.6)	160 (13.9)	76 (6.6)	59 (5.1)	1151
7	502 (51.1)	132 (13.4)	129 (13.1)	79 (8.0)	60 (6.1)	983
8	408 (50.6)	113 (14.0)	104 (12.9)	68 (8.4)	53 (6.6)	806
9	318 (49.3)	87 (13.5)	88 (13.6)	52 (8.1)	37 (5.7)	645
10	249 (48.5)	80 (15.6)	62 (12.1)	47 (9.2)	32 (6.2)	513

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.4

Frequency of Sleep Latency Symptom by Annual Visit

Dichotomized Sleep Latency as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	1647 (87.1)	230 (12.2)	1890
2	1553 (84.9)	248 (13.6)	1829
3	1471 (84.6)	210 (12.1)	1739
4	1307 (81.5)	211 (13.2)	1604
5	1154 (81.0)	152 (10.7)	1424
6	894 (77.7)	135 (11.7)	1151
7	763 (77.6)	139 (14.1)	983
8	625 (77.5)	121 (15.0)	806
9	493 (76.4)	89 (13.8)	645
10	391 (76.2)	79 (15.4)	513

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.5

Frequency of WASO Symptom by Annual Visit

Dichotomized WASO as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	1389 (73.5)	489 (25.9)	1890
2	1261(68.9)	539 (29.5)	1829
3	1159 (66.7)	522 (30.0)	1739
4	1011 (63.0)	508 (31.7)	1604
5	904 (63.5)	402 (28.2)	1424
6	660 (57.3)	368 (32.0)	1151
7	566 (57.6)	335 (34.1)	983
8	459 (57.0)	287 (35.6)	806
9	356 (55.2)	226 (35.0)	645
10	285 (55.6)	185 (36.1)	513

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.6

Frequency of WASO by Annual Visit

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total N *
1	660 (34.9)	368 (19.5)	361 (19.1)	235 (12.4)	254 (13.4)	1890
2	579 (31.7)	330 (18.0)	352 (19.3)	255 (13.9)	284 (15.5)	1829
3	514 (29.6)	299 (17.2)	346(19.9)	250 (14.4)	272 (15.6)	1739
4	453 (28.2)	272 (17.0)	286 (17.8)	262 (16.3)	246 (15.3)	1604
5	381 (26.8)	227 (15.9)	296 (20.8)	194 (13.6)	208 (14.6)	1424
6	284 (24.7)	158 (13.7)	218 (18.9)	164 (14.3)	204 (17.7)	1151
7	257 (26.1)	147 (15.0)	162 (16.5)	152 (15.5)	183 (18.6)	983
8	191 (23.7)	113 (14.0)	155 (19.2)	117 (14.5)	170 (21.1)	806
9	141 (21.9)	105 (16.3)	110 (17.1)	97 (15.0)	129 (20.0)	645
10	113 (22.0)	76 (14.8)	96 (18.7)	79 (15.4)	106 (20.7)	513

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.7

Frequency of Early Awakenings by Annual Visit

Dichotomized Early Awakenings as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	1634 (86.5)	245 (13.0)	1890
2	1524 (83.3)	276 (15.1)	1829
3	1414 (81.3)	266 (15.3)	1739
4	1267 (79.0)	251 (15.6)	1604
5	1114 (78.2)	191 (13.4)	1424
6	858 (74.5)	171 (14.9)	1151
7	737 (75.0)	165 (16.8)	983
8	616 (76.4)	130 (16.1)	806
9	486 (75.4)	96 (14.9)	645
10	386 (75.2)	84 (16.4)	513

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.8

Frequency of Early Awakenings by Annual Visit

Likert Response Scale: Frequency of Symptom in Past 2 Weeks						
Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total N *
1	949 (50.2)	399 (21.1)	286 (15.1)	133 (7.0)	112 (5.9)	1890
2	881 (48.2)	361 (19.7)	282 (15.4)	154 (8.4)	122 (6.7)	1829
3	801 (46.1)	355 (20.4)	258 (14.8)	151 (8.7)	115 (6.6)	1739
4	716 (44.6)	301 (18.8)	250 (15.6)	150 (9.4)	101 (6.3)	1604
5	593 (41.6)	283 (19.9)	238 (16.7)	102 (7.2)	89 (6.3)	1424
6	476 (41.4)	193 (16.8)	189 (16.4)	93 (8.1)	78 (6.8)	1151
7	419 (42.6)	168 (17.1)	150 (15.3)	92 (9.4)	73 (7.4)	983
8	343 (42.6)	141 (17.5)	132 (16.4)	73 (9.1)	57 (7.1)	806
9	268 (41.6)	111 (17.2)	107 (16.6)	54 (8.4)	42 (6.5)	645
10	212 (41.3)	88 (17.2)	86 (16.8)	46 (9.0)	38 (7.4)	513

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.9

Frequency of Typical Night's Sleep by Annual Visit

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	Restful n (%)	Average Quality n (%)	Restless n (%)	Very Restless n (%)	Total Sample N*
1	673 (35.6)	769 (40.7)	361 (19.1)	76 (4.0)	1890
2	611 (33.4)	758 (41.4)	344 (18.8)	87 (4.8)	1829
3	545 (31.3)	728 (41.9)	333 (19.2)	72 (4.1)	1739
4	375 (23.4)	863 (53.8)	237 (14.8)	43 (2.7)	1604
5	289 (20.3)	746 (52.4)	234 (16.4)	36 (2.5)	1424
6	237 (20.6)	554 (48.1)	197 (17.1)	41 (3.6)	1151
7	204 (20.8)	484 (49.2)	182 (18.5)	32 (3.3)	983
8	139 (17.3)	374 (46.4)	135 (16.8)	20 (2.5)	806
9	120 (18.6)	321 (49.8)	106 (16.4)	32 (5.0)	645
10	114 (22.2)	234 (45.6)	97 (18.9)	25 (4.9)	513

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.10

Frequency of Typical Night Sleep by Annual Visit

Dichotomized as Good versus Poor Sleep Quality:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	Good Sleep Quality Restful/Average Quality n (%)	Poor Sleep Quality Restless/Very Restless n (%)	Total Sample N*
1	1442 (76.3)	437 (23.1)	1890
2	1369 (74.8)	431 (23.6)	1829
3	1273 (73.2)	405 (23.3)	1739
4	1238 (77.2)	280 (17.5)	1604
5	1035 (72.7)	270 (19.0)	1424
6	791 (68.7)	238 (20.7)	1151
7	688 (70.0)	214 (21.8)	983
8	513 (63.7)	155 (19.2)	806
9	441 (68.4)	138 (21.4)	645
10	348 (67.8)	122 (23.8)	513

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.11

Frequency of Any Insomnia Variable by Annual Visit

Early Perimenopausal Group

Dichotomized SL,WASO, A as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N
1	1196 (69.49)	525 (30.51)	1721
2	1025 (66.78)	510 (33.22)	1535
3	893 (65.28)	475 (34.72)	1368
4	725 (63.93)	409 (36.07)	1134
5	596 (65.57)	313 (34.43)	909
6	422 (63.36)	244 (36.64)	666
7	328 (62.96)	193 (37.04)	521
8	223 (59.63)	151 (40.37)	374
9	146 (58.40)	104 (41.60)	250
10	95 (61.29)	60 (38.71)	155

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.12

Frequency of Sleep Latency by Annual Visit

Early Perimenopause Group

Dichotomized Sleep Latency as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	1515 (88.03)	206 (11.97)	1721
2	1335 (86.86)	202 (13.14)	1537
3	1212 (88.53)	157 (11.47)	1369
4	988 (87.05)	147 (12.95)	1135
5	807 (88.78)	102 (11.22)	909
6	595 (89.34)	71 (10.66)	666
7	459 (87.93)	63 (12.07)	522
8	322 (86.10)	52 (13.90)	374
9	222 (88.80)	28 (11.20)	250
10	139 (89.68)	16 (10.32)	155

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.13

Frequency of Sleep Latency Symptom by Annual Visit

Early Perimenopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total N *
1	964 (56.01)	301 (17.49)	250 (14.53)	113 (6.57)	93 (5.40)	1721
2	825 (53.68)	304 (19.78)	206 (13.40)	117 (7.61)	85 (5.53)	1537
3	741 (54.13)	257 (18.77)	214 (15.63)	75 (5.48)	82 (5.99)	1369
4	664 (58.50)	175 (15.42)	149 (13.13)	92 (8.11)	55(4.85)	1135
5	506 (55.67)	172 (18.92)	129 (14.19)	65 (7.15)	37 (4.07)	909
6	399 (59.91)	95 (14.26)	101 (15.17)	35 (5.26)	36 (5.41)	666
7	322 (61.69)	72 (13.79)	65 (12.45)	39 (7.47)	24 (4.60)	522
8	232 (62.03)	51 (13.64)	39 (10.43)	24 (6.42)	28 (7.49)	374
9	145 (58.00)	40 (16.00)	37 (14.80)	17 (6.80)	11 (4.40)	250
10	89 (57.42)	26 (16.77)	24 (15.48)	10 (6.45)	6 (3.87)	155

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.14

Frequency of WASO by Annual Visit

Early Perimenopause Group

Dichotomized WASO as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	1280 (74.33)	442 (25.67)	1722
2	1100 (71.61)	436 (28.39)	1536
3	973 (71.07)	396 (28.93)	1369
4	781 (68.75)	355 (31.25)	1136
5	653 (71.84)	256 (28.16)	909
6	455 (68.42)	210 (31.58)	665
7	355 (68.14)	166 (31.86)	521
8	246 (65.78)	128 (34.22)	374
9	158 (63.20)	92 (36.80)	250
10	105 (67.74)	50 (32.26)	155

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.15

Frequency of WASO by Annual Visit

Early Perimenopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total N *
1	608 (35.31)	339 (19.69)	333 (19.34)	219 (12.72)	223 (12.95)	1722
2	520 (33.85)	284 (18.49)	296 (19.27)	213 (13.87)	223 (14.52)	1536
3	439 (32.07)	247 (18.04)	287 (20.96)	205 (14.97)	191 (13.95)	1369
4	358 (31.51)	214 (18.84)	209 (18.40)	197 (17.34)	158 (13.91)	1136
5	281 (30.91)	164 (18.04)	208 (22.88)	138 (15.18)	118 (12.98)	909
6	210 (31.58)	107 (16.09)	138 (20.75)	99 (14.89)	111 (16.69)	665
7	167 (32.05)	92 (17.66)	96 (18.43)	82 (15.74)	84 (16.12)	521
8	116 (31.02)	55 (14.71)	75 (20.05)	48 (12.83)	80 (21.39)	374
9	63 (25.20)	54 (21.60)	41 (16.40)	41 (16.40)	51 (20.40)	250
10	46 (29.68)	26 (16.77)	33 (21.29)	26 (16.77)	24 (15.48)	155

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.16

Frequency of Early Morning Awakenings by Annual Visit

Early Perimenopause Group

Dichotomized Early Morning Awakenings as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	1501 (87.12)	222 (12.88)	1723
2	1320 (85.94)	216 (14.06)	1536
3	1160 (84.80)	208 (15.20)	1368
4	965 (85.02)	170 (14.98)	1135
5	800 (88.01)	109 (11.99)	909
6	575 (86.34)	91 (13.66)	666
7	440 (84.29)	82 (15.71)	522
8	315 (84.22)	59 (15.78)	374
9	218 (87.20)	32 (12.80)	250
10	128 (82.58)	27 (17.42)	155

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.17

Frequency of Early Morning Awakenings by Annual Visit

Early Perimenopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total N *
1	870 (50.49)	363 (21.07)	268 (15.55)	123 (7.14)	99 (5.75)	1723
2	767 (49.93)	310 (20.18)	243 (15.82)	120 (7.81)	96 (6.25)	1536
3	661 (48.32)	299 (21.86)	200 (14.62)	120 (8.77)	88 (6.43)	1368
4	542 (47.75)	233 (20.53)	190 (16.74)	109 (9.60)	61 (5.37)	1135
5	425 (46.75)	200 (22.00)	175 (19.25)	67 (7.37)	42 (4.62)	909
6	324 (48.65)	125 (18.77)	126 (18.92)	52 (7.81)	39 (5.86)	666
7	263 (50.38)	98 (18.77)	79 (15.13)	45 (8.62)	37 (7.09)	522
8	185 (49.47)	70 (18.72)	60 (16.04)	34 (9.09)	25 (6.68)	374
9	110 (44.00)	52 (20.80)	56 (22.40)	19 (7.60)	13 (5.20)	250
10	73 (47.10)	28 (18.06)	27 (17.42)	18 (11.61)	9 (5.81)	155

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.18

Frequency of Typical Night's Sleep by Annual Visit

Early Perimenopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	Restful n (%)	Average Quality n (%)	Restless n (%)	Very Restless n (%)	Total Sample N*
1	613 (35.58)	714 (41.44)	326 (18.92)	70 (4.06)	1723
2	528 (34.35)	661 (43.01)	276 (17.96)	72 (4.68)	1537
3	457 (33.46)	592 (43.34)	264 (19.33)	53 (3.88)	1366
4	283 (24.93)	666 (58.68)	162 (14.27)	24 (2.11)	1135
5	217 (23.87)	521 (57.32)	150 (16.50)	21 (2.31)	909
6	164 (24.62)	363 (54.50)	111 (16.67)	28 (4.20)	666
7	132 (25.29)	290 (55.56)	88 (16.86)	12 (2.30)	522
8	90 (24.13)	204 (54.69)	73 (19.57)	6 (1.61)	373
9	62 (24.80)	138 (55.20)	39 (15.60)	11 (4.40)	250
10	44 (28.39)	74 (47.74)	31 (20.00)	6 (3.87)	155

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.19

Frequency of Typical Night Sleep by Annual Visit

Early Perimenopause Group

Dichotomized as Good versus Poor Sleep Quality:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	Good Sleep Quality Restful/Average Quality n (%)	Poor Sleep Quality Restless/Very Restless n (%)	Total Sample N*
1	1327 (77.0)	396 (23.0)	1723
2	1189 (77.4)	348 (22.6)	1537
3	1049 (76.8)	317 (23.2)	1366
4	949 (83.6)	186 (16.4)	1135
5	738 (81.2)	171 (18.8)	909
6	527 (79.1)	139 (20.9)	666
7	422 (80.9)	100 (19.2)	522
8	294 (78.8)	79 (21.2)	373
9	200 (80.0)	50 (20.0)	250
10	118 (76.1)	37 (23.9)	155

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.20

Frequency of Any Insomnia Variable by Annual Visit

Late Perimenopause Group

Dichotomized SL,WASO, A as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N*
1	85 (68.55)	39 (31.45)	124
2	116 (57.14)	87 (42.86)	203
3	125 (54.82)	103 (45.18)	228
4	158 (58.74)	111 (41.26)	269
5	155 (59.39)	106 (40.61)	261
6	116 (52.49)	105 (47.51)	221
7	107 (50.00)	107 (50.00)	214
8	108 (57.14)	81 (42.86)	189
9	84 (56.38)	65 (43.62)	149
10	67 (52.34)	61 (47.66)	128

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.21

Frequency of Sleep Latency by Annual Visit

Late Perimenopause Group

Dichotomized Sleep Latency as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N*
1	106 (85.48)	18 (14.52)	124
2	174 (85.71)	29 (14.29)	203
3	193 (84.65)	35 (15.35)	228
4	227 (84.39)	42 (15.61)	269
5	232 (88.89)	29 (11.11)	261
6	192 (86.88)	29 (13.12)	221
7	173 (80.84)	41 (19.16)	214
8	159 (84.13)	30 (15.87)	189
9	124 (83.22)	25 (16.78)	149
10	101 (78.91)	27 (21.09)	128

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.22

Frequency of Sleep Latency Symptom by Annual Visit

Late Perimenopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total N*
1	74 (59.68)	19 (15.32)	13 (10.48)	10 (8.06)	8 (6.45)	124
2	107 (52.71)	31 (15.27)	36 (17.73)	17 (8.37)	12 (5.91)	203
3	121 (53.07)	39 (17.11)	33 (14.47)	16 (7.02)	19 (8.33)	228
4	143 (53.16)	44 (16.36)	40 (14.87)	20 (7.43)	22 (8.18)	269
5	133 (50.96)	51 (19.54)	48 (18.39)	12 (4.60)	17 (6.51)	261
6	113 (51.13)	39 (17.65)	40 (18.10)	22 (9.95)	7 (3.17)	221
7	98 (45.79)	37 (17.29)	38 (17.76)	23 (10.75)	18 (8.41)	214
8	85 (44.97)	38 (20.11)	36 (19.05)	19 (10.05)	11 (5.82)	189
9	79 (53.02)	23 (15.44)	22 (14.77)	15 (10.07)	10 (6.71)	149
10	65 (50.78)	24 (18.75)	12 (9.38)	16 (12.50)	11 (8.59)	128

