Hablemos de *Ginecología*

Manejo del insomnio durante la menopausia

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La **menopausia** es el periodo en la vida de la mujer donde existe el **cese de la menstruación debido al agotamiento de los folículos ováricos**.

Epidemiología

La prevalencia del insomnio a nivel mundial se estima que es del 11%, la prevalencia del insomnio se va modificando a lo largo de la vida de las mujeres, a partir de los 15 años, **el riesgo de insomnio se incrementa en un 28%, durante la perimenopausia**, el riesgo se estima entre el 16 y 47% para finalmente tener una prevalencia del 35 al 60% durante la menopausia.

Comorbilidades médicas

Las comorbilidades más frecuentes del insomnio durante la menopausia son las enfermedades metabólicas como la **diabetes, neuropatía diabética y la deficiencia de vitamina D; los trastornos psiquiátricos como la depresión y ansiedad.** Es frecuente que existan varios trastornos del sueño durante la menopausia, como el **síndrome de piernas inquietas**, además el riesgo de **apnea obstructiva del sueño** en esta etapa de la vida de la mujer es el mismo que el riesgo que en los hombres.

Síntomas de la menopausia

Casi **hasta el 90% de las mujeres** refiere la presencia de síntomas vasomotores, los cuales se presentan de forma predominante por la noche, lo que incrementa la presencia de despertares nocturnos (insomnio intermedio), los problemas del sueño se presentan hasta en el 60%, así como variaciones en el humor (78%), dolor de cabeza (70%), síntomas genitourinarios (30%), entre otros.

Arquitectura del sueño

Se caracteriza por la presencia de 4 fases:

- **Fase N1 de sueño**, es la transición entre la vigilia y el sueño, las ondas electroencefalográficas que representan esta fase son ondas alfa (8-14 Hz) y ondas theta (4-8 Hz).
- **Fase N2 de sueño**, los elementos electroencefalográficos característicos de esta fase son los husos de sueño (cuya función se ha asociado a la memoria) y los complejos K.
- **Fase N3 de sueño**, es la fase de sueño más profunda donde se presentan ondas delta (1-3 Hz).
- **Fase Sueño MOR**, antes conocido como el sueño paradójico se caracteriza por la presencia ondas beta (12-30 Hz), las cuales también se encuentran en vigilia.

Estrógenos y Progesterona

A lo largo de la vida de la mujer, estas hormonas se relacionan con **cambios estructurales en el sueño**. En la infancia la duración del tiempo total del sueño es mayor a diferencia del resto de las etapas de la vida en la mujer, durante el embarazo existe un gran incremento en el tiempo despierto posterior al inicio de sueño (WASO), durante el tercer trimestre de embarazo existe una reducción en el tiempo total de sueño, reducción de la duración del sueño MOR y del WASO.

Durante el ciclo menstrual el pico de estrógenos durante la ovulación se asocia a un **incremento del sueño NoMOR**, el cual coincide con el pico de progesterona de la fase lútea.

En resumen, los **estrógenos se asocian con una disminución de la latencia de inicio de sueño**, reducción en la presencia de despertares nocturnos e incremento en el tiempo total de sueño. La progesterona es un agonista GABA, la administración como terapia hormonal de reemplazo puede mejorar la duración y calidad de sueño a través del incremento del sueño de ondas lentas además de ser un promotor de la función respiratoria.

Cambios en la arquitectura del sueño durante la menopausia

La eficiencia de sueño en mujeres jóvenes se estima que es del 94% y ésta disminuye hasta el 80% durante el periodo de la menopausia. Existe un **incremento en el WASO**, disminución en la fase de sueño de ondas lentas y sueño MOR, así como una disminución en el tiempo total del sueño.

Por sí solo los síntomas vasomotores dan origen a un **sueño fragmentado**, incremento en el tiempo despierto posterior al inicio de sueño, aumento en la latencia de inicio de sueño y una disminución en la latencia de inicio de sueño MOR.

Tratamiento del insomnio durante la menopausia

El **tratamiento no farmacológico** consiste en la terapia cognitivo-conductual dirigida al insomnio, como no farmacológico.

Este último depende de los síntomas que acompañan al insomnio, en cualquier caso que se presente el insomnio, se debe evaluar la presencia comórbida de algún episodio depresivo o de ansiedad; en caso de estar presentes se debe evaluar la necesidad de iniciar un **tratamiento antidepresivo**; el siguiente paso es descartar la presencia de síntomas vasomotores y el beneficio de implementar un tratamiento de reemplazo hormonal.
Una vez evaluados los pasos anteriores, es necesario tomar en cuenta el momento en el cual se presenta el insomnio; si es insomnio inicial, de mantenimiento y/o terminal. Dentro del grupo de **medicamentos hipnóticos** disponibles que tenemos para el manejo del insomnio se encuentran los fármacos no benzodiacepínicos, melatonina y las benzodiacepinas.

Review Article

Menopause and Sleep Disorders

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Submitted: 19-Jan-2022
Revised: 02-Feb-2022
Accepted: 02-Feb-2022
Published: 02-May-2022

Abstract

Women are likely to suffer from sleep disorders more in comparison to men during menopause and with advancing age. The incidence of sleep disorders ranges from 16% to 47% at peri-menopause and 35%–60% at postmenopause. Insomnia with or without associated anxiety or low lying depression and Mood disorder is most common associated manifestations. Sleep disorders and insomnia largely remain a clinical diagnosis based on the subjective complaints of patients. Benzodiazepines remain the mainstay of the treatment in majority of the sleep disorders including chronic or acute insomnia. Treatment of associated anxiety, depression, or psychosis is most important. Tricyclic antidepressant, Selective Serotonin Reuptake Inhibitors (SSRI), Melatonin, Duloxetine, Fluoxetine, Imipramine, Nortriptyline or Amitriptyline and other drugs such as Eszopiclone, Escitalopram, Gabapentin, Quiteiapine, Citalopram, Mirtazapine followed by long-acting Melatonin and Ramelteon, also are very useful for the management of various sleep disorders. Hormone replacement therapy presently lacks concrete evidence to be used in menopausal women for sleep disorder. Sleep hygiene practices, self-hypnosis, meditation, and exercise play a very important role.

Keywords: *Anxiety obstructive sleep apnea, insomnia, menopause, mood disorders, sleep disorders*

Introduction

With the changes in the biological life cycles and the extreme hormonal change and with advancing age, women are at an increased risk for sleep disturbances such as insomnia, poor sleep quality, and sleep deprivation, as well as sleep disorders such as OSA, restless legs syndrome (RLS), depression, and various mood and anxiety-related disorders.[1] There is emerging evidence that menopause-associated hormone loss contributes to this elevated risk of sleep disorders, but age is also an important factor.[2] The current review will discuss various aspects of menopause and sleep disorder in light of available scientific evidence.

Epidemiology

The incidence increases from 16%–42% to 39%–47% at peri-menopause and 35%–60% at postmenopause. Difficulty in sleeping has been reported in 38% of the elderly women's and age-adjusted rates have been reported highest in the late perimenopausal (45.4%) and surgically postmenopausal (47.6%) women.[3] Studies have reported that 33%–51% of women show a dramatic increase in sleep disturbance in the mid-life years, a time when they enter menopause, i.e., during transition from peri-menopause to menopause.[4]

The menopausal transition is associated with rise in insomnia-related symptoms, particularly difficulty in staying asleep, which has a negative impact on the quality of life. Vasomotor symptoms (VMS) are a key component of sleep disruption during the said transition.[5] Further, studies have shown a high association between fibromyalgia and early, late perimenopause and surgical menopause to be one of the another factors for high incidence of sleep disorder occur during transition of menopause.[6]

Access this article online

Quick Response Code:

Website: www.jmidlifehealth.org

DOI: 10.4103/jmh.jmh_18_22

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How to cite this article: Tandon VR, Sharma S, Mahajan A, Mahajan A, Tandon A. Menopause and sleep disorders. J Mid-life Health 2022;13:26-33.

Associated Co-Morbidity and Risk Factors

The most commonly encountered co-morbid disease with sleep disorders in menopausal women includes restless leg syndrome, periodic leg movement syndrome, depression, and anxiety. Epidemiological studies state that women experience sleep-related difficulties and depressive symptoms around times usually when there is alteration in the levels of sex hormones such as at the time of puberty and menopause.[7] Further, the sleep disorders during menopause can be an independent risk associated with arterial stiffness in menopause and can result into higher incidence of cardiovascular-related morbidity and mortality.[8]

Obstructive sleep apnea (OSA) is another very common comorbid condition associated with sleep disorder. It is a chronic adult disorder which is characterized by episodes of recurrent upper-airway obstruction, accompanied by frequent reopening of the airway during sleep.

OSA is associated with oxidative stress, intermittent hypoxia, sympathetic overactivity, thus leading to high cardiovascular mortality and morbidity. It is more common in males than females, and this is attributed to the differences in anatomy and functional respiratory components. However, women take over men after menopause as far incidence of OSA is concerned.[9] OSA has also enhanced the risk of systemic arterial hypertension and arrhythmias, especially atrial fibrillation. Further, one of the studies has suggested the association of sleep disturbance among postmenopausal women and increase incident cardiovascular disease and type 2 diabetes.[10] Similarly, another study conducted by Im *et al*.[11] supported significant associations of type 2 diabetes mellitus with sleep-related manifestations among midlife women.

Further, in postmenopausal women, high BMI and abdominal obesity are sources of sleep disturbances, decreasing deep sleep, and sleep efficiency while increasing the risk of OSA.[12]

It is also well known that the prevalence of sleep-disordered breathing (SDB) among postmenopausal women is increased in patients with obesity or metabolic comorbidities. Metabolic comorbidities thus contribute to SDB regardless of the degree of obesity.[13] Further, conditions such as gastro-esophageal reflux disease, diabetic neuropathy, vitamin D deficiency, and related muscle cramps also have been found associated with sleep disorder among postmenopausal women. Many drugs such as beta-blockers, bronchodilators, corticosteroids, diuretics, stimulating antidepressants, central nervous system stimulants also are known to affect the sleep quality adversely.

Gender Difference for Sleep Disorders

Women usually have a better quality of sleep as compared to men, which is evident by longer sleep times, shorter sleep-onset latency, and higher sleep efficiency. Despite all this, women generally tend to have more sleep-related complaints than men. The amount of slow-wave sleep slowly declines with age both in men as well as women.

Normal physiologic periods, which are associated with alteration in hormone levels such as puberty, menstruation, pregnancy, and menopause, all are associated with alterations in the sleep patterns. Studies of insomnia support a female preponderance, with increased divergence of prevalence among men and women in the elderly age group. RLS also has a slight female predominance, while rapid eye movement sleep behavior disorder and Kleine–Levin syndrome are more frequently seen in men.[14]

There are many ways in which women experience sleep differently from men. The new research is unraveling the novel aspects of sleep pathology in women and the significance of sex hormones in determining the sleep regulation as well as arousals and possibly the etiology of sleep-related disorders.

Moreover, studies indicate that during the periods of hormonal alterations, women get predisposed to various sleep-related disturbances like decline in sleep quality and sleep deprivation, as well as other sleep disorders such as OSA, RLS, and insomnia.[1]

Women are more likely than men to complain of insomnia, headache, irritability, and fatigue than the typical symptoms of loud snoring and breathing cessation during sleep.

Premenopause versus Postmenopause and Sleep Disorder

Compared with pre/perimenopausal women, postmenopausal women were more often reported to have difficulty in the onset of sleep and possible sleep-onset insomnia disorder. Postmenopausal women were also more likely to screen positive for OSA in comparison to premenopausal women. The two groups did not vary on sleep dissatisfaction, daytime somnolence, sleep-maintenance insomnia disorder, and rest less leg syndrome.[15]

In another study, total sleep time in pre- and postmenopausal women was similar but shorter than in young women. Sleep efficiency followed the same pattern, being 93.4% in young women, 84.3% in premenopausal and 80.2% in postmenopausal. Pre- and

postmenopausal women had decreased slow-wave sleep (duration or activity) and increased wake time after sleep onset (duration or frequency). Insomnia complaints were more frequent after the menopause. Sleepiness and mood scores were almost comparable in all age groups. Reaction speeds declined with increasing age. After the menopause, better cognitive performance was associated with more rapid eye movement sleep.

Objective sleep measures varied to a significant extent among the young and postmenopausal women. These variations might be more because of the physiological process of aging than the rapid changes throughout the menopause since similar sleep patterns were already present in the premenopausal women. The complaints regarding increase in the duration of sleep after menopause were not associated with disturbances in the objective sleep quality, mood, or cognitive performance.[16]

Pathogenesis

Circadian rhythm is an internal biological clock which initiates commencement and monitoring of various physiological processes. This circadian pacemaker is located in the suprachiasmatic nucleus present in the hypothalamus. The circadian clock undergoes many changes throughout the life, at both physiological and molecular levels. The existence of sex differences does exist, and so the consequences of sleep disturbances associated with menopause are a good example. Endogenous secretion of melatonin decreases with increase in age and varies with gender, and in menopausal women, it is associated with a significant reduction in the melatonin levels, thus affecting the sleep patterns.[17]

The level of melatonin decrease (especially at nighttime) with age, more so during the peri- menopausal period. Postmenopausal women usually have increased sleep latency time as well as more awakenings during the middle of the night and in the early morning. Although these sleep-related complaints in menopause may be multifactorial (such as poor sleep hygiene, depression, primary sleep disorders, SDB, fibromyalgia), decreased melatonin secretion and the disturbance in the circadian oscillator system are also of substantial relevance, both with regard to the sleep-disturbing symptoms and to the direct impairment of sleep regulation. These sleep disorders have been treated by hormonal supplementation with melatonin along with improvement in sleep hygiene and the support of this hypothesis is that melatonin is an important determinant of sleep in advancing age and in menopause which ultimately decides the quality and quantity of sleep.[18] Thus, the endogenous secretion of melatonin decreases with aging across among women, menopause is associated with a significant reduction in melatonin levels.[19,20]

Reproductive hormones have an overall protective effect on sleep apnea in women of premenopausal age group. Progesterone stimulates the benzodiazepine receptors, gamma-aminobutyric acid receptors and thus induces sleep and works as anxiolytic. Premenstrual falls in progesterone levels are associated with sleep disturbance. Similar has been postulated to be responsible for increased incidence of sleep disorder during peri-menopasual and postmenopausal period.

Similarly, estrogen is involved in norepinephrine, serotonin, and acetylcholine metabolism. It increases the rapid eye moment (REM) sleep, total sleep time and decrease sleep latency, and spontaneous arousals. It is also known to have a thermoregulatory effect at night and indirectly improves sleep. Further, by regulating 5HT, it may also exert antidepressant effect and indirectly also contribute in improving sleep quality.

Spectrum of Clinical Presentation

Sleep disorders in the menopause are common. Although these disorders may be directly because of the menopause and/or due to the associated VMS, the etiology being multifactorial, which includes wide array of associated conditions. They may simply emerge as a part of the physiological process of aging and not being particularly related to decrease in estrogen levels or, alternatively, because of other conditions such as breathing or limb movement syndromes, depression, anxiety, co-morbid medical diseases, medication, pain and/or psychosocial factors. The wide spectrum of sleep disorders encountered in menopausal women include insomnia, nocturnal breathing disturbances, and the associated sleep disorders that accompany the restless leg syndrome, periodic leg movement syndrome, depression, and anxiety.[21]

Chronic insomnia (difficulty in sleep for >3 weeks) is usually common among postmenopausal women and is often associated with anxiety, depression or pscychosis, or mood disorders. If not treated adequately along with treatment of associated problem at least for 3 to 6 months may be very commonly associated with withdrawal or rebound insomnia. Incidence of short-term insomnia (difficulty in sleep for 3–21 days) is more common overall, but higher incidence during transition period of menopause is observed. It may require treatment for more than 3 weeks in majority of the cases.

Transient insomnia (difficulty in sleep for 1–3 days) can be encountered with equal propensity in younger age

women, peri-menopause or menopause. May require treatment for few days or may not require treatment at all.[22]

Insomnia is very common among the postmenopausal women age group and further increases the risk of depression in this already-vulnerable population.[23]

The relatively less common sleep disorders during peri-menopausal or menopausal women's include, Bruxism: Involuntarily grinding or clenching of the teeth while sleeping; Hypopnea syndrome: Abnormally shallow breathing or slow respiratory rate while sleeping; Narcolepsy excessive daytime sleepiness; Cataplexy a sudden weakness in the motor muscles that can result in collapse to the floor; Night terror/sleep terror disorder: abrupt awakening from sleep with terror*;* Parasomnias: disruptive sleep-related events involving inappropriate actions during sleep stages - sleep walking; Periodic limb movement disorder*:* Sudden involuntary movement of arms and/or legs during sleep, for example kicking the legs. Also known as nocturnal myoclonus; Rapid eye movement behavior disorder*:* Acting out violent or dramatic dreams while in REM sleep; RLS An irresistible urge to move legs; *Sleep paralysis*: is characterized by temporary paralysis of the body shortly before or after sleep. Sleep paralysis may be accompanied by visual, auditory or tactile hallucinations; Sleepwalking\ or somnambulism; Nocturia: A frequent urge to the bathroom to urinate at night for quite a couple of times. It differs from enuresis, or bed-wetting, in which the person is not aroused and still sleeping, but the bladder nevertheless empties and Somniphobia*:* a state of extreme anxiety and fear for even the thought of going to sleep.

Screening and Investigations

Since sleep disorders in postmenopausal women cannot be attributed to hormone changes only, as there are other disorders which can cause sleep problems in these women. Thus, it is very important to have comprehensive for all other associated possible comorbid conditions which can independently affect the sleep.

Further, sleep disorders and insomnia still largely remain a clinical diagnosis based on the subjective complaints of patients. The most commonly used tools for the evaluation of associated depression and anxiety are Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale.

Careful assessment be made by taking proper history not to establish clinical diagnosis of insomnia or sleep disorder but also to have an assessment regarding common comorbid condition. An accurate and detailed history from the patient, patient's partner, or family member combined with a sleep questionnaire can help in eliciting critical information. Most sleep-related complaints fall into three categories: insomnia, excessive sleepiness, or abnormal behaviors during sleep. First, the chief complaint is to be carefully evaluated like when symptom(s) started, any particular pattern of symptoms since onset, and other contributing factors (medical, environmental, occupational, psychological/stress, lifestyle choices) that may have predisposed to or precipitated the illness. Assess the impact of the sleep complaint on patient's life, and inquire about his or her meal and sleep schedules, sleep hygiene, restless legs sensation, snoring, witnessing of any apneic episodes, sweating, coughing, gasping/choking/snoring, dryness of the mouth, bruxism, excessive movements during sleep, periodic limb movements, any abnormal behaviors during sleep, daytime sleepiness, presence of cataplexy, sleep paralysis, and hypnagogic or hypnapompic hallucinations. Then, evaluate about the caffeine intake, alcohol and nicotine use, as well as use of illicit drugs. Review the pertinent medical/surgical/psychiatric history and past treatments, and their efficacy or lack thereof. Carefully evaluate if there is any family history of sleep disorders (snoring, OSAS, narcolepsy, RLS). Laboratory tests rarely performed to assess and therefore treat sleep disorders include the polysomnogram (PSG), multiple sleep latency test, maintenance of wakefulness test, actigraphy, video-PSG, and electroencephalography (EEG), including 24-h ambulatory EEG.

PSG is a complete, nocturnal, laboratory-based monitoring, which simultaneously records numerous variables during sleep. It includes various modalities such as electrocardiogram, sleep staging (EEG), electro-oculogram, submental electromyogram (EMG), nasal or oral airflow, respiratory efforts, oximetry, anterior tibialis EMG, and position monitoring. Depending upon the clinical diagnosis, additional parameters may be added: transcutaneous CO2 monitoring or end-tidal gas analysis; extremity muscle activity; motor activity movement; extended video-EEG; penile tumescence; esophageal pressure; gastroesophageal reflux; snoring; and continuous blood pressure recording.[24]

Management

Benzodiazepine hypnotics and the newer agents zolpidem, zopiclone, and zaleplon are preferred over barbiturates. Benzodiazepine compounds with a shorter half-life are favored in patients with sleep-onset insomnia. These compounds are considered appropriate for the elderly population

because of a decreased risk of accidental falls and respiratory depression.

Benzodiazepines which have longer half-lives are favored for patients who have significant daytime anxiety and who might be able to tolerate the next-day sedation but would otherwise be impaired further by rebound daytime anxiety. These benzodiazepines also are appropriate for patients receiving treatment for major depressive episodes because the short-acting agents can worsen early-morning awakening. However, longer-acting benzodiazepines can be associated with next-day cognitive impairment or delayed daytime cognitive impairment (after 2 to 4 weeks of treatment) as a result of drug accumulation with repeated administration.

Still Benzodiazepines remain the mainstay of the treatment in majority of the sleep disorders including chronic insomnia. Treatment of associated anxiety, depression, or pscychosis is important and sedatives being used as adjunct and be discontinued gradually after 3 to 6 months is the main line of treatment. However, risk of tolerance and abuse is maximum among chronic insomniacs. A slowly eliminated drug is preferable because of the rebound insomnia and withdrawal symptoms associated with such drugs.

Fort the management of short-term insomnia, lowest effective dose of Benzodiazepines, 30 minute before sleep after three night acceptable sleep, skip few doses and then use 2 to 4 time a week not more than 3 weeks is the treatment strategy recommended these days.

Similarly, for the transient insomnia, use of low dose Benzodiazepines, with short duration of action for 2 to 3 nights preferably newer non-BZD hypnotics has increased due to their rapid onset of action, minimal next-day impairment, and absence of cumulation or minimum possibility of rebound insomnia on stopping.[18]

However, it is also to understand that sedative and hypnotic are absolute safe in elderly. Clinician should always try to look for other associated factors like anxiety depression, dementia, loneliness, and loss of family support while treating sleep disorders. Smaller than usual dose of short acting BDZ, e.g., Oxazepam are to be preferred. If BDZ not tolerated, then use of non-Benzodiazepines like Zolpidem and Zoleplon are recommended.

