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Optimizing Sleep across the Menopausal Transition

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Abstract

Women frequently experience sleep disturbances, particularly nighttime awakenings, as they transition menopause and enter post-menopause. Sleep is essential for optimal functioning and health. Persistent and distressing sleep disturbances across menopause can negatively impact daytime functioning, productivity, and increase risk for mental and physical health conditions. While multiple factors can disturb sleep, two unique factors in the context of menopause are vasomotor symptoms and the changing reproductive hormone environment. Vasomotor symptoms are associated with sleep disturbances and contribute significantly to awakenings and amount of time spent awake during the night. Even after accounting for vasomotor and depressive symptoms, lower estradiol and higher follicle stimulating hormone levels, indicative of menopause, are associated with sleep disturbance, particularly awakenings, suggesting that the hormone environment may directly affect sleep. Management strategies for clinically-significant menopausal sleep disturbances include cognitive behavioral therapy for insomnia, which is effective and durable in treating menopausal insomnia. Hormone therapy alleviates sleep disturbances, particularly in the presence of disruptive vasomotor symptoms. Sleep disturbances have a significant impact on women's functioning and health and there is a need for further research of the underlying mechanisms to advance effective preventative and treatment strategies that ensure optimal health and wellbeing of midlife women.

Keywords

menopause; climacteric; subjective sleep quality; sleep architecture; polysomnography; vasomotor symptoms; hot flashes; depressive symptoms

INTRODUCTION

Menopause is an important transition point from a reproductive to a nonreproductive stage of life encompassed within the normal aging process for women. Menopause occurs at a median age of 51.4 years,¹ but can range between 40 and 58 years of age. The transition to menopause and post-menopause can be associated with the emergence of

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several symptoms, including sleep disturbances, which have a major impact on longterm health, healthcare utilization, quality of life, and work productivity. Sleep disturbance can arise due to multiple factors, including underlying physical and mental health conditions, medications, personal life stressors, socioeconomic factors, as well as factors specifically related to menopause (e.g. vasomotor symptoms). For some women, sleep disturbances that are already present before menopause can become exacerbated during this time. Surgical menopause can be associated with more severe sleep disturbances than natural menopause, as reviewed elsewhere.³ Here, I provide an overview of sleep disturbance in the natural menopausal transition, focusing on its association with vasomotor symptoms and the underlying changes in female reproductive hormones. I also highlight current treatment options. Sleep disturbance significantly affects functioning and health in the context of menopause and there is a need for further research of the underlying mechanisms to advance effective preventative and treatment strategies that ensure optimal health and wellbeing of midlife women.

THE MENOPAUSAL TRANSITION

Natural menopause is defined as the time of the final menstrual period, confirmed to be present after 12 months of amenorrhea, resulting from depletion of ovarian follicles. There are complex changes in the central nervous and endocrine systems across menopause, such that it is not defined by one event but rather as a transitionary phase encompassing several years before and after the final menstrual period.⁴ The menopausal transition is defined by Stages of Reproductive Aging Workshop (STRAW^{6, 7}) criteria. The early menopausal transition is marked by a persistent difference of 7 days or more in the length of consecutive menstrual cycles and the late menopausal transition is marked by the occurrence of amenorrhea of ≥ 60 days, increased variability in cycle length, and follicle stimulating hormone (FSH) levels ≥ 25 IU/l.⁷ Early postmenopause describes the first two years after menopause, with increasing FSH and decreasing estradiol levels, until hormone levels finally stabilize.⁷ While hormonal changes roughly map onto the STRAW stages, changes are non-linear over time⁸ and ovulatory menstrual cycles can still occur,⁹ adding to the inter-individual variability in hormonal patterns across the menopause transition.^{10,11} Vasomotor symptoms (hot flashes, night sweats) typically emerge in the late reproductive stage or early menopausal transition and peak in the late menopausal transition and first 2 years after menopause.¹² Peri-menopause encompasses the menopausal transition and the first year after the final menstrual period.