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.23

Frequency of WASO by Annual Visit

Late Perimenopause Group

Dichotomized WASO as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N*
1	90 (72.58)	34 (27.42)	124
2	126 (62.07)	77 (37.93)	203
3	139 (60.96)	89 (39.04)	228
4	166 (61.71)	103 (38.29)	269
5	169 (64.75)	92 (35.25)	261
6	125 (56.56)	96 (43.44)	221
7	117 (54.67)	97 (45.33)	214
8	116 (61.38)	73 (38.62)	189
9	91 (61.07)	58 (38.93)	149
10	78 (60.94)	50 (39.06)	128

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.24

Frequency of WASO by Annual Visit

Late Perimenopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total Sample N*
1	41 (33.06)	25 (20.16)	24 (19.35)	11 (8.87)	23 (18.55)	124
2	47 (23.15)	31 (15.27)	48 (23.65)	31 (15.27)	46 (22.66)	203
3	57 (25.00)	37 (16.23)	45 (19.74)	31 (13.60)	58 (25.44)	228
4	65 (24.16)	43 (15.99)	58 (21.56)	47 (17.47)	56 (20.82)	269
5	70 (26.82)	41 (15.71)	58 (22.22)	36 (13.79)	56 (21.46)	261
6	50 (22.62)	31 (14.03)	44 (19.91)	42 (19.00)	54 (24.43)	221
7	52 (24.30)	29 (13.55)	36 (16.82)	43 (20.09)	54 (25.23)	214
8	44 (23.28)	31 (16.40)	41 (21.69)	34 (17.99)	39 (20.63)	189
9	39 (26.17)	23 (15.44)	29 (19.46)	28 (18.79)	30 (20.13)	149
10	30 (23.44)	25 (19.53)	23 (17.97)	18 (14.06)	32 (25.00)	128

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.25

Frequency of Early Morning Awakenings by Annual Visit

Late Perimenopause Group

Dichotomized Early Morning Awakenings as per AASM criteria: Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N*
1	108 (87.10)	16 (12.90)	124
2	161 (79.31)	42 (20.69)	203
3	187 (82.02)	41 (17.98)	228
4	216 (80.30)	53 (19.70)	269
5	210 (80.46)	51 (19.54)	261
6	182 (82.35)	39 (17.65)	221
7	166 (77.57)	48 (22.43)	214
8	156 (82.54)	33 (17.46)	189
9	129 (86.58)	20 (13.42)	149
10	108 (84.38)	20 (15.63)	128

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.26

Frequency of Early Morning Awakenings by Annual Visit

Late Perimenopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total Sample N*
1	65 (52.42)	31 (25.00)	12 (9.68)	8 (6.45)	8 (6.45)	124
2	89 (43.84)	38 (18.72)	34 (16.75)	26 (12.81)	16 (7.88)	203
3	101 (44.30)	42 (18.42)	44 (19.30)	24 (10.53)	17 (7.46)	228
4	129 (47.96)	45 (16.73)	42 (15.61)	26 (9.67)	27 (10.04)	269
5	119 (45.59)	50 (19.16)	41 (15.71)	18 (6.90)	33 (12.64)	261
6	105 (47.51)	38 (17.19)	39 (17.65)	27 (12.22)	12 (5.43)	221
7	91 (42.52)	38 (17.76)	37 (17.29)	24 (11.21)	24 (11.21)	214
8	84 (44.44)	39 (20.63)	33 (17.46)	17 (8.99)	16 (8.47)	189
9	75 (50.34)	31 (20.81)	23 (15.44)	12 (8.05)	8 (5.37)	149
10	59 (46.09)	23 (17.97)	26 (20.31)	10 (7.81)	10 (7.81)	128

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.27

Frequency of Typical Night's Sleep by Annual Visit

Late Perimenopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	Restful n (%)	Average Quality n (%)	Restless n (%)	Very Restless n (%)	Total Sample N*
1	48 (38.71)	45 (36.29)	26 (20.97)	5 (4.03)	124
2	66 (32.67)	71 (35.15)	54 (26.73)	11 (5.45)	202
3	55 (24.12)	107 (46.93)	51 (22.37)	15 (6.58)	228
4	70 (26.02)	137 (50.93)	50 (18.59)	12 (4.46)	269
5	47 (18.08)	153 (58.85)	49 (18.85)	11 (4.23)	260
6	51 (23.08)	114 (51.58)	50 (22.62)	6 (2.71)	221
7	39 (18.22)	110 (51.40)	55 (25.70)	10 (4.67)	214
8	36 (19.05)	113 (59.79)	30 (15.87)	10 (5.29)	189
9	31 (20.81)	89 (59.73)	25 (16.78)	4 (2.68)	149
10	29 (22.66)	61 (47.66)	36 (28.13)	2 (1.56)	128

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.28

Frequency of Typical Night Sleep by Annual Visit

Late Perimenopause Group

Dichotomized as Good versus Poor Sleep Quality:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	Good Sleep Quality Restful/Average Quality n (%)	Poor Sleep Quality Restless/Very Restless n (%)	Total Sample N*
1	93 (75.0)	31 (25.0)	124
2	137 (67.8)	65 (32.2)	202
3	162 (71.1)	66 (29.0)	228
4	207 (77.0)	62 (23.0)	269
5	200 (76.9)	60 (23.1)	260
6	165 (74.7)	56 (25.3)	221
7	149 (69.6)	65 (30.4)	214
8	149 (78.8)	40 (21.2)	189
9	120 (80.5)	29 (19.5)	149
10	90 (70.3)	38 (29.7)	128

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.29

Frequency of Any Insomnia Variable by Annual Visit

Surgical Menopause Group

Dichotomized SL,WASO, A as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N*
1	18 (56.25)	14 (43.75)	32
2	30 (49.18)	31 (50.82)	61
3	43 (51.19)	41 (48.81)	84
4	61 (53.51)	53 (46.49)	114
5	70 (51.85)	65 (48.15)	135
6	69 (48.59)	73 (51.41)	142
7	86 (51.81)	80 (48.19)	166
8	79 (43.17)	104 (56.83)	183
9	91 (49.73)	92 (50.27)	183
10	92 (49.20)	95 (50.80)	187

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.30

Frequency of Sleep Latency by Annual Visit

Surgical Menopause Group

Dichotomized Sleep Latency as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N*
1	26 (81.25)	6 (18.75)	32
2	44 (72.13)	17 (27.87)	61
3	66 (78.57)	18 (21.43)	84
4	92 (80.70)	22 (19.30)	114
5	115 (84.56)	21 (15.44)	136
6	107 (75.35)	35 (24.65)	142
7	131 (78.92)	35 (21.08)	166
8	144 (78.69)	39 (21.31)	183
9	147 (80.33)	36 (19.67)	183
10	151 (80.75)	36 (19.25)	187

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.31

Frequency of Sleep Latency Symptom by Annual Visit

Surgical Menopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total N *
1	17 (53.13)	4 (12.50)	5 (15.63)	2 (6.25)	4 (12.50)	32
2	26 (42.62)	10 (16.39)	8 (13.11)	9 (14.75)	8 (13.11)	61
3	42 (50.00)	13 (15.48)	11 (13.10)	10 (11.90)	8 (9.52)	84
4	45 (39.47)	25 (21.93)	22 (19.30)	10 (8.77)	12 (10.53)	114
5	67 (49.26)	25 (18.38)	23 (16.91)	8 (5.88)	13 (9.56)	136
6	65 (45.77)	23 (16.20)	19 (13.38)	19 (13.38)	16 (11.27)	142
7	82 (49.40)	23 (13.86)	26 (15.66)	17 (10.24)	18 (10.84)	166
8	91 (49.73)	24 (13.11)	29 (15.85)	25 (13.66)	14 (7.65)	183
9	94 (51.37)	24 (13.11)	29 (15.85)	20 (10.93)	16 (8.74)	183
10	95 (50.80)	30 (16.04)	26 (13.90)	21 (11.23)	15 (8.02)	187

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.32

Frequency of WASO by Annual Visit

Surgical Menopause Group

Dichotomized Awakenings as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	19 (59.38)	13 (40.63)	32
2	35 (57.38)	26 (42.62)	61
3	47 (55.95)	37 (44.05)	84
4	64 (56.14)	50 (43.86)	114
5	82 (60.29)	54 (39.71)	136
6	80 (56.34)	62 (43.66)	142
7	94 (56.63)	72 (43.37)	166
8	97 (53.01)	86 (46.99)	183
9	107 (58.47)	76 (41.53)	183
10	102 (54.55)	85 (45.45)	187

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.33

Frequency of WASO by Annual Visit

Surgical Menopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total Sample N*
1	11 (34.38)	4 (12.50)	4 (12.50)	5 (15.63)	8 (25.00)	32
2	12 (19.67)	15 (24.59)	8 (13.11)	11 (18.03)	15 (24.59)	61
3	18 (21.43)	15 (17.86)	14 (16.67)	14 (16.67)	23 (27.38)	84
4	30 (26.32)	15 (13.16)	19 (16.67)	18 (15.79)	32 (28.07)	114
5	30 (22.06)	22 (16.18)	30 (22.06)	20 (14.71)	34 (25.00)	136
6	24 (16.90)	20 (14.08)	36 (25.35)	23 (16.20)	39 (27.46)	142
7	38 (22.89)	26 (15.66)	30 (18.07)	27 (16.27)	45 (27.11)	166
8	31 (16.94)	27 (14.75)	39 (21.31)	35 (19.13)	51 (27.87)	183
9	39 (21.31)	28 (15.30)	40 (21.86)	28 (15.30)	48 (26.23)	183
10	37 (19.79)	25 (13.37)	40 (21.39)	35 (18.72)	50 (26.74)	187

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.34

Frequency of Early Morning Awakenings by Annual Visit

Surgical Menopause Group

Dichotomized WASO as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N*
1	25 (78.13)	7 (21.88)	32
2	43 (70.49)	18 (29.51)	61
3	67 (79.76)	17 (20.24)	84
4	86 (75.44)	28 (24.56)	114
5	104 (77.04)	31 (22.96)	135
6	101 (71.13)	41 (28.87)	142
7	131 (78.92)	35 (21.08)	166
8	145 (79.23)	38 (20.77)	183
9	139 (75.96)	44 (24.04)	183
10	150 (80.21)	37 (19.79)	187

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.35

Frequency of Early Morning Awakenings by Annual Visit

Surgical Menopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total N *
1	14 (43.75)	5 (15.63)	6 (18.75)	2 (6.25)	5 (15.63)	32
2	25 (40.98)	13 (21.31)	5 (8.20)	8 (13.11)	10 (16.39)	61
3	39 (46.43)	14 (16.67)	14 (16.67)	7 (8.33)	10 (11.90)	84
4	45 (39.47)	23 (20.18)	18 (15.79)	15 (13.16)	13 (11.40)	114
5	49 (36.30)	33 (24.44)	22 (16.30)	17 (12.59)	14 (10.37)	135
6	47 (33.10)	30 (21.13)	24 (16.90)	14 (9.86)	27 (19.01)	142
7	65 (39.16)	32 (19.28)	34 (20.48)	23 (13.86)	12 (7.23)	166
8	74 (40.44)	32 (17.49)	39 (21.31)	22 (12.02)	16 (8.74)	183
9	83 (45.36)	28 (15.30)	28 (15.30)	23 (12.57)	21 (11.48)	183
10	80 (42.78)	37 (19.79)	33 (17.65)	18 (9.63)	19 (10.16)	187

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.36

Frequency of Typical Night's Sleep by Annual Visit

Surgical Menopause Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	Restful n (%)	Average Quality n (%)	Restless n (%)	Very Restless n (%)	Total Sample N *
1	12 (37.50)	10 (31.25)	9 (28.13)	1 (3.13)	32
2	17 (27.87)	26 (42.62)	14 (22.95)	4 (6.56)	61
3	33 (39.29)	29 (34.52)	18 (21.43)	4 (4.76)	84
4	22 (19.30)	60 (52.63)	25 (21.93)	7 (6.14)	114
5	25 (18.38)	72 (52.94)	35 (25.74)	4 (2.94)	136
6	22 (15.49)	77 (54.23)	36 (25.35)	7 (4.93)	142
7	33 (19.88)	84 (50.60)	39 (23.49)	10 (6.02)	166
8	13 (12.26)	57 (53.77)	32 (30.19)	4 (3.77)	106
9	27 (15.00)	94 (52.22)	42 (23.33)	17 (9.44)	180
10	41 (21.93)	99 (52.94)	30 (16.04)	17 (9.09)	187

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.37

Frequency of Typical Night Sleep by Annual Visit

Surgical Menopause Group

Dichotomized as Good versus Poor Sleep Quality:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	Good Sleep Quality Restful/Average Quality n (%)	Poor Sleep Quality Restless/Very Restless n (%)	Total Sample N*
1	22 (68.75)	10 (31.26)	32
2	43 (70.49)	18 (29.51)	61
3	62 (73.81)	22 (26.19)	84
4	82 (71.93)	32 (28.07)	114
5	97 (71.32)	39 (28.68)	136
6	99 (69.72)	43 (30.28)	142
7	117 (70.48)	49 (29.51)	166
8	70 (66.03)	36 (33.96)	106
9	121 (67.22)	59 (32.77)	180
10	140 (74.87)	47 (25.13)	187

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.38

Frequency of Any Insomnia Variable by Annual Visit

Surgical Menopause with HRT Group

Dichotomized SL,WASO, A as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N*
1	12 (63.16)	7 (36.84)	19
2	17 (44.74)	21 (55.26)	38
3	27 (52.94)	24 (47.06)	51
4	33 (50.77)	32 (49.23)	65
5	39 (49.37)	40 (50.63)	79
6	32 (48.48)	34 (51.52)	66
7	30 (56.60)	23 (43.40)	53
8	15 (39.47)	23 (60.53)	38
9	17 (60.71)	11 (39.29)	28
10	18 (62.07)	11 (37.93)	29

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.39

Frequency of Sleep Latency by Annual Visit

Surgical Menopause with HRT Group

Dichotomized Sleep Latency as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N*
1	15 (78.95)	4 (21.05)	19
2	27 (71.05)	11 (28.95)	38
3	40 (78.43)	11 (21.57)	51
4	55 (84.62)	10 (15.38)	65
5	68 (85.00)	12 (15.00)	80
6	53 (80.30)	13 (19.70)	66
7	46 (86.79)	7 (13.21)	53
8	33 (86.84)	5 (13.16)	38
9	25 (89.29)	3 (10.71)	28
10	26 (89.66)	3 (10.34)	29

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.40

Frequency of Sleep Latency Symptom by Annual Visit

Surgical Menopause with HRT Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total Sample N*
1	10 (52.63)	3 (15.79)	2 (10.53)	1 (5.26)	3 (15.79)	19
2	15 (39.47)	5 (13.16)	7 (18.42)	8 (21.05)	3 (7.89)	38
3	24 (47.06)	8 (15.69)	8 (15.69)	6 (11.76)	5 (9.80)	51
4	26 (40.00)	14 (21.54)	15 (23.08)	5 (7.69)	5 (7.69)	65
5	43 (53.75)	16 (20.00)	9 (11.25)	5 (6.25)	7 (8.75)	80
6	33 (50.00)	13 (19.70)	7 (10.61)	8 (12.12)	5 (7.58)	66
7	29 (54.72)	8 (15.09)	9 (16.98)	3 (5.66)	4 (7.55)	53
8	19 (50.00)	8 (21.05)	6 (15.79)	3 (7.89)	2 (5.26)	38
9	18 (64.29)	4 (14.29)	3 (10.71)	3 (10.71)	0 (0.00)	28
10	22 (75.86)	3 (10.34)	1 (3.45)	2 (6.90)	1 (3.45)	29

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.41

Frequency of WASO by Annual Visit

Surgical Menopause with HRT Group

Dichotomized WASO as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	13 (68.42)	6 (31.58)	19
2	22 (57.89)	16 (42.11)	38
3	30 (58.82)	21 (41.18)	51
4	36 (55.38)	29 (44.62)	65
5	50 (62.50)	30 (37.50)	80
6	39 (59.09)	27 (40.91)	66
7	32 (60.38)	21 (39.62)	53
8	18 (47.37)	20 (52.63)	38
9	18 (64.29)	10 (35.71)	28
10	19 (65.52)	10 (34.48)	29