Further, clinician must remember that among this venerable population there is high possibility of drug interactions, if already on other drugs. The risk of fall and fractures increases in elderly on the long-term hypnotic therapy. Thus, fall and fracture prevention techniques should be encouraged to those patients and planned to start short-term benzodiazepines preferably. Treatment of associated anxiety, depression, or psychosis is important and for this use of sedatives as adjunct and discontinue gradually after 3 to 6 months should always be the approach in such cases. Risk of tolerance and chances of abuse are maximum among the chronic insomniacs. A slowly eliminated drug is preferable because rebound insomnia and withdrawal symptoms are least marked with such drugs.

For the management of other Sleep disorders Mono-therapy or in combination following drugs can be used very effectively, i.e., Tricyclic antidepressant, SSRI, Melatonin, Duloxetine, fluoxetine, Imipramine, Nortriptyline or amitriptyline.

Other drugs which may be useful are Eszopiclone, escitalopram, gabapentin, isoflavones, valerian, quiteiapine XL, citalopram, mirtazapine followed by long-acting melatonin, ramelteon, Pycnogenol, may also be considered depending on the additional requirement.[25-28]

Menopausal hormone therapy improves the quality of sleep in women along with improvement in concomitant VMS.[25] Women suffering from insomnia related to VMS can be treated with hormone replacement therapy (HRT). Oestrogen itself may also have an antidepressant as well as a direct sleep effect.[26]

Welton *et al*.,[29] Sarti *et al*.,[30] in their respective studies suggested that hormone therapy to be superior over placebo in improvising sleep disorders among postmenopausal women.

Gambacciani *et al*.[31] in their study reported that low estrogen dose may have a value in the treatment of menopausal women in which sleep disturbances may be a symptom of estrogen deprivation. Low-dose estrogen associated with low-dose micronized progesterone may especially benefit women who complain of disturbed sleep.

Kagan *et al*.[32] in their study suggested that a single-capsule 17β-estradiol-progesterone significantly improved MOS-Sleep parameters from baseline to week 12, which was sustained for up to 12 months, and was associated with a very low incidence of somnolence.

Similarly, Ensrud *et al*.[33] suggested that among perimenopausal and postmenopausal women with hot flashes, both low dose oral estradiol and low-dose venlafaxine compared with placebo modestly reduced insomnia symptoms and improved subjective sleep quality.

However, few contrary results were also reported by Lindberg *et al*.[34] Mirer *et al*.[35] which failed to establish any superiority of hormonal therapy over placebo in sleep disorders both in premenopausal or postmenopausal women's.

Lindberg *et al.* in their study also reported that there is no evidence that female sex hormone changes during menopause per se are able to explain the increase in SDB in midlife women and HRT may not have any beneficial effect on SDB.[34]

Mirer *et al*.[35] in their study suggested that hormone therapy was negatively associated with SDB. The association of hormone therapy and SDB was heterogeneous ($P < 0.01$); apnea-hypopnea index among users was 15% lower in the early period but similar to nonusers in the late.

The study of Shahar *et al*.[36] also reported the inverse association between hormone use and SDB, particularly among women 50 to 59 years old.

In another recent study, estradiol levels were significantly elevated in non-OSA than in OSA patients ($P < 0.05$). Reduced estradiol levels were correlated with an increased risk of OSA among depressed perimenopausal and postmenopausal women. However, study did not evaluate any effect of HRT on OSA.[37]

Manber *et al*.[38] in their pilot study to evaluate the impact of estrogen and estrogen plus progesterone HRT on mild-to-moderate SDB in postmenopausal women suggested that estrogen to have a substantial beneficial effect on measures of SDB in postmenopausal women. Overall, no additional benefit was seen with the addition of progesterone. In fact, progesterone attenuated the beneficial effects of estrogen in 4 out of the 6 participants.

Since there is lack of consistency in studies partly due to difference in preparations of hormone, age, symptomatology, type of menopause and in light of few recent studies concluding HT to offer no significant advantage in sleep disorders and further due to recent debate surrounding use of HT in menopause due to established risk of breast cancer, cardiovascular risk, ovarian cancers etc., presently HT is not recommended as line of treatment for sleep disorders among postmenopausal women's by the current guidelines of Indian Menopause society.[39]

Nonpharmacological Treatment

Self-Hypnosis is a non-pharmacological treatment for poor sleep and hot flashes in menopausal women. The goal of hypnosis is to help educate and train the subjects to perform self-hypnosis to alleviate the underlying symptoms.

The use of hypnosis as a treatment for poor sleep has shown benefits for both acute and chronic insomnia. There were clinically meaningful improvements in reducing the perception of poor sleep quality in 50%–77% of women across time.[40]

Cognitive therapy is aimed at changing patients belief and attitude about insomnia. Combined cognitive and behavioral technique beside changing patients beliefs, have the behavioral component which may include stimulus control and or sleep restriction therapy with or without the use of relaxation therapy helps majority of postmenopausal women's suffering from chronic insomnia. Progressive muscle relaxation training also helps in some of the patients dramatically. Further, stimulus control therapy, sleep restriction therapy are also some important techniques which help many patients successfully.

Beside this, sleep hygiene preventive practices need to be advocated for overall benefit to postmenopausal patients of sleep disorders. Sleep only when sleepy, if you can't fall asleep within 20 minutes, get up and do something boring until you feel sleepy, don't take naps. Stay away from caffeine, nicotine, and alcohol at least 4–6 h before bed; Have a light meal before bed; Avoid sleep in day; Stimulus control; Establish regular bedtime; Make sure your bed and bedroom are quiet and comfortable; Avoid too much of water before sleep; Wear comfortable clothes; Switch off mobile phones; Don't try to recall events of the day; Don't worry for the next day; Dead man position-good sleep; Develop a regular bed time; Moderate exercise help in good sleep; Warm milk is useful as it contain d-tryptophan which decrease onset time of sleep; Training in relaxation and meditation help.

Conclusion

Women are likely to suffer from sleep disorders more in comparison to men during menopause and with advancing age. Insomnia with or without associated anxiety or low lying depression is most common manifestation. Sleep disorders and insomnia still largely remain a clinical diagnosis based on the subjective complaints of patients. Benzodiazepines remain the mainstay of the treatment in majority of the sleep disorders including chronic insomnia. Treatment of associated anxiety, depression, or psychosis is most important. HRT presently lacks concrete evidence to be used in menopausal women for sleep disorder. Sleep hygiene preventive practices, self hypnosis, medication, and exercise play a very important role.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Journal of
Clinical Medicine

MDPI

Review

Insomnia in Postmenopausal Women: How to Approach and Treat It?

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Abstract: Insomnia is one of the major complaints of menopausal women with advancing age and may be complexly related to a variety of causes. However, there is still a lack of standards on the general approach and treatment for insomnia in menopausal women. The aim of this review is to summarize recent pathogenic theories of sleep disturbance in the menopausal period and discuss the approach and management of insomnia in postmenopausal women. Sleep disturbances in menopausal women may be associated with physical and psychiatric factors and other comorbid diseases. Careful history taking and multidisciplinary physical and psychosocial evaluation are necessary and, in particular, comorbidities related to sleep disorders, such as obstructive sleep apnea, must be taken into consideration. A unique aspect of insomnia in postmenopausal women is that menopausal symptoms due to hormonal decline can be closely related to sleep disturbances. Therefore, menopausal hormone therapy (MHT) should be considered as the treatment of choice among pharmacological treatments following cognitive behavioral therapy, which is suggested as the first-line treatment in the general population insomnia treatment guidelines. Additionally, melatonin and 5HT-based drugs, which have fewer side effects, along with MHT should be preferentially recommended in menopausal women.

Keywords: hot flushes; insomnia; menopause; sleep disorder; menopausal hormonal therapy

Citation: Jeon, G.-H. Insomnia in Postmenopausal Women: How to Approach and Treat It? *J. Clin. Med.* **2024**, *13*, 428. https://doi.org/10.3390/jcm13020428

Academic Editor: Błażej Męczekalski

Received: 21 November 2023
Revised: 3 January 2024
Accepted: 10 January 2024
Published: 12 January 2024

1. Introduction

With the decline of reproductive hormones in the menopausal transition period, a substantial number of women experience physiological and psychological changes. Sleep disturbance is one of the major complaints of menopausal women with advancing age. Menopausal women also frequently experience other typical menopausal symptoms, including hot flashes (HFs), night sweats, palpitations, mood changes, anxiety, and depression, which also increase the risk of developing sleep problems [1]. Indeed, various sleep problems, such as decreased sleep duration, poor sleep quality, and early morning awakenings, commonly begin in the menopausal period [2]. It is reported that women in menopausal transition or menopause suffer from sleep disturbance or insomnia, ranging from 35% to 60%, and a significant number of women experience severe symptoms that impair daytime functioning [3]. Sleep disturbance can cause fatigue, somnolence, mood disorders, memory impairment, lack of attention, and even accidents, which can lead to behavioral, occupational, and social problems [4]. Recent studies revealed that insomnia is also associated with significant medical problems, such as cardiovascular disease, diabetes, and an increased risk of mortality [5]. In addition to menopause, it has been reported that women have specific periods related to vulnerability to sleep disorders, such as the menstrual cycle and pregnancy, suggesting a link between sleep disorders and female hormones [6,7]. As such, insomnia is closely related to hormonal changes and, although it is a major menopausal symptom, there are currently no universal guidelines for treating insomnia in menopausal women. Recently, Proserpio et al. also reviewed the mechanism and treatment of insomnia in menopausal women, with similar content to this

review [8]; however, this review categorizes the causes and treatment of sleep disorders in menopausal women to make it easier to approach clinically and contains updated contents on menopausal hormone therapy (MHT), melatonin, and orexin antagonist. This review will summarize recent pathogenic theories of sleep disturbance, including hormonal changes during the menopausal period, and discuss the approach and management of insomnia in postmenopausal women.

2. Insomnia and Sleep Disorders: Definition

Insomnia is defined as difficulties falling asleep or maintaining sleep, which result in daytime impairment, despite adequate opportunity and circumstances to sleep. Chronic insomnia disorder is defined when it occurs at least three times per week for three months, according to the International Classification of Sleep Disorders, Third Edition (ICSD-3). Insomnia was traditionally approached as a primary or secondary (comorbid) disorder, provoked by physical problems or psychosocial factors, etc. (as will be discussed later in the Insomnia Etiology Section), but there were issues of uncertainty with the nature of the associations and the direction of causality in comorbid insomnia cases; thus, all insomnia diagnoses were consolidated under chronic insomnia disorder [9]. In addition to insomnia, obstructive sleep apnea (OSA), which is classified as a sleep-related breathing disorder, restless legs syndrome (RLS), and periodic movement disorder are major certain comorbid diseases encountered in sleep disorders in postmenopausal women. Indeed, insomnia and sleep-related breathing disorders are the two most common sleep disorders [9,10]. Other sleep disorders that are less common or unrelated in menopause include circadian rhythm sleep–wake disorder, narcolepsy, idiopathic hypersomnia, cataplexy, night terrors, parasomnias, and sleep paralysis [11].

3. Sleep Disturbance across Menopause: Epidemiology

Middle-aged women have increasing complaints of sleep disorders as they enter menopausal transition and the menopausal period. The incidence rates of sleep problems show 39–47% in peri-menopausal and 35–60% in postmenopausal women, compared to 16–42% in premenopausal women [3]. Although sleep deteriorates with age and is affected by many physical problems (lower back pain, musculoskeletal disorders, urinary symptoms, hot flushes (HFs), etc.), mood disorders and psychosocial factors, socioeconomic, and racial/ethnic factors [10,12], an independent relationship between menopausal stages and sleep disturbance, controlled for the effects of aging and other confounders, was shown in a meta-analysis of 24 cross-sectional studies [13]. In addition, the incidence of sleep-related breathing and movement disorders also increases in postmenopausal women due to age and obesity, as discussed later.

Meanwhile, women who had undergone surgical menopause and were not taking hormone therapy had the highest prevalence of sleep disturbance compared with natural menopausal transitional women, independent of age or years since surgery. The most common sleep complaint in these women was reported as frequent awakenings during sleep in the longitudinal analysis of the Study of Women's Health Across the Nation (SWAN) [3]. Regarding the predictors of poor sleep quality during menopause, it has been reported that depressive symptoms, personal crisis, perceived health impairments, and frequent night sweats are related [14]. In a cohort study that followed a population-based sample for over one year, Lebland et al. reported that the greatest risk of developing insomnia was a previous insomnia episode, and thus premenopausal sleep status can also be considered as an important factor in predicting postmenopausal insomnia [15].

4. Insomnia and Menopause: Pathogenesis and Etiology

Sleep disturbance in postmenopausal women is pathophysiologically multifactorial (Table 1). Physiologically, it may be strongly associated with menopause symptoms, such as HFs and night sweats that can be experienced along with female hormonal changes [16], and psychiatrically, with mood disorders, anxiety, and depression [10]. In addition, fam-

ily/economic/social stress, obesity, ill health, and drug and alcohol intake are common causes of sleep problems in middle-aged women, and commonly encountered comorbid diseases with sleep disorders include OSA, RLS, and periodic leg movement syndrome. After menopause, the prevalence of OSA increases due to weight gain and changes in fat distribution from increased testosterone production and decreased female hormones, and the incidence of RLS increases [14,17]. There is limited data showing that basic physiological changes, such as alterations in the circadian system and decreased melatonin secretion due to aging itself, also contribute to sleep difficulties in menopause [18].

Table 1. Etiology of sleep disorders in menopause.

Physiologic/Physical
Age
Circadian rhythm modifications
Decreased melatonin secretion
Female sexual hormone changes
Decreased estrogen and progesterone, increased FSH
Menopausal symptoms
Hot flushes, night sweats
Others
Bladder problems,
Ill health, chronic pain—musculoskeletal disorders, osteoarthritis, fibromyalgia, cancer, etc.
Poor sleep hygiene/circumstances
Medication, coffee, smoking
Psychiatric/Psycho-social
Mood disorder—depression
Anxiety
Illegal drugs, alcohol intake
Others—familial/economic/social problem: stress, bereavement, divorce, unemployment, finances, etc.
Comorbid diseases with sleep disorders
Obstructive sleep apnea
Restless legs syndrome
Periodic limb movement syndrome
Others
Circadian rhythm sleep–wake disorder
Narcolepsy, idiopathic hypersomnia
Parasomnias

FSH: follicle-stimulating hormone.

4.1. Reproductive Hormonal Changes

Previous studies have reported beneficial effects of female sexual hormones on sleep. Estrogen blocks wake-promoting neurotransmitters, such as acetylcholine, histamine, norepinephrine, serotonin, and dopamine [19], and is known to have a thermoregulatory effect of regulating the lowest body temperature during the night, which provides good conditions for falling asleep [20]. Overall, estrogen seems to increase the rapid eye movement sleep and total sleep time and decrease sleep latency and awakenings after sleep [21]. Estrogen may also exert an antidepressant effect by regulating 5HT [22]. Progesterone stimulates benzodiazepine receptors, causing the release of gamma-aminobutyric acid (GABA), a sedating neurotransmitter, and thus induces sleep favoring non-rapid eye movement sleep [23,24]. Progesterone is also known to exert an anxiolytic and respiratory stimulant effect [24,25], which may also help promote good sleep.

Several population studies showed an association between reproductive hormone levels, including estradiol, FSH, and inhibin B, and sleep quality or sleep disruption in menopausal transition women [3,17,26–29]; however, their findings are inconsistent, and

correlation with objective polysomnographic indices has also not been clearly demonstrated. The isolation of hormonal effects seems to be challenging because there are multiple influencing factors, such as high variability of their measurements across the menopausal transition.

4.2. Vasomotor Symptoms

HFs are a physiological result of peripheral and central temperature increases due to lowered estrogen levels. HFs are common complaints, reported by up to 80% of menopausal women [30], accompanied by increased body temperature during the nighttime and night sweats, which lead to sleep disturbance. A recent study found that 69.4% of HFs interfered with sleep [31], and an increase in HFs was common during early sleep (N1) and wake, typically preceding or occurring simultaneously with nighttime awakenings [32]. The SWAN data showed that women with moderate to severe HFs had a higher risk of frequent nocturnal awakenings compared to women without HFs [33]. Indeed, Campbell and Murphy reported that insomnia was present in 29% of menopausal women with HFs vs. 11% in those without HFs [34].

4.3. Mood Disorders

The relationship between sleep and mood disorders is well established in the general population. It has been reported that up to 90% of patients with major depressive disorder have sleep problems [35], and that symptoms of depression and anxiety are associated with self-reported poor sleep, in the setting of a non-psychiatric population [36]. Women are at increased risk of developing major depressive disorder during the menopausal transition, especially if they suffer from HFs [10]. It was postulated that HFs disrupt sleep, intrusive anxious thoughts during nocturnal awakenings trigger daytime mood symptoms (domino effect), and depression links with insomnia, in a vicious cycle [37]. Additionally, Vousoura et al. found that HFs and depressive symptoms were associated with different patterns of sleep disturbance, with HFs being related to frequent awakening during sleep, whereas depression was uniquely associated with difficulty falling asleep and waking up earlier than desired [38].

4.4. Circadian Rhythm Modifications/Decreased Melatonin Secretion

Circadian rhythm is an internal biologic clock for commencing and monitoring of various physiological processes, including the sleep/wake time schedule. This circadian pacemaker, located in the hypothalamic suprachiasmatic nuclei and the circadian clock, undergoes substantial changes throughout life. Melatonin, synthesized in the pineal gland, also regulates the circadian rhythm by detecting changes in the length of day and night or seasonal sunlight hours [39]. Aging itself is associated with both circadian rhythm alterations and decreased melatonin secretion and, in particular, women have been shown to experience greater sleep difficulties—difficulty falling asleep and waking up earlier than desired—due to a significant decrease in melatonin levels following menopause as well as aging [18,39]. Sex steroids modulate the sleep-favoring effects of melatonin, such as peripheral vasodilation and thermoregulation; therefore, in menopausal women, the decline in female hormones facilitates the occurrence of insomnia [40]. Additionally, the gradual decrease in melatonin along with the steep decrease in estrogen concentration during menopause have been reported to contribute to insomnia in postmenopausal women [41].

5. Assessment of Insomnia in Menopausal Women

The diagnosis of insomnia is mainly performed clinically based on the subjective complaints of the patient, and in menopausal women, insomnia commonly occurs as a secondary disorder to physical and psychiatric problems, underlying other sleep disorders, such as OSA or RLS [10,11]. Therefore, careful assessment by proper history taking is important to exclude the comorbid factors. A detailed history from patients and family members using sleep questionnaires and diaries, including the onset of insomnia, pattern and

frequency (number of nights/week) of insomnia symptoms, sleep/awake schedule, frequency and bother from menopausal symptoms (HFs and night sweats), and contributing factors or diseases, should be performed. The impact of the sleep complaint on the patient's life, daytime sleepiness, sleep hygiene, and physical symptoms—snoring, any apneic episodes, dryness of mouth, sweating, restless legs sensation, and periodic limb movements—suggesting other sleep disorders, such as OSA, RLS, etc., should be assessed. The medical, surgical, and psychiatric history, and medications and caffeine/alcohol/nicotine/ illicit drug use, are also reviewed [11,42]. Although a polysomnography (PSG) is not generally an essential test for the assessment of insomnia, in menopausal women suffering from persisting sleep disturbances suggesting primary insomnia or other sleep disorders, such as OSA, PSG and a comprehensive assessment are needed [10,43]. Detailed contents of these comorbid diseases with sleep disorders are considered outside the scope of this review, which highlights primary or secondary insomnia in postmenopausal women.

6. Management of Insomnia in Menopausal Women

First of all, individual treatment for the identified underlying disease or condition of insomnia is generally necessary, but insomnia after the menopausal transition may be associated with multiple overlapping factors, so management can be complicated and requires individualized treatment. In cases related with multiple sleep disorder factors, such as moderate to severe HFs, depression, and OSA, combined treatments can be considered. The main treatment options for menopausal women with insomnia include non-pharmacological treatment and pharmacological treatment, which are represented by cognitive behavioral therapy for insomnia (CBT-I) and MHT/non-hormonal pharmacological treatment, respectively [42,44]. According to the clinical practice guidelines of the American Academy of Sleep Medicine (AASM) and the European Sleep Research Society (ESRS) for the treatment of insomnia, CBT-I is the first-line intervention for all patients with chronic insomnia, and similar considerations should be given to menopausal women with insomnia. A pharmacological treatment can be offered if CBT-I is not effective or unavailable [44,45]. In patients with OSA, non-pharmacological therapy—continuous positive airway pressure or an oral appliance—should be applied according to the severity of disorder. In addition, in the cases of RLS, triggering factors such as coffee, nicotine, alcohol, antidepressants, and antihypertensive drugs should firstly be avoided, and dopaminergic agonists are the first-line treatment for moderate to severe disease [10]. An example of a flowchart for diagnosing and treating insomnia in postmenopausal women, reflecting medical history and related symptoms, is provided in Figure 1.