SLEEP HEALTH

Sleep is essential for overall health and emotional well-being.^{13,14} Sleep health is a multidimensional construct that promotes physical and mental well-being¹⁵ and is comprised of six key dimensions, including regularity (getting in and out of bed at similar times each day), subjective satisfaction (feeling satisfied with one's sleep), alertness during waking hours (ability to stay awake during the day without dozing), appropriate timing (sleeping between 2:00 a.m. and 4:00 a.m.), high efficiency (being awake for less than 30 minutes each night after trying to fall asleep), and sleep duration (obtaining between 6 and 8 hours of sleep per night).¹⁵ Better sleep health is associated with better physical and

mental health outcomes as well as better quality of life,¹⁶ with a wide range of positive effects, including strengthening of immunity,¹⁷ optimal brain and cognitive functioning,¹⁸ and well-regulated energy metabolism¹⁹ (Figure 1). Conversely, sleep disturbance implies poor sleep health and negatively affects various physiological systems, and is associated with adverse health outcomes including cardiovascular disease,²⁰ obesity & diabetes,²¹ all-cause mortality,²² and psychological disorders such as depression.²³

Sleep can be assessed using several methodological approaches, including surveys and daily diaries, wearables and research-grade actigraphy, and polysomnography (PSG). PSG allows for the objective assessment of sleep and quantification of sleep stages including rapid eye movement (REM) sleep and slow wave sleep (SWS) by measuring brain activity (electroencephalography, EEG), eye activity, and muscle activity. These data are continuous and detailed, thus informing mechanisms and physiology of sleep. However, assessments using questionnaires and sleep diaries are still essential in providing valuable information regarding an individual's perception of their sleep,²⁴ which drives treatment seeking behavior. Use of wearables and actigraphy can also provide important longitudinal data about patterns of sleep-wake activity over weeks or months. Combinations of PSG, self-report, and wearable technology/actigraphy assessments can provide complementary information about sleep in the context of menopause. Assessment of the presence of sleep disorders including obstructive sleep apnea (OSA) and restless legs syndrome requires additional clinical evaluation.

SLEEP QUALITY DURING THE MENOPAUSAL TRANSITION

Between 40–60% of women report having sleep disturbances during the menopausal transition and postmenopause^{26–31} This greater prevalence of sleep disturbance in the menopausal transition relative to pre-menopause is evident from several cross-sectional and longitudinal studies (reviewed in³²) even after controlling for age and across different populations.³³ Sleep disturbance is a common symptom for which women seek care in the menopausal transition,³⁴ and is linked with functional impairment, poor quality of life, and increased healthcare use.^{35,36} Sleep disturbance in midlife women is associated with risk of unemployment and \$2.2 billion/year in lost productivity.³⁷ It also has long-term negative effects on mental health, with increased risk for persistent depression,³⁸ and poor physical health, notably poor cardiovascular health³⁹: Shorter sleep duration, poorer sleep quality, and greater severity of insomnia in postmenopausal women are all associated with worse cardiovascular health as assessed with the American Heart Association Life's Simple 7 scores.⁴⁰

The most common sleep-related complaint is nighttime awakenings. Longitudinal data from several studies, including the Study on Women's Health Across the Nation (SWAN), have confirmed that women transitioning from premenopause through the menopausal transition have higher odds of reporting waking up several times compared to women who have not yet transitioned, after adjusting for demographics and health-related factors.^{28,41–43} 40% of women in the late menopausal transition report waking several times, and this percentage remains stable into post-menopause.⁴⁴ Sleep disturbance in the menopausal transition could be a consequence of several factors,³ including aging-related factors, psychosocial stress

and socioeconomic factors, mental and physical health comorbidities, as well as menopause-related factors of vasomotor symptoms^{28,30} and reproductive hormone changes (decrease in estradiol and increase in FSH).²⁸