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.42

Frequency of WASO by Annual Visit

Surgical Menopause with HRT Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total Sample N*
1	8 (42.11)	3 (15.79)	2 (10.53)	2 (10.53)	4 (21.05)	19
2	10 (26.32)	6 (15.79)	6 (15.79)	8 (21.05)	8 (21.05)	38
3	11 (21.57)	11 (21.57)	8 (15.69)	7 (13.73)	14 (27.45)	51
4	17 (26.15)	9 (13.85)	10 (15.38)	13 (20.00)	16 (24.62)	65
5	20 (25.00)	11 (13.75)	19 (23.75)	9 (11.25)	21 (26.25)	80
6	9 (13.64)	12 (18.18)	18 (27.27)	10 (15.15)	17 (25.76)	66
7	16 (30.19)	8 (15.09)	8 (15.09)	8 (15.09)	13 (24.53)	53
8	5 (13.16)	5 (13.16)	8 (21.05)	9 (23.68)	11 (28.95)	38
9	4 (14.29)	8 (28.57)	6 (21.43)	4 (14.29)	6 (21.43)	28
10	7 (24.14)	6 (20.69)	6 (20.69)	2 (6.90)	8 (27.59)	29

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.43

Frequency of Early Morning Awakenings by Annual Visit

Surgical Menopause with HRT Group

Dichotomized Early Morning Awakenings as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	13 (68.42)	6 (31.58)	19
2	27 (71.05)	11 (28.95)	38
3	41 (80.39)	10 (19.61)	51
4	50 (76.92)	15 (23.08)	65
5	57 (72.15)	22 (27.85)	79
6	46 (69.70)	20 (30.30)	66
7	43 (81.13)	10 (18.87)	53
8	32 (84.21)	6 (15.79)	38
9	23 (82.14)	5 (17.86)	28
10	25 (86.21)	4 (13.79)	29

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.44

Frequency of Early Morning Awakenings by Annual Visit

Surgical Menopause with HRT Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total N *
1	9 (47.37)	1 (5.26)	3 (15.79)	2 (10.53)	4 (21.05)	19
2	16 (42.11)	6 (15.79)	5 (13.16)	6 (15.79)	5 (13.16)	38
3	23 (45.10)	8 (15.69)	10 (19.61)	4 (7.84)	6 (11.76)	51
4	25 (38.46)	11 (16.92)	14 (21.54)	7 (10.77)	8 (12.31)	65
5	31 (39.24)	18 (22.78)	8 (10.13)	13 (16.46)	9 (11.39)	79
6	21 (31.82)	15 (22.73)	10 (15.15)	8 (12.12)	12 (18.18)	66
7	19 (35.85)	14 (26.42)	10 (18.87)	7 (13.21)	3 (5.66)	53
8	15 (39.47)	8 (21.05)	9 (23.68)	2 (5.26)	4 (10.53)	38
9	11 (39.29)	6 (21.43)	6 (21.43)	5 (17.86)	0 (00.00)	28
10	12 (41.38)	6 (20.69)	7 (24.14)	1 (3.45)	3 (10.34)	29

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.45

Frequency of Typical Night's Sleep by Annual Visit

Surgical Menopause with HRT Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	Restful n (%)	Average Quality n (%)	Restless n (%)	Very Restless n (%)	Total Sample N *
1	8 (42.11)	7 (36.84)	4 (21.05)	0 (0.00)	19
2	13 (34.21)	16 (42.11)	8 (21.05)	1 (2.63)	38
3	20 (39.22)	19 (37.25)	9 (17.65)	3 (5.88)	51
4	12 (18.46)	37 (56.92)	12 (18.46)	4 (6.15)	65
5	15 (18.75)	41 (51.25)	22 (27.50)	2 (2.50)	80
6	12 (18.18)	36 (54.55)	15 (22.73)	3 (4.55)	66
7	9 (16.98)	32 (60.38)	10 (18.87)	2 (3.77)	53
8	0 (0.00)	8 (66.67)	4 (33.33)	0 (0.00)	12
9	3 (10.71)	20 (71.43)	5 (17.86)	0 (0.00)	28
10	6 (20.69)	17 (58.62)	4 (13.79)	2 (6.90)	29

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.46

Frequency of Typical Night Sleep by Annual Visit

Surgical Menopause with HRT Group

Dichotomized as Good versus Poor Sleep Quality:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	Good Sleep Quality Restful/Average Quality n (%)	Poor Sleep Quality Restless/Very Restless n (%)	Total Sample N*
1	15 (79.0)	4 (21.0)	19
2	29 (76.3)	9 (23.7)	38
3	39 (76.5)	11 (23.5)	51
4	49 (75.4)	16 (24.6)	65
5	56 (70.0)	24 (30.0)	80
6	48 (72.7)	18 (27.3)	66
7	41 (77.4)	12 (22.6)	53
8	8 (66.7)	4 (33.3)	12
9	23 (82.1)	5 (17.9)	28
10	23 (79.3)	6 (20.7)	29

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.47

Frequency of Any Insomnia Variable by Annual Visit

Surgical Menopause with No HRT Group

Dichotomized SL,WASO, A as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	6 (46.15)	7 (53.85)	13
2	13 (56.52)	10 (43.48)	23
3	16 (48.48)	17 (51.52)	33
4	28 (57.14)	21 (42.86)	49
5	31 (55.36)	25 (44.64)	56
6	37 (48.68)	39 (51.32)	76
7	56 (49.56)	57 (50.44)	113
8	64 (44.14)	81 (55.86)	145
9	74 (47.74)	81 (52.26)	155
10	74 (46.84)	84 (53.16)	158

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.48

Frequency of Sleep Latency by Annual Visit

Surgical Menopause with No HRT Group

Dichotomized Sleep Latency as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	11 (84.62)	2 (15.38)	13
2	17 (73.91)	6 (26.09)	23
3	26 (78.79)	7 (21.21)	33
4	37 (75.51)	12 (24.49)	49
5	47 (83.93)	9 (16.07)	56
6	54 (71.05)	22 (28.95)	76
7	85 (75.22)	28 (24.78)	113
8	111 (76.55)	34 (23.45)	145
9	122 (78.71)	33 (21.29)	155
10	125 (79.11)	33 (20.89	158

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.49

Frequency of Sleep Latency Symptom by Annual Visit

Surgical Menopause with No HRT Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total Sample N*
1	7 (53.85)	1 (7.69)	3 (23.08)	1 (7.69)	1 (7.69)	13
2	11 (47.83)	5 (21.74)	1 (4.35)	1 (4.35)	5 (21.74)	23
3	18 (54.55)	5 (15.15)	3 (9.09)	4 (12.12)	3 (9.09)	33
4	19 (38.78)	11 (22.45)	7 (14.29)	5 (10.20)	7 (14.29)	49
5	24 (42.86)	9 (16.07)	14 (25.00)	3 (5.36)	6 (10.71)	56
6	32 (42.11)	10 (13.16)	12 (15.79)	11 (14.47)	11 (14.47)	76
7	53 (46.90)	15 (13.27)	17 (15.04)	14 (12.39)	14 (12.39)	113
8	72 (49.66)	16 (11.03)	23 (15.86)	22 (15.17)	12 (8.28)	145
9	76 (49.03)	20 (12.90)	26 (16.77)	17 (10.97)	16 (10.32)	155
10	73 (46.20)	27 (17.09)	25 (15.82)	19 (12.03)	14 (8.86)	158

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.50

Frequency of WASO by Annual Visit

Surgical Menopause with No HRT Group

Dichotomized WASO as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N*
1	6 (46.15)	7 (53.85)	13
2	13 (56.52)	10 (43.48)	23
3	17 (51.52)	16 (48.48)	33
4	28 (57.14)	21 (42.86)	49
5	32 (57.14)	24 (42.86)	56
6	41 (53.95)	35 (46.05)	76
7	62 (54.87)	51 (45.13)	113
8	79 (54.48)	66 (45.52)	145
9	89 (57.42)	66 (42.58)	155
10	83 (52.53)	75 (47.47)	158

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.51

Frequency of WASO by Annual Visit

Surgical Menopause with No HRT Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total Sample N*
1	3 (23.08)	1 (7.69)	2 (15.38)	3 (23.08)	4 (30.77)	13
2	2 (8.70)	9 (39.13)	2 (8.70)	3 (13.04)	7 (30.43)	23
3	7 (21.21)	4 (12.12)	6 (18.18)	7 (21.21)	9 (27.27)	33
4	13 (26.53)	6 (12.24)	9 (18.37)	5 (10.20)	16 (32.65)	49
5	10 (17.86)	11 (19.64)	11 (19.64)	11 (19.64)	13 (23.21)	56
6	15 (19.74)	8 (10.53)	18 (23.68)	13 (17.11)	22 (28.95)	76
7	22 (19.47)	18 (15.93)	22 (19.47)	19 (16.81)	32 (28.32)	113
8	26 (17.93)	22 (15.17)	31 (21.38)	26 (17.93)	40 (27.59)	145
9	35 (22.58)	20 (12.90)	34 (21.94)	24 (15.48)	42 (27.10)	155
10	30 (18.99)	19 (12.03)	34 (21.52)	33 (20.89)	42 (26.58)	158

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.52

Frequency of Early Morning Awakenings by Annual Visit

Surgical Menopause with No HRT Group

Dichotomized Early Morning Awakenings as per AASM criteria:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	No < 3 times per week n (%)	Yes ≥ 3 times per week n (%)	Total Sample N *
1	12 (92.31)	1 (7.69)	13
2	16 (69.57)	7 (30.43)	23
3	26 (78.79)	7 (21.21)	33
4	36 (73.47)	13 (26.53)	49
5	47 (83.93)	9 (16.07)	56
6	55 (72.37)	21 (27.63)	76
7	88 (77.88)	25 (22.12)	113
8	113 (77.93)	32 (22.07)	145
9	116 (74.84)	39 (25.16)	155
10	125 (79.11)	33 (20.89)	158

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.53

Frequency of Early Morning Awakenings by Annual Visit

Surgical Menopause with No HRT Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	None n (%)	<1 n (%)	1-2 n (%)	3-4 n (%)	>5 n (%)	Total Sample N*
1	5 (38.46)	4 (30.77)	3 (23.08)	0 (00.00)	1 (7.69)	13
2	9 (39.13)	7 (30.43)	0 (00.00)	2 (8.70)	5 (21.74)	23
3	16 (48.48)	6 (18.18)	4 (12.12)	3 (9.09)	4 (12.12)	33
4	20 (40.82)	12 (24.49)	4 (8.16)	8 (16.33)	5 (10.20)	49
5	18 (32.14)	15 (26.79)	14 (25.00)	4 (7.14)	5 (8.93)	56
6	26 (34.21)	15 (19.74)	14 (18.42)	6 (7.89)	15 (19.74)	76
7	46 (40.71)	18 (15.93)	24 (21.24)	16 (14.16)	9 (7.96)	113
8	59 (40.69)	24 (16.55)	30 (20.69)	20 (13.79)	12 (8.28)	145
9	72 (46.45)	22 (14.19)	22 (14.19)	18 (11.61)	21 (13.55)	155
10	68 (43.04)	31 (19.62)	26 (16.46)	17 (10.76)	16 (10.13)	158

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.54

Frequency of Typical Night's Sleep by Annual Visit

Surgical Menopause with No HRT Group

Likert Response Scale: Frequency of Symptom in Past 2 Weeks

Annual Visit #	Restful n (%)	Average Quality n (%)	Restless n (%)	Very Restless n (%)	Total Sample N *
1	4 (30.77)	3 (23.08)	5 (38.46)	1 (7.69)	13
2	4 (17.39)	10 (43.48)	6 (26.09)	3 (13.04)	23
3	13 (39.39)	10 (30.30)	9 (27.27)	1 (3.03)	33
4	10 (20.41)	23 (46.94)	13 (26.53)	3 (6.12)	49
5	10 (17.86)	31 (55.36)	13 (23.21)	2 (3.57)	56
6	10 (13.16)	41 (53.95)	21 (27.63)	4 (5.26)	76
7	24 (21.24)	52 (46.02)	29 (25.66)	8 (7.08)	113
8	13 (13.83)	49 (52.13)	28 (29.79	4 (4.26)	94
9	24 (15.79)	74 (48.68)	37 (24.34)	17 (11.18)	152
10	35 (22.15)	82 (51.90)	26 (16.46)	15 (9.49)	158

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.55

Frequency of Typical Night Sleep by Annual Visit

Surgical Menopause with No HRT Group

Dichotomized as Good versus Poor Sleep Quality:

Frequency of Symptom in Past 2 Weeks

Annual Visit #	Good Sleep Quality Restful/Average Quality n (%)	Poor Sleep Quality Restless/Very Restless n (%)	Total Sample N*
1	7 (58.9)	6 (46.2)	13
2	14 (60.9)	9 (39.1)	23
3	23 (69.7)	10 (30.3)	33
4	33 (67.4)	16 (29.7)	49
5	41 (73.2)	15 (26.8)	56
6	51 (67.1)	25 (32.9)	76
7	76 (67.3)	37 (32.8)	113
8	62 (66.0)	32 (34.1)	94
9	98 (64.5)	54 (35.5)	152
10	117 (74.0)	41 (26.0)	158

* Respondents with complete data for the variable. Diminishing sample size across study period reflects participants who complete study participation due to menopause.

Table 4.56

Differences in Insomnia Symptoms Before and After Surgical Menopause

Variable	n	Mean	Std Dev	p *
Difficulty falling asleep (SL)	204	-0.03	1.22	0.73
Wake after sleep onset (WASO)	204	-0.13	1.49	0.22
Early Awakenings (A)	204	0.10	1.50	0.35
Sleep Quality (SQ)	199	0.02	0.83	0.73

*Statistical significance, $p < 0.05$ level of significance

Table 4.57

Differences in Dichotomized Insomnia Symptoms Before and After Surgical Menopause

Variable	*n*	*Pre- SM (%)*	*Post- SM (%)*	*p**
Difficulty Falling Asleep (SL)	*204*	*19.61*	*17.16*	*0.3841*
Wake After Sleep Onset (WASO)	*204*	*37.25*	*40.20*	*0.4308*
Early Awakenings (A)	*204*	*21.57*	*19.12*	*0.4751*
Sleep Quality (SQ)	*199*	*28.64*	*25.13*	*0.2967*
Any Symptom of Insomnia	*204*	*42.65*	*45.10*	*0.5221*

*Statistical Procedure Used: McNemar's Test, $p < 0.05$ level of significance

Table 4.58

Differences in Dichotomized Insomnia Symptoms Before and After Surgical Menopause

With HRT Group

Variable	*n*	*Pre- SM (%)*	*Post- SM (%)*	*p**
Difficulty Falling Asleep (SL)				
Wake After Sleep Onset (WASO)	*91*	*39.56*	*39.56*	*1.00*
Early Awakenings (A)	*91*	*20.88*	*21.98*	*0.8415*
Sleep Quality (SQ)	*90*	*34.44*	*30.00*	*0.4142*
Any Symptom of Insomnia	*91*	*46.15*	*48.35*	*0.6949*

*Statistical Procedure Used: McNemar's Test, $p < 0.05$ level of significance

Table 4.59

Differences in Dichotomized Insomnia Symptoms Before and After Surgical Menopause

Without HRT Group

Variable	*n*	*Pre- SM (%)*	*Post- SM (%)*	*p**
Difficulty Falling Asleep (SL)				
Wake After Sleep	*111*	*35.14*	*40.54*	*0.2888*
Onset (WASO)				
Early Awakenings (A)	*111*	*21.62*	*17.12*	*0.2971*
Sleep Quality (SQ)	*107*	*23.36*	*21.50*	*0.6547*
Any Symptom of Insomnia	*111*	*39.64*	*42.34*	*0.6121*

*Statistical Procedure Used: McNemar's Test, $p < 0.05$ level of significance

Table 4.60

Multivariable Regression Analysis Predicting Chronic Insomnia

Variable	Model 1		Model 2		Model 3		Model 4	
	p Full Model	p Reduced Model	p Full Model	P Reduced Model	p Full Model	p Reduced Model	P Full Model	P Reduced model
Cold sweats	0.99	_____	_____	_____	_____	_____	_____	_____
Night sweats	0.03	0.0007	<0.0001	0.0004	0.0008	0.0004	0.006	<0.001
Hot Flashes	0.15	_____	_____	_____	_____	_____	_____	_____
Menopausal Status	<0.001	<0.0001	<0.0001	<0.0001	0.0012	<0.0001	0.0053	<0.001
Depression	0.0002	<0.0001	0.0005	0.0001	0.0053	0.0001	0.0121	<0.001
Rotating Shifts	0.94	_____	_____	_____	_____	_____	_____	_____
BMI	0.01	<0.0001	0.0002	<0.0001	0.0004	<0.001	0.0031	<0.001
Age 5 year bins			0.0011	0.0013	0.003	0.0013	0.0750	0.0002
Race/ethnicity			0.3166	_____	_____	_____	_____	_____
Income Level			0.8811	_____	_____	_____	_____	_____
Education level			0.5594	_____	_____	_____	_____	_____