6.1. Non-Pharmacological Treatment

CBT-I is a treatment that includes cognitive therapy to change patients' beliefs and attitudes about sleep and behavioral techniques to improve their insomnia, which typically includes sleep hygiene education to provide better sleep conditions, sleep restriction therapy to increase sleep efficiency, stimulus control therapy to adjust the relationship between sleep and sleep stimulation conditions, relaxation training to promote a good sleep, and cognitive therapy to correct dysfunctional thinking about sleep [46,47]. A meta-analysis and systematic review published by Trauer et al. in 2015 suggested that CBT-I intervention was effective in the general population with chronic insomnia [48]. Recent studies of a randomized controlled trial (RCT) with peri- and post-menopausal women with insomnia have reported that CBT-I improved insomnia and reduced HFs' interference, as well. CBT-I in menopausal women resulted in significant improvements in self-reported insomnia symptoms, sleep latency, sleep quality, and wake time after sleep compared to the menopause education protocol [49]. In a pooled analysis of data from 4 RCTs, which compared the effects of pharmacologic and non-pharmacologic interventions on insomnia and HFs in 546 peri- and post-menopausal women, CBT-I was also found to be more effective for reducing insomnia symptoms in women with HFs compared with other pharmacologic or exercise treatments [50]. In addition to CBT-I as a non-pharmacological

treatment method for insomnia, light therapy and exercise therapy are also expected to be effective in treating insomnia. Light therapy is helpful in stabilizing the circadian rhythm, and exercise therapy is helpful in strengthening sleep homeostasis and improving sleep latency and maintenance [51,52]. The ESRS insomnia treatment guidelines currently suggest light therapy and exercise therapy as adjuvant treatments for insomnia [45], and these can also be considered as non-pharmacological treatment methods. A brief description of CBT-I, the first-line intervention for chronic insomnia patients, is provided in the following sections [46,47].

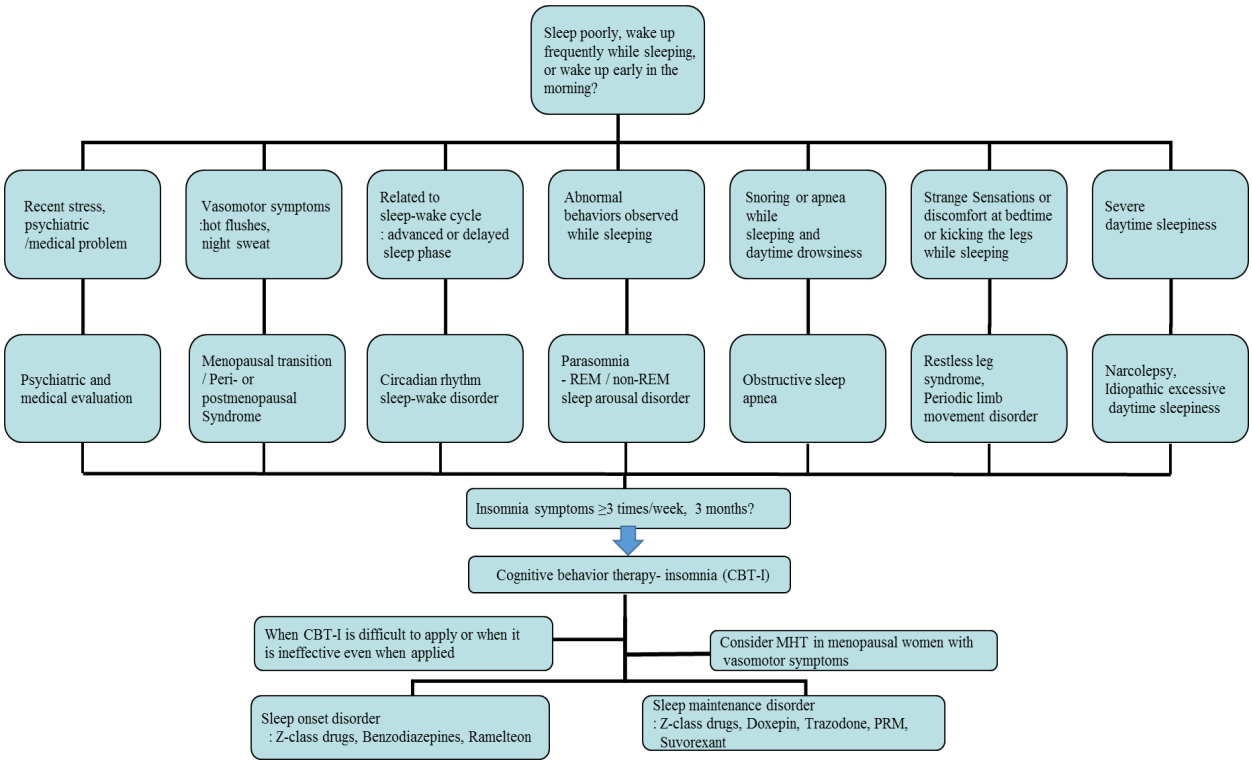

Figure 1. An example of a flowchart for diagnosing and treating insomnia, reflecting patient history and related symptoms, in postmenopausal women. REM: rapid eye movement; MHT: menopausal hormone therapy; PRM: prolonged-release melatonin.

6.1.1. Sleep Hygiene Education

Sleep hygiene education teaches patients about behavioral and environmental factors to improve sleep, as follows: ensuring the sleep environment is quiet and at a temperature suitable for sleeping, establishing a regular bedtime, adequate exercise and exposure to sunlight, avoiding caffeine in the afternoon and excessive fluids, alcohol, and nicotine at bedtime, limiting naps to 30 min, limiting bedtime screen use, etc.

6.1.2. Sleep Restriction Therapy and Stimulus Control Therapy

These behavioral treatments of insomnia are for breaking the maladaptive connection between going to sleep and the hyperarousal state. Sleep restriction therapy considers the patient's actual sleep time and limits the time spent in bed to increase the sleep desire. Monitoring the sleep and wake times every day and trying to stay in bed only during sleep can improve sleep efficiency. Stimulus control therapy involves breaking the relationship between being in the bedroom and negative aspects of sleep, such as lying in bed only when tired and using the bed only for sleeping.

6.1.3. Relaxation Training

Relaxation training is used to control thought patterns and somatic tension that interferes with sleep. This relaxation-based intervention, alternating contraction of muscles with relaxation, is achieved through progressive muscle relaxation, abdominal breathing, etc.

6.1.4. Cognitive Therapy

Cognitive therapy examines negative beliefs or dysfunctional thoughts about sleep, such as the belief that insomnia will persist, excessive worry or obsession with sleep, trying to lie down and sleep beforehand, etc., and replaces them with rational thoughts or facts by setting a realistic amount or quality of sleep.

6.2. Menopausal Hormone Therapy

Based on the identified roles of reproductive hormones in sleep and the theory that vasomotor symptoms (VMS), such as HFs, in menopause cause insomnia, as discussed above, MHT can be an important treatment for insomnia in menopausal women with hot flashes. Indeed, a meta-analysis including 15,468 women from 42 trials published in 2017 showed that MHT improved sleep quality in menopausal women with VMS, along with improvement in concomitant VMS. There was no significant difference when women without VMS were analyzed separately or combined in this study [53]. However, several previous studies exploring the effects of estrogen and progesterone on sleep efficiency have shown mixed results. While some studies suggested that hormone therapy, such as low-dose estrogen with micronized progesterone or drospirenone, 17β-estradiol-progesterone, and low-dose oral estradiol and venlafaxine, reduced insomnia symptoms compared with a placebo [54–58], some contrary results were also reported, which failed to identify any superiority of MHT over the placebo [59,60]. Even studies favoring the effectiveness of MHT mainly showed improvements in subjective sleep quality and tended to show inconsistent results in objective PSG variables [61–63]. This lack of consistency is due to the heterogeneity of the trials regarding differences in study populations, age, definitions of menopausal stages, types of menopause, preparations of hormones, and unstandardized sleep scales; therefore, there is a limitation of overall certainty in the evidence of the MHT effects on sleep disturbances [11,53]. Nevertheless, based on the fact that MHT is effective for HFs in peri- and post-menopausal women and helps improve quality of life, there is an emerging view that MHT can be considered as the first-line treatment when insomnia is suspected to be part of VMS, and it is better to first evaluate the response of MHT and then consider other treatments for insomnia in menopausal women with VMS [64]. In the same context, it was reported that the degree of improvement in VMS was an important predictor of insomnia improvement [65]. Considering the bidirectional relationship between insomnia and depression, it is difficult to determine whether insomnia in postmenopausal women is related to the high prevalence of clinical depression or depressed mood during that period or due to menopause itself. The only way to differentiate may be a trial of MHT and consideration of other therapy if insomnia or depression persists after three months of successful MHT [64]. Before using MHT to relieve insomnia in menopausal women, it is important to monitor the side effects of MHT, such as thromboembolic events and breast cancer, and whether the benefits outweigh the risks should be evaluated. Additionally, there are recent studies showing that transdermal treatment was the safest type of hormone therapy in the assessment of risk of venous thromboembolism [66], and micronized progesterone was more effective for improving sleep, as well as reducing HFs [67], which suggests to consider transdermal estradiol and micronized progesterone for the patients at risk of thromboembolism.

6.3. Non-Hormonal Pharmacological Treatment

In the general population, including menopausal women, when it is difficult to apply the recommended first-line treatment of CBT-I or when it is ineffective even when

applied, the following non-hormonal pharmacological treatments can be considered for treating insomnia.

6.3.1. Benzodiazepines and Z-Class Drugs

Benzodiazepines (triazolam, temazepam, and estazolam) and Z-class drugs (zolpidem, zopiclone, and zaleplon) act as agonists of the benzodiazepine receptor component of the $GABA_A$ receptor complex and are commonly used for treating insomnia. Z-class drugs are known to have relatively fewer side effects compared to benzodiazepines, as they are made to mainly bind selectively to type 1 GABA-A receptors and produce only a sleeping effect [68]. Studies have shown that benzodiazepines and Z-class drugs reduce sleep latency, increase total sleep time, reduce awakenings during sleep, and improve sleep quality [44,69]. Considering the pharmacological properties, Z-class drugs with a short half-life (zolpidem IR and eszopiclone) or short-acting benzodiazepines (triazolam) are used for sleep onset disorder, and Z-class drugs such as zolpidem CR and eszopiclone, long-acting benzodiazepines, and antidepressants are appropriately selected and used for sleep maintenance disorder or early awakening [44,70].

In menopausal women with insomnia, several RCTs for Z-class drugs have also reported that zolpidem increased the total sleep time and decreased the wake time after sleep onset and number of awakenings [71], and eszopiclone was effective in the treatment of insomnia, as well as VMS [72]. However, these agents are suggested for short-term use for $\leq$4 weeks at the lowest dose in adults with insomnia due to their unproven long-term efficacy, the risk of tolerance, and the potential for dependence and abuse, according to the AASM and ESRS practice guidelines [44,45]. Common side effects of benzodiazepines and Z-class drugs include headache, dizziness, and daytime sleepiness and drowsiness, and in particular, the elderly are at increased risk of side effects such as cognitive function impairment, delirium, and falls and fractures due to the muscle relaxation effect, although Z-class drugs have relatively fewer side effects compared to benzodiazepines [73]. It is not clear to what extent these sedative hypnotics impact insomnia in postmenopausal women, but considering that older women are more vulnerable to fractures, more caution is needed when prescribing them to older women [74]. Indeed, meta-analyses showed that the use of benzodiazepines or Z-class drugs was associated with an increased risk of falls and fractures in older adults [75,76].

Zolpidem, a Z-class drug, is currently the most commonly used drug for chronic insomnia, and the AASM also suggests the use of zolpidem in adults with sleep onset and sleep maintenance disorders. Additionally, benzodiazepines are recommended as the main treatment for some sleep disorders such as REM sleep behavior disorder, restless legs syndrome, and periodic limb movement disorder, while in patients with sleep apnea, the use of benzodiazepines and Z-class drugs can worsen the symptoms [77–79].

6.3.2. Antidepressants

Given that insomnia is highly implicated in depression, antidepressants can be considered for treating insomnia in menopausal women with comorbid depression. Moreover, antidepressants, such as serotonin and norepinephrine reuptake inhibitors (SSRIs and SNRIs), are valid treatments for VMS in menopausal women with contraindication to MHT [80,81]. Ensrud et al. reported that escitalopram was effective for insomnia in a RCT of 205 peri- and post-menopausal women with HFs [82]. Mirtazapine is also known to be useful in cases of not only insomnia but also depression, which has a sleep-inducing effect and increased slow-wave sleep effect, along with side effects such as appetite, weight gain, and dry mouth [83]. However, there are limited studies on the direct effects of these antidepressants on insomnia; therefore, using antidepressants to treat sleep disruption for women without depression should not be recommended [70]. Nevertheless, some antidepressants that can currently be used for sleep regulation include doxepin and trazodone. Doxepin is the only tricyclic antidepressant approved by the U.S. Food and Drug Administration (FDA) as a treatment for insomnia. When doxepin was administered at 3 mg or 6 mg, the

awakening time after hypnosis, total sleep time, and sleep efficiency were significantly improved compared to the placebo control group, and a meta-analysis demonstrated that it was effective in treating sleep maintenance disorders [84]. Trazodone, a blockade of the serotonin 5-HT2A receptor and histamine H1-adrenergic receptors, was also found to be effective for insomnia in a meta-analysis study [85]. It is used as an off-label sleep medicine at low doses of 25–50 mg, and is known to be helpful for sleep maintenance disorders rather than sleep initiation [86]. Compared to benzodiazepines or Z-class drugs, doxepin and trazodone have an advantage in terms of side effects, as these drugs are less prone to abuse or dependence, and the risk of falling is relatively low, so they may be advantageous when prescribed to the elderly [44,86].

6.3.3. Melatonin

Melatonin basically advances the sleep cycle and has a sleep-favoring effect. Supplementation with melatonin has been reported to improve insomnia symptoms and mood disorders in postmenopausal women without serious side effects [87,88]. A prolonged-release melatonin (PRM) agent (2 mg) was approved for patients with primary insomnia over 55 years old for short-term use in some European countries [89]. Unlike existing melatonin preparations, which did not have sufficient effects due to their short half-life of 35 to 50 min, the prolonged-release formulation can improve the sleep structure by maintaining the concentration over 8 to 10 h, similar to the pattern of melatonin secretion in the body [90]. However, clinical trials among the elderly, including menopausal women, had inconsistent results, not only in the quality of sleep, but also in menopausal symptoms [88,90–92]. AASM and ESRS practice guidelines did not recommended the use of melatonin preparations for sleep onset insomnia or sleep maintenance insomnia due to insufficient evidence on their effectiveness, in which the guidelines comprehensively reviewed melatonin without clearly distinguishing between prolonged-release agents and short-acting agents and judging their respective effectiveness. Considering that there are not enough studies conducted on PRM yet, additional research on PRM drugs seems necessary. However, PRM does not act on GABA receptors, so it has fewer side effects, such as cognitive decline, falls, rebound insomnia, dependence, tolerance, and withdrawal symptoms, compared to benzodiazepines or Z-class drugs, making it an effective alternative to conventional sleep drugs for the elderly population, including menopausal women [93].

Ramelteon is a melatonin receptor (MT1 and MT2) agonist that was reported to be effective in improving sleep quality and efficiency as a result of a meta-analysis study, and it was approved by the U.S. FDA for the treatment of insomnia. The AASM practice guidelines also recommended that it can be used for sleep onset insomnia [44].

6.3.4. Orexin Antagonist and Gabapentin

Orexin is a neuropeptide that plays an important role in promoting wakefulness and impairing thermoregulation and plasma level of orexin increases after menopause. Suvorexant, an orexin OX1 and OX2 receptor antagonist, was approved by the U.S. FDA as a treatment for insomnia in 2014, and the AASM suggested that suvorexant could be used for sleep maintenance disorder. Rahman et al. found that suvorexant was a well-tolerated and efficacious treatment for middle-aged women with VMS-associated insomnia, and it reduced VMS in a double-blinded RCT [94].

Gabapentin is widely known as one of the non-hormonal treatments for VMS in menopausal women. Yurcheshen et al. demonstrated that gabapentin improved sleep quality in menopausal women with HFs at a dose of 300 mg, three times daily, in a RCT [95], and positive effects of gabapentin on nighttime awakenings and sleep-enhancing actions were also observed in the hypothesized novel sleep disorder, LUNA, associated with low serum estradiol causing nighttime awakening [96]. Studies on orexin antagonists and gabapentin are limited, so their precise roles need to be further established.

7. Conclusions

Diagnosis of insomnia in menopausal women is largely performed based on the subjective complaints of patients and may be complexly related to a variety of causes, including changes in female hormones, aging, weight gain, psychosocial problems, and alcohol and drug use. Careful history taking and multidisciplinary physical and psychosocial evaluation are necessary and, in particular, comorbidities related to sleep disorders, such as OSA, must be taken into consideration. Additionally, a unique aspect of insomnia in postmenopausal women is that menopausal symptoms (HFs, mood disorders, musculoskeletal symptoms, and pain) due to hormonal decline can be closely related to sleep disturbances. Therefore, menopausal hormone therapy (MHT) should be considered as the treatment of choice among pharmacological treatments, following cognitive behavioral therapy, which is suggested as the first-line treatment in the general population insomnia treatment guidelines. Additionally, melatonin and 5HT-based drugs, which have fewer side effects, along with MHT should be preferentially recommended in menopausal women. However, there is still a lack of standards on the general approach and treatment for insomnia in menopausal women, and more large-scale prospective studies are needed for further insight on the roles of various treatments for insomnia in menopausal women. Thus, until then, menopausal women with insomnia also need an individualized approach and treatment (MHT, prolonged-release melatonin, 5HT-based drugs, etc.) under the premise that CBT should be used as the first-line treatment, following the treatment guidelines of insomnia for the general population.

Funding: This work was supported by the National Research Foundation of Korea (NRF) Grant, funded by the Korean government (MSIT) (No. 2022R1G1A1011532).

Conflicts of Interest: The author declares no conflicts of interest.

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HHS Public Access

Author manuscript

Curr Psychiatry Rev. Author manuscript; available in PMC 2016 January 01.

Published in final edited form as:

Curr Psychiatry Rev. 2015 ; 11(1): 63–83. doi:10.2174/1573400510666140929194848.

Treatment of Insomnia, Insomnia Symptoms, and Obstructive Sleep Apnea During and After Menopause: Therapeutic Approaches

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Abstract

Understanding sleep complaints among menopausal women is an emerging area of clinical and research interest. Several recent reviews have focused on mechanisms of menopausal insomnia and symptoms. In this review, we present a discussion on the most relevant and recent publications on the treatment of sleep disorders for menopausal women, with a focus on menopause-related insomnia, insomnia symptoms, and obstructive sleep apnea. We discuss both nonpharmacological and pharmacological treatments, including cognitive-behavioral therapy for insomnia (CBT-I), complementary and alternative medicine, hormone replacement therapy, sedative hypnotics, antidepressants, and continuous positive airway pressure. In addition, we briefly discuss methods and considerations of assessment of sleep disorders in menopausal women.

Keywords

complementary and alternative medicine; insomnia; insomnia symptoms; menopause; obstructive sleep apnea; pharmacology; sleep disorders

Introduction

Menopause, defined as the cessation of menstruation for at least one year, is due to the degeneration of ovaries and follicles, in addition to fluctuating ovarian hormone levels.

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Decreased ovarian function precedes menopause in the climacteric or peri-menopausal period. Menstrual cycle changes and vasomotor symptoms decline at a gradual rate, long before menses cease. Psychological and physiological issues often accompany menopause-related vasomotor changes in the form of hot flashes, bleeding irregularities, sexual dysfunction, mood changes, cognitive declines and/or sleep disturbance [1, 2].

As the 470 million postmenopausal women worldwide increases by 1.5 million women annually, and expected to reach a total of 1.2 billion by 2030, approximately 50 – 85% of these women will experience menopause-related vasomotor symptoms [1, 3, 4]. There is a wide variability in the duration of menopause-related symptoms, with many women reporting symptoms decreasing within one year of menopause, while other women complain of persistent vasomotor symptoms for up to, or more than thirty years [5]. Complaints of sleep disturbance, usually in the form of intermittent awakenings, are one of the frequently reported behavioral symptoms of menopause. Studies utilizing diagnostic tools of wrist actigraphy and the Insomnia Severity Index (ISI) have justified insomnia as a prevalent concern in this population [6-10]. Clinical diagnoses of moderate to severe insomnia have been demonstrated in 9.5 - 33% of peri- or postmenopausal women [6, 7]. Large population-based studies confirm these findings, demonstrating 28 - 64% of peri- or postmenopausal women report insomnia symptoms [8, 9].

Beyond its prevalence, sleep disturbance in menopausal women is also associated with negative consequences in numerous domains. Bolge et al.'s [10] survey of 141 postmenopausal women with sleep disturbance and 1305 premenopausal women without insomnia, depicted that sleep disturbance was significantly correlated with occupational impairment and increased visits to the emergency room. Other associations with menopause-related sleep difficulties include mood disturbance, hot flashes, hypertension, use of anti-hypertensive medication, melatonin acrophase offset, and lower global functioning [2].

Objective sleep research utilizing polysomnography (PSG) has documented decreased sleep efficiency, with increased sleep onset latency and increased wakefulness after sleep onset in postmenopausal women compared to premenopausal women [11, 12]. There are many possible factors that can contribute to this phenomenon, including the co-occurrence of hot flashes and mood symptomology [13]. In addition, sleep disruption in menopause may be exacerbated or caused by primary sleep disorders such as obstructive sleep apnea (OSA) [14]. OSA is defined by an apnea hypopnea index of 5, indicating at least 5 complete or partial obstructions of the airway per hour, usually resulting in an awakening [15]. Signs and symptoms of OSA include loud snoring, daytime sleepiness, shortness or gasping for breath, witnessed apnea episodes, dry mouth and morning headaches.

Although the exact mechanism is not clear, studies have demonstrated an increased risk for OSA after the menopausal transition. One large population-based study of 589 women in the Wisconsin Sleep Cohort Study demonstrated 3.5 times risk of OSA in post-menopausal compared to pre-menopausal women, when controlling for age, body composition and lifestyle as confounding variables [16]. One hospital-based study [17] found that although pre- and postmenopausal women present with similar signs and symptoms when referred to sleep studies, the prevalence of sleep-disordered breathing tended to be higher (86.2%

versus 79.4%, respectively) and more severe (68.1% versus 35.8%, respectively) in postmenopausal versus premenopausal women. It has been proposed that decreases in levels of progesterone, a respiratory stimulant, are implicated to increase the risk for sleep disordered breathing (SBD) [18].