Despite the overwhelming evidence that women, on average, report more sleep disturbances as they transition menopause, PSG studies that have compared groups of women at different life stages have not necessarily found evidence of objective sleep disturbance. Some reported no differences in sleep architecture between pre- and post-menopausal women,^{45–47} others found more deep SWS in peri- and post-menopausal women than pre-menopausal women,^{48–50} or differences only in the sleep EEG (more high frequency beta EEG activity, suggesting greater cortical hyperarousal) in late-perimenopausal and postmenopausal women compared with pre-menopausal and early peri-menopausal women.⁴⁵ In their longitudinal study of changes in PSG measures across the menopausal transition, Lempio and colleagues⁴⁹ reported that women had less total sleep time and more wakefulness after sleep onset (WASO) 6 years after a baseline visit after adjusting for vasomotor symptoms, BMI, and mood. These changes in sleep were linked with advancing age rather than increased FSH levels. A possible explanation for disparate findings between subjective and objective sleep measures could be the high inter-individual variability in the extent of sleep disturbances along with variability in hormone trajectories, duration of the menopausal transition, and life experiences all of which can interact to affect sleep and dilute any potential group differences in the smaller samples of women typically studied with PSG. Indeed, an analysis of trajectories for waking up several times at least 3 nights per week reported by women in the SWAN study across their natural final menstrual period showed that there were four clusters, with group 1 (37.9%) having low prevalence, group 2 (28.4%) having moderate prevalence, group 3 (15.3%) having increasing prevalence, and group 4 (18.4%) having a high prevalence of problems waking several times across the final menstrual period.⁵¹ Thus, not all women have the same sleep experience as they transition menopause, with some already having moderate-high sleep disturbance before the approach to the final menstrual period.

One quarter of women experience severe sleep disturbances in the context of the menopausal transition that impact daytime functioning, qualifying them for a diagnosis of insomnia.³² Sleep disturbance in women with menopausal insomnia is not isolated to self-reported symptoms since they also have more PSG-measured WASO, poorer sleep efficiency, and a short sleep duration compared to good sleeper controls, also in the menopausal transition.⁵² One factor that contributed to their PSG-measured sleep disturbances was nocturnal hot flashes, which matches the literature linking chronic insomnia symptoms with more severe hot flashes.³⁰

RELATIONSHIP BETWEEN VASOMOTOR SYMPTOMS AND SLEEP DISTURBANCE

Vasomotor symptoms affect up to 80% of women during the menopausal transition and into post-menopause.⁵³ Data from SWAN show a median duration for vasomotor symptoms of 7.4 years,⁵⁴ although there is wide individual variability in timing of symptom onset,

persistence, and daily frequency.^{55,56} A hot flash is a sensation of heat, sweating, flushing, anxiety, and chills lasting 3–10 min⁵⁷ and is characterized by peripheral vasodilation and sweating to increase heat loss, which are components of the classic heat dissipation response.⁵⁸ Hot flashes emerge as estrogen levels decline but their mechanism is more complex, with evidence implicating involvement of central noradrenergic activity^{53,59,60} and hypothalamic kisspeptin, neurokinin B and dynorphin (KNDy) neuron activity.⁶¹ KNDy neurons project to structures critical for body temperature regulation, and their effects on temperature regulation are sensitive to estrogen.⁶² This discovery is leading to the development of potential non-hormonal pharmacological treatments that antagonize neurokinin B/neurokinin-3 receptor (NK3R) signaling pathways for the treatment of vasomotor symptoms.⁶³

Self-reported vasomotor symptoms are consistently associated with poorer self-reported sleep quality and chronic insomnia.³ Longitudinal SWAN data show that women with moderate-severe hot flashes are almost three times more likely to report sleep disturbance (frequent nocturnal awakenings) compared to women without hot flashes.⁴⁴ Also, effective treatment of vasomotor symptoms with hormone therapy reduces sleep disturbance.^{26,31,64,34}