Diabetes	0.765	_____	_____	_____
Hypertension	0.123	_____	_____	_____
Alcohol Use	0.4731	_____	_____	_____
Marital Status	0.132	_____	_____	_____
Stroke			0.5236	0.4475
Myocardial Infarction/ Angina			0.4740	0.3003
Overall Health			0.2238	0.7343
Smoker			0.1506	_____
Exercise			0.3452	0.0394

Note combined alcohol variable based on Annual Visit 1 data, all other variables from baseline data collection visit, Statistical significance $p<0.10$

Table 4.61

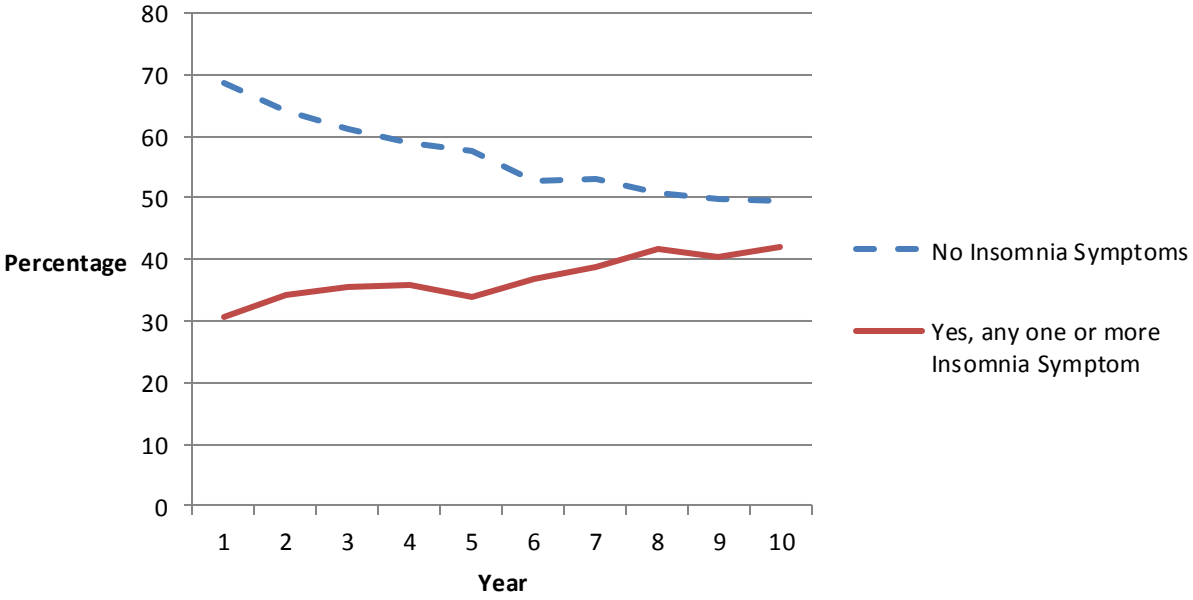
Final Predictors of Chronic Insomnia in Perimenopausal Women

Variable	p *	Unit	SE	95% CI	
				LL	UL
Night sweats	0.002	1.00	1.257	1.115	1.418
Menopausal Status	<0.0001	1.00	1.510	1.252	1.822
Depression	<0.0001	1.00	1.521	1.237	1.871
BMI	<0.0001	5.00	1.139	1.073	1.208
Exercise	0.0047	1.00	1.322	1.089	1.604
Age	0.0010	1.00	0.783	0.676	0.906

Note Exercise variable dichotomized to look at % of participants who exercised more than once a week, age at baseline categorized in 5-year increments: 40-44/45-49/50
Statistical significance p<0.10

Figures

Figure 4.1
Dichotomized Insomnia Symptoms Together



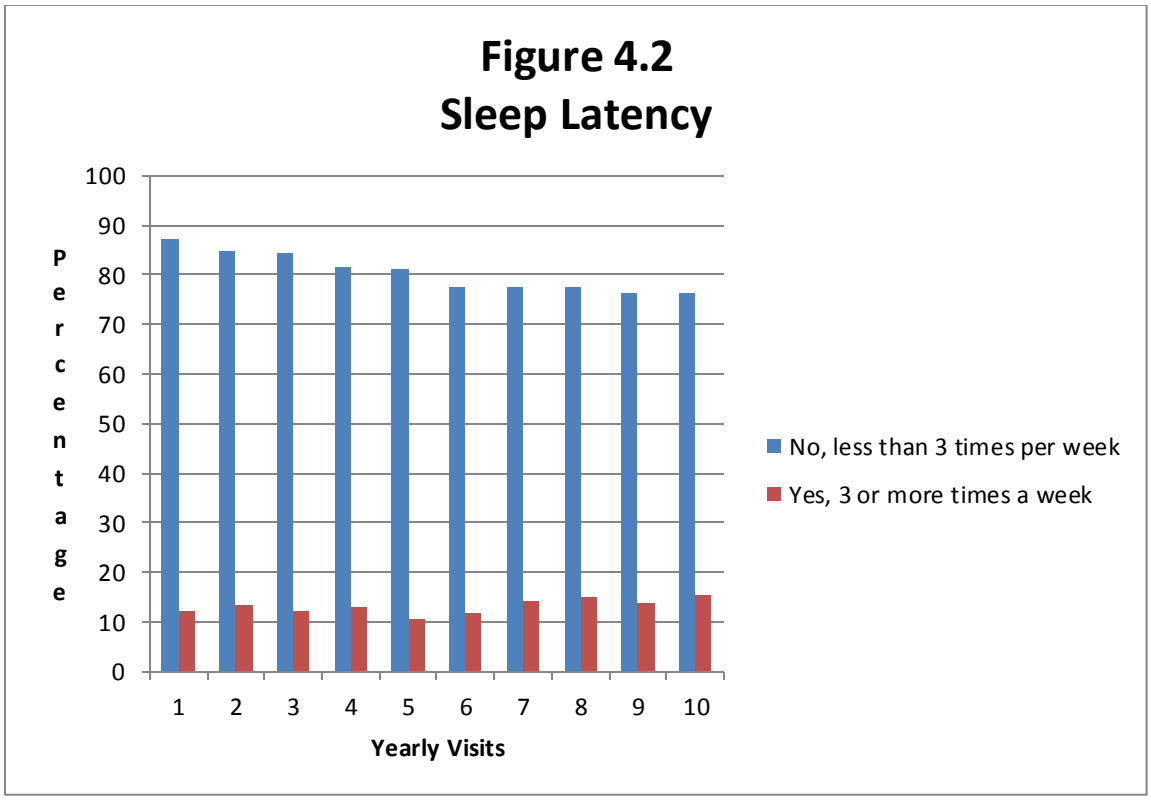


Figure 4.2
Sleep Latency
Percentage
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
Yearly Visits
No, less than 3 times per week
Yes, 3 or more times a week

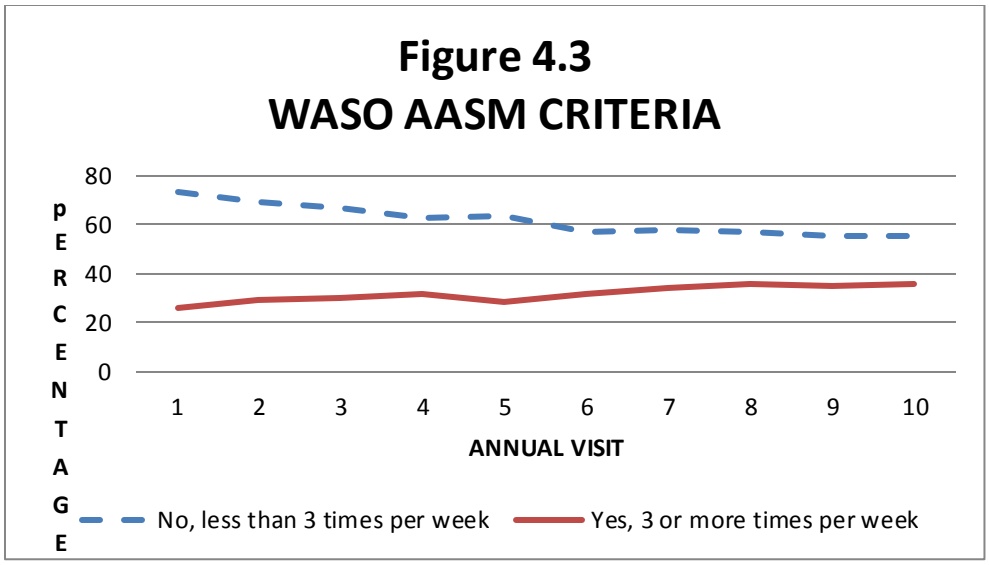


Figure 4.3
WASO AASM CRITERIA
80
60
40
20
0
PERCENTAGE
1
2
3
4
5
6
7
8
9
10
ANNUAL VISIT
No, less than 3 times per week
Yes, 3 or more times per week

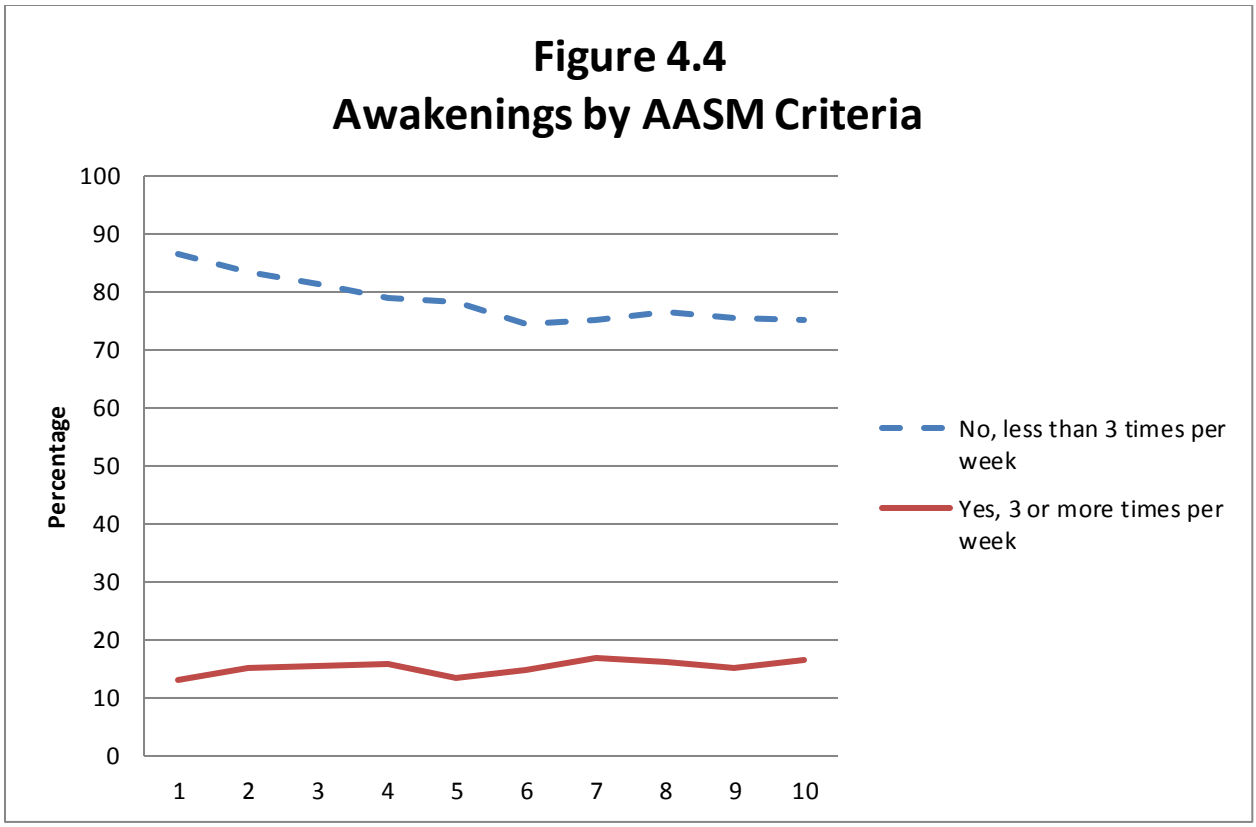


Figure 4.4
Awakenings by AASM Criteria
Percentage
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
No, less than 3 times per week
Yes, 3 or more times per week

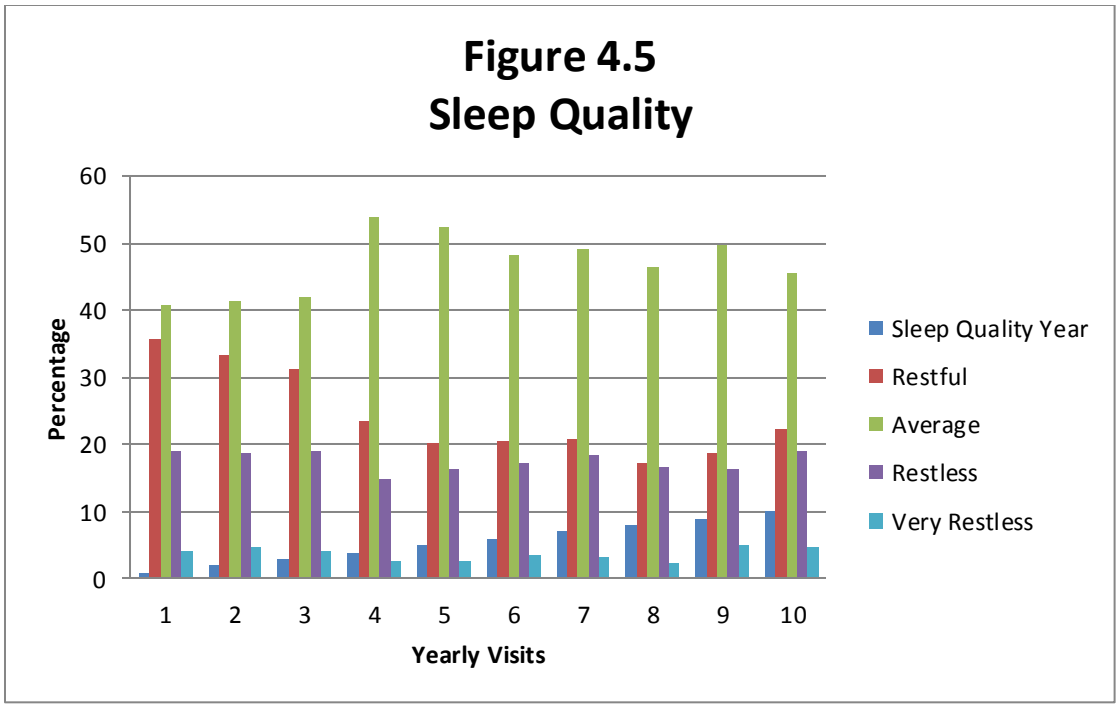
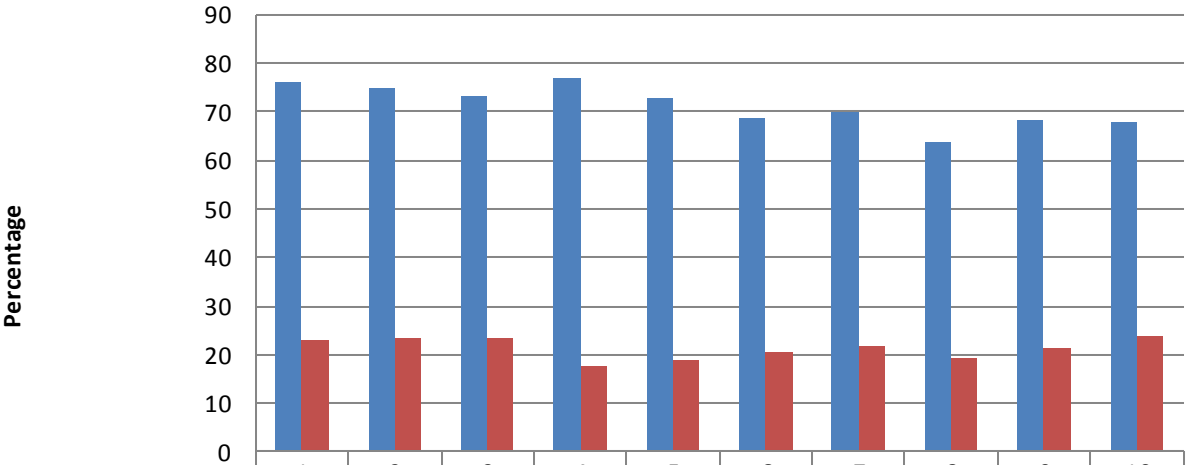