Sleep disturbances during menopause are additionally implicated in the high prevalence of clinical depression and depressed mood during and after the menopause transition [19, 20]. The relationship between sleep and depression can be described as bidirectional: sleep disturbance can be both a consequence of clinical depression as well as an instigator of depressed mood. Previous studies have demonstrated that sleep disturbance mediates the expression of depressed mood in peri- and postmenopausal women [19-21]. It has also been suggested that depression provides an additive effect on sleep disturbance in this population [22]. Clark and colleagues, however, found no relationship between sleep disturbance and depressed mood in peri- and postmenopausal women [23]. Regardless of mechanism, depressed mood is implicated in the treatment of menopause related insomnia and sleep disturbance. In terms of treatment, there are no specific studies examining treatment of comorbid insomnia and depression in peri- or postmenopausal women. There are several studies, however, that examine treatment for sleep disturbance and comorbid conditions, including depression, and found that treatments for sleep disturbance enhanced treatment of depression or alleviated depressed symptoms altogether [24-26].

Methods

This review summarizes current findings on the assessment and treatment of menopause-related sleep disorders. This review was completed through a systematic review of the literature regarding the treatment of insomnia and obstructive sleep apnea in peri- and post-menopausal women. The databases searched included PsycINFO, PsycNET, MEDLINE, and PubMed. Keywords used in the search included “menopause,” “insomnia,” “sleep disorder,” “pharmacology” and “alternative medicine.” A thorough and systematic examination of the literature was completed for each subsection of the paper. Studies included in the following review are summarized in Tables 2-4, according to the sleep issue it examines.

Diagnostic Considerations

Discussions of the diagnostic complexities of insomnia are quite common. Sleep can be disturbed for a variety of reasons. It can be affected by comorbidities. In addition, sleep disturbance can cause and/or exacerbate comorbidities. The duration of sleep disturbance can be variable, from days to lifelong. All these variables pose a challenge to defining insomnia as a distinct disorder. In the case of hot flashes and insomnia symptoms coinciding with menopause, the understanding of insomnia may be formidable. According to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) [27] if a patient concurrently meets criteria for Primary Insomnia (such as 1 month of sleep disturbance and clinically significant distress or impairment), and experiences hot flashes, the diagnosis for primary insomnia may be ruled out, as these symptoms would be deemed due to a general medical condition. If the insomnia began prior to the hot flashes, or potentially precipitated

or exacerbated the vasomotor symptoms, however, a diagnosis of Sleep Disorder Due to a General Medical Condition, Insomnia Type, may not adequately capture the important features and resulting treatment considerations.

The recent revision of the DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) [28] attempts to encompass the bidirectional nature of insomnia and increased the minimum duration of symptoms from one to three months. The DSM-5 combines both primary and secondary insomnia into Insomnia Disorder, with specifications for comorbidities. The DSM-5's nullification of causality in the diagnosis expresses the complex diagnostic nature of insomnia, where true causality cannot always be established. The DSM-5's classification of Insomnia Disorder suggests that regardless of cause, the patient's insomnia need to be a focus of treatment to improve the patient's condition, other comorbidities, and quality of life.

Although treatment considerations should minimize consideration of causality in the treatment of insomnia, qualitative distinctions are still important considerations. Severe, chronic insomnia and mild, transient insomnia have different implications for treatment. For the purposes of this treatment review, we will investigate studies inculcating individuals with full diagnostic criteria for insomnia, denoted by the term *insomnia* [29]. Due to the paucity of studies utilizing the diagnostic criteria of the DSM-5's Insomnia Disorder, *insomnia* will refer to the qualitative aspects of the diagnosis of insomnia in accordance with the DSM-IV, such as the duration and impact requirements. We will additionally review studies attempting to treat individuals with symptoms of sleep disturbance, without fulfilling the complete criteria, which will be termed *insomnia symptoms* [29].

Assessment and Intervention

Subjective Assessments: Conducting a Clinical Interview

The essential diagnostic tool for insomnia is a clinical interview. Information collected during the clinical interview should provide sufficient information about the nature and impact of the insomnia symptoms, the developmental course, and specific features to assist the clinician in arriving at a diagnosis and formulating treatment recommendations. Inquiry about comorbid medical and psychiatric conditions, social history, and other menopausal complaints (hot flashes, night sweats, incontinence, diminished libido, vaginal dryness, fatigue, depressed mood) can also be informative [15, 30].

Administering other self-report questionnaires, such as the Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index, or the Epworth Sleepiness Scale [31] may also help determine severity of symptoms and level of sleepiness that may be associated with other sleep disorders, such as OSA. The ISI is a particularly robust diagnostic tool, as it is validated to encompass the diagnostic criteria of the DSM-IV [32] (See Table 1 for a list of the self-report measures utilized for menopause-related sleep issues).

Objective Assessments: Polysomnography and wrist actigraphy

PSG and wrist actigraphy provide two objective measures of sleep quality. PSG utilizes night electroencephalography (EEG), electromyography and electrooculography to detect

brain wave, movement and eye rhythm changes to demonstrate sleep cycles. The American Academy of Sleep Medicine (AASM) recommends PSG as the ideal diagnostic tool for sleep breathing disturbances, periodic limb movements and overall sleep disturbance [33]. Alternatively, wrist actigraphy utilizes a portable watch device to detect movement for multiple nights at a time. Wrist actigraphy has been validated as an accurate diagnostic tool for insomnia [34] and periodic limb movements [35]. Although not used for the diagnosis of insomnia, PSG is used to rule out other sleep-related disorders, such as OSA and periodic limb movements, to therefore confirm a primary diagnosis of insomnia [33, 35].

Insomnia

Non-pharmacological Treatments

Cognitive Behavioral Therapy for Insomnia (CBT-I)—Hormonal fluctuation and vasomotor symptoms such as night sweats may be the initial cause of insomnia symptoms, but physiological arousals, behavioral conditioning, and misguided coping attempts appear to prolong insomnia [36], as described by Spielman and Glovinsky's three factor model of insomnia [37]. Spielman [37] posits that chronic insomnia can develop when poor sleep is induced by physical factors (i.e., hot flashes) or other disposing factors, is precipitated by life stressors, and is perpetuated by maladaptive coping strategies. According to this model, postmenopausal women's distress about poor sleep can lead to dysfunctional efforts to induce sleep and can cause conditioned arousal, whereby the bed becomes a cue for arousal rather than sleep. These behavioral factors can maintain the sleep problem even after the causative effects of vasomotor symptoms have been eliminated [36]. CBT-I teaches skills to undermine the cognitive and behavioral factors that maintain insomnia, regardless of the cause.

CBT-I is a brief and effective non-pharmacological intervention for insomnia. CBTI is a structured, skill-focused psychotherapy that consists of cognitive therapy (challenging irrational/distorted beliefs about sleep); behavioral techniques (sleep restriction, stimulus control therapy, relaxation techniques) and sleep education about sleep hygiene. The techniques of cognitive behavioral therapy have been applied to menopausal symptoms (e.g., hot flashes, depression), thus providing the opportunity to create a multicomponent behavioral intervention targeting multiple menopausal symptoms. A description of each CBTI component and some ways they could be potentially tailored to menopausal women is outlined below.

Sleep Restriction: Sleep restriction involves limiting the amount of time spent in bed to the amount of actual total sleep time, which is typically derived from 1 to 2 weeks of sleep diary data. It is usually indicated in patients whose sleep efficiency (total sleep time/time in bed × 100) is less than 85%. Sleep restriction systematically reduces time in bed to a degree that is less than the patient is accustomed to, thus utilizing the homeostatic drive of sleep to increase sleep consolidation. The patient's sleep efficiency is carefully monitored in subsequent follow-up sessions and modified throughout treatment based on sleep diary information and patient report.

Stimulus Control: The main objective of stimulus control is to have the patient limit the amount of time spent awake in bed and re-associate the bed and bedroom with sleep to regulate sleep–wake schedules. The guidelines that are discussed with the patient include the following: 1) only going to bed when sleepy; 2) using the bed and bedroom only for sleep and sexual activity; 3) leaving the bed and bedroom if unable to fall asleep for longer than 15 to 20 minutes, and return only when sleepy; and 4) keeping a fixed wake time in the morning every day.

Cognitive Therapy: Cognitive therapy is designed to challenge maladaptive beliefs and attitudes that serve to maintain insomnia (e.g., “If I don't get my 8 hours sleep, I'm useless.”). Worrying, faulty attributions, or unrealistic expectations of sleep may lead to increased emotional arousal, and thus lead to additional sleep disturbance, reinforcing the beliefs, and causing a vicious cycle. Challenging dysfunctional thoughts associated with sleep is believed to decrease the anxiety and arousal associated with insomnia. The first step is to increase the patient's aware of his/her dysfunctional thoughts of sleep, which is usually done through self-monitoring or questionnaires. Once sleep cognitions are identified, the next task is to help the patient challenge dysfunctional thoughts through guided discovery and collaborative empiricism. Instead of regarding cognitions as an absolute truth, the patient is encouraged to view his/her thoughts as one of the many possible interpretations (e.g., “I don't even know whether I'll get good sleep tonight.”). The final step is to replace dysfunctional cognitions with more adaptive, realistic, and alternative interpretations based on past evidence (e.g., “ Although it is difficult to function the next day after a poor night's sleep, I have historically been able to get most important tasks of the day done.”

In addition, menopausal women experiencing hot flashes may also have maladaptive thoughts related to hot flashes (e.g., “If I had a hot flash and someone noticed, it would be awful and humiliating.”). By applying cognitive therapy techniques to menopause related cognitions, women can be taught to apply these skills to unhelpful thoughts about hot flashes. Women who cope with hot flashes by using disclosure to others or self-talk (e.g., “Letting the flash pass without being hooked by the feelings”) report less distress about hot flashes.

Relaxation Training: Relaxation techniques can be effective in reducing physiological hyperarousal related to sleep disturbance. Relaxation provides a method for decreasing arousal prior to initiating sleep. Common relaxation techniques include progressive muscle relaxation, which involves alternately tensing and relaxing different muscle groups in the body; deep breathing techniques, which involve diaphragmatic breathing; body scanning, which involves focusing on a body-part sequence that covers the whole body; and autogenic training, which involves visualizing a peaceful scene and repeating autogenic phrases to deepen the relaxation response.

Sleep Hygiene: Although there is insufficient evidence for sleep hygiene to be an option for single therapy, it is usually provided in conjunction with other treatment modalities. Sleep hygiene consists of recommending a variety of behaviors and tending to environmental factors (e.g., light, bedroom temperature) that are conducive to sleep and may decrease discomfort related to nocturnal hot flashes. Examples of sleep hygiene instructions include

wearing lighter pajamas to bed and keeping a second pair near the bed, using lighter bedding and layering, keeping the ambient room temperature cool, keeping a fan nearby and a cool beverage near the bed, limiting caffeine products throughout the day, avoiding alcohol and smoking, and obtaining exercise away from bedtime (> 4 hours).

CBT-I has been shown to be more efficacious than zopiclone for short- and long-term management of adult insomnia [38]. CBT-I has also been shown to be efficacious for the treatment of insomnia [39] in randomized trials comparing CBT-I to sedative hypnotics in older adults [40]. Furthermore, CBT-I is virtually side effect free, while sedative hypnotics may be accompanied by cognitive or gastrointestinal side effects [38,39]. CBT-I may be beneficial for insomnia in menopausal women; however, to date, no randomized clinical trials have been conducted to examine efficacy of CBT-I in menopausal women or special treatment considerations in this population.

Complementary and Alternative Medicine

Yoga: Recent attention has been given to the efficacy of yoga-based protocols on reducing menopause-related vasomotor symptoms [41, 42]. There are, however, few studies focusing on the benefits of yoga on menopause-related insomnia. One randomized clinical trial with 44 postmenopausal women by Afonso et al. [41] demonstrated that both a standardized yoga intervention and a passive stretching active control intervention significantly reduced incidences of insomnia as assessed by the ISI. Yoga additionally decreased anxiety, depression, vasomotor symptoms and menopause-related quality of life scores. Furthermore, when compared against the wait-list control group, yoga significantly decreased insomnia symptomology, vasomotor symptoms and menopause-related quality of life scores. Yoga appears to be a promising treatment option for the alleviation of menopause-related insomnia; however, larger randomized trials with objective insomnia and sleep measurements, such as actigraphy and PSG, are needed to confirm its therapeutic benefits.

Therapeutic Massage: In addition to yoga, the effectiveness therapeutic massage (TM) has been investigated in attenuating symptoms of menopause-related insomnia. TM is the manipulation of deeper layers of muscle and connective tissue using various techniques, to enhance function and aid in the healing process, decrease muscle reflex activity, inhibit motor-neuron excitability, and promote relaxation and well being. In a recent pilot study evaluating the effectiveness of TM on seven postmenopausal women with insomnia (difficulty falling asleep or insomnia symptoms at least three times a week), Oliveira and colleagues [43] found that the administration of sixteen, bi-weekly, hour-long TM sessions was correlated with a decrease in the severity of subjective insomnia and anxiety-depressive symptoms, as measured with sleep diaries, the Beck Depression Inventory (BDI), and the State Trait Anxiety Inventory (STAI). Further, they found a decrease in REM latency and increased percent time spent in deeper stage 3 sleep, as measured by PSG before and after TM. Upon one-year follow-up, two participants reported insomnia relapse, two reported better sleep than before treatment, and three reported no problems with sleep. Although this finding is potentially promising, larger studies of randomized, placebo-controlled design are needed to draw more definite conclusions about the clinical significance of TM for menopausal insomnia.

Auricular acupressure: An additional alternative medicinal treatment for alleviating insomnia is auricular acupressure (AA). AA is based on an ancient Chinese technique that utilizes pressure on discrete pressure points in the ear to stimulate bodily function [44]. In a study of 45 Taiwanese women with postmenopausal insomnia who received a four-week course of daily AA therapy using five bilateral magnetized pellets, Kung et al. [44] found significant increases in subjective sleep quality based on the PSQI.. The authors conclude that AA intervention may contribute to the improvement of postmenopausal insomnia by increasing parasympathetic cardiac activity while decreasing sympathetic cardiac activity. The lack of randomly assigned control group, however, was a major limitation of this study.

Exercise: Llanas et al. [45]'s reported on two case studies used PSG to assess a physiotherapeutic treatment on postmenopausal related insomnia. The exercise treatment was composed of active stretching, passive stretching, active strengthening, and massage therapy. The treatment occurred for two ninety-minute sessions, twice a week for six months. The authors posit that exercise and fitness would exert positive effects on menopausal insomnia. They found that one patient experienced a significant increase in REM sleep and in total sleep efficiency, while the other patient experienced a reduction in sleep latency and an increase in slow wave sleep.

Pharmacological Treatments

Hormone Replacement Therapy—Vasomotor symptoms begin when the menstrual cycle ceases, as a result of reduced estrogen and progesterone levels. This hormonal reduction is associated with the onset of menopausal symptoms, such as hot flashes, irritability, depressed mood, fatigue, and insomnia. Physiologically, hot flashes occur when lowered estrogen levels cause peripheral and central temperature increases. Primary pharmacological treatments for menopause-related vasomotor symptoms including insomnia revolve around replacing the diminished levels of estrogen and/or progesterone levels. The added estrogen contributes to sleep through metabolizing norepinephrine, serotonin and acetylcholine, which consequently increases REM cycles [46]. Antonijevic, et al. [47] confirmed mild REM sleep increases with PSG in 11 postmenopausal women administered with estrogen. Progesterone stimulates benzodiazepine receptors, causing the release of gamma-aminobutyric acid (GABA), a sedating neurotransmitter that can potentially facilitate sleep [46]. Taken together, the menopause facilitated fluctuations and ultimate decline in estrogen and progesterone can impact sleep.

There is a paucity of studies exploring the direct effects of hormone replacement therapy (HRT) on sleep; however, some studies provide evidence of characteristic sleep reduction variables. Randomized controlled trials that have explored the effects of estrogen and progesterone on sleep efficiency have resulted in mixed results. Some studies found significant subjective sleep disturbance alleviation using estrogen replacement therapies [48, 49] while others found polysomnographic evidence of slightly increased REM sleep and shorter sleep latencies compared to placebo [50, 51]. These studies are limited by their small sample sizes. Other studies, however, found no significant sleep differences between estrogen administered and non-estrogen administered patients through analysis of multiple PSG recording nights [52, 53].

Progesterone/estrogen combination studies have demonstrated small subjective sleep quality improvements, with one study [54] utilizing PSG recordings and a placebo control group finding no significant sleep quality differences. Montplaiser et al. [55] compared an estrogen only group to an estrogen and micronized progesterone group utilizing PSG. They found the combination group significantly reduced participant's sleep efficiency by 8%, with the estrogen-only group showing no effects [55]. Saletu et al.'s [56] randomized, placebo and estrogen/progesterone treatment study on 55 postmenopausal women diagnosed with insomnia displayed moderate, yet non-significant improvements in wakefulness after sleep onset when measured with PSG post-treatment. Although there were no objective improvements, there were significant improvements regarding subjective ratings of sleep quality and wakefulness.

HRT's inconclusive treatment properties were further complicated by the Women's Health Initiative's (WHI) revelation, which indicated a 29% increased risk of heart disease and 26% increased risk of breast cancer [57]. Although there is no significant risk of death from HRT, these statistics are undoubtedly concerning. As a result, the WHI recommended a maximum of 5 years of HRT at low doses. One large sample survey (n=1876) [58] of women seeking alternatives to HRT reported other side effects, including breast tenderness, abnormal bleeding and increased body weight. The risks and side effects of HRT have caused much concern among patients experiencing vasomotor symptoms, and therefore many peri- and postmenopausal women are seeking alternatives to HRT [46].

Sedative hypnotics

Benzodiazepine and Non-benzodiazepine Hypnotics: A short-acting non-benzodiazepine hypnotic may be warranted for short-term use for acute, initial insomnia. Tolerance, withdrawal, dependence, and exacerbation of depression may occur when hypnotics are used longer than 2 weeks, and the discontinuation of treatment may elicit rebound insomnia [59]. Furthermore, somnambulism and complex sleep behaviors have emerged in the literature as a notable, but rare, side effect of sedative hypnotics [60-63]. The side effects of zolpidem, a popular non-benzodiazepine hypnotic, have been noted by the United States Food and Drug Administration, and in 2013, they released a public drug safety warning about the next day impairments [64]. They recommend reducing the doses of zolpidem to the lowest effective dose possible, 5mg, especially in women [64]. It is important to note that many of the studies evaluating zolpidem use prior recommended doses, and may not be reflective of its current efficacy and side effect profile in women. Although the long-term effects of hypnotics are unknown, increased mortality has been linked with hypnotic use [65, 66]. Zaleplon (Sonata) and zolpidem (Ambien) are more effective in treating problems with initiating sleep, but less effective with problems maintaining sleep. Soares et al. [67] enrolled 410 peri- or early postmenopausal women with insomnia (aged 40-60 years) in a double-blind, placebo-controlled study and found eszopiclone (Lunesta 3 mg) significantly decreased ISI scores, in addition to improved mood, quality of life, and menopause-related symptoms.

In a recent randomized, placebo-controlled crossover trial by Joffe and colleagues [68]; sleep, mood, hot flashes, and quality of life were examined in 59 peri- and postmenopausal

women, ages 40-65, with sleep onset and/or sleep maintenance insomnia, with co-occurring hot flashes, and depressive and/or anxiety symptoms. The authors found that eszopiclone reduced insomnia severity and improved all sleep parameters, depressive and anxiety symptoms, quality of life, and nighttime hot flashes compared to placebo. A limitation of this study was the relative homogenous sample of women, which was mostly comprised of Caucasian, postmenopausal, non-obese women whom reported few hot flashes at baseline. Additionally, women treated with hormonal therapy or antidepressants were not excluded from the study. Finally, outcomes were not measured beyond the 11-week trial and it was thus difficult to conclude if the improvements in insomnia and other vasomotor symptoms remained over time. These newer generation non-benzodiazepines have less tolerance, withdrawal, and dependence liability than traditional benzodiazepines, thereby reducing abuse potential. However, they still have habit-forming properties, and long-term use remains undesirable [69].

Zolpidem indicated favorable improvements on subjective sleep quality in a four-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group, outpatient study [70] on 141 peri- and postmenopausal women complaining of sleep maintenance difficulty in addition to nocturnal hot flashes, hot flashes or night sweats. Dorsey and colleagues [70] found that those in the zolpidem group reported significantly increased total sleep time, decreased wake time after sleep onset, and decreased number of awakenings throughout the duration of the study compared to those in the placebo group. Those in the zolpidem group did not report a significant improvement in quality of life or ability to function, and also experienced significantly more incidences of dizziness (8.8%), backache (7.4%), and irritability (4.4%). Despite the side effects of zolpidem and the observed placebo effect, the authors conclude that zolpidem was a generally safe and effective treatment for menopause-related insomnia, as measured by self-report in this cohort of peri- and postmenopausal women.

Ramelteon—Several other psychopharmacological approaches have emerged in the field of insomnia treatment. In a six-week, prospective, open-label trial of ramelteon (8 mg), a selective melatonin receptor agonist, Dobkin and colleagues [71] observed significant improvements in latency to sleep onset, total sleep time and sleep efficiency from sleep diary data in 20 healthy peri- and postmenopausal American women with insomnia. Using self-report measures, they also found improvements in sleep quality, sleep impairment, daytime functioning, quality of life and mood. There was a non-significant effect of ramelteon on wake after sleep onset (WASO), which is the primary complaint in menopausal women experiencing hot flashes. The investigators observed no tolerance or rebound over the course of the trial and only 40% of women reported side effects, most of which were mild. However, because this was an uncontrolled, non-randomized pilot study, in which 6 out of 20 participants dropped out, no objective sleep data was collected and the results are thus inconclusive.