Associations between vasomotor symptoms and objective sleep disturbance (PSG or actigraphy) are less consistent.²⁶ Several studies have not found an association between vasomotor symptoms and overall objective sleep quality.^{46,50,65–68} Another study that examined hot flash events and PSG awakenings showed a time of night effect: physiological hot flashes (measured with sternal skin conductance) were more likely to precede PSG awakenings in the first half of the night but awakenings were more likely to precede hot flashes in the second half of the night.⁶⁹ Others, including our own work have found that the majority of nocturnal physiological hot flash events are linked with PSG awakenings, regardless of time of night, and/or with more WASO.^{70–72} For example, we found that 69% of nocturnal hot flashes were associated with an awakening/arousal (Figure 2) and wake-time associated with hot flashes contributed an average of 27% to total wakefulness after sleep onset.⁷¹ Similarly, in an experimental model of new-onset hot flashes in young premenopausal women treated with a gonadotropin-releasing hormone agonist that simulates menopause, 66% of objectively measured vasomotor symptoms were associated with an awakening.⁷² The strong overlap in timing between many hot flash events and awakenings suggests there may be a common mechanism within the central nervous system in response to estrogen withdrawal, although further work is needed to investigate this possibility.

Taken together, nocturnal hot flashes play a key role in sleep disturbance, although there is substantial individual variability and not all women who have menopause-related sleep problems complain of hot flashes²⁶ and not all hot flashes trigger an awakening. It is therefore important to consider other factors that could be associated with sleep disturbances, including the direct effect of reproductive hormone changes.

RELATIONSHIP BETWEEN REPRODUCTIVE HORMONES AND SLEEP DISTURBANCE

Work in animal models shows that ovarian hormones, including estradiol, regulate female sleep.⁷³ However, the underlying neurobiological substrates, mechanisms, and pathways remain unknown,⁷⁴ and further work is needed to define the neural circuits involved,⁷⁵ considering circadian timing and reproductive stage, especially given some of the paradoxical effects⁷⁶ of estradiol on sleep-wake behavior in rodents versus women. Estradiol is a neuroactive steroid and there are estrogen receptors in sleep and arousal-regulating nuclei, including the preoptic area of the hypothalamus, suprachiasmatic nucleus, and locus coeruleus.⁷⁴ Estradiol (and other hormones of the hypothalamic-pituitary-ovarian axis), therefore, may influence sleep-wake regulation directly, for example by influencing adenosinergic actions in the preoptic area (a sleep-promoting nucleus) to affect sleep homeostasis⁷⁶ or by influencing arousal systems in the lateral hypothalamus (rich in hypocretin-releasing neurons, which promote wakefulness),⁷⁴ or the locus coeruleus (primary site of norepinephrine, involved in arousal).⁷⁴ Estradiol could also act indirectly to influence sleep via other systems, including thermosensory and thermoregulatory sites in the hypothalamus, which overlap with sleep-active sites.⁷⁷

Knowledge about the effects of reproductive hormones on sleep in midlife women comes from observational and interventional studies, including randomized controlled trials of hormone therapy, however findings are mixed and many studies have had limitations in sample size, infrequent hormone sampling, inadequate control of covariates, and varied in assessment tools of sleep (self-report, PSG).⁷⁵ The longitudinal SWAN study that addressed many limitations, found that decreasing estradiol and increasing FSH levels across the menopausal transition were associated with higher odds of reported frequent awakenings²⁸ and that a greater rate of change in FSH was associated with poorer sleep quality.⁷⁸ Also, the 13-year prospective Melbourne Women's Midlife Health Project found that a steeper declining slope in estradiol was associated with more severe sleep problems.⁸ In contrast, the SWAN PSG sub-study found that a more rapid rate of change in FSH was associated with higher amount of SWS and longer total sleep time during follow-up,⁷⁸ suggesting there may be varied relationships between sleep continuity and sleep architecture measures and female reproductive hormone changes. A cross-sectional study of a combined sample of reproductive age and still cycling women in the menopausal transition found that higher FSH concentrations were associated with more PSG-measured WASO, after adjusting for age and BMI.⁷⁹ Recently, Coborn and colleagues advanced understanding of relationships between reproductive hormone changes and sleep by tracking daily sleep assessments and weekly hormone levels across 8-weeks in perimenopausal women.⁸⁰ They showed an association between more self-reported nightly awakenings and lower estradiol (especially when in the post-menopausal range) and higher FSH levels, independent of vasomotor or depressive symptoms.⁸⁰ These data suggest that the hormonal milieu of the menopausal transition is associated with sleep discontinuity, in particular.⁸⁰