Figure 4.5
Sleep Quality
60
50
40
30
20
10
0
Percentage
1
2
3
4
5
6
7
8
9
10
Yearly Visits
Sleep Quality Year
Restful
Average
Restless
Very Restless

Figure 4.6
Dichotomized Annual Sleep Quality



	1	2	3	4	5	6	7	8	9	10
Good Sleep Quality	76.3	74.85	73.2	77.18	72.68	68.72	69.99	63.65	68.37	67.83
Poor Sleep Quality	23.12	23.57	23.29	17.46	18.96	20.68	21.77	19.23	21.39	23.78

Figure 4.7
Dichotomized Insomnia Variable
Early Perimenopause

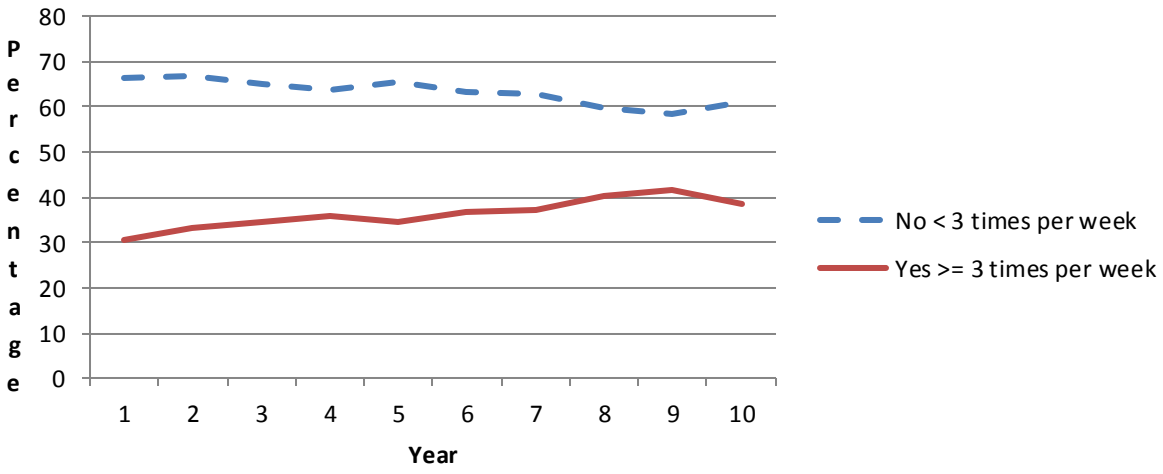


Figure 4.8
Dichotomized Insomnia Variable
Late Perimenopause

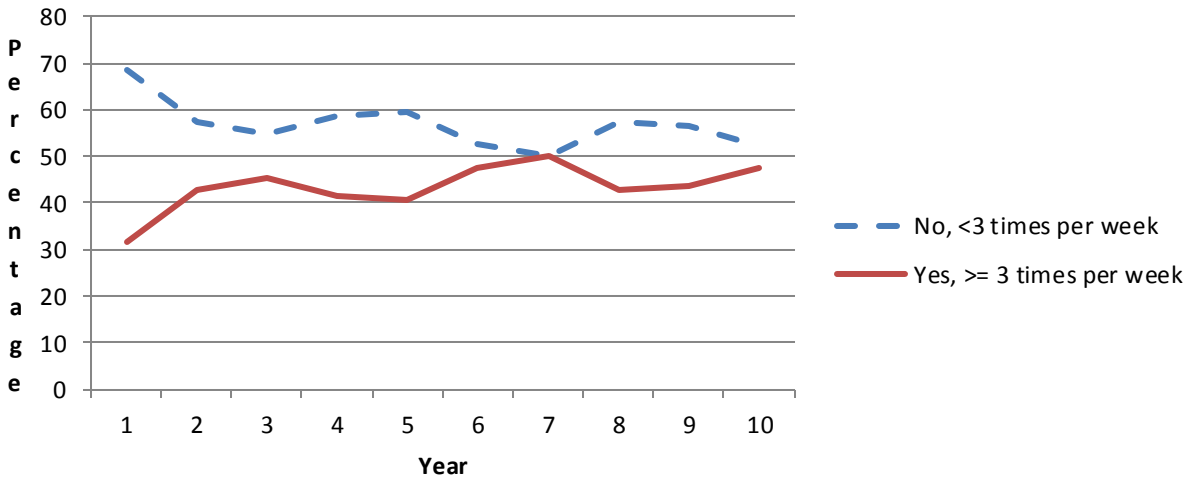


Figure 4.9
Dichotomized
Annual Sleep Quality Late Perimenopause

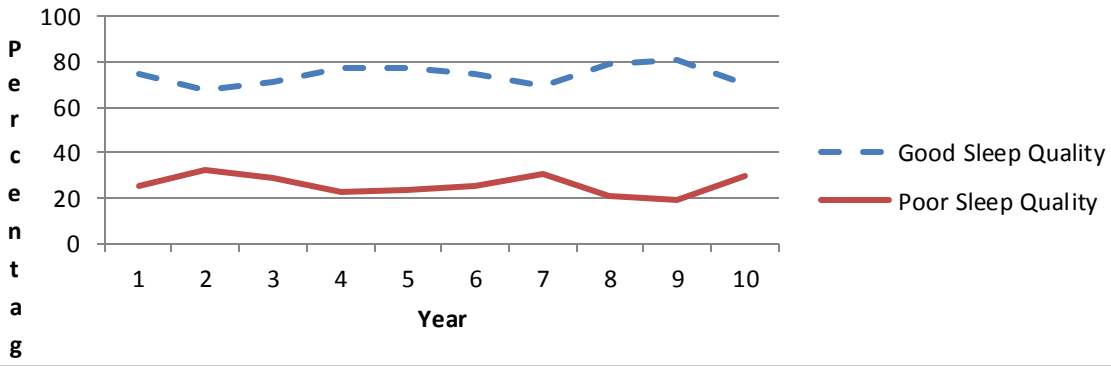


Figure 4.10
Frequency of Any Insomnia Variable
Surgical Menopause Group

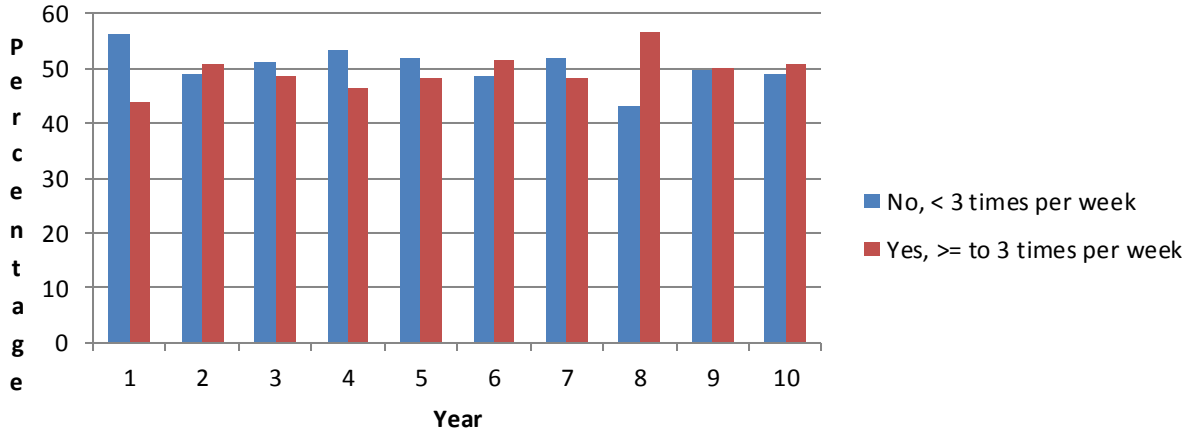


Figure 4.11

Dichotomized

Annual Sleep Quailty Surgical Menopause

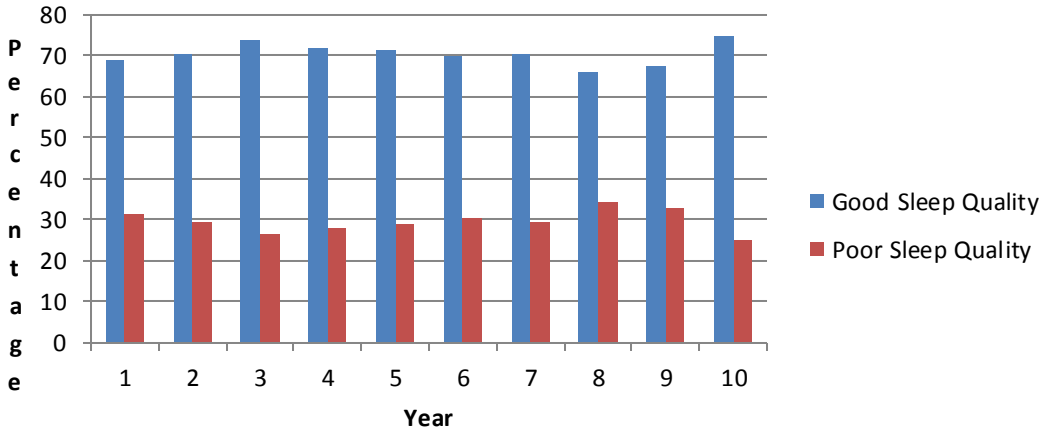
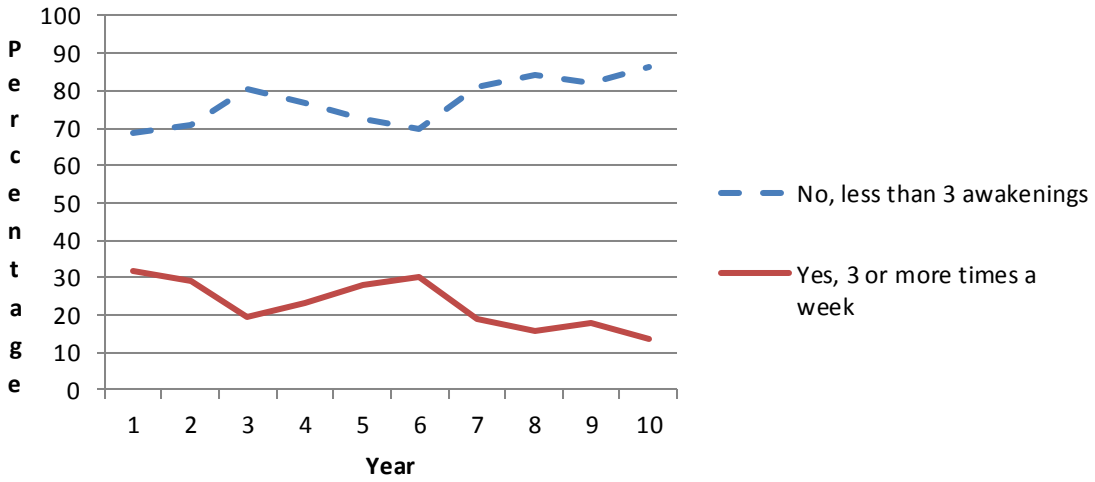


Figure 4.12
Early Morning Awakenings by AASM Criteria
Surgical Menopause with HRT



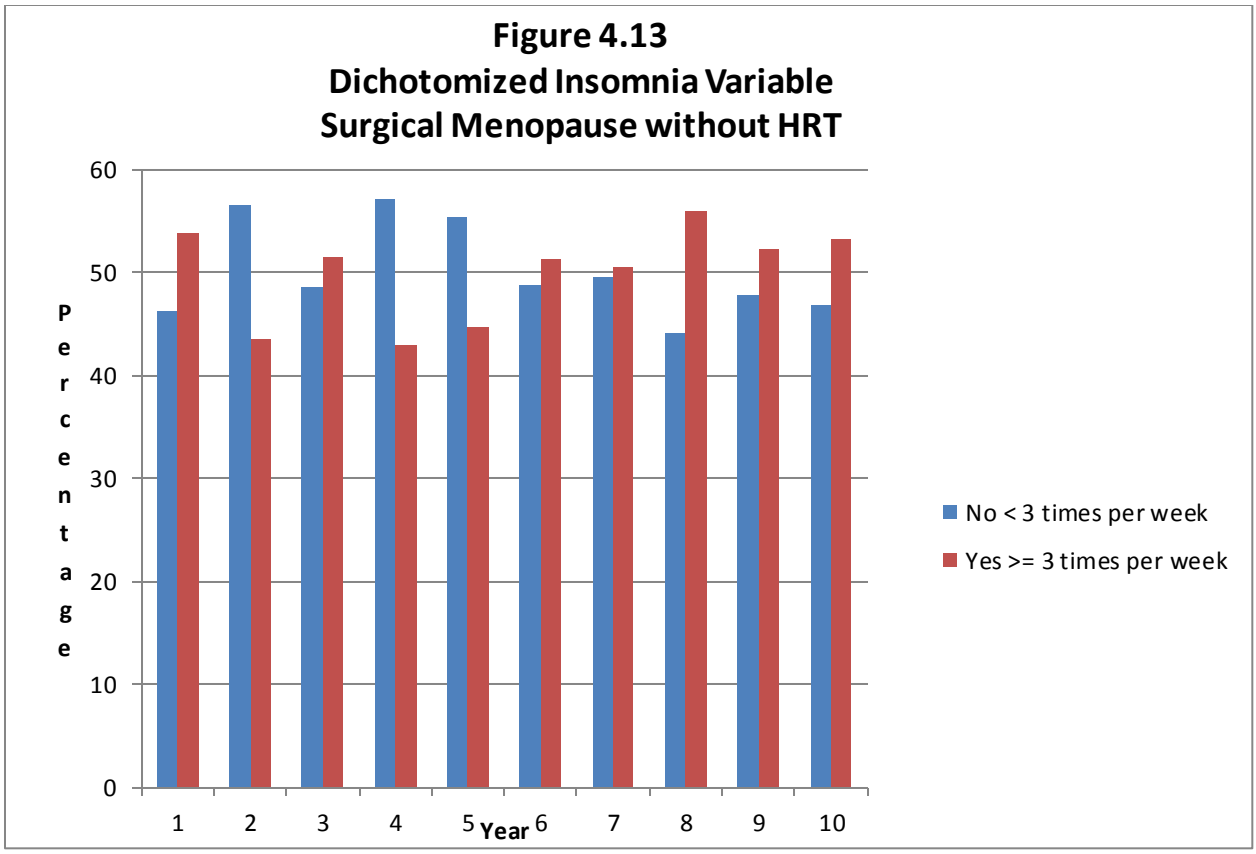


Figure 4.13
Dichotomized Insomnia Variable
Surgical Menopause without HRT
Percentage
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
Year
No < 3 times per week
Yes >= 3 times per week

Chapter 5 Discussion

The purpose of this study was to describe the prevalence of insomnia in all perimenopausal women. Secondly the prevalence of insomnia among women in different stages of perimenopause was examined to discern if there was a difference of self-reported insomnia symptoms in women progressing naturally versus surgically to menopause. Additionally, predictors of chronic insomnia in perimenopausal women were examined. A major finding of the study was that 31% to 42% of all perimenopausal women in the sample had diagnosable insomnia according to the American Academy of Sleep Medicine (AASM) criteria. This figure is higher than the prevalence in the general population in which 15% to 20% have a short-term insomnia disorder lasting less than three months (http://www.sleepeducation.com/news/2014/03/10/insomnia-awareness-day-facts-and-stats).