Integrated Cognitive Behavioral Therapy for Insomnia (CBT-I) and Brief Sedative Hypnotic Use—Morin et al. [72] investigated a novel 2 stage protocol utilizing brief sedative hypnotic use and CBT-I. In a prospective, randomized controlled trial

involving 2-stage therapy for 160 adults with persistent insomnia (mean insomnia duration of 16.4 (±13.6) years) patients treated with combined therapy initially, followed by CBT-I alone obtained the best long-term outcomes. This was evidenced by higher remission rates (68%) at the six-month follow-up compared with patients who continued to take zolpidem (42%) during extended therapy. During the initial six-week treatment phase, the investigators found the main effect of CBT-I was on improving sleep latency, wakefulness after sleep onset, and sleep efficiency. Nevertheless, during the 6-month extended therapy phase and six-month follow-up period, combined therapy produced a higher remission rate compared with CBT-I alone (56% vs 43%). The authors conclude that during acute therapy, the addition of hypnotic medication to CBT-I produced added benefits, which are optimized by discontinuing medication during maintenance CBT-I in long-term treatment. Although this study did not examine the treatment of insomnia specifically in menopausal women, 60.6% of participants were female, and mean age (SD) for participants was 50 (10.1) years. An additional strength of this study was the use of both subjective and objective measures of sleep (daily sleep diaries and seven nights of PSG). The homogeneous sample limits the generalizability of these findings, since all patients were Caucasian, employed (73.3%), and predominantly married or in a common-law relationship (68.1%).

Antidepressants—Selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRIs and SNRIs) have proven to be efficacious in mitigating menopause-related depression [73]. Other randomized, controlled trials have demonstrated modest capabilities of various antidepressants in reducing hot flashes [74]. There are limited studies on the direct effects of antidepressants on insomnia. Ensrud et al. [75] recently investigated escitalopram (Lexapro)'s effects on insomnia in a randomized, controlled clinical trial of 205 peri- and postmenopausal women with hot flashes and without major depression. At week eight, escitalopram was more effective than placebo in decreasing ISI scores (41% decrease vs. 21% decrease) and PSQI scores (32% decrease vs. 17% decrease) relative to baseline scores. There was no significant difference in the presence of newly emergent adverse events between groups. The results of this study are limited by its short duration, and thus more research is needed to justify the use of antidepressants for insomnia treatment.

Insomnia Symptoms

Non-pharmacological Treatments

Cognitive Behavioral Therapy—Many therapies have been investigated for their abilities to reduce night sweats, which would aid in decreasing sleep awakenings, and thus indirectly target insomnia symptoms. Cognitive behavioral therapy may have an additive effect for post-menopausal insomnia symptoms by providing education and teaching skills to cope with climacteric symptoms associated with menopausal symptoms. CBT for the treatment of climatic symptoms (CBT-C) may include (1) psychoeducation, which involves shared discussion around symptoms and experiences of menopause; (2) cognitive strategies that assist women in identifying and re-evaluating negative and/or catastrophic thoughts about themselves, the menopausal transition, their hot flashes and other menopausal symptoms; (3) behavioral strategies which involves increasing women's participation in health related activities such as relaxation (e.g., paced respiration), regular exercise, and

eliminating behaviors that might exacerbate hot flashes (e.g., rushing, smoking, alcohol intake, caffeine intake, and spicy food intake); and (4) monitoring hot flashes and night sweats daily [76]. A group format CBT-C (for hot flashes, insomnia symptoms, and depression) has been applied peri- and postmenopausal women with promising results. Green et al. recently applied CBT-C to an 8 person pilot trial and found significant reductions in frequency and interference of hot flashes, depression, anxiety and quality of life [77]. Sleep disruption as assessed by the PSQI was reduced post-treatment, but the decreased scores were not significant [77]. Mann et al. tested the efficacy of a group CBT-C format on 96 women displaying menopausal symptoms after breast cancer treatment [78]. Compared to the control group, the CBT group demonstrated significant reductions in insomnia symptoms and depressed mood as assessed by a self-report measure at 20 weeks follow-up [78]. There were no significant reductions in hot flashes both post-treatment and at 20 weeks follow-up [78]. Results from this study are limited in application to peri- and postmenopausal women, as menopausal status was never confirmed in the study participants. In general, more research is needed on the effects of CBT-C on menopause related insomnia symptoms.

Mindfulness-based stress reduction—Mindfulness-based stress reduction (MBSR) has been explored in its capacity to reduce vasomotor symptoms, in addition to subjective insomnia symptoms, with moderate success. In a randomized trial of 110 peri- and post-menopausal women (47 to 69 years old) experiencing an average of 5 or more moderate to severe hot flashes and/or night sweats per day in the past week, Carmody and colleagues [79] found that women receiving MBSR, compared to those in the wait-list control group experienced clinically significant improvements in the degree of bother from hot flashes and night sweats in the previous 24 hours. Furthermore, the MBSR group also experienced improvements in subjective sleep quality, menopause-related quality of life, anxiety, and perceived stress. Improvements were maintained at 3 months post treatment without any "booster" intervention. Major limitations of this study include the lack of an active control group, a homogenous sample of mostly Caucasian and educated women, and that only 63% of women provided 80% or more of bothersome ratings in their hot flash diaries.

Complementary and Alternative Medicine

Acupuncture: Researchers have investigated acupuncture as a potential treatment for decreasing vasomotor and sleep problems [80]. In a multicenter, randomized, controlled trial of 267 post-menopausal Norwegian women, Borud et al. [80] found that 10 sessions of individualized acupuncture treatment paired with advice on self-care significantly decreased hot flash frequency and intensity compared to the control group. Furthermore, acupuncture improved sleep and somatic symptom dimensions of the Women's Health Questionnaire. Nevertheless, the external validity of this study is questionable, as more than 60% of the participants had previously used acupuncture and were thus self-selecting. Furthermore, due to the nature of acupuncture treatment, double-blind, sham-controlled studies are difficult to design and implement. This study suggests, however, that acupuncture and self-care can relieve hot flash intensity and frequency as well as increase health-related quality of life, including sleep measures, in postmenopausal women.

Isoflavens (soy): Hachul et al. [81] in a randomized controlled trial of 37 postmenopausal Brazilian women (age 50 to 65) found that 80 mg of soy-derived isoflavones taken daily for 4 months significantly improved sleep efficiency, as measured by baseline and post-treatment PSG (from 77.9% to 83.9% in isoflavone group versus 77.6% to 81.2% in placebo group), decreased the intensity and number of hot flashes, and decreased the frequency of subjective insomnia symptoms (89.5% to 36.9% in isoflavone group; 94.7% to 63.2% in placebo group). Measuring objective sleep efficiency with PSG is a strength of the study, but the small sample size (n=37) is a limitation.

In a recent randomized, controlled study of 634 Italian women with typical menopausal symptoms and mild psychoaffective/insomnia symptoms not requiring psychopharmacological therapy, Agosta et al. [82] found that a 12-week treatment of a soy isoflavones mixture (n=300) was effective in improving hot flushing, nocturnal sweating with awakenings, palpitations and vaginal dryness. Additionally, the group receiving magnolia bark extract, a natural anxiolytic, in addition to the soy treatment (n=334), showed improvement on psycho-affective symptoms associated with menopause, including anxiety, irritability and insomnia symptoms. Rates of adverse events were minimal and similar between both groups.

Omega-3 Supplements: Beyond soy, omega-3 supplements have gained popularity for treatment of a variety of issues, including hot flashes [83]. The pharmacodynamics are not completely understood, with research implicating the serotonin and dopamine systems in its pathways [84]. Nevertheless, due to its widespread accessibility, peri- and postmenopausal women use these supplements to reduce their hot flashes [83]. After mixed efficacy results from small-scale pilot studies, Cohen et al. [84] set out to examine the efficacy of omega-3 supplements for hot flashes and insomnia symptoms within a structured, large-scale (n=355), multi-site, randomized control trial. Upon examination of the results, the investigators found no significant differences between the omega-3 supplement group and the control group on hot flashes per day, bother of hot flashes, ISI scores and PSQI scores [84]. This study is limited by its breadth, as it attempted to analyze the efficacies of exercise, yoga and omega-3 within the same groups [84].

Black cohosh (Cimicifuga racemosa, syn.: Actaea racemosa): Black cohosh has become a popular herbal alternative to HRT for alleviating vasomotor symptoms, especially in European and Asian countries [85, 86]. The exact pharmacodynamic properties of black cohosh have not been established, with some studies suggesting a selective estrogen effect [87], and others describing a serotonergic and dopaminergic receptor blocking effect [88]. Many studies have demonstrated significant hot flash reductions in self-report measures [88, 89], with few directly investigating sleep symptoms. In one recent randomized clinical evaluation of a black cohosh and ginseng based supplement, Rotem et al. [90] substantiated considerable decreases on a sleep intensity question relative to a placebo group (70% decrease vs. 21% decrease) after 12 weeks of treatment. Additionally, this black cohosh mixture was more effective than placebo in decreasing hot flash mean scores (73% decrease vs. 38% decrease) and night sweats mean scores (69% decrease vs. 29% decrease) relative to baseline scores. Although these significant results denote efficacy of black cohosh, the

final results are questionable due to high drop out rates from both placebo and treatment groups, small group sizes, and non-significant differences before week 12 measurements.

A Hungarian study [91] on 2016 women presenting vasomotor complaints and who had rejected HRT or for whom HRT was contraindicated, demonstrated modest, but significant reductions on a insomnia symptom question (2.17 points) using Ramifemin, a popular black cohosh mixture. This study was limited by its lack of placebo group, its homogenous response rate and the questionable validity of its self-report menopause measure [91]. As both studies illustrate, the methodological concerns with black cohosh mixture prevent us from recommending this supplement for reducing menopause-related insomnia symptoms.

Pharmacological Treatments

Hormone Replacement Therapy (HRT)—The efficacy of HRT for sleep and mood disturbances remains unclear, with some studies finding no benefit and others yielding positive results. Exogenous estrogen reportedly decreases sleep latency and awakenings after sleep onset, while increasing total sleep time, presumably due to decreases in hot flashes [92]. The marked subjective improvement in sleep with HRT [92], however, is contrasted with a lack of consistent sleep improvement when assessed with PSG [93]. Estrogen is the drug of choice when treating hot flashes, but its efficacy in treating insomnia symptoms is unclear. In a thorough review of the literature, Parry et al. [94] noted that compared to placebo, treatment with estrogen reduces frequency and duration of night-time wakefulness, increases amount of REM sleep, decreases hot flash frequency and improves mood. Treatment with conjugated estrogen appears to reduce sleep latency, increase REM minutes and percent, improve vasomotor symptoms and objective/subjective sleep efficiency and sleep quality. Similarly, transdermal estradiol is also associated with increased sleep quality, reduced sleep latency and number of awakenings, and improvement in somatic, mood and vasomotor symptoms.

Additionally, Hachul et al. [95] examined the effects of estrogen and progesterone on sleep in 33 postmenopausal women, finding the combination of estrogen and progesterone to be more effective than estrogen alone in decreasing the prevalence of periodic limb movements (PLM; 8.1% vs. 2.1%), hot flashes (14.2% vs. 0%) and bruxism (11.1% vs. 0%). Nevertheless, the authors found both estrogen and estrogen/progesterone to be effective in decreasing arousals and sleep fragmentation [95].

Recent work by Kalleinen and colleagues [96] on 17 premenopausal (aged 45-51 years) and 18 postmenopausal (aged 58-70 years) women who slept in a laboratory for two nights before and after 6 months of estrogen-progestin treatment (EPT) disputes this trend. Compared to placebo, premenopausal women receiving EPT had more awakenings from stage 1 sleep, and postmenopausal women with EPT had a greater total number of awakenings and decreased slow wave activity than the corresponding placebo group. While the limited findings were mostly unfavorable to EPT, one cannot conclude that EPT deteriorates sleep more than placebo. Although this study showed that neither middle-aged cycling premenopausal women nor older postmenopausal women benefit from estrogen-progestin treatment in terms of their sleep quality, treatment with progesterone alone has shown significant reductions in time spent intermittently awake [97]. Further a significant

increase in REM sleep in the first third of the night in postmenopausal women was seen with progesterone treatment [97].

Furthermore, in a study [98] examining the effects of estradiol or estradiol/progesterone treatment on sleep quality, mood, depressive and menopausal symptoms in older healthy women who have undergone hysterectomies, Heinrich and Wolf also reported no significant effects. This placebo-controlled double-blind study examined the effects of estradiol (2 mg), estradiol plus progesterone (100 mg) or placebo at baseline, at 4 weeks and 24 weeks, using three questionnaires. The results indicated no effect on mood, well-being, menopausal symptoms, sleep quality and depressive symptoms.

In a multi-site, population based study of 3,123 postmenopausal community-dwelling aged women, Tranah and colleagues [99] found that postmenopausal women currently using HRT, compared to past HRT users and those who have never used HRT, had improved sleep quality for two of five actigraphy measures: shorter wake after sleep onset (WASO) and fewer long-wake (5 minutes or longer) episodes, both of which are related to sleep fragmentation. Sleep efficiency, sleep latency, and nap-time did not differ between the three groups. One limitation of this study was that actigraphy was only measured for 4 days. Additional limitations included several significant demographic differences between the groups with current HRT users slightly younger and more likely to be married, never HRT users more likely to have a higher BMI and more medical conditions, and past HRT users more likely to score higher on an anxiety scale.

In a prospective, randomized controlled trial of low-dose HRT on qualify of life, metabolic parameters, and blood pressure in 70 healthy, post-menopausal Caucasian women, Gambacciani and colleagues [100] found that participants who took beta-estradiol (1 mg/day; E2) plus drospirenone (2 mg/day; DRSP) for 6 to 12 weeks, compared to those in the control group, experienced significant improvements in sleep problems, vasomotor and somatic symptoms, anxiety/fears, depressed mood, and sexual behavior as measured by the Women's Health Questionnaire. Three months after treatment, the researchers also found that E2+DRSP treatment significantly decreased waist circumference, blood insulin values, and systolic blood pressure. This study was limited by the small, homogeneous sample, lack of a placebo control, high drop-out rate in the control versus treatment group during the 3-month follow-up phase (42.8% vs 8.6%), and failure to control for behavioral modifications (e.g. in diet or exercise) that may have confounded findings.

Antidepressants—Using antidepressants to treat sleep disruption in the absence of depression is not recommended [101]. Their mechanisms for treating insomnia include blocking wake-promoting neurotransmitters (acetylcholine, histamine, norepinephrine, serotonin, and dopamine) for sleep enhancement. Among them, the main sedating effects are caused by the anticholinergic and antihistamine effects [102]. Some antidepressants and mood stabilizers (e.g., venlafaxine, gabapentin) may ameliorate mood and vasomotor symptoms but may aggravate insomnia symptoms. Escitalopram (an SSRI) was more effective than estrogen and progesterone therapy in improving depressive symptoms in peri- and postmenopausal women, while having a positive impact on other menopause-related symptoms [103]. Although serotonin was shown to be ineffective in treating vasomotor

symptoms [104], SSRIs like duloxetine appear to significantly improve menopausal sleep, mood, vasomotor, and physical symptoms [105]. In a double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy in the treatment of vasomotor symptoms in menopause, Archer et al. [106] found that hot flash severity and nighttime awakenings were significantly reduced at weeks 4 and 12 in postmenopausal women (n= 458) experiencing 50 or more moderate to severe hot flushes per week. All three groups showed a reduction in hot flashes from baseline to week 12, with the group receiving 100 mg/d achieving 65.4% reduction, the group receiving 150 mg/d achieving a 66.6% reduction, while the placebo group had a 50.8% reduction. This study reported a higher number of adverse events in the active groups in week one only. Their findings provide evidence of an effective non-hormonal treatment for menopausal hot flashes associated with nocturnal sleep fragmentation.

Recently, an SSRI named paroxetine (trade name Brisdelle) received approval by the United States Food and Drug Administration (FDA) to treat moderate to severe menopause related hot flashes [107]. Paroxetine CR is the first non-hormonal treatment for hot flashes approved by the FDA. The FDA based its decision on two randomized control trials. The studies [108] randomized 165 postmenopausal women to one of three groups: placebo, 12.5mg/d or 25.0/mg/d. The study was conducted in 17 sites across the United States, including urban, suburban and rural clinics. At the end of 6 weeks, paroxetine CR significantly reduced frequency and severity of hot flashes by around 20% more than placebo. Although insomnia symptoms were not directly measured, 14.3% of study participants taking paroxetine reported insomnia symptoms as an adverse side effect to the treatment. The second study [109] entered 151 postmenopausal women into a randomized crossover control design, utilizing both 10mg and 20mg doses of paroxetine CR. More than 80% of the patient population was breast cancer survivors, while the first study contained only 7.3%. Similar to the first study, both doses of paroxetine significantly decreased hot flash frequency and severity, up to 30% more than placebo after 9 weeks of treatment. The authors in both studies conclude that the low dose paroxetine is recommended for clinical use due to higher levels of tolerability and compliance. This study was limited by its high drop out rate (29%). In terms of insomnia symptoms, the low dose paroxetine was the only group to display significant sleep improvements relative to the placebo group. The complete effects of paroxetine remain to be examined utilizing more objective sleep measures.

Other antidepressents beyond SSRIs have been examined for their insomnia symptom relief. The FDA recently approved doxepin, a tricyclic antidepressant with antihistamine effects, for the treatment of primary and comorbid chronic insomnia, [110]. In the high dose range, doxepine has anti-histamine, anticholinergic, anti-serotonergic and anti-adrenergic effects, but in hypnotic doses (<10 mg), it has a relatively pure anti-histamine effect. Doxepin has been shown to have both sleep initiation and maintenance improvements in the nights following use in several randomized control trials in both middle and older aged adults, as assessed by PSG [111-115]. As of yet, doxepin has not been tested in menopausal related insomnia symptoms.

Other sedating antidepressents have been evaluated in connection to menopause related insomnia symptoms, such as trazodone and mirtazapine, but they are not FDA approved for

the treatment of insomnia without comorbid depression [110]. Trazadone was the most widely used medication for insomnia until 2002, but despite its popular use, there are limited studies focused on efficacy and safety of insomnia without depression [116-118]. In terms of menopausal related insomnia symptoms without depression, there are a few studies examining its efficacy [119] Pansini et al. [119] showed significantly reduced subjective insomnia symptoms in postmenopausal women, as assessed by the Kupperman Menopausal Index. The study is limited by uncontrolled sample of 25 women; many had comorbid depression and anxiety, and it is unclear if the remission in affective symptoms mediated the decrease in insomnia symptoms. At the present state of the research, trazadone is not recommended for treatment of menopausal related insomnia symptoms without depression.

Mirtazapine, similarly sedating antidepressant, has shown some mild evidence to treat menopause related depression that is unresponsive to HRT [120]. Dolev [121] exhibited significant sleep improvements in 11 case studies of perimenopausal women taking mirtazapine in combination with prolonged release melatonin. Although this is not evidence for its efficacy, it does show that there may be developments in the treatment of menopause related insomnia symptoms using antidepressents. Of note, 63% of the women experienced significant weight gain as a side effect to treatment, most of which reduced following the treatment. Despite their sedating effects, use of antidepressents are generally not advised for routine use in menopause-related insomnia symptoms without depression, as the sedating effects tend to be short live and side effects are common.

Sleep apnea and sleep-disordered breathing

Non-pharmacological Treatments

Continuous Positive Airway Pressure—Exploring treatment options for menopause-related SDB is an important endeavor, as postmenopausal women are almost 3 times more likely to display OSA and other SDB abnormalities [122]. Various treatment modalities are used to alleviate snoring, OSA, and SDB. Much like insomnia, rigorous evaluation and a detailed history are important aspects of diagnosing sleep-related breathing disorders. A full overnight PSG with EEG, EOG, EMG, a temperature regulated thermistor, a pressure regulated thermocouple, and respiratory effort belts are the standard for diagnosing OSA, although 4 channel monitoring devices can diagnose patients, especially those with a high pre-test probability for OSA

Continuous positive airway pressure (CPAP) and auto-CPAP have been shown to be efficacious, and are the treatment of choice for OSA [123]. Problems arise with CPAP treatment for menopause-related SDB, as many people find the equipment cumbersome, and compliance reports indicate only 40 - 50% of patients prescribed CPAP are adherent [124, 125]. The effectiveness of CPAP requires that patients use their device on a regular nightly basis. To further complicate CPAP use in postmenopausal women, the few gender studies conducted on CPAP compliance indicate that women tend to be less compliant with CPAP [126, 127], with increased age being an additional factor implicated with non-compliance [126]. McArdle et al.'s [128] longitudinal on 1211 patients prescribed with CPAP found that patients who refused CPAP were more likely to be female and referred by a specialist, two factors that would apply to postmenopausal women seeking sleep apnea treatment. Although

many factors weigh against postmenopausal CPAP, women diagnosed with OSA with an AHI over 5 should be advised to adhere to use CPAP using psychoeducation and support tools, as CPAP is non-invasive and efficacious.

When comparing CPAP against CBT-I for comorbid insomnia and SDB, one study found a differential effect of each treatment in postmenopausal women. For postmenopausal patients with both chronic insomnia and upper airway resistant syndrome (UARS), a milder SDB issue, the study demonstrated that CBT-I the optimal treatment for reducing sleep latency, while SDB treatment (nasal CPAP or radiofrequency/turbinactomy) is the optimal treatment for relieving daytime fatigue was [129]. Both types of treatment should be taken into consideration for a patient presenting with comorbid insomnia and SDB.