MANAGEMENT OF SLEEP DISTURBANCE

Sleep disturbance in women transitioning menopause and post-menopause is common, however, it is not universal and varies between women in chronicity and severity. Some women may have a pre-existing sleep problem, which could be exacerbated as they transition and enter post-menopause. Greater awareness and public education about sleep disturbances that may arise in the context of menopause as well as management options is needed for women to be fully informed. Healthcare providers should inquire about sleep, recognizing that it is a window to health and that improving sleep can have multiple longterm positive benefits for daytime functioning, mood, and physical health. Sleep can be evaluated with a sleep history assessment⁸¹ or sleep diary,⁸² and women should be questioned about the timing of sleep disturbances in relation to changes in bleeding patterns and menopausal symptoms like hot flashes and night sweats. In cases where sleep disturbance is distressing with a negative effect on functioning and quality of life, treatment options should be considered. Women should be screened for underlying medical conditions and primary sleep disorders, which increase in prevalence in women after menopause.³ Medical conditions as well as use of medications become more common with advancing age and may lead to sleep disturbances.⁸³ Post-menopausal women have a more than 3-fold increased risk of severe obstructive sleep apnea compared with pre-menopausal women, after adjusting for confounding factors including age, BMI, and smoking.⁸⁴ Apneas and periodic limb movements disrupt sleep and were shown to be the best predictors for poorer PSG-defined sleep quality in peri- and post-menopausal women reporting sleep disturbances.⁸⁵ Continuous positive airway pressure is the treatment of choice for obstructive sleep apnea, and healthy lifestyle changes (e.g. weight loss and exercise) should also be implemented. Patients with comorbid sleep-disordered breathing and insomnia may benefit from concomitant cognitive behavioral therapy for insomnia (CBT-I).⁸⁶

There is a growing number of options for managing menopausal sleep disturbances including cognitive-behavioral therapy for insomnia, hormonal and non-hormonal pharmacological medication as well as non-pharmacological and self-management strategies, as reviewed in detail elsewhere.^{26,32,35,87} CBT-I, comprised of behavioral, cognitive, and educational components, is the primary intervention for patients with chronic insomnia,⁸⁸ and is superior to sleep medication alone in the long-term.⁸⁹ CBT-I has been shown in randomized controlled trials to be effective in treating insomnia in peri- and/or post-menopausal women.^{90,91} In the MsFlash study, 8-weeks of CBT-I delivered via telephone led to a greater reduction in insomnia symptoms and also reduced sleep-related interference from hot flashes compared with a menopause education control condition, with improvements maintained at 6 months post-treatment.⁹¹ Another controlled trial of CBT-I delivered face-to-face by a specialist to women diagnosed with insomnia disorder that either developed or worsened within 6 months of menopause also showed high efficacy relative to control (sleep hygiene education).⁹⁰ Women treated with CBT-I showed large reductions in insomnia symptoms, increases in total sleep time, and high remission rates (>50%) that were maintained 6 months later. A single component of CBT-I (sleep restriction therapy for 2 weeks) was also highly effective in alleviating insomnia symptoms, although CBT-I had better long-term outcomes.⁹⁰ In this same group, CBT-I and sleep restriction therapy

also reduced depressive symptoms, dysfunctional beliefs about sleep, and presleep somatic hyperarousal, and improved daytime function, quality of life, and work performance, with stronger effects for CBT-I.^{92,93} Taken together, these results are supportive for the use of CBT-I for successfully treating menopausal insomnia and concomitant subclinical depressive symptoms.