Population studies report that the prevalence of short-term insomnia in women can range from 15.9% (Morin et al., 2011) to 21% (National Sleep Foundation, 2007). Based on these findings perimenopausal women have exceedingly higher rates of insomnia than women of all ages and the general North American population. In this study, late perimenopausal women had significantly more self-reported insomnia symptoms and higher prevalence of diagnosable insomnia when compared to early perimenopausal women. There were no significant differences in self-reported insomnia symptoms between women progressing naturally versus surgically to menopause. However, women that had undergone surgical menopause self-reported similar frequencies of insomnia symptoms and prevalence of diagnosable insomnia as

late perimenopausal women. Perimenopausal status was an independent predictor of chronic insomnia. In addition to perimenopausal status, night sweats, depression, BMI, and exercising more than once a week were found to be independent predictors of chronic insomnia in the perimenopausal sample. Age was found to influence chronic insomnia in perimenopausal women with an inverse effect; as women age, their odds of developing chronic insomnia diminished with every five year increase in age. The following discussion will focus on the four major findings from the study, the limitations and strengths of the study, clinical implications and will conclude with recommendations for future research.

Insomnia in All Perimenopausal Women

Sleep disturbances are the most frequent self-reported complaint in mid-life women (Berg, Larson, & Pasvogel, 2008) with previous research showing that sleep disturbances increase with age and women report more sleep disturbances than men (Zhang & Wing, 2006). In this study, at least a third of the perimenopausal sample self-reported any one symptom of insomnia at a frequency ≥ three times per week over a two week period. Using the AASM criteria for diagnosable insomnia, the frequency of self-reported insomnia symptoms identified in this secondary analysis suggests a high rate of diagnosable insomnia among perimenopausal women. Insomnia has a negative impact on health outcomes, confers cardiometabolic consequences, and increases the risk of depression and hypertension (Joffe, Massler & Sharkey, 2010; Matthews et al., 2014; Serrano & Wamaock, 2007). Grandner, Jackson, Pak and Gehrman (2012) reported a significant risk for obesity, diabetes, myocardial infarction and coronary artery disease among adults reporting insomnia. In addition quality of life and functional

outcomes such as decreased work productivity are associated with sleep disturbances (Linton & Bryngelsson, 2000). A prior study reported that adults with insomnia had insomnia related healthcare costs about $1253 per year more than patients without insomnia (Ozminkowski et al., 2007). Perimenopausal women in the world will reach 500 million in the next 10 years and are at high risk for poor health outcomes and poor quality of life/functional outcomes which are costly. Heath care related costs associated with insomnia are 15 billion dollars annually (http://www.insomnia.net/research/cost/). It is estimated that due to drowsy workers, lost work productivity and absenteeism costs the US government 150 billion dollars (http://www.insomnia.net/research/cost/). For these reasons, combined with the high prevalence of insomnia in perimenopausal women, it is imperative to recognize diagnosable insomnia in this population through insomnia risk screening. In addition, the fields of women's health and sleep need to prioritize insomnia as an under recognized and under reported diagnosis in perimenopausal women. Previous studies have examined isolated symptoms of insomnia but few studies have examined symptoms as a diagnosable insomnia category to better understand the sleep symptom clusters in perimenopausal women (Hollander et al., 2001: Kravitz et al., 2003; Kravitz et al., 2008: Pien at al., 2008). This current study has identified the prevalence of insomnia and chronic insomnia in a large sample of perimenopausal women. To our knowledge, no prior studies have reported the prevalence of this significant public health problem: diagnosable insomnia in perimenopausal women.

At any time across the ten year study period, at least 17% of the perimenopausal sample categorized their sleep quality as poor. Wake after sleep onset (WASO)

increased over the study period and perimenopausal women self-reported more early morning awakenings as they progressed through perimenopause. These findings are consistent with other studies (Berg, Larson & Pasvogel, 2008; Terauchi et al., 2012). Kravitz et al (2003) reported findings from a cross sectional study that difficulty sleeping was highest among perimenopausal women compared to pre-perimenopausal and postmenopausal women. The current study further supports the finding that sleep quality worsens during perimenopause; the current study also adds to the state of the science about the prevalence of insomnia in this population (Blumel et al., 2012; Hollander et al., 2001; Terauchi et al., 2010). To our knowledge this is the first study to examine insomnia symptoms longitudinally to describe the prevalence of insomnia in a large sample (N=3302). The findings suggest perimenopausal women are at high risk for developing chronic insomnia.

Insomnia Prevalence By Perimenopausal Stages

Studies support the fact that approximately half of all perimenopausal women suffer from sleep disturbances (NSF, 2007); however few studies have examined insomnia per se in this population. It is unclear from the extant literature if there is a stage of perimenopause when sleep disturbances are more prevalent. Previous cross-sectional studies have shown that perimenopausal women do report more self-reported sleep disturbances than pre-perimenopausal and postmenopausal women (Kravitz et al., 2003; Xu et al., 2011). Hollander and colleagues (2001) reported a higher odds of poor sleep quality in perimenopausal women when compared to postmenopausal women in a secondary analysis of the Penn Ovarian Aging Study; reporting that increased hot flashes were found to predict poor sleep and diminishing estradiol levels

and perimenopausal status were related at each of the three assessment periods . This finding expands on the previous results from the Penn Ovarian Aging Study which did not find a significant relationship between sleep quality and menopausal status but did report a significant relationship between menopausal symptoms, such as hot flashes and depressive symptoms, and identified such menopausal symptoms were predictors of sleep quality in perimenopausal women (Pien et al., 2008).

The results of the current study identified that self-reported symptoms of insomnia vary by perimenopausal stage (i.e., early versus late). Early perimenopausal women self-reported any one symptom of insomnia 31% to 39% of the time during the ten year study period. Late perimenopausal women self-reported any one symptom of insomnia 31% to 48% of the time during the ten year study period. These findings suggest that as women progress through perimenopause, the prevalence of self-reported insomnia symptoms increase. The odds of late perimenopausal women self-reporting any one insomnia symptom was 1.3 times greater than the early menopausal women. This finding suggests that women in late perimenopause have a higher incidence of insomnia symptoms and as early perimenopausal women progress to late perimenopause, sleep disturbances increase.

For any reported symptoms, (SL, WASO, A, SQ), women in the late perimenopausal stage had a higher frequency of self-reported insomnia symptoms than the early perimenopausal women in this study. Late perimenopausal women had significantly more difficulty initiating sleep (↑SL), significantly more nighttime awakenings (WASO), and early morning awakenings (A) and increased frequency of self-reported poor sleep quality than early perimenopausal women. As women

progressed from early to late perimenopause, the adjusted odds of poor sleep quality were 1.3 times that of early perimenopause. The transition from early to late perimenopause is therefore likely to be a major precipitating factor in the development of chronic insomnia. Although not all studies of insomnia symptoms in mid-life women show an effect for menopausal status, the negative studies do not examine all symptoms of insomnia but symptoms in isolation and have much smaller sample sizes than the current study (Hollander et al., 2001; Pien et al., 2008; Shaver et al., 1988)

Insomnia Prevalence in Surgical Menopause

Surgical menopause changes the normal progression to menopause. Women that have undergone surgical menopause have more reported more vasomotor symptoms than women progressing naturally to menopause (Benshushan et al., 2009; Chubaty et al., 2011). How and if surgical menopause affects sleep disturbances in the perimenopausal population is not known. It is known, however, that surgical menopause negatively impacts health-related quality of life (Bhattacharya & Jha, 2010). Chubaty et al., (2011) reported that in women taking hormone replacement therapy (HRT) after surgical menopause, sleep disturbances did not differ from the women not taking HRT after surgical menopause. Topatan and Yildiz (2012) reported that sleep disturbances had a significant negative impact on women who had undergone surgical menopause. What is known to date about insomnia symptoms in women who undergo surgical menopause is significantly limited by studies examining these symptoms in isolation and without categorizing the reproductive stage of the women undergoing the surgery. The current study explicitly examined if differences in insomnia symptoms

exist among perimenopausal women progressing naturally versus surgically to menopause.

During the 10 year study interval, 44% to 51% of the surgical menopause group (N=187) self-reported any one symptom of insomnia at a frequency of ≥ 3 nights per week over a two week interval. This frequency of insomnia symptoms meets the AASM criteria for insomnia; therefore, surgical menopausal women have a high incidence of diagnosable insomnia. Difficulty initiating sleep (↑SL) did not increase in frequency over the ten year study period. Wake after sleep onset (WASO) increased by 5% over the ten year study interval. There was minimal change for awakenings (A) over the ten year study period with both the single and dichotomized awakenings variable. At any given point over the decade long study, at least 25% of the surgical menopausal women self-reported poor sleep quality. Our finding supports previous research that reported a positive correlation for sleep disturbances in women who had surgical menopause and were not treated with HRT (Kravitz et al., 2003). There was not a significant difference between women in the surgical menopause group taking HRT or not taking HRT in the present study. Additionally, there was not a significant difference in self-reported insomnia or insomnia symptoms before versus after surgical menopause. Though this finding was unexpected based on *a priori* assumptions, the absence of differences in insomnia symptoms before and after surgical menopause may be explained by perimenopausal stage at the time of surgical menopause.

In this study, *a priori* assumptions asserted that a difference in self-reported insomnia symptoms would exist between perimenopausal women progressing naturally to menopause when compared to perimenopausal women who had undergone surgical

menopause. This assumption was not fully supported. There was not a significant difference between the late perimenopause group and the surgical menopause group in overall insomnia prevalence. The adjusted odds of having any one symptom of insomnia were 1.3 times greater in the surgical menopause group versus the early perimenopause group. These findings suggest that perimenopausal stage is an important determinant of insomnia symptoms. To more fully explain these findings, the stage of perimenopause at surgery is required. In the current study, perimenopausal stage at surgery was not available.

Predictors of Chronic Insomnia

Chronic insomnia is prevalent in 10% of the American population (http://www.sleepeducation.com/news/2014/03/10/insomnia-awareness-day-facts-and-stats). Chronic insomnia prevalence has been reported in mid-life women to be 43.6% in a multinational study (Blumel et al., 2012). Our study provides evidence that perimenopausal status is an independent predictor of chronic insomnia in mid-life women. Compared to previous studies conducted among perimenopausal women, the study is novel in several aspects. First the study data was from a longitudinal study, with data accrued over a ten year interval from a large heterogeneous sample (N=3302). To our knowledge, this is the largest analysis of longitudinal data focused on insomnia prevalence in perimenopausal women. Secondly our study utilized all four symptoms of insomnia measured as frequency of symptoms, and utilized the AASM criteria for diagnosable insomnia to determine the prevalence of both insomnia and chronic insomnia in the study sample. Finally, the current study included variables that specifically address evidence-based factors of influence on insomnia and explored

additional theoretical-based factors of influence on insomnia to extend the field's understanding of important predictors of chronic insomnia in perimenopausal women. In the current study, chronic insomnia was defined as persistence of any insomnia symptoms for at least two consecutive annual data collection points. This strict definition permitted evaluation of the most persistent symptoms of insomnia and not acute/transient insomnia. The current study findings are supported by previous studies (Kravitz et al., 2008; Ohayon, 2006) and expands on earlier studies to include the outcome of diagnosable chronic insomnia in a perimenopausal sample.

Vasomotor symptoms (VMS) have been reported to positively correlate with sleep disturbances in previous studies (Berg, Larson & Pasvogel, 2008; Kantola et al., 1999; Ohayon, 2006). In our study night sweats, a vasomotor symptom, was an independent predictor of chronic insomnia in perimenopausal women. Interestingly though, other vasomotor symptoms including hot flashes and cold sweats were not significant predictors of chronic insomnia. Ohayon (2006) used a single time varying summary variable for vasomotor symptoms that incorporated hot flashes/flushes, cold sweats, and night sweats. Although the frequency categories measured in the Ohayon study were the same as in the present study, collapsing all vasomotor symptoms into one index that incorporated all VMS likely masks the effect of individual symptoms that are important influential factors on insomnia. Blumel and associates (2012) reported a positive relationship between sleep disturbances and vasomotor symptoms. Our study separated the VMS, rather than collapsing the VMS into one variable, to importantly differentiate which VMS are significantly influential on chronic insomnia. Women with night sweats should be screened for symptoms of insomnia.

Obesity, especially a greater waist to hip ratio, is associated with insomnia in women (McCarthy et al., 2012; Owens & Matthews, 1998). The current study findings are consistent with the earlier reports; for every five unit increase in Body Mass Index (BMI), perimenopausal women in this study had 1.1 increased odds for chronic insomnia. Clearly, an increase in BMI increases the risk of chronic insomnia. This finding and knowing that chronic insomnia is also associated with diabetes, cardiovascular disease (Grandner et al., 2012) and insulin resistance (Van Cauter, 2011), which are also related to an increased BMI, emphasizes that perimenopausal women need to be encouraged to maintain a healthy weight through diet and exercise.

Exercise in our study was surprisingly an independent predictor of chronic insomnia. Perimenopausal women who exercised more than once a week at baseline data collection were 1.3 times more likely to have chronic insomnia. These results need further exploration. Traditionally exercise is widely believed to improve sleep but many of the studies have utilized good sleepers to make this declaration (Youngstedt & Kline, 2006); other studies find no relationship between exercise and sleep (Pien et al., 2008; Woods & Mitchell, 2010). Though evidence to date is not consistent for how exercise may influence insomnia, several considerations must be acknowledged for the current study. These include: 1) time of day of exercise was not measured; 2) exercise intensity level was not known; 3) history of physical activity or habitual nature of exercise was not known; and 4) exercise was measured as a self-reported measure. These extraneous variables may lessen the validity of the findings for exercise and chronic insomnia in the current study. Until the effect of exercise on insomnia is further examined, and considering the fact women with increasing BMI have a higher risk for

chronic insomnia, perimenopausal women should continue to moderately exercise. Future studies of exercise and sleep should be completed to further explore this finding.

Finally, as the sample aged (i.e., every five year increase from baseline age) women had 20% lower odds of chronic insomnia. This finding is surprising since sleep problems increase with age and women are more susceptible to sleep problems at all ages than men (Polo-Kantola, 2010). This could be related to the gradual and final resolution of VMS. Symptoms related to the perimenopausal transition typically resolve within six months to two years (Freeman et al., 2007; Woods & Mitchell). Although this is believed to be true, symptoms may persist for up to 30 years (Kronenberg, 1990). Insomnia in older adults is common however sleep needs do not decline with age (http://sleepfoundation.org/sleep-topics/aging-and-sleep). It is possible that due to the relative limited range of age (m=45.9 yrs. ± 2.69) of participants in the current study, these results are not generalizable to non-perimenopausal women. It is known that while many women believe that less sleep is normal with increasing age, they also believe that lack of sleep is a problem (Byles, Mishra & Harris, 2005).

Study Limitations and Strengths

There are several study limitations that must be considered when interpreting the results. One limitation is the absence of objective measures of sleep quality, or even a validated measure of subjective sleep quality, to validate self-reported sleep quality. Previous studies have shown discrepancies between objective and subjective sleep data in menopausal women (Boulet et al., 21994; Polo-Kantola et al., 1999). In addition, sleep diaries were not used to supplement the four dependent sleep variables (SL, WASO, A, SQ); sleep diaries could have supported the Likert based response

items. Subjective sleep disturbances are no less important than objectively measured sleep disturbances, such as actigraphy or polysomnography. Yet, the combination of objective and subjective measures of sleep disturbances in this population may importantly enrich our understanding of sleep symptoms in order that effective symptom management strategies can be designed. In addition, the inability to control for confounding variables such as environmental factors that disrupt sleep, use of pharmacologic and non-pharmacologic sleep aids and site specific data due to the nature of available data from the public repository are limitations of this study.

A second limitation is related to sampling weights of the study. When complex sampling designs are utilized, it is important to utilize sampling weights to permit researchers to obtain accurate population estimates (Kneipp & Yarandi, 2002). Sampling designs in large survey data sets can affect the validity of the study results and therefore conclusions be erroneous. Incorporating sampling weights into the analysis of the study is important to obtain valid estimates for the study population. The outcome of using non-weighted data can result in study findings that are statistically significant but not clinically significant. Sampling weights are a statistical correction factor that compensates for over- or under-represented stratum within a population as well as non-response bias (Smith et al., 2011). Sample weights are applied to the sample to obtain population estimates that reflect the U. S. population. Sample weight is the inverse probability of being selected for the sample. This method corrects for over- and under-sampling of certain members of the sample so that the data is representative of the entire large population (Smith et al., 2011). Sampling weights are used to compensate for the following; 1) unequal probabilities of selection, 2)

compensate for non-response and 3) adjust the sample distribution for key variables of interest to make it conform to a known population distribution. According to the SWAN code books, data was not weighted. SWAN recruitment procedures did over-sample minority groups and sample weights should be applied to compensate for this. In conclusion, sample weights are used to avoid producing biased estimates from the study population. Sampling weights were not used in the analysis of this study; therefore the results must be cautiously considered for generalization.