Pharmacological Treatments

Hormone Replacement Therapy—Based on assertions that higher premenopausal estrogen and progesterone levels might account for the lower incidence of breathing-related sleep disorders in premenopausal women relative to postmenopausal women, a number of studies have tested whether administration of estrogen and progesterone might decrease SDB in menopausal women, with inconsistent results. Pickett et al. [53] found the combination of estrogen and progestin significantly decreased the number and duration of apnea/hypopneas in a randomized PSG based study. Similarly, Saaresranta et al. [130] observed that estrogen use and an especially high serum estradiol concentration predicted higher mean overnight arterial oxyhemoglobin saturation, which suggests estrogen therapy may have favorable respiratory effects. CPAP therapy, however, was found to be more successful than estrogen therapy in reducing episodes of apneas and hypopneas. Other studies show no significant improvements in the number of apneas in post-menopausal women with sleep apnea when treated with estrogen and/or medroxyprogesterone [131]. In a 2003 study using PSG, Polo-Kantola and colleagues [132] found that estrogen replacement therapy only had a minor effect on sleep apnea and no effect on partial airway obstruction in 62 post-menopausal women. Further, research on pharmacological suppression of estrogen and progesterone in healthy young women have demonstrated that although participants subjectively noticed some increased snoring, there was no increase in PSG measured arousals or sleep fragmentation to suggest that lack of hormones leads to SDB [133]. Thus, while hormonal changes that occur during the menopausal transition may increase risk of apnea, sleep quality appear to be only slightly improved by exogenous administration of hormone therapy.

CONCLUSION

In the peri- and postmenopausal population, insomnia, hot flashes, and depression are closely interrelated and should be taken into account when considering treatment options. Insomnia and insomnia symptoms relating to hot flashes should be inquired about in gynecological primary care settings with menopausal women. If insomnia is present, menopausal patients should be referred to a board certified sleep physician, sleep center, or behavioral sleep medicine specialist. Cognitive-behavioral therapy for insomnia alone or with pharmacological interventions appears to be a promising treatment for menopausal

insomnia; however, the efficacy remains unknown until randomized clinical trials are conducted.

Complementary and alternative treatments such as yoga, TM and exercise may be helpful as a complement to other treatments for insomnia, but as of yet have not proved their efficacy as stand-alone treatments. If pharmacological interventions are warranted for insomnia treatment, HRT may be effective for some women, particularly those with vasomotor symptoms. A short-acting nonbenzodiazepine hypnotic, like zolpidem and zaleplon, may be used in the short term (less than two weeks) for acute insomnia, but not recommended for long-term use. Antidepressants such as SSRIs, appear to be effective in treating insomnia in menopausal women, presumably by relieving underlying depression. Secondary insomnia symptoms should be treated within the framework of other symptoms. MBSR presents as an effective non-pharmacological treatment for insomnia symptoms, in addition to cognitive behavioral therapy for climacteric symptoms. More research is needed to determine if they can be prescribed as standalone treatments. Soy and black cohosh remain questionable standalone treatments for insomnia symptoms due to methodological concerns. HRT should be considered carefully for treatment of insomnia symptoms with vasomotor symptoms. When considering treatment with HRT, menopausal women should discuss the benefits and risks with their physicians. Estrogen and progestins should be used at the lowest doses for the shortest duration needed to achieve treatment goals. Paroxetine is the only antidepressant that is FDA approved for hot flash treatment and may be efficacious. It is important to remember that insomnia and SDB, the two most common sleep disorders, are best managed by providers with sleep medicine expertise. If patients report symptoms consistent with SDB, OSA, RLS, PLMS, or other sleep disorders, a referral to a sleep specialist is recommended. If both SDB and insomnia are contemporaneously diagnosed, CPAP is considered the standard of treatment recommended treatment in menopausal women and should be attempted first before trying alternatives.

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Table 1

Self-Report Measures

Self-Report Measure	Insomnia or Symptoms	Focus of Attention	Number of Questions	Type of Questions	Cutoff Scores	
Insomnia Severity Index (ISI)	Insomnia, validated with the DSM-IV	Nature, severity and impact of insomnia.	7	5-point Likert scale 0 = “No problem” - 4 = “Very severe problem”	0-7 = No insomnia 8-14 = Subthreshold insomnia 15-21 = Moderate insomnia 22-28 = Severe insomnia	
Pittsburgh Sleep Quality Index (PSQI)	Insomnia symptoms.	Nature and severity of sleep quality disturbances.	19	Open ended questions and various 4-point Likert scales.	0-5 = Good sleep quality >5 = Poor sleep quality	
Epworth Sleepiness Scale (ESS)		Insomnia and sleep-disordered breathing symptoms.	Daytime sleepiness as a result of sleep disturbance.	8	4-point Likert Scale 0 = “No chance of dozing” - 4 = “High chance of dozing”	0-9 = Normal sleepiness 10-15 = Clinical levels of fatigue 16-24 = Severe clinical levels of fatigue
Sleep and/or Hot Flash Diary		Insomnia and/or hot flash symptoms	Nature and quality of sleep quality disturbance.	At least 4, depending on author's purpose and specificity of inquiry.	Mostly open ended question, asking questions about incidence times and numbers, sleep and wake times, hours of sleep, number of occurrences of activities and/or beverages during the day, severity ratings, etc.	No official score method, but depending on purposes, total sleep time, wake after sleep onset, average bedtime, average number of hot flashes, average severity rating, fatigue levels, etc.
Menopause Rating Scale (MRS)		Insomnia symptoms	Quality of menopause related symptoms	11, 1 for sleep.	5-point Likert scale 0 = “None” - 4 = “Very severe”	Continuous with higher scores indicating higher severity. Three subscales and total score: Psychological symptoms (depressed, irritable, anxious, exhausted), Somato-vegetative symptoms (sweating/ flush, cardiac sleeping disorders, joint and

Self-Report Measure	Insomnia or Symptoms	Focus of Attention	Number of Questions	Type of Questions	Cutoff Scores	
						muscle), and Urogenital symptoms (Sexual problems, urinary complaints, vaginal dryness)
Women's Health Questionnaire (WHQ)		Insomnia symptoms	Quality of health related symptoms prevalent in middle aged women	36, 3 for sleep.	4-point Likert scale 0 = "No, no at all - 4 = "Yes, definitely"	Continuous with higher scores indicating higher severity. 11 subscales: Depressed mood, somatic symptoms, anxiety/fears, vasomotor symptoms, sleep problems, sexual behavior, menstrual symptoms, memory/ concentration, attractiveness.

Table 2

Insomnia Treatment Studies

Study author	Treatment Assessed	Population	Group design and initial sample size	Treatment length	Attrition rates	Follow up	Outcome measure	Results
Afonso et al. (2012)	Yoga	Postmenopausal women	Randomized; Tx1 = Yoga (n=15) Tx2 = Passive Stretching (n=14) Tx3 = Wait list control (n=15)	2 sessions a week for 16 weeks.	0%	No	ISI	Both yoga and passive stretching significantly decreased insomnia scores compared to the control.
Oliveira et al. (2011)	Therapeutic Massage	Postmenopausal women	Pilot; Tx = Therapeutic massage (n=7)	2 sessions a week for 8 weeks	0%	1 year	Sleep diary and PSG	Post treatment: Sleep Diary showed increased sleep latency and subjective sleep quality. PSG showed increased REM latency and increased stage 3 sleep. 1 year follow-up: 2 subjectively improved since post-treatment, 3 maintained sleep improvements, 2 relapsed.
Kung et al. (2011)	Auricular acupuncture	Postmenopausal women	Tx = Auricular acupuncture (n=45)	Nightly for 4 weeks	0%	No	PSQI	Increases in total sleep duration and sleep efficiency, and decreases in sleep latency.
Antonijevic et al. (2000)	Estrogen replacement therapy	Postmenopausal women	Within subject; Tx = Estrogen patch (n=11)	Two patches per week, two weeks	0%	No	PSG	Increases in total minutes of REM sleep.
Schiff et al. (1972)	Estrogen replacement therapy	Postmenopausal women	Randomized, double blind; Tx1 = Oral estrogen (n=9) Tx2 = Placebo control (n=7)	One month	0%	No	PSG	Increases in REM sleep and decreases in sleep latency.
Bliwase (1992)	Estrogen replacement therapy	Elderly women	Subjective separation into “good sleepers” (n=22) and “poor sleepers” (n=16)	No treatment	N/A	No	PSG	Using estrogen did not differentiate good from poor sleepers.
Pickett et al. (1989)	Progesterone and estrogen replacement therapy	Postmenopausal women	Tx = Combined oral estrogen and progesterone	7 days	0%	No	PSG	No differences before and after administration of hormones.

Study author	Treatment Assessed	Population	Group design and initial sample size	Treatment length	Attrition rates	Follow up	Outcome measure	Results
Purdie et al. (1995)	Progesterone and estrogen replacement therapy	Postmenopausal women	Randomized; Tx1 = Combined oral estrogen and progesterone (n-16) Tx2 = Placebo control (n=14)	12 weeks	0%	No	PSG	No significant differences between groups.
Montplaisir et al. (2001)	Estrogen compared with combined estrogen and progesterone replacement therapies	Postmenopausal women	Randomized; Tx1 = Oral estrogen (n=11) Tx2 = Combined oral estrogen and progesterone (n=10)	6 months	0%	No	PSG	Combination estrogen and progesterone increased sleep efficiency by 8%, while estrogen alone showed no effects on sleep efficiency.
Saletu et al. (2001)	Progesterone and estrogen replacement therapy	Postmenopausal women diagnosed with insomnia	Within subject; Tx1 = Placebo control Tx2 = Combined oral estrogen and progesterone (n=55)	4 months	0%	No	PSG and subjective report	Combination estrogen and progesterone depicted moderate, yet non-significant improvements in wake-time after sleep onset, sleep initiation and sleep maintenance sampled by PSG, while subjective improvements of wakefulness and efficiency were reported.
Soares et al. (2006)	Eszopiclone (Lunesta)	Peri- or early postmenopausal women diagnosed with insomnia related to the menopausal transition	Randomized; Tx1 = Eszopiclone 3mg (n=201) Tx2 = Placebo (n=209)	4 weeks	12.4%	No	ISI	58% of those treated with eszopiclone displayed a reduction of ISI score to “non significant clinical insomnia”, versus 35% of the placebo group.
Joffe et al. (2006)	Eszopiclone (Lunesta)	Peri- and postmenopausal women	Randomized, crossover; Tx1 = Eszopiclone 3mg (n=30) Tx2 = Placebo (n=29)	11 weeks	22%	No	ISI and sleep diaries	Compared with placebo, eszopiclone reduced the ISI score by 8.7 ± 1.4 more points on eszopiclone than on placebo, without a significant time-by-treatment interaction. The sleep diary revealed significant sleep latency reductions without significant time-by-treatment interactions, but sleep efficiency, wake-time after sleep onset and total sleep time did display significant

Study author	Treatment Assessed	Population	Group design and initial sample size	Treatment length	Attrition rates	Follow up	Outcome measure	Results
								time-by-treatment interactions. time-by-treatment interactions.
Dorsey et al. (2004)	Zolpidem (Ambien)	Peri- and postmenopausal women diagnosed with insomnia related to the menopausal transition	Randomized; Tx1 = Zolpidem 10mg (n=68) Tx2 = Placebo (n=73)	4 weeks	11%	No	Subjective sleep reports	Zolpidem group reported significantly increased total sleep time, decreased wake time after sleep onset, and decreased number of awakenings compared to those in the placebo group.
Ensrud et al. (2012)	Escitalopram (Lexapro)	Peri- and postmenopausal women with hot flashes	Randomized; Tx1 = Escitalopram 10-20mg (n=104) Tx2 = Placebo (n=101)	8 weeks	5%	No	ISI and PSQI	Escitalopram was more effective than placebo in decreasing ISI scores (41% decrease vs. 21% decrease) and PSQI scores (32% decrease vs. 17% decrease) relative to baseline scores.

Table 3

Insomnia Symptom Treatment Studies

Study author	Treatment Assessed	Population	Group design and initial sample size	Treatment length	Attrition rates	Follow up	Outcome measure	Results
Keefer & Blanchard (2005)	Group CBT for Climactic Symptoms	Peri- and postmenopausal women experiencing vasomotor symptoms	Tx1 = Group CBT-C (n=11) Tx2 = Waitlist Control/Delay ed CBT-C (n=8)	8 weeks	0%	No	Daily vasomotor symptom diary	Compared with the waitlist control group, the CBT-C group displayed significantly less total vasomotor symptoms, although the effect was moderate.
Green et al. (2013)	Group CBT	Peri- and postmenopausal women experiencing vasomotor symptoms	Pilot; Tx = CBT (n=8)	10 weeks	0%	No	Hot flash diary Interference Scale and PSQI	The group CBT treatment significantly reduced hot flashes, depressed mood and anxiety, but results were not significant for sleep disturbance.
Mann et al. (2012)	Group CBT	Women experiencing menopausal symptoms after breast cancer treatment	Randomized; Tx1 = CBT (n=47) Tx2 = Usual care (n=49)	6 weeks	17%	2 week and 20 week	Women's Health Questionnaire	Compared to the control group, the CBT group demonstrated significant reductions up in sleep disturbance and depressed mood at 20 week follow-up, but not in hot flashes.
Carmody et al. (2011)	Mindfulness-Based Stress Reduction	Late perimenopausal and early postmenopausal women experiencing vasomotor symptoms	Randomized; Tx1 = MBSR (n=57) Tx2 = Wait list control (n=53)	8 weeks	9.3%	1, 12, 16, 20 week follow ups.	Daily hot flash diary	In the MBSR group, there was a significant reduction in the degree of bother of the hot flashes at 9 weeks (14.7% vs. 6.7%) and at 20 weeks (21.6% vs. 10.5%), compared with the control group. Although there was a significant difference between MBSR and control in

Study author	Treatment Assessed	Population	Group design and initial sample size	Treatment length	Attrition rates	Follow up	Outcome measure	Results
								perceived sleep quality, the within subjec
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								perceived sleep quality, the within subjec
Borud et al. (2009)	Acupuncture	Postmenopausal women experiencing vasomotor symptoms	Randomized; Tx1 = Acupuncture (n=134) Tx2 = Wait list control (n=133)	12 weeks	7%	No	Daily hot flash diary	In the acupuncture group, there was a significant, albeit mild, reduction in the frequency of hot flashes per 24 hours, compared with the control group (5.8 vs. 3.7). In addition, there was a significant increase in hours of sleep in the acupuncture group, compared to the control group (0.42 hours vs. 0.14 hours).
Hacul et al. (2011)	Isovlavones (soy)	Postmenopausal women with sleep disturbance	Randomized; Tx1 = Oral isoflavones (80mg; n=19) Tx2 = Oral placebo (n=19)	16 weeks	2%	No	PSG	Relative to the placebo control group, the isoflavones group demonstrated significant improvements in sleep efficiency (from 77.9% to 83.9% vs. 77.6% to 81.2%), decreases in the intensity and number of hot flashes, and decreases the frequency of subjective insomnia (89.5% to 36.9% vs. 94.7% to 63.2%)
Cohen et al. (2013)	Omega-3 Supplements	Peri- and postmenopausal women with vasomotor symptoms	Randomized; Tx1 = Oral omega-3 (n=177) Tx2 = Oral placebo (n=178)	12 weeks	2%	No	ISI and PSQI	No significant differences between the omega-3 group in vasomotor or sleep

Study author	Treatment Assessed	Population	Group design and initial sample size	Treatment length	Attrition rates	Follow up	Outcome measure	Results
								variables, relative to control.
Rotem & Kaplan (2007)	Black cohosh	Peri- and postmenopausal women with vasomotor symptoms	Randomized; Tx1 = Oral black cohosh preparation (n=25) Tx2 = Oral placebo (n=25)	12 weeks	30%	No	Subjective sleep quality rating	Relative to the placebo control group, the black cohosh group demonstrated significant increases sleep quality scores (70% increase vs. 21% increase), decreases in hot flash mean scores (73% decrease vs. 38% decrease) and decreases in night sweats mean scores (69% decrease vs. 29% decrease)
Vermes, Banhidy & Acs (2005)	Black cohosh	Peri- and postmenopausal women	Tx1 = Oral black cohosh preparation (n=2016)	12 weeks	0%	No	Kupperman Menopausal Index	Black cohosh led to significant decreases in the insomnia item scores.
Hachul et al. (2008)	Estrogen compared with combined estrogen and progesterone compared with progesterone replacement therapies	Postmenopausal women	Randomized; Tx1 = Oral estrogen for 12 weeks, followed by estrogen and progesterone for 12 weeks (n=14) Tx2 = Oral placebo for 12 weeks, followed by progesterone for 12 weeks (n=19)	24 weeks	0%	No	PSG	Objective sleep factors (efficiencies, latencies) were not significantly improved, but the combination of estrogen and progesterone to be more effective than estrogen alone in decreasing the prevalence of PLM (8.1% vs. 2.1%), hot flashes (14.2% vs. 0%) and bruxism (11.1% vs. 0%). However, hormone therapy decreased the prevalence of arousal in both groups

Study author	Treatment Assessed	Population	Group design and initial sample size	Treatment length	Attrition rates	Follow up	Outcome measure	Results
Kalleinen et al. (2008)	Estrogen and progesterone therapy	Pre- and postmenopausal women	Randomized; Premenopausal Tx1 = Oral cyclic estrogen and progesterone (n=9) Tx2 = Oral placebo (n=8) Postmenopausal Tx1 = Oral continuous estrogen and progesterone (n=9) Tx2 = Oral placebo (n=9)	6 months	11%	No	PSG	Sleep quality measure were not significantly benefited from estrogen and progesterone therapy in neither premenopausal nor postmenopausal women, compared to placebo.
Schussler et al. (2008)	Progesterone Replacement Therapy	Postmenopausal women who did not report poor sleep as motivation for the study	Randomized, crossover; Tx1 = Oral progesterone for 3 weeks followed by 2 week washout followed by placebo for 3 weeks (n=5) Tx2 = Oral placebo for 3 weeks followed by 2 week washout followed by progesterone for 3 weeks (n=5)	8 weeks	0%	No	PSG	Progesterone alone depicted significant reductions in time spent awake and a significant increase in REM sleep in the first third of the night, compared to placebo effects.
Heinrich & Wolf (2005)	Estrogen compared with combined estrogen and progesterone replacement therapies	Postmenopausal women	Randomized; Tx1 = Oral estradiol (n=12) Tx2 = Oral estradiol and progesterone (n=10) Tx3 = Oral placebo (n=13)	24 weeks	31% (prior to analysis)	No	Subjective sleep report (in a depression questionnaire)	There were no significant differences on sleep quality between the three groups.
Tranah et al. (2010)	Present hormone therapy users compared with past hormone therapy users compared with no hormone therapy users	Postmenopausal women	Naturalistic; Tx1 = Present hormone therapy users (n=424) Tx2 = Past hormone therapy users (n=1,289)	4 consecutive 24 hour periods	N/A	No	Actigraphy	Postmenopausal women currently using HT, compared to past HT users and those who have never used HT, had improved sleep quality for

Study author	Treatment Assessed	Population	Group design and initial sample size	Treatment length	Attrition rates	Follow up	Outcome measure	Results
			Tx3 = No hormone therapy users (n=1,410) Tx3 = No hormone therapy users (n=1,410) Tx3 = No hormone therapy users (n=1,410)					two of five actigraphy measures: shorter wake after sleep onset (WASO) and fewer long-wake (5 minutes or longer) episodes. Sleep efficiency (SE), sleep latency, and nap-time did not differ between the three groups
Gambacciani et al. (2011)	Estrogen and progesterone replacement therapy	Postmenopausal women	Randomized; Tx1 = Oral estradiol and drosperinone (n=35) Tx2 = Oral calcium (n=35)	12 weeks	26%	3 months	Women's Health Questionnaire	At 12 weeks, the estradiol and drosperinone group experienced significant improvements in sleep problems, vasomotor and somatic symptoms, compared to those in the control group.
Soares et al. (2006)	Escitalopram (Lexapro) compared with estrogen and progesterone replacement therapy	Peri- and postmenopausal women with depressive disorders and menopause related symptoms	Randomized; Tx1 = Oral escitalopram (10-20mg; n=20) Tx2 = Oral ethinyl estradiol and norethindrone acetate (n=20)	8 weeks	l0%	No	PSQI	Both treatment groups experienced significant increases in sleep variables, however there was no significant differences between the two treatments.
Joffe et al. (2007)	Duloxetine	Postmenopausal women with Major Depressive Disoder	Pilot; Tx1 = Oral duloxetine (60-120mg; n=20)	8 weeks	25%	No	PSQI	Duloxetine led to significant increases in sleep measures.
Stearns et al. (2003)	Paroxetine (Brisdelle)	Postmenopausal women	Randomized; Tx1 = Oral placebo (n=56) Tx2 = Oral paroxetine (12.5mg; n=51)	6 weeks	15.8%	No	Daily hot flash diary.	Both high and low dose paroxetine significantly decreased hot flash frequency and severity relative to

Study author	Treatment Assessed	Population	Group design and initial sample size	Treatment length	Attrition rates	Follow up	Outcome measure	Results
			Tx3 = Oral paroxetine (25mg; n=58) Tx3 = Oral paroxetine (25mg; n=58) Tx3 = Oral paroxetine (25mg; n=58)					placebo. Low dose displayed highest tolerability and compliance ratings.
Stearns et a. (2007)	Paroxetine (Brisdelle)	Postmenopausal women, with 80% cancer survivors	Randomized crossover; Tx1 = Oral paroxetine (10mg) followed by placebo (n=37) Tx2 = Oral placebo followed by paroxetine (10mg; n=39) Tx3 = Oral paroxetine (20mg) followed by placebo (n=38) Tx4 = Oral placebo followed by paroxetine (20mg; n=37)	9 weeks	29%	No	Daily hot flash diary and Medical Outcomes Study Sleep Problems Index	Both high and low dose paroxetine significantly decreased hot flash frequency and severity relative to placebo. Low dose displayed highest tolerability and compliance ratings. Low dose was the only treatment that significantly reduced sleep symptoms relative to placebo.
Pansini et al. (1994)	Trazadone	Postmenopausal women	Pilot; Tx1=Oral trazadone (75mg; n=25)	3 months	0%	No	Kupperman Menopausal Index	Trazadone led to significant decreases in insomnia, anxiety and irritability scores. The intensity of hot flushes appeared reduced, but was not statistically significant.
Dobkin et al. (2009)	Ramelteon (Rozeram)	Peri- and postmenopausal women with sleep latency insomnia	Open label pilot; Tx1 = Ramelteon 8mg (n=20)	6 weeks	30%	No	Sleep diary	Ramelteon was effective in improving subjective reports of sleep latency, total sleep time, and sleep quality.
Dolev (2011)	Mirtazapine followed by prolonged-release melatonin add-on	Perimenopausal women with insomnia symptoms without depression	Case studies: Tx1=Oral Mirtazapine (15mg) followed by PRN oral prolonged release	3 months	0%	No	PSQI	The mirtazapine/ melatonin combination led to significant decreases in global insomnia scores,

Study author	Treatment Assessed	Population	Group design and initial sample size	Treatment length	Attrition rates	Follow up	Outcome measure	Results
			melatonin (2 mg; n=11) melatonin (2 mg; n=11)					as well as sleep latency time.