Hormone therapy (estrogen/progestin or estrogen alone for women after a hysterectomy) is the most effective treatment for menopausal symptoms such as severe vasomotor symptoms, however, its risk profile differs between women and current guidance recommends that treatment be individualized to maximize benefits and minimize risks.⁹⁴ Several studies have evaluated the effect of hormone therapy on sleep. While some studies found no benefit, the majority of good quality randomized controlled trials found that hormone therapy reduced sleep disturbances.⁷⁵ Hormone therapy may be particularly beneficial for women with sleep disturbances associated with nocturnal hot flashes, although a recent controlled trial showed that transdermal estrogen therapy plus intermittent progesterone reduced sleep disturbances over a 12-month treatment period, independent of vasomotor symptom bother and depressive symptoms, in perimenopausal women.⁹⁵ Non-hormonal pharmacological options for treating hot flashes and associated insomnia symptoms are available when hormone therapy is contra-indicated or not preferred, including low-dose selective serotonin/serotonin norepinephrine reuptake inhibitors, although the side-effect profiles of these medications need to be considered before use.³

CONCLUSION

Sleep disturbances, particularly difficulties maintaining sleep, frequently arise or worsen as women transition menopause and enter post-menopause. When these sleep disturbances are distressing and prolonged, they can negatively affect daytime functioning, quality of life, productivity, and longterm physical and mental health. Vasomotor symptoms are a key factor that disturb sleep in peri- and post-menopausal women, contributing specifically to sleep-maintenance difficulties. The changes in the hormone milieu across the menopausal transition, with declining estradiol and increasing FSH, are also directly linked with sleep disturbances, even after accounting for vasomotor and depressive symptoms. Beyond the disruptive effects to sleep continuity of these menopause-specific factors, sleep disturbances can arise from primary sleep disorders, mood disturbance, medical conditions, medications, or life stressors. Women should be informed about sleep disturbances in the context of menopause as well as management options when symptoms are distressing. These sleep disturbances vary in severity, chronicity, and etiology and treatment options need to be tailored to the individual.

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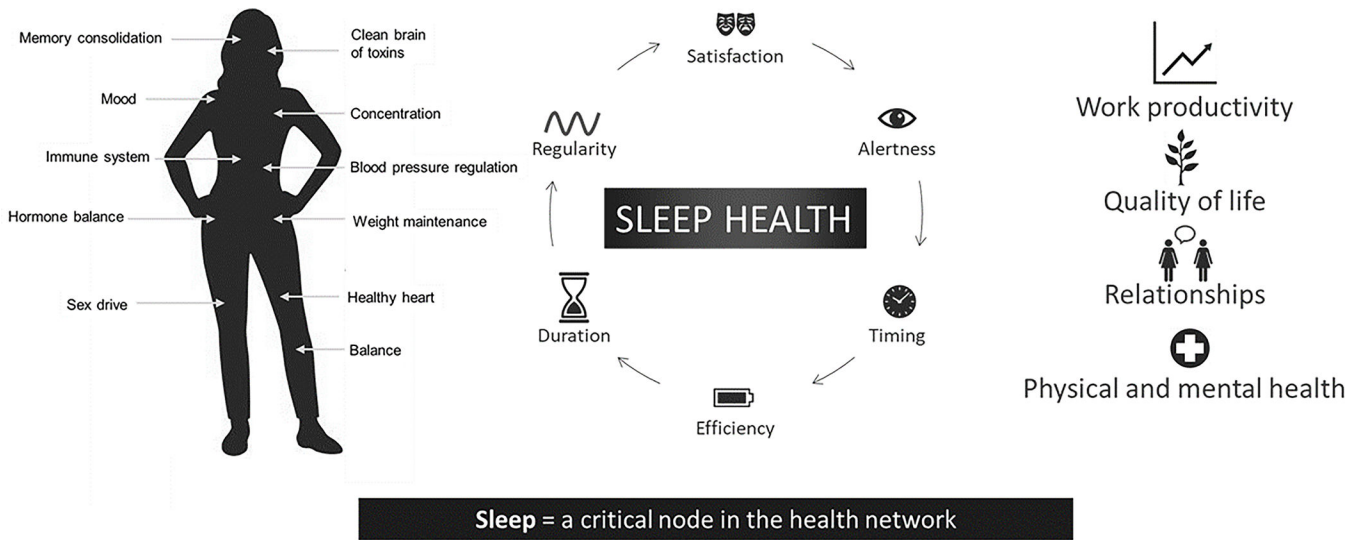


Figure 1: Schematic showing the multiple dimensions of sleep health as defined in: *Byssse DJ. Sleep health: can we define it? Does it matter? Sleep 2014;37:9–17.* Sleep health is essential for multiple functions, including weight maintenance, cardiovascular health, cognitive function, and mood. When sleep is disturbed, multiple systems are affected.