This study was a secondary analysis of an existing dataset; this study approach has several limitations. The major limitation is the data was not collected specifically for the study research questions. For example, the sleep quality variable was measured with a single question. The sleep quality variable assessed by one question could have resulted in data analysis issues such as under or over identification. Having only one question measure subjective sleep quality may not have adequately measured the concept. To improve the measure of sleep quality, future studies are needed that use a validated sleep quality measurement tool such as the Pittsburgh Sleep Quality Index. It is understandable that due to respondent burden this was not feasible for the parent study.

Another measurement limitation identified was that nightly hot flashes were not measured in the dataset. Night sweats was included in the vasomotor symptom cluster and night sweats can result from nocturnal hot flashes and cold sweats; however this is an assumption. Night sweats was determined to be an independent predictor of chronic insomnia in the study. Additionally skin temperature was not collected; in this study, this decision may have been due to employing such a complex measure in a very large

sample. Skin temperature as a physiologic measurement could validate the self-reported hot flashes. Future studies should include a question rating the occurrence of nocturnal hot flashes similarly to the other vasomotor symptoms in addition to physiologic measures of vasomotor symptoms.

The self-report format of the original survey for both independent and dependent variables may have resulted in self-report bias. In addition the repeated measures included in the longitudinal survey could have resulted in response bias. Self-report measures are widely accepted in the evaluation and treatment of insomnia. So, while the use of self-report is a methodological concern, there is no apparent reason to believe these results are different from previously reported findings in the extant literature based solely on the concern for self-reported measures of the primary variables which may introduce recall bias and response bias with a repeated measures design.

Although this study has limitations, it also has strengths. The longitudinal design of the parent study allowed for repeated measures of the dependent variables through the perimenopausal period over a 10 year period. This allowed us to examine the transitory nature of insomnia by perimenopausal stage as well as compare these variables before and after surgical menopause. To our knowledge, no other study to date has examined this phenomenon. The SWAN study has an additional three years of data, which when publically released can be used to further extend the current study interval in subsequent analyses. The large sample size allowed for an in depth examination of insomnia and perimenopausal stages. The sampling method captured community dwelling, multi-ethnic, mid-life women progressing to menopause. The

SWAN longitudinal study included multiple factors that have been associated with sleep disturbances to support the current study's aims; SWAN also maintained an exceptional retention rate for the sample. Examining insomnia in relation to other covariables, specific to mid-life women, provides a detailed understanding of the relationship between perimenopausal stage and the development of chronic insomnia in the target population.

Clinical Implications

This study was based on longitudinal and self-report data and does not establish causality between perimenopausal stage and insomnia. Despite this fact, the study findings have implications for clinical practice. Examining the prevalence of insomnia in perimenopausal women, particularly women in early and late perimenopause, is absent in the sleep literature. This study begins to address the gap by identifying a stage in perimenopause when insomnia is highly prevalent. It is well established in the literature that women experience more insomnia than men in the general population. Additionally, research is beginning to investigate the changes in endogenous reproductive hormones during perimenopause and the effect on VMS and sleep; this study adds to the existing literature by examining perimenopausal stages and insomnia symptoms. Although additional studies are required, the findings of this study indicate that assessment of the sleep patterns and problems of perimenopausal women is clinically necessary. It is important for primary care providers as well as gynecology and obstetrics providers to initiate screenings for insomnia in this high risk population. Screenings should at a minimum consist of the four sleep questions used by this study; alternatively, validated insomnia instruments could be employed in these clinical

settings to identify perimenopausal women at risk for insomnia and chronic insomnia. Such an approach will support the much needed conversation among providers and mid-life women about the risk and negative health outcomes associated with chronic insomnia.

This study, through the combination of two conceptual models, has established the Perimenopausal Insomnia Symptom Management Model (PISSM). This study examined insomnia symptoms in perimenopausal women and provides several important findings; 1) Perimenopausal women report sleep disturbances and as reported, equate to diagnosable insomnia, 2) Perimenopause is likely a precipitating event related to sleep disturbances, and 3) Late perimenopausal stage might be the perpetuating factor related to chronic insomnia. Future studies are needed to address both predisposing and perpetuating factors in perimenopausal women and further explore the use of the Perimenopausal Insomnia Symptom Management Model.

Recommended Future Research

This is the first study to use the Perimenopausal Insomnia Symptom Management Model (PISSM). PISSM supports addressing insomnia symptoms individually and as clusters over time to discern predisposing, precipitating and perpetuating factors in the development of chronic insomnia. Evidence clearly suggests that women have more predisposing factors for insomnia than men (Ozminkowski, Wang & Walsh, 2007). In the current study, 27% of women were identified as having chronic insomnia; this is a much higher prevalence rate of insomnia than in the general population (AASM, 2008). To date, it is unclear why perimenopausal women are predisposed to chronic insomnia. Future studies should include physiologic measures,

such as endogenous hormone levels, and objective measures of sleep, which are important methodological considerations in order for the field to better understand the trajectory of hormonal and sleep changes during the transition to menopause.

The current study was based on subjective sleep data. This a commonly employed method used in sleep research. However, the use of both subjective and objective sleep data would further strengthen study results by permitting validation of subjective sleep data. In addition to sleep questionnaires, sleep diary data would complement the survey questions. The use of actigraphy, or accelerometry, in addition to the subjective sleep measures would further strengthen subsequent studies, particularly for understanding the relationship between sleep/insomnia and activity/exercise. In a large sample such as SWAN, the feasibility and participant burden for concurrent sleep diary data collection and actigraphy were likely reasons why these measurement strategies were not employed. Also, the SWAN study was not designed to specifically focus on sleep in perimenopausal women. Future studies that focus on the phenomenon of insomnia in perimenopausal women may consider a more complete and robust sleep data collection approach to validate the findings of the current study and extend knowledge about this phenomenon.

Future opportunities for measuring sleep-related variables and outcomes abound in this era of rapidly advancing technology, largely impacted by use of mobile devices in everyday life, wearable sensors, and 24/7 data assessment techniques. An innovative data collection method would be to use a Pebble Smartwatch, which includes both accelerometry and an open platform for programming brief surveys; study participants can simply answer the four sleep questions upon arising from sleep in the morning and

respond to daily activity surveys/sleep diaries while accelerometry is concurrently used to measure wake/sleep and activity. This approach affords researchers the opportunity to have real-time data over a period of a study interval with minimal participant burden. Future work in this area will capitalize on exciting, new technology in multidisciplinary team approaches to further extend our knowledge of insomnia in perimenopausal women and importantly further develop insights for symptom management strategies for this target population.

Additional post-hoc analyses should be completed on the data already obtained to clarify some outcomes from the study. When comparing the naturally progressing perimenopausal women, early and late, to the surgical menopause group, the data was separated by stage for analysis. The question remains would the results have been similar if the stages of perimenopause were not categorized and the analysis completed between two groups (natural vs surgical). Additionally, to examine the true trajectory of insomnia in perimenopausal women, within-subject analyses for the ten year interval period may be explored to specifically evaluate progression of insomnia and insomnia symptoms. Careful attention would need to be given to attrition related to surgical menopause and menopause. These post-hoc analyses are being considered to further delineate if differences in insomnia exist between natural and surgical menopausal women. Such analyses offer additional and important insight for the evaluation and treatment of insomnia in perimenopausal women.

Conclusion

Understanding the prevalence of insomnia in perimenopausal women is a critical consideration given the sheer numbers of women entering perimenopause in the next

decade(United States Census Bureau, 2010) and the negative health outcomes associated with chronic insomnia(Grandner et al., 2012; Van Cauter, 2011). The Institute of Medicine estimates that between 50 and 70 million American adults have a sleep disorder (IOM, 2006) and yet most of these remain undiagnosed (Baran & Chevin, 2009).

This study begins to address the prevalence of insomnia in perimenopausal women transitioning to menopause and specifically addresses the importance of perimenopausal stage as an influential factor on insomnia symptoms and chronic insomnia. Findings from this study have clear implications for the screening of perimenopausal women for insomnia and insomnia symptoms; further, based on the findings, it is imperative that perimenopausal women approaching or in late stage perimenopausal be considered as high risk for insomnia. Clinical screening of sleep disturbances and insomnia in perimenopausal women is crucial to preventing the development of chronic insomnia. A strategic priority of Healthy People 2020 is to "increase public knowledge of how adequate sleep and treatment of sleep disorders improve health, productivity, wellness, quality of life, and safety on roads and in the workplace" (htttp://healthpeople.gov/2020/topics-objectives/topic/sleep-health). Screening perimenopausal women for symptoms of insomnia is consistent with this sleep health priority.

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Whiteman, M. K., Hills, S. D., Jamieson, D. J., Morrow, B., Podgomik, M. N., Brett, K. M., & Marchbanks, P. A. (2008). Inpatient hysterectomy in the United States, 2000-2004. *American Journal of Obstetrics and Gynecology*, *198*(1), e1-7.

Wild, R. A. (2007). Introduction to a special issue on surgical menopause. Menopause, *14*(3), 556-561.

Woods, N. F., & Mitchell, E. S. (2005). Symptoms during the perimenopause: Prevalence, severity, trajectory, and significance in women's lives. *The Journal of Medicine*, *118*(12B), 14S-24S.

Xu, M., Belanger, L., Ivers, H., Guay, B., Zhang, J., & Morin, C. M. (2011). Comparison of subjective and objective sleep quality in menopausal and non-menopausal women with insomnia. *Sleep Medicine*, *12*, 65-69.

Yazdi, Z., Sadeghniiat-Haghighi, K., Loukzadeh, Z., Elmizadeh, K., & Abbasi, M. (2014). Prevalence of sleep disorders and their impact on occupational performance: A comparison between shift workers and nonshift workers. *Sleep Disorders*, 1-5.

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Zhang, B., & Wing, Y. (2006). Sex differences in insomnia: A meta-analysis. *Sleep*, *29*(1), 85-93.

Appendix A

SWAN Data Access Application

SWAN Data Access Application

SWAN encourages investigators currently not affiliated with one of the SWAN sites or coordinating center to join us in analyzing and reporting results from the largest, most comprehensive database of the menopausal transition ever constructed. It should be noted that SWAN cannot provide analytic assistance with your proposed analyses. If you are interested in working with us, please submit your application to the coordinating center care of Joyce Monroe at swanaccess@edc.pitt.edu.

Required for submission:

1. CV
2. Application Form
3. Letter of support from an investigator who knows your work if you consider yourself an early stage investigator (new investigator within ten years of completing terminal research degree or within ten years of completing medical residency).

Application:

Name: __Colleen Ciano__MSN, RN, PhD (c)_____

Address : ___253 N. Oak Street_____

__Lititz, PA 17543_____

_____

Telephone: _908-596-0108_____

E-mail: __clc5477@psu.edu_____

1. What areas of SWAN are you interested in working with?

I am interested in looking at the impact of perimenopause and surgical menopause that occurs during perimenopause and its impact on the insomnia trajectory.

Sleep disturbances in the perimenopausal period are highly prevalent. Evidence to date has focused on the natural progression to menopause. Few studies have specifically addressed surgical menopause and sleep. The perimenopausal population is large and the risk of insomnia is likely high in perimenopausal women who have undergone surgical menopause related to the abrupt hormone changes occurring after the surgical procedure. This study will address this gap in the evidence by describing the insomnia trajectory in women with surgical menopause. This research will importantly contribute new knowledge about insomnia and its trajectory in perimenopausal women who have undergone surgical menopause.

2. What papers already published by SWAN relate closest to your area(s) of interest? (The P&P status report on the SWAN web site can be used to view what has already been done and other projects that are in the works.)

Harlow, S. D., Crawford, S. L., Sommer, B., & Greendale, G. A. (2000). Self-defined menopausal status in a multi-ethnic sample of midlife women. *Maturitas*, *36*, 93-112.

Gold, E. B., Bromberger, J., Crawford, S., Samuels, S., Greendale, G. A., Harlow, S. D., & Skurnick, J. (2001). Factors associated with age at natural menopause in a multiethnic sample of midlife women. *American Journal of Epidemiology*, *153*(9), 865-874.

Gold, E. B., Colvin, A., Avis, N., Bromberger, J., Greendale, G. A., Powell, L., ... Matthews, K. (2006). Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: Study of women's health across the nation. *American Journal of Public Health*, *96*(7), 1226-1235.

Avis, N. A., Stellato, R., Crawford, S., Bromberger, J., Ganz, P., Cain, V., & Kagawa-Singer, M. (2001). Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Social Science and Medicine*, *52*, 345-356.

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Hollander, L. E., Freeman, E. W., Sammel, M. D., Berlin, J. A., Grisso, J. A., & Battistini, M. (2001). Sleep quality, estradiol levels, and behavioral factors in late reproductive age women. *Obstetrics and Gynecology*, *98*(3), 391-397.

Kravitz, H. M., Ganz, P. A., Bromberger, J., Powell, L. H., Sutton-Tyrrell, K., & Meyer, P. M. (2003). Sleep difficulty in women at midlife: A community survey of sleep and the menopausal transition. *Menopause*, *10*, 19-28.

Kravitz, H. M., & Joffe, H. (2011). Sleep during the perimenopause: A SWAN story. *Obstetrics and gynecology clinics of North America*, *38*, 567-586.

Kravitz, H. M., Zhao, X., Bromberger, J. T., Gold, E. B., Hall, M. H., Matthews, K. A., & Sowers, M. R. (2008). Sleep disturbance during the menopausal transition in a multi-ethinic community sample of women. *Sleep*, *31*(7), 979-990.

Sommer, B., Avis, N., Meyer, P., Ory, M., Madden, T., Kagawa-Singer, M., … Adler, S. (1999). Attitudes toward menopause and aging across ethnic/racial groups. *Psychosomatic Medicine*, *61*, 868-875.

Sowers, M., Pope, S., Welch, G., Sternfeld, B., & Albrecht, G. (2001). The association of menopause and physical functionng in women at midlife. *Journal of American Geriatrics Society*, *49*, 1485-1492.

Troxel, W. M., Buyesse, D. J., & Hall, M. (2009). Marital happiness and sleep disturbances in a multi-ethnic sample of middle-aged women. *Behavioral Sleep Medicine*, *7*, 2-19.

3. What specific research questions would you like to explore in SWAN that are not addressed by prior SWAN publications or currently approved concept proposals?

Research Questions:

1. What is the trajectory of insomnia in all perimenopausal women?
    1a. When do perimenopausal women report insomnia symptoms?
    1b. In perimenopausal women, is there a change in insomnia symptoms after surgical menopause?
2. What is the trajectory of insomnia in perimenopausal women who have undergone surgical menopause?
    2a. Is there a difference in insomnia symptoms, among perimenopausal women when comparing perimenopausal women who have undergone surgical menopause and women that progress naturally to menopause?
3. What are the risk factors for developing insomnia among perimenopausal women?

4. What data management and analytic resources are available to you?

a. Are you sufficiently fluent with data management and statistical analysis to be able to construct your dataset and perform analyses on your own? If yes, please elaborate briefly on the types of longitudinal analyses you can do.

b. If you would not do your own analyses, who would perform the analyses for you and what is the analyst's level of experience?

5. If you consider yourself an early stage investigator (new investigator within ten years of completing terminal research degree or within ten years of completing medical residency), please provide a summary of the mentorship that is available to you at your home institution.

a. What is the expertise of your mentor(s) and how does this relate to your potential project?

b. Do your mentors have sufficient time and interest in your project to be included as a coauthor in the resulting manuscript?

c. Please include a letter of support from your primary mentor if this letter should include why this project is a good match for your area, a statement of confidence that the project will be carried to completion and the mentor's willingness to support you with your chosen project.

6. If you consider yourself an established investigator, please describe whether or not you would like to involve other investigators that you mentor in the project that you propose.