Table 4

Sleep Disordered Breathing Treatment Studies

Study author	Treatment Assessed	Population	Group design and initial sample size	Treatment length	Attrition rates	Follow up	Outcome measure	Results
Guilleminault et al. (2002)	Cognitive behavioral therapy for insomnia (CBT:I) and respiratory treatments (CPAP or turbinactomy)	Postmenopausal women with chronic insomnia. Half had Upper Airway Resistance Syndrome	Randomized; Tx1 = UARS group with respiratory treatment (n=15 CPAP; n=15 turbinactomy) Tx2 = UARS group with CBT:I treatment (n=32) Tx3 = Normal breathers with immediate CBT:I (n=34) Tx4 = Normal breathers with delayed CBT:I (n=34)	6 months between baseline and post treatment assessments. CBT:I was 6 sessions over 8 weeks.	2%	No	Subjective sleep quality Visual Analog Scales, 7 days of actigraphy, PSG, and sleep logs.	Respiratory treatments in patients with UARS, significantly decreased complaints of daytime fatigue, compared to the other groups. Regardless of the presence of UARS, CBT:I decreased sleep latency, compared to respiratory treatments and control.
Pickett et al. (1989)	Estrogen and progesterone replacement therapy	Women with complete overihysterectomy	Tx1 = 7 days of oral placebo followed by 7 days of oral estrogen and progesterone (n=9)	14 days	0%	No	PSG	Estrogen and progesterone led to significant decreases in the average number of sleep disordered events (apnea-hypopnea index).
Saaresranta et al. (2006)	Estrogen replacement therapy (oral, gel, and/or patch)	Postmenopausal women with hysterectomy	Non-randomized; Tx1 = No estrogen (n=11) Tx2 = Previous estrogen use (n=22) Tx3 = Present short term estrogen use (n=11) Tx4 = Continuous estrogen use (n=22)	5 years	3%	No	PSG	Long term estrogen use predicts higher mean overnight arterial oxyhemoglobin saturation levels and lower numbers of sleep disordered events (apnea-hypopnea index).
Polo-Kantola et al. (2003)	Estrogen replacement therapy	Postmenopausal women with hysterectomy	Randomized, crossover; Tx1 = Transdermal estrogen for 3 months followed by 1 month washout followed by placebo for 3 months (n=30) Tx2 = Transdermal placebo for 3 months followed by 1 month washout followed by estrogen for 3 months (n=32)	7 months		No	PSG through static charge sensitive bed	Marginal, but non-significant improvements in sleep disordered symptoms after treatment with estrogen.

Meta-Analysis of Quantitative Sleep Parameters From Childhood to Old Age in Healthy Individuals: Developing Normative Sleep Values Across the Human Lifespan

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Objectives: The purposes of this study were to identify age-related changes in objectively recorded sleep patterns across the human life span in healthy individuals and to clarify whether sleep latency and percentages of stage 1, stage 2, and rapid eye movement (REM) sleep significantly change with age.

Design: Review of literature of articles published between 1960 and 2003 in peer-reviewed journals and meta-analysis.

Participants: 65 studies representing 3,577 subjects aged 5 years to 102 years.

Measurement: The research reports included in this meta-analysis met the following criteria: (1) included nonclinical participants aged 5 years or older; (2) included measures of sleep characteristics by "all night" polysomnography or actigraphy on sleep latency, sleep efficiency, total sleep time, stage 1 sleep, stage 2 sleep, slow-wave sleep, REM sleep, REM latency, or minutes awake after sleep onset; (3) included numeric presentation of the data; and (4) were published between 1960 and 2003 in peer-reviewed journals.

Results: In children and adolescents, total sleep time decreased with age only in studies performed on school days. Percentage of slow-wave sleep was significantly negatively correlated with age. Percentages of stage 2 and REM sleep significantly changed with age. In adults, total sleep time, sleep efficiency, percentage of slow-wave sleep, percentage of REM sleep, and REM latency all significantly decreased with age, while sleep latency, percentage of stage 1 sleep, percentage of stage 2 sleep, and wake after sleep onset significantly increased with age. However, only sleep efficiency continued to significantly decrease after 60 years of age. The magnitudes of the effect sizes noted changed depending on whether or not studied participants were screened for mental disorders, organic diseases, use of drug or alcohol, obstructive sleep apnea syndrome, or other sleep disorders.

Conclusions: In adults, it appeared that sleep latency, percentages of stage 1 and stage 2 significantly increased with age while percentage of REM sleep decreased. However, effect sizes for the different sleep parameters were greatly modified by the quality of subject screening, diminishing or even masking age associations with different sleep parameters. The number of studies that examined the evolution of sleep parameters with age are scant among school-aged children, adolescents, and middle-aged adults. There are also very few studies that examined the effect of race on polysomnographic sleep parameters.

Key Words: meta-analysis, PSG, psychiatric disorders, sleep disorders, moderator analysis

Citation: Ohayon MM; Carskadon MA; Guilleminault C; Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *SLEEP* 2004;27(7):1255-73.

INTRODUCTION

SLEEP PATTERNS EVOLVE ACROSS THE NORMAL AGING PROCESS IN COMPLEX WAYS. Changes in sleep patterns across childhood and adolescence, for example, are related not only to chronologic age but also to maturation stage. Few studies, however, have made comprehensive analyses of these 2 aspects in adolescents.[1] Similarly, chronologic age in elderly people does not always match physiologic age. Therefore, changes in sleep patterns may happen earlier, ie, at a younger age, for some individuals or at an older age for others. Further, epidemiologic and other studies suggest that much of the sleep disturbance typically seen in old age is likely the result of medical comorbidities than age per se.[2-6]

Nevertheless, 4 age-related changes have been consistently demonstrated in polysomnographic (PSG) studies of sleep architecture: total sleep time (TST),[7-29] sleep efficiency,[7,9-14,17-23,25-29,30-36] and slow-wave sleep (SWS)[7,8,10,12-18,21-28,31,33,35,37-39] all decrease, while wake after sleep onset (WASO)[12-14,16,17,19,21,23,28,29, 32,33,36,37,40] increases with age.

However, a number of PSG sleep characteristics remain uncertain as regard their evolution with age: (1) sleep latency has been reported to increase with age in some studies,[10,13,26,31,40] while several other studies have found no significant changes with age.[8,9,12,14,16,17,20-23,28,29,32,33,35-37,39,41] Likewise, a number of studies have found no significant differences with age for (2) percentage of stage 1[9,25,26,35,39,42] and (3) stage 2 sleep[9,13,20,22,23,25,33,35,36,42,43] while many others have reported an increase with age of these stages.[7,8,12,17,27,28,31] (4) Similarly, rapid eye movement (REM) sleep has been reported to decrease with age in several stud-

Disclosure Statement

This is not an industry supported study. Dr. Ohayon has received support from Eli Lilly and the American Academy of Sleep Medicine; and has received guest speaker honorarium from Eli Lilly, Excerpta Medica, and Pfizer Inc. Dr. Carskadon has received support from Sepracor; and is a consultant for Cephalon, Inc. Drs. Guilleminault and Vitiello have indicated no financial conflicts of interest.

Submitted for publication March 2004
Accepted for publication July 2004

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ies[7,8,10-12,14,16-18,20,21,23-26,28,31,33,37,38,44] while many other studies have found no such association with age.[9,13,15,19,22,27,34-36,39-43]

Why such discrepancies between the studies? Several factors may be responsible for the difficulties identifying age trends in sleep architecture of apparently healthy subjects, including for example, small sample sizes; inconsistency in controlling factors that may influence sleep, such as mental or physical illness; uncontrolled use of alcohol, drugs, or medications; or insufficient screening for sleep disorders.

The purposes of this study were to better define normative sleep across the human life span by identifying age-related changes in objectively recorded sleep patterns in healthy individuals using meta-analyses. More specifically, this study aimed to clarify whether sleep latency, percentages of stage 1 and stage 2 sleep, and percentage of REM sleep change with age and in which direction. It also aimed to verify to what extent lack of control over key variables modify the observed age changes in sleep patterns.

METHODS

The target population studies for these meta-analyses included all studies that met the following criteria:

1. Included nonclinical participants aged 5 years or older; the lower limit of 5 years was chosen to include only school-aged children
2. Included measures of sleep characteristics by "all-night" PSG or actigraphy on 1 or more of the following variables: sleep latency, sleep efficiency, TST, stage 1 sleep, stage 2 sleep, SWS, REM sleep, REM latency, and minutes of WASO
3. Included data presented numerically
4. Was published between 1960 and 2003 in peer-reviewed journals (unpublished works, dissertations, chapters, and abstracts were not included)

Databases searched were PubMed, PsyInfo, and Science Citation Index. Search terms were *sleep* with *normal*, *normative*, and *healthy*. In addition, references cited in retrieved reports were screened for additional reports. More than 4,000 reports were first screened for inclusion criteria and reduced to 585 reports. Subsequently, if a research report referred to the same data, only the most complete data set was taken, and the other papers were discarded.

Overall, 65 studies met all inclusion criteria. These studies represented 3,577 subjects aged 5 years to 102 years. The research reports devoted to children and adolescents totaled 1,186 subjects aged between 5 years and 19 years. The research reports on adults included 2,391 participants aged 19 years or older.

Procedures

Each accepted research report was reviewed and coded according to 6 criteria

1. At least 1 target variable (TST, sleep latency, sleep efficiency, WASO, REM sleep, stage 1 sleep, stage 2 sleep, SWS) was present
2. The sample was well described (number of subjects, recruitment procedure, etc)
3. Statistical analytic results were reported for at least 1 target variable (for example, F value, *r* value, etc);
4. Central tendency measures (eg, mean) and measures of variability were reported for at least 1 target variable;
5. Sexes were identified, and data summarized for each
6. Age was identified, and data summarized for age groups

Research reports with positive answers to criteria 1 to 4 and positive answers on criteria 5 or 6 were analyzed with a detailed checklist composed of 15 items summarizing the key elements of the articles: background, participants, intervention, selection criteria, objectives, outcomes, sample size, composition of the sample, variables assessed, statistical methods, and key results. As a rule, when the studies included 2 or more nights of PSG recording, the first-night results were discarded from the meta-analysis. When the results for each night were presented, night-1 results were discarded, and the data were averaged for all the other nights.

Statistical Analyses

Calculation of Effect Sizes

Effect sizes are indices that measure the magnitude of the differences between 2 groups. Effect sizes can be measured in 2 ways: (1) as the standardized differences between 2 groups or (2) as the correlation between an independent variable classification and individual scores on the dependent variable (effect size correlation). For this study, we measured standardized differences between 2 groups by calculating Cohen's d.[45] The simplest formula of Cohen's d is defined as the difference between means (M1 – M2) divided by the SD of either group. Furthermore, since the different groups in the selected studies are presumed to come from the same population (healthy individuals), pooled SD was used instead.[46] The pooled SD is the root mean square of the 2 SD. The formula is then: $d = M_1 - M_2 / \sigma_{pooled}$ where $\sigma_{pooled} = \sqrt{[(\sigma_1^2 + \sigma_2^2) / 2]}$.

Some studies did not provide means and SD for the key variables; therefore, effect size had to be calculated from other statistical tests reported, such as correlation coefficients, *t* tests, or analyses of variance.

Analyses of Effect Sizes

Effect sizes for each study were analyzed using Comprehensive Meta Analysis, a software package developed by Biostat (Englewood, NJ). The software provides a correction of effect sizes for sampling errors,[47] particularly important since most studies had small sample sizes. The formula given by Hedges and Olkin[47] was used: unbiased estimate of $d = d \times (1 - [3 / \{4 (M_1 + M_2)-9\}])$. Values of d are interpreted according to Cohen guidelines:[45] effect sizes at .2 are considered small, at .5 are considered medium, and are large at .8. In the text, as a general rule, a positive value of the effect size indicates an *increase with age* of the studied variable while a negative value indicates a *decrease with age*. The closer an effect size is to 0, the smaller is the age difference.

The *Q* statistic, a homogeneity test, was calculated to assess the dispersion of individual outcomes vis-à-vis the combined effect. The *Q* statistic has an approximate χ^2 distribution with *k*-1 degrees of freedom where *k* is the number of effect sizes. When *Q* is significant, it indicates that the variation is greater than expected by sampling error and that analyses of moderators should be done. Therefore, 7 moderator variables that might influence sleep parameters were also collected: mental illness, physical illness, drugs or alcohol use, sleep apnea, other sleep

disorders, sex, and polysomnographic recordings performed according a fixed sleep-wake schedule or based on habitual sleep patterns. For children and adolescents, the time of the recording (school day vs nonschool day) was also collected. These moderators were used to calculate to what extent their presence (or absence) modified the different effect sizes. Alpha was set to .05 for all analyses, and the confidence intervals to 95%.

RESULTS

Only 10.8% of the studies were conducted in 1975 or earlier; 16.9% were performed between 1976 and 1985; 33.8% of studies were carried out between 1986 and 1995; and 38.5% between 1996 and 2003. Table 1 presents the number of studies and subjects involved for each moderator variables.

Studies in Children and Adolescents

Data collection of objective sleep parameters was relatively infrequent in children and adolescents. A total of 18 studies presenting numeric data on TST and sleep stages were found from 1972 to 2003 (Table 2). In addition, the instrumentation used to collect sleep data varied. Eleven studies used in-laboratory PSG recording. Two studies used an ambulatory monitoring system,[55,58] and 5 studies used actigraphy, 1 of them using both in-laboratory polysomnographic recording and actigraphy.[57,60-62,64] The 18 studies were performed in different contexts. Five studies were done only on school days,[53,58,60-62] 3 studies were performed on week ends or during summer time,[54,52,59] and 2 studies included both school days and nonschool days.[57,64] Eight studies did not specify the time of the year.

Studies in Adults

Forty-seven studies using either PSG or actigraphy recording of sleep parameters in healthy adults were retained. A listing of these studies can be found in Table 3. In these studies, 17 (36.2%) compared sleep parameters of elderly adults to those observed in young adults (mostly subjects in their 20s). Seven (14.9%) compared young, middle-aged, and elderly subjects, 3 studies compared middle-aged subjects to elderly, 11 other studies were limited to young and middle-aged adults, and 9 included only elderly subjects. Most of the studies included both men and women but rarely reported values for each sex. Thirteen studies included only men and 1 study only women.

Six studies reported results based on a single night of polysomnographic recording (Table 3). In the other studies, the first night was for habituation to the laboratory, and the analyses were carried on the other nights. All but 5 of the PSG studies used the Rechtschaffen and Kales criteria[75] for sleep-stage scoring.

Overall Age-Related Trends

To describe age-related changes, we plotted mean values of each of sleep variables (TST; sleep latency; sleep efficiency; percentage of S1, S2, SWS, and REM sleep; and REM latency) as a function of age. The method of least squares was used to fit exponential equations to the data. Figure 1 presents the data and Table 4 the details of the equations. As is seen, sleep latency and percentage of S1, S2, and REM sleep had a low proportion of variance explained by age only (11% or less).

As can be observed, TST (r = -.76, P < .0001), sleep efficiency (r = -.82, P < .0001), percentage of SWS (r = -.56, P < .0001), and percentage of REM sleep (r = -.34, P < .0001) each showed a significant decrease with age. On the other hand, sleep latency (r = .16, P < .0001), percentage of stage 1 sleep (r = .16, P < .0001), percentage of stage 2 sleep (r = .34, P < .0001), and WASO (r = .75, P < .0001) each increased with age.

Magnitude of Effect Sizes

Table 5 and 6 provide information about the effect sizes calculated for each of the 9 sleep variables studied, the number of studies and subjects involved, the mean weighted effect sizes with 95% confidence intervals, and the Q values of homogeneity tests.

Age Trends for Children and Adolescents

In children and adolescents, TST (n = 1360), percentage of SWS (n = 585), and REM latency (n = 447) were negatively correlated with age, which indicated that as the children are aging, these sleep variables are decreasing (Table 5). Percentage of stage 2 sleep (n = 572) was positively related to age, indicating that percentage of stage 2 increases with age. The effect size was in the small range for percentage of REM sleep, indicating that the differences between children and adolescents, although significant, were not so large (about 2%). Effect sizes were in the medium range for TST, percentage stage 2 sleep, REM latency, and SWS. The decrease in SWS and the increase in percentage of stage 2 were about 7% per 5-year period between 5 and 15 years of age. Sleep latency, sleep efficiency, and percentage of stage 1 sleep had nonsignificant effect sizes.

Table 1—Number of Studies and Subjects Involved for Each Moderator in Adult Samples

	Studies, no.	Subjects, no.		
		Total	Men	Women
Total	47	2391	1474	917
Sex comparison	17	1045	506	539
Use of habitual sleep patterns for polysomnography	26	1382	849	533
Participants screened for				
Mental illness	28	1801	1059	742
Physical illness	38	1913	1113	800
Drugs or alcohol use	31	1622	961	661
Sleep apnea	15	670	368	302
Other sleep disorders	29	1382	849	533

Age Trends for Adults

In adults, all sleep parameters had effect sizes significantly different from 0. The effect size was in the large range for TST, sleep efficiency, percentage of SWS, and WASO; medium for REM percentage; and small for percentage of stage 1 sleep and REM latency. Total sleep time, sleep efficiency, percentage of SWS, percentage of REM sleep, and REM latency were negatively correlated with age. This pattern indicates an age-related decrease in these sleep variables.

As seen in Figure 1a, TST (n = 2009) linearly decreased with age with a loss of about 10 minutes per decade of age. Similarly, percentage of SWS (n = 1544) linearly decreased at a rate of about 2% per decade of age. The decrease in sleep efficiency (n = 1738) was more evident from 40 years of age: a 3% decrease per decade of age can be observed until very old age. The decrease in percentage of REM sleep (n = 1986) was subtler and was more obvious when young adults were compared to individuals 60 years of age or older, where a 4% discrepancy can be observed between these 2 groups.