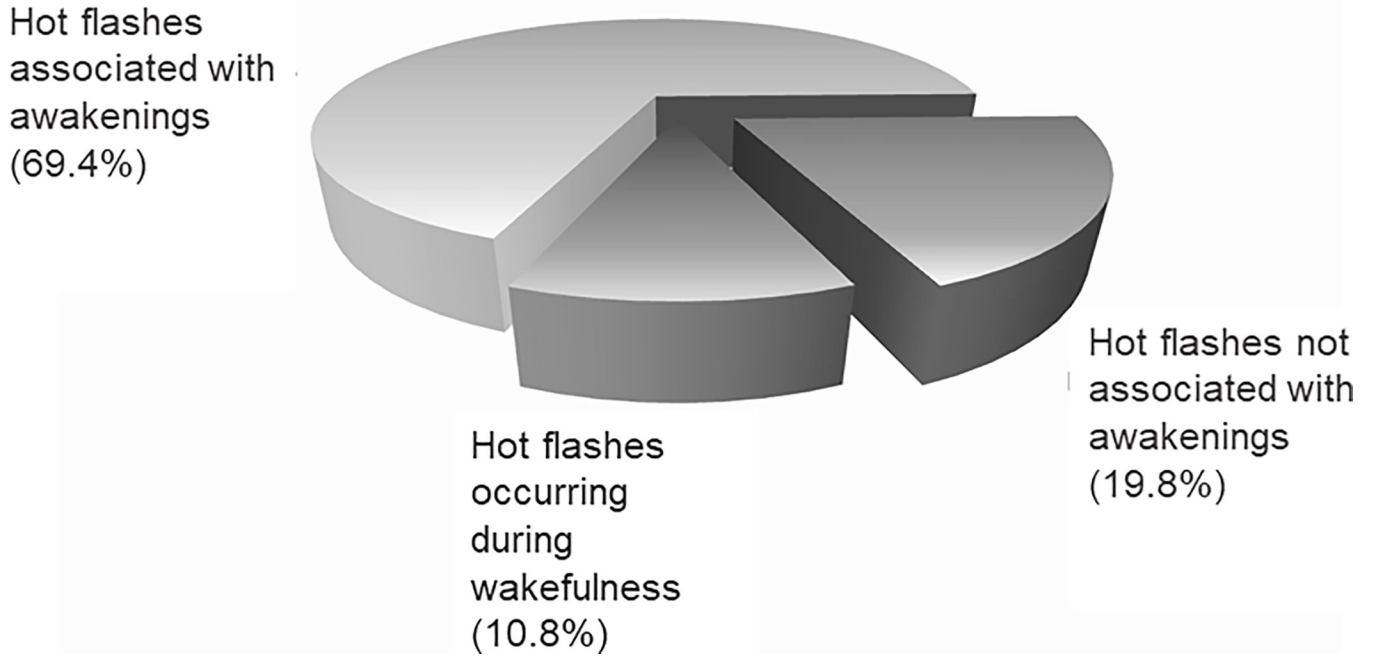


Figure 2.

In a sample of 34 perimenopausal women with physiological hot flashes detected from sternal skin conductance measures during overnight polysomnography recordings ($n = 222$ hot flash events), an awakening occurred within a 3-min window around the onset of the hot flash in 69.4% of events. Sleep was undisturbed in 19.8% of hot flash events, and the remainder (10.8%) occurred when the woman was already awake. Data taken from *de Zambotti M, Colrain IM, Javitz HS, Baker FC. Magnitude of the impact of hot flashes on sleep in perimenopausal women. Fertil Steril. 2014 Dec;102(6):1708–15.*