Appendix B

SWAN Data Access Forms

Material Transfer Agreement (MTA)

Letter of Understanding from Applicant Investigator and Institution to the Repository
Name of Investigator:
Name of Institution:
Institutional Address:
I (the investigator named above) and my institution (named above) hereby apply to be provided materials from the SWAN Repository.
We agree to the following terms:
1) We will provide the results of measurements or genetic analyses developed from the materials provided from the Repository in a form that is compatible with the existing database and Repository requirements. These will be provided within six months of publishing any analyses on measurements or genetic markers, or within three years of the end of a funded period, or other agreed upon timeline if these data have not been published.
2) We agree and understand that the data generated by Repository applicants may be subsequently provided to SWAN Core Study investigators or other approved applicant investigators following the incorporation of the data into the Repository database.
3) We agree not to provide or re-distribute any of the original data or any of the specimen materials from the Repository to anyone who is not or has not been approved to have access to the data or the materials. Furthermore, we agree not to provide the results of any measurements, genetic markers or polymorphisms to other investigators without the expressed knowledge and documented approval of the Repository. This clause does not prohibit publication of work, including reference to the data and materials, but it does prohibit distribution of material to any third party.
4) We agree, after the receipt of the data or materials from the Repository, to provide an annual report of our progress and an annual inventory of any unused serum, plasma, DNA or cells that until such time that all data and specimens have been returned to the Repository or depleted. This progress report and inventory will include documentation as to the storage, freeze thaw and utilization history that accompanies any of the samples.
5) We agree to forward in an agreed upon and timely manner any unused materials to other Repository-approved investigators or return these materials to the Repository within 60 days as directed by the Repository.
6) We agree to acknowledge the SWAN Core Study, the Repository and their support from the National Institutes of Health in any publication or public presentation of the results of work based in the data and the materials from the Repository.
7) We agree that this project is not in conflict with the standing Repository informed consent that 1) the investigators will have a local IRB document that addresses the potential need to provide genetic counseling; and 2) there is limited likelihood that the proposed line of investigation will lead to the need for further clinical evaluation and/or genetic counseling in affected SWAN participants. (DNA or genetics data recipients only)

SWAN Repository
Data Use Agreement
Name of Investigator:
Name of Institution:
Institutional Address:
I (the investigator named above) and my institution (named above) hereby apply to be provided data from the University of Michigan, on behalf of the SWAN Repository ("Repository").
We agree to the following terms:
1) That data from the Repository will be used only for the approved Research Proposal **#NUM, "STUDY TITLE"** with documentation indicating approval by an Institutional Review Board ("IRB").

2) All data provided to the applicant can be linked by a common ID number. However, we understand that the data will be recoded so as to reduce the likelihood of being able to link with other identifying data in the SWAN databases.

3) Not to attempt to identify, approach, contact or communicate with any participant in the SWAN Core Study for whom data may be accessible through the Repository. We agree that communication with participants must only come through contacting the SWAN Steering Committee, outlining the nature of the communication and then following procedures of the SWAN Core Study.

4) Not to provide, allow access to, distribute, sell, barter, trade, or in any way transfer any of the data from the Repository to anyone who has not been approved to have access to the data through this agreement and as covered by the IRBs pertaining to this approved use of the data. We further agree to use appropriate safeguards to prevent the use or disclosure of the data without express written approval of the Repository.

5) Not to provide the results of any measurements, genetic markers or polymorphisms to other investigators without the expressed knowledge and documented approval of the Repository. This clause does not prohibit publication of work, including reference to the data, but it does prohibit distribution of data to any third party.

6) To immediately report to the Repository any use or disclosure of data or information not authorized by this Agreement.

7) To make the Repository Organization, the Repository Advisory Group and the National Institutes of Health a party to any discussions that may potentially lead to patents or the assignment of intellectual property rights that may result from, or are in any way related to, having access to the provided data.

8) To provide an annual report of our progress to the SWAN Repository, due on the first business calendar day of the signed agreement for the consecutive years.

9) To acknowledge the SWAN Core Study, the SWAN Repository (AG017719) and their support from the National Institutes of Health in any publication or public presentation of the results of work based on the data from the Repository. We also agree to submit all publications to PubMed Central (FOR PMCID #) as required by NIH Public Access policy.

10) To be responsible for the appropriate and ethical use of the data provided to us from the Repository by our collaborators, colleagues and employees.

Edited 03/27/2013

CONCEPT PROPOSAL FOR SUBMISSION TO P&P

This form is used to propose a new writing group. Please save this document to disk (hard drive or flash drive). Once completed, please submit via email to the Coordinating Center P&P Administrator (swanaccess@edc.pitt.edu) and the P&P Chair (Howard Kravitz, Hkravitz@rush.edu) when proposing a new Writing Group

Please use the TAB Key or the mouse to navigate the form. The Alphabet "X" Key on the keyboard or the mouse can be used to select the Check Boxes

Writing Group Number:

Priority Paper: No

SWAN Story: No

Is the submission a revision of a previously approved concept sheet? No
If yes, is the concept sheet open for sign up? N/A

Submission Date (mm/dd/yyyy)**:**

Working Title:

Individual Submitting Proposal *(last name, first name)***:**

Is this concept proposal related to a doctoral dissertation or thesis? No
If yes, have other concept proposals been submitted in relation to this dissertation or thesis? N/A
If yes, what number(s)?
If yes, how many papers will be generated from this concept sheet?
If more than one, please describe the expected contents of each paper:

Committee (Committee(s) affiliation is required)**:**

- ☐ Bone Committee
- ☐ Cardiovascular Committee
- ☐ Design Committee
- ☐ Lifestyles, Symptoms and Behavior Committee
- ☐ Pharmacoepidemiology Committee
- ☐ Reproductive History
- ☐ Vitamin D Working Group
- ☐ Repository (attach review & approval letter)
- ☐ Calendar Working Group
- ☐ Daily Hormone Study Working Group
- ☐ Genetics Committee
- ☐ Ovarian Markers Committee
- ☐ Physical Function Committee
- ☐ Ultrasound Committee
- ☐ Ancillary Study, please specify

Writing Group Chair *(last name, first name)***:**

Edited 03/27/2013

Site of Writing Group Chair:

Alternate Chair (If applicable)**:**

Sponsor (If individual submitting or the Chair is not a SWAN investigator)**:**

Co Authors (Tentative Writing Group Members)**:**

Background *(If this is related to a dissertation or thesis proposal, please list other SWAN concept sheets/manuscripts and discuss how your proposal relates to these SWAN concept sheets/manuscripts)*:

Research Hypothesis:

Primary Question (Please restate Research Hypothesis in LAY language)**:**

Sample to Be Used:

Exclusion Criteria:

Dependent / Outcome Variables (Please list variable names)**:**

Independent Variables: (Please list variable names)**:**

Covariates (Please list variable names)**:**

Data Source (Select all that apply)**:**

- ☐ Baseline
- ☐ Core/Source (n=3302)
- ☐ DHS
- ☐ Follow-Up 01
- ☐ Follow-Up 03
- ☐ Follow-Up 05
- ☐ Follow-Up 07
- ☐ Follow-Up 09
- ☐ Follow-Up 10
- ☐ Follow-Up 12
- ☐ Longitudinal Cardiovascular
- ☐ Longitudinal Whole Body Data
- ☐ Site(s)-Specific
- ☐ Cohort Only Screener (n=3290)
- ☐ Cross-sectional Screener (n=16,065)
- ☐ Focus Group
- ☐ Follow-Up 02
- ☐ Follow-Up 04
- ☐ Follow-Up 06
- ☐ Follow-Up 08
- ☐ Follow-Up 09 New Jersey
- ☐ Visit 11 Interim Contact
- ☐ Longitudinal Bone Mineral Density
- ☐ Longitudinal Diabetes
- ☐ Menstrual Calendar
- ☐ Other, please specify

Analytic Design (Select all that apply)**:**

Edited 03/27/2013

- ☐ Case-Control
- ☐ Longitudinal
- ☐ Overview/Summary
- ☐ Cross-sectional
- ☐ Methods

Analytic Support (Please select only one): ☐ CC ☐ At the Site

Statistician Name:

Approach to Analysis (Please provide a description for how the data will be analyzed, including statistical tests and models to be used; ***if follow up visit 06 data or beyond will be used***, please explain how NJ data will be analyzed):

The following are important SWAN issues that should be addressed in the approach to analysis section. In order to confirm that you addressed these issues in your methods please check the items that apply to your proposal:

- ☐ If follow up 06 data or beyond were used the handling of New Jersey data was addressed
- ☐ If longitudinal data analysis, have you described how variables are measured and used over time
- ☐ Site and Race/Ethnicity have been included as covariates
- ☐ Hormone use was addressed
- ☐ If using endogenous hormone data, cycle day has been included as a covariate
- ☐ The handling of menopause status was addressed (surgical menopause & unknown menopausal status)
- ☐ Transformed variables, where necessary, were described
- ☐ Created variables were described

Keywords:

Timeline:

Analysis Complete (mm/yyyy):
Draft to Co Authors (mm/yyyy):
Final Draft Approved by Co Authors (mm/yyyy):
Submit Checklist & Manuscript to P&P (mm/yyyy):
Submit to Journal (mm/yyyy):

Additional Comments / Notes:

Appendix C

Ethical Consultation

Research Ethics Consultation Report

Consult requester:	Colleen Ciano, Phd candidate, Penn State College of Nursing
Primary consultant:	Joshua Crites, PhD (Director, Research Ethics Consultation Service, Penn State College of Medicine)
Other contacts:	Janice Penrod, Phd, RN (Director, Center for Nursing Research, Penn State College of Nursing)
	Amy Sawyer, PhD, RN (Assistant Professor of Nursing, Penn State College of Nursing; dissertation advisor for Colleen Ciano)

Background and Ethical Analysis

The primary ethical question in this consultation request is whether there are any ethical reasons for not using a publicly available data set as the basis for subsequent analysis associated with a dissertation, given that the source of that data (Study of Women's Health Across the Nation, or SWAN) had formally disapproved a request by the author of that dissertation, Colleen Ciano, for access to the "private" data.

Per the SWAN website (http://www.swanstudy.org), "investigators currently not affiliated with one of the SWAN sites or coordinating centers…may register for SWAN database access." Ms. Ciano followed this process, including an extended email conversation with members of the SWAN study but ultimately was not granted data access on the grounds that her project was very similar to several questions that SWAN investigators were already researching and that her use of SWAN data therefore would be "duplicative" of research internal to the SWAN project (personal communication from the Chair of the SWAN study and Ms. Ciano).

The SWAN study is, in part, an NIH-funded research project. As such, it is subject to NIH policy statements regarding the availability of research results including publications, data, unique research resources, and intellectual property (http://grants.nih.gov/grants/policy/nihgps_2013/nihgps_ch8.htm#_Toc271264947). The way I understand this policy, there is a wide range of mechanisms by which an NIH-funded project may satisfactorily make its results public. It is worth noting that this policy pertains to the *results* of NIH-funded research. This means that in many situations, there are no Federal requirements

for sharing data prior to publication, or, by a more liberal reading, that requirements to share data are satisfied by the publication of research results.

Using this framework as the basis for a (brief) ethical analysis, it is clear that: 1) there is no evidence of data hoarding or other breach of research integrity given that SWAN has a mechanism for applying for access and that they are making large parts of their research data publicly available via a third party website, and 2) there are no ethical prohibitions against using the publicly available data to answer questions for which access to the "private" data was refused.

Assessment/Recommendations

While the SWAN research group may have rightful control of access to their own research data, there is no ethical precedence (or practical mechanism) for limiting access to publicly available data. It would indeed by of ethical (and likely regulatory) concern for any research team to attempt to limit access to data it had put out into the public domain. To be sure, I do not see any evidence of that occurring in this situation. It may be lamentable that SWAN leadership has not opened themselves to assisting with a project they view as scientifically important and with supporting the education and training of a young investigator. However much of a lost opportunity this represents for all involved, it does not appear to be unethical.

Given that the SWAN group has made data available in the public domain, and in light of the fact that this data set includes adequate data to support statistical power calculations for Ms. Ciano's project, there is little evidence that using this data set would not be ethically supportable.

Specific Recommendations:

1) It is ethically supportable to move forward with this project, using the publicly available data set. While access to the "private" data set has been refused by the SWAN research group, there is not sufficient evidence to believe that this is intended to limit access to the publicly available data. In other words, in the opinion of this consultant, it would not be unethical to move forward with this dissertation project using the publicly available data.
2) That being said, it is this consultant's recommendation to continue exploration of possibilities of collaboration with SWAN investigators. The purpose of doing so is two-fold. First, there seems to be a strong potential of educational benefit for Colleen to work

with investigators whose work closely aligns with her own interests and with whom she is likely to work in the future. Second, it is my recommendation to consider additional efforts to establish working relationships with SWAN researchers to maximize the impact of Colleen's work. It is true that science advances by the confirmation (or disconfirmation) of others' work, but, as a budding researcher, it is important for Colleen to begin building a research portfolio that is not merely redundant of the work of others. Understanding that Colleen has expended significant preliminary work in the preparation of her dissertation proposal, it would be worthwhile for her, in conversation with the dissertation committee, to explore this consideration.

Please do not hesitate to contact Josh Crites with additional questions or further clarification.

Electronically signed: **Joshua S. Crites, PhD**

Director, Research Ethics Consultation Service

Co-Director, Clinical Ethics Consultation Service

Assistant Professor, Department of Humanities

Penn State Milton S. Hershey Medical Center

Penn State College of Medicine

Mail Code H134

500 University Drive

P.O. Box 850

Hershey, PA 17033-0850

email: jcrites@hmc.psu.edu

phone: (717) 531-8778

Appendix D

Protection of Human Subjects

PENNSTATE

Vice President for Research
Office for Research Protections

The Pennsylvania State University
The 330 Building, Suite 205
University Park, PA 16802

Phone : (814) 865-1775
Fax: (814) 863-8699
Email : orprotections@psu.edu
Web : www.research.psu.edu/orp

NOT HUMAN RESEARCH

Date: November 7, 2014

From: Courtney Whetzel, IRB Analyst

To: Colleen Ciano

Type of Submission:	Initial Study
Title of Study:	The Impact of Perimenopause on the Insomnia Trajectory
Principal Investigator:	Colleen Ciano
Study ID:	STUDY00001371
Submission ID:	STUDY00001371
Funding:	College of Nursing
Review Level:	

The Office for Research Protections determined that the proposed activity, as described in the above-referenced submission, does not meet the definition of human subject research as defined in 45 CFR 46.102(d) and/or (f). Institutional Review Board (IRB) review and approval is not required.

The IRB requires notification and review if there are any proposed changes to the activities described in the IRB submission that may affect this determination. If changes are being considered and there are questions about whether IRB review is needed, please contact the Office for Research Protections.

This correspondence should be maintained with your records.

Vita
Colleen L. Ciano MSN, RN

EDUCATION:

Millersville University, **Master of Science Nursing**, Nursing Education 2010
Monmouth University, **Bachelor of Science**; Major, Nursing 1998
Ann May School of Nursing, **Diploma**, Nursing 1994

ACADEMIC POSITIONS:

Instructor of Nursing, College of Nursing,
The Pennsylvania State University, Middletown, PA 2013 -Present
Instructor of Nursing, Immaculata University, Malvern, PA 2010-2014
Adjunct Clinical Instructor, HACC , Lancaster, PA 2006-2014
Practical Nursing Instructor, LCCTC, Willow Street, PA 2008-2011

PROFESSIONAL POSITIONS:

Staff Nurse, Postpartum Unit, The Reading Hospital, Reading, PA 2012- Present
Staff Nurse, LDRP, Mainline Health Systems, Paoli, PA 2011-2012
Staff Nurse/Clinical Educator, L&D, Lancaster General Health 2006-2008
Staff Nurse, LDRP, CentraState Medical Center, Freehold, NJ 2003-2006

REFEREED PRESENTATIONS:

Ciano, C, King, TS, Hupcey, JE, Wright, RR, Sawyer, AM (2015). The prevalence of insomnia in perimenopausal women. Women's Health Conference, Hershey, PA: April 2015 (Accepted oral presentation).

Ciano, C, King, TS, Hupcey, JE, Wright, RR, Sawyer, AM (2015). The impact of surgical menopause on the insomnia trajectory in perimenopausal women. Eastern Nursing Research Society Annual Scientific Sessions, Eastern Nursing Research Society, Washington, D.C.: April 2015 (Accepted poster presentation).

Watach, AJ, **Ciano, C**, Sawyer, AM (2015). CPAP adherence in children and adolescents with obstructive sleep apnea. Eastern Nursing Research Society Annual Scientific Sessions, Eastern Nursing Research Society, Washington, D.C.: April 2015 (Accepted poster presentation).

Ciano, C (2013). Sleep quality in perimenopausal women. Eastern Nursing Research Society Annual Scientific Sessions, Eastern Nursing Research Society, Boston, MA.: April 2013.

CLINICAL PUBLICATIONS AND NON REFEREED JOURNALS:

Goldsmith, C, Sawyer, AM, **Ciano C** (2014). An Update: Insomnia: Sleepless in America (July 2014). Falls Church, VA: Gannett Healthcare Group. http://ce.nurse.com/course/ce426/insomnia-sleepless-in-america/

Goldsmith, C, **Ciano, C** (2014). Perimenopause: Is it Hot in Here or is it Just Me? (October 2014). Falls Church, VA: Gannett Healthcare Group.