On the other hand, sleep latency (n = 1436), percentages of stage 1 (n = 1072) and stage 2 sleep (n = 1133), and WASO (n = 1012) increased with age, as indicated by significant positive effect-size values. As illustrated in Figure 1a, and showing a small effect size, sleep latency increased very progressively with age and became more obvious after 65 years of age. The same observations can be made for percentages of stage 1 and stage 2

Table 2—Studies Using Polysomnography or Actigraphy to Assess Sleep Parameters in Normal Healthy Children and Adolescents

First author, year	Country	Sample	Measures	Variables Provided
Williams, 1972[48]	USA	28 boys 8-15 years	PSG, 3 nights	S1, S2, S3, S4, REM
Karacan, 1975[49]	USA	7 boys & 10 girls 12.5-15.8 years	PSG, 3 nights	TST, SL, SE, S1, S2, S3, S4, REM
Orr, 1977[50]	USA	13 children 6-16 years	PSG, 3 nights	TST, S1, S2, S3, S4, REM
Benoit, 1978[51]	France	13 boys & 8 girls 5-12 years	PSG, 2 nights	TST, S1, S2, S3, S4, REM
Carskadon, 1980[52]	USA	11 boys 10.2-15.7 years 8 girls 10.9-15.8 years Recorded 3 summers	PSG, 3 nights, MSLT	TST, SL, S2, SWS, REM
Coble, 1984 [53]	USA	42 boys & 45 girls 6.0-15.11 years	PSG, 3 nights during school year	TST, TSA, SL, SE, S1, S2, S3, S4, REM
Goetz, 1987[54]	USA	24 boys & 16 girls mean age 15.6 ± 1.5 years	PSG, 3 Nights	TST, TSA, SL, SE, S1, S2, S3, S4, REM
Palm, 1989[55]	Sweden	9 boys & 9 girls 8-12 years	AMS, 50 hours	TST, TSA, SL, SE, S1, S2, S3, S4, REM, NNW
Acebo, 1996[56]	USA	23 boys 13.3 ± 2.1 years 22 girls 13.8 ± 1.8 years	PSG, 1 night	TST, TSA, SL, SE, S1, S2, S3, S4, REM
Carskadon, 1998[57]	USA	15 boys & 25 girls 14-16.2 years	Actigraphy, 2 weeks + PSG, 1 night	TST, TSA, SL, S1, S2, S3, S4, REM, bedtime, wake-up time
Stores, 1998[58]	UK	30 boys & 30 girls 5-16 years	AMS, 1 night	TST, SL, SE, S1, S2, S3, S4, REM, NNW
Laberge, 2000[59]	Canada	19 boys 13.9-17 years	PSG, 2 nights	TST, SL, SE, S1, S2, SWS, REM
Sadeh, 2000[60]	Israel	72 boys & 68 girls 7.2-11.8 years	Actigraphy, 5 school nights	TST, TSA, SL, SE, MWT, NNW
Aronen, 2001[61]	Finland	33 boys & 33 girls 5-12 years	Actigraphy, 5 school nights	TSA, SL, SE
Gaudreau, 2001[26]	Canada	16 boys & 8 girls 6-16 years	PSG, 1 night	TST, SL, SE, S1, S2, S3, S4, REM
Paavonen, 2002[62]	Finland	6 boys & 14 girls 7.3-13.3 years	Actigraphy, 3 school nights	TSA, SL, SE
Bruni, 2002[63]	Italy	6 boys & 4 girls 6-10 years	PSG, 2 nights	TST, TSA, SL, SE, S1, S2, S3, S4, REM
Wolfson, 2003[64]	USA	106 boys & 196 girls 13.8-19.9 years	Actigraphy, sleep questionnaire, sleep diary	TSA, bedtime, wake-up time (school-days, weekends)

PSG refers to polysomnography; MSLT, Multiple Sleep Latency Test; AMS, ambulatory monitoring system; S1, stage 1 sleep; S2, stage 2 sleep; S3, stage 3 sleep; S4, stage 4 sleep; REM, rapid eye movement; TST, total sleep time; TSA, time spent asleep; SL, sleep latency; SE, sleep efficiency; SWS, slow-wave sleep; MWT, morning wake time; NNW, number of night awakenings

Table 3—Studies Using Polysomnography or Actigraphy to Assess Sleep Parameters in Normal Healthy Adults

First author, year	Country	Sample	Measures	Variables provided
Feinberg, 1967[40]	USA	9 men and 6 women mean age 77.0 years 9 men and 6 women mean age 26.6 years	PSG, 1 night	TST, SL, SE, REM, WASO
Kahn, 1969[44]	USA	16 men, 71-95 years	PSG, 4-5 nights	TST, SE, S1, S2, S3, S4, REM
Kahn, 1970[30]	USA	10 women, 66-87 years	PSG, 4-5 nights	TST, SE, S1, S2, S3, S4, REM
Williams, 1972[7]	USA	10 men, 41-46 years 11 men, 60-69 years 10 men, 13-15 years	PSG, 3 nights	TST, SE, S2, S3, S4, REM
Brezinova, 1975[8]	Scotland	5 men and 9 women mean age 55 years 6 men and 4 women mean age 22 years	PSG, 10 nights	TST, SL, S1,S2,SWS, REM
Gaillard, 1978[9]	Switzerland	18 men and 22 women 19-30 years	PSG, 3 nights	TST, SL, SE, S1, S2, S3, S4, REM
Gillin 1981[10]	USA	21 men & 15 women 15-64 years	PSG, 3 nights	TST, SL, SE, SWS, REM
Hayashi, 1982[31]	Japan	5 men and 10 women 73-92 years 13 men, 19-22 years	PSG, 3 nights	SL, SE, S1, S2, S3, S4, REM
Webb, 1982[42]	USA	40 men & 40 women 50-60 years 16 men & 16 women 20-30 years	PSG, 3 nights	S1, S2, S3, S4, REM
Krieger, 1983[65]	USA	10 men & 10 women 20-30 years 11 men & 9 women 53-76 years	PSG, 2 nights	SWS, REM
Bixler, 1984[32]	USA	40 men and 60 women mean age 45.4 years	PSG, 4 nights	TST, SL, SE, WASO
Berry, 1985[66]	USA	55 men & 64 women 50-70 years	PSG, 5 nights	TST, SE, S1, S2, S3, S4, RM
Naifeh, 1987[33]	USA	5 men and 6 women 61-81 years 6 men and 6 women 30-39 years	PSG, 4 nights	TST, SL, SE, S1, S2, SWS, REM, WASO
Zeplin, 1987[37]	USA	9 men and 9 women 57-71 years 9 men and 9 women 18-23 years	PSG, 3 nights	SL, SWS, REM, WASO
Hoch, 1988[41]	USA	9 men and 10 women 60-82 years	PSG, 2 x 3 nights	TST, SL, SE, REM, WASO
Schiavi, 1988[11]	USA	40 men, 23-73 years	PSG, 3 nights	TST, SE, REM
Bonnet, 1989[67]	USA	12 men, 55-70 years 12 men, 18-28 years	PSG, 4 nights (data from baseline night after 1 night habituation)	TST, SL, S1, S2, S3, S4, REM, WASO
Dijk, 1989[68]	Netherland	13 men & 15 women 19-28 years	PSG, 2 nights	TST, S1, S2, S3, S4, REM
Brendel, 1990[12]	USA	6 men and 4 women mean age 83.0 years 10 men and 4 women mean age 23.9 years	PSG, 3 nights	TST, SL, SE, S1, S2, S3, S4, SWS, REM, WASO
Hoch, 1990[34]	USA	49 men and 56 women 60-91 years	PSG, 3 nights	TST, SE, REM
Vitiello, 1990[69]	USA	11 men and 13 women mean age 63.6 years	PSG, 3 nights	TST, SL, SE, S1, S2, SWS, REM, WASO
Van Coevorden, 1991[38]	Belgium	8 men, 67-84 years 8 men, 20-27 years	PSG, 3 nights	TST, SWS, REM
Lauer, 1991[13]	Germany	26 men and 25 women mean age 38.3 years	PSG, 3 nights	TST, SL, SE, S1, S2, SWS, REM, WASO

Table 3 continued

Monk, 1991[14]	USA	16 men and 18 women mean age 83.1 years 21 men and 9 women mean age 25.5 years	PSG, 2 nights	TST, SL, SE, SWS, REM, WASO
Burger, 1992[15]	USA	30 men, 20-79 years	PSG, 1 night	TST, SWS, REM
Buysse, 1992[16]	USA	16 men and 18 women mean age 83.1 years 21 men and 9 women mean age 25.5 years	PSG, 2 nights	TST, SL, SWS, REM, WASO
Hirshkowitz, 1992 [17]	USA	186 men 20 years or older	PSG, 2 nights	TST, SL, SE, S1, S2, SWS, REM, WASO
Monk, 1992[18]	USA	20 men and 25 women 71-91 years 10 men and 11 women 19-28 years	PSG, 2 nights	TST, SE, SWS, REM
Schiavi, 1992[19]	USA	67 men 45-74 years	PSG, 4 nights	TST, SE, REM, WASO
Wauquier 1992[70]	Netherland	7 men & 7 women 88-102 years	AMS, 48 hours	TST, SE, SL, REM
Hoch, 1994[20]	USA	21 men and 29 women 61.1-89.2 years	PSG, 3 nights	TST, SL, SE, S1, S2, SWS, REM, WASO
Frank, 1995[21]	USA	8 men, mean age 65 years 8 men, mean age 25 years	PSG, 1 night	TST, SL, SE, SWS, REM, WASO
Landolt, 1996[22]	Switzerland	8 men, 20-26 years 8 men, 57-64 years	PSG, 1 night	TST, SL, SE, S1, S2, SWS, REM
Vitiello, 1996[71]	USA	45 men and 68 women mean age 69.1 years	PSG, 3 nights	TST, SL, SE, SWS, REM, WASO
Ehlers, 1997[39]	USA	33 men & 28 women 20-40 years	PSG, 3 nights	TST, SL, SE, S1, S2, SWS, REM, WASO
Haimov, 1997[35]	Israel	17 men, 65-78 years 8 men, 19-26 years	PSG, 1 night	TST, SL, SE, S1, S2, SWS, REM
Martin, 1997[72]	UK	7 men and 5 women mean age 25 years	PSG, 2 x 2 nights	TST, SE, S1, S2, SWS, REM
Parrino, 1998[23]	Italy	20 men and 20 women ≥ 10 years	PSG, 2 nights	TST, SL, SE, S1, S2, S3, S4, REM, WASO
Rao, 1999[36]	USA	35 men and 38 women mean age between 24.2 and 42 years	PSG, 2 nights	TST, SL, SE, S1, S2, S3, S4, REM, WASO
Spiegel, 1999[73]	Switzerland	20 men and 10 women T1: 63.1 years T2: 77.1 years	PSG, 2 nights	SL, S1, S2, SWS, REM, WASO
Armitage, 2000[74]	USA	15 men & 8 women 22-40 years	PSG, 2 nights	TST, SL, S1, S2, SWS, REM
Van Cauter, 2000[24]	USA	149 men 16-93 years	PSG, 2 nights	TST, SWS, REM
Murphy, 2000[43]	USA	5 men & 9 women 19-28 years 6 men & 5 women 60-82 years	PSG, 5 nights	S1, S2, SWS, REM
Carrier, 2001[25]	USA	53 men & 47 women 20-60 years	PSG, 3 nights	TST, SE, S1, S2, SWS, REM
Gaudreau, 2001[26]	Canada	20 men & 10 women 19-60 years	PSG, 1 night	TST, SL, SE, S1, S2, SWS, REM
Nicolas, 2001[27]	France	17 men and 19 women 10-69 years	PSG, 2 night	TST, SE, S1, S2, SWS, REM
Crowley, 2002[28]	Australia	8 men and 6 women mean age 21.4 years 11 men and 9 women mean age 75.5 years	PSG, 2 nights	TST, SL, SE, S1, S2, SWS, REM, WASO
Yoon, 2003[29]	USA	22 men and 38 women mean age 66.2 years 26 men and 47 women mean age 23.5 years	Actigraphy, 1 week	TST, SL, SE, WASO

PSG refers to polysomnography; AMS, ambulatory monitoring system; TST, total sleep time; SL, sleep latency; SE, sleep efficiency; REM, rapid eye movement; WASO, wake after sleep onset; S1, stage 1 sleep; S2, stage 2 sleep; S3, stage 3 sleep; S4, stage 4 sleep; SWS, slow-wave sleep.

sleep. In both cases, there was an increase of about 5% between 20 and 70 years, which translated into small effect sizes. On the other hand, the effect size was large for WASO. It can be seen in Figure 1e that WASO consistently increased about 10 minutes per decade of age from 30 years.

All the homogeneity statistics (Q statistic) were significant (Table 6), indicating that factors other than aging may be responsible for the observed differences. Results of the moderator analyses are reported in Tables 7, 8, and 9.

Table 4—Equations Relating Sleep Variables to Age in Studies Using In-laboratory Recordings

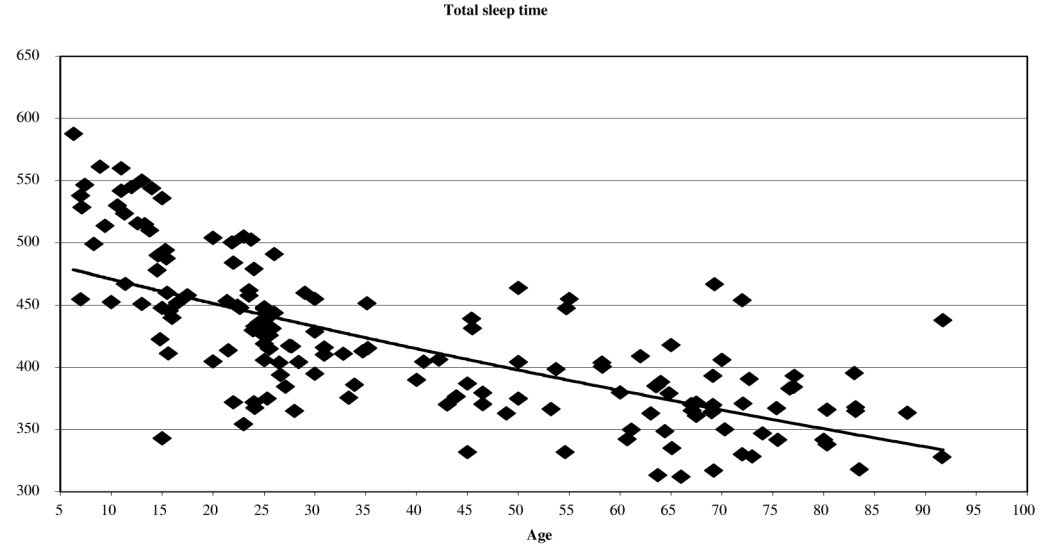
Variables	N	EEG b	PVE
TST	2890	-0.004	59
Sleep latency	2465	0.002	2
SE %	2843	-0.003	63
Stage 1 %	2140	0.003	2
Stage 2 %	2185	0.003	11
SWS %	2907	-0.016	34
REM %	3063	-0.003	10
REM latency	2220	-0.008	50
WASO	1698	0.029	60

EEG refers to electroencephalogram; TST, total sleep time; REM, rapid eye movement; WASO, wake after sleep onset; PVE, proportion of variance explained

Impact of Moderator Variables

Total Sleep Time

In children and adolescents, the relation between age and TST was moderated by the recording methods; studies that used in-laboratory PSG found significantly larger correlations than those using actigraphy (z statistic for contrast: -7.92; $P < .0001$). Similarly, the relation between age and TST was moderated by the time of recording. Studies that took place during school days (z statistic for contrast: -7.60; $P < .0001$) had larger correlations than those that were done on nonschool days. The results showed that TST decreased with age only when recordings took place on school days. On nonschool days, TST remained the same from childhood to the end of adolescence.



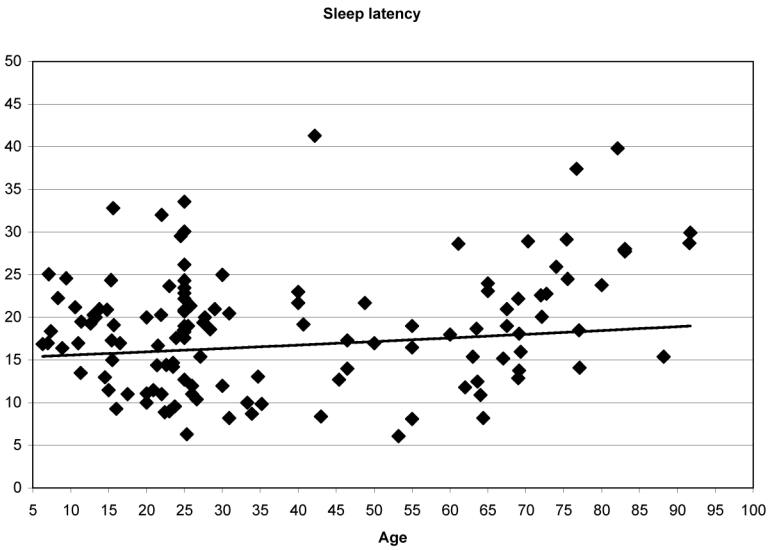


Figure 1a—Age-related trends for total sleep time (minutes) and sleep latency (minutes). Lines represent the exponential equations fitted for data from samples

In adults, exclusion of subjects with mental disorders produced a larger effect size, indicating a greater association between TST and aging when researchers excluded participants with a mental disorder compared to studies that kept such participants. The same effect on TST was observed when researchers excluded participants with physical illnesses, drug or alcohol use, or sleep apnea, or other sleep disorders (Table 7). Studies that kept habitual sleep patterns for the night of the PSG recording also produced a larger effect size than when researchers imposed the schedule for lights off and on. Effect size was larger in women than in men, indicating a greater association between declining TST and aging among women.

We also verified that the sample composition in terms of age—ie, elderly only (60 years or older); young, middle-aged, and elderly subjects; or samples composed of young adults and elderly subjects—produced different results. The association between TST and age was higher in studies that compared young adults with middle-aged and young adults with elderly subjects. The association was nonsignificant when the researchers included only participants 60 years or older. This indicates that TST did not continue to significantly decline among older subjects.

Sleep Efficiency

Similar to the pattern seen for TST, adult studies that excluded participants with mental disorders, physical illnesses, sleep apnea, or other sleep disorders obtained a greater association between sleep efficiency and age compared to studies that included these participants. Inclusion or exclusion of drugs or alcohol had no appreciable influence on effect sizes. Again, effect size was larger in women than in men, indicating a greater association between declining sleep efficiency and aging among women. The examination of sample composition showed that, once again, a larger effect size was found in studies that compared young with elderly adults and young with middle-aged subjects; however, in contrast to what was observed for TST, sleep efficiency continued to significantly decrease with age in the "elderly only" samples where a medium effect size was observed.

Sleep Latency

As seen in Table 7, adult studies that included participants with physical illnesses or with other sleep disorders had nonsignificant effect size for sleep latency, indicating that sleep latency did not

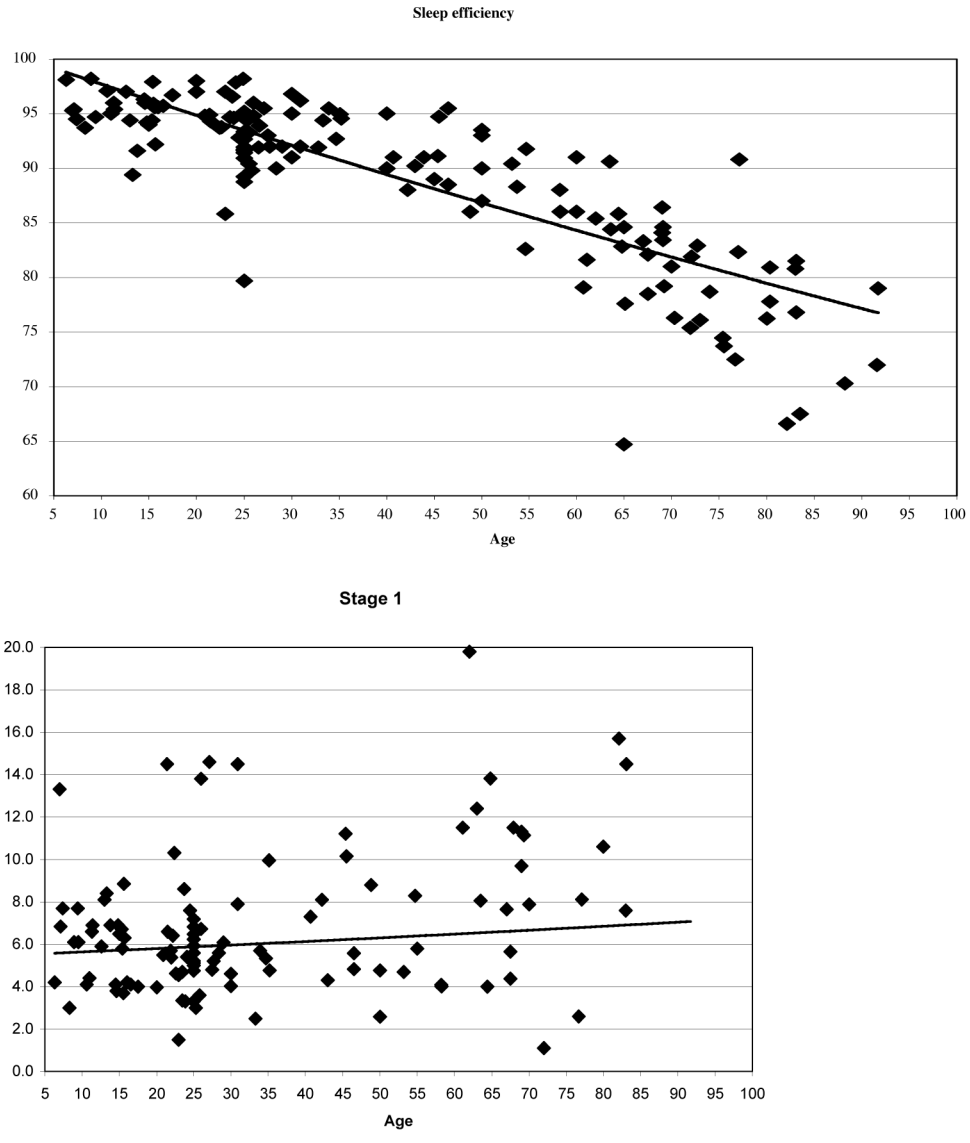


Figure 1b—Age-related trends for sleep efficiency and percentage of stage 1 sleep. Lines represent the exponential equations fitted for data from samples.

change with age. In contrast, studies that took care to exclude such participants had medium positive effect sizes, indicating that sleep latency increased with age. Studies that included subjects with sleep apnea had significant positive effect sizes, while those that excluded them had nonsignificant effect sizes. Again, sample composition in terms of participants' ages produced different effect sizes: studies that included only elderly subjects and those that included young, middle-aged, and elderly subjects had nonsignificant effect sizes. Only when researchers compared very young adults to elderly participants was a positive association observed between sleep latency and getting older.

Percentage of Stage 1 Sleep

Moderator analyses in adults showed that the association between percentage of stage 1 sleep and age is greater when researchers excluded participants with a mental disorder, sleep apnea or other sleep disorders or taking drugs or alcohol (Table 8). On the other hand, inclusion or exclusion of participants with a physical illness had no impact on effect size. Larger effect size was obtained when the association between increasing percentage of stage 1 sleep and aging was limited to women compared to when it was limited to men. Again, larger effect sizes were obtained when studies included only young and middle-aged participants or young and elderly participants.

Percentage of Stage 2 Sleep

In children and adolescents studies, as well as in adult studies, percentage of stage 2 sleep significantly increased with age.

The relation between age and percentage of stage 2 sleep in children and adolescents was somewhat influenced by the day of recording (Table 5). Studies that took place during school days (z statistic for contrast: 3.05; $P < .0001$) had smaller effect sizes than those that were done on nonschool days (z statistic for contrast: 2.83; $P < .01$) or those for which there was no indication for the time of the year (z statistic for contrast: 4.39; $P < .0001$).

In adult samples, studies that excluded participants with mental disorders, physical illnesses, drug or alcohol use, sleep apnea, or other sleep disorders obtained larger effect sizes between aging and percentage of stage 2 sleep, while studies that kept those participants had nonsignificant effect sizes. Similarly, stud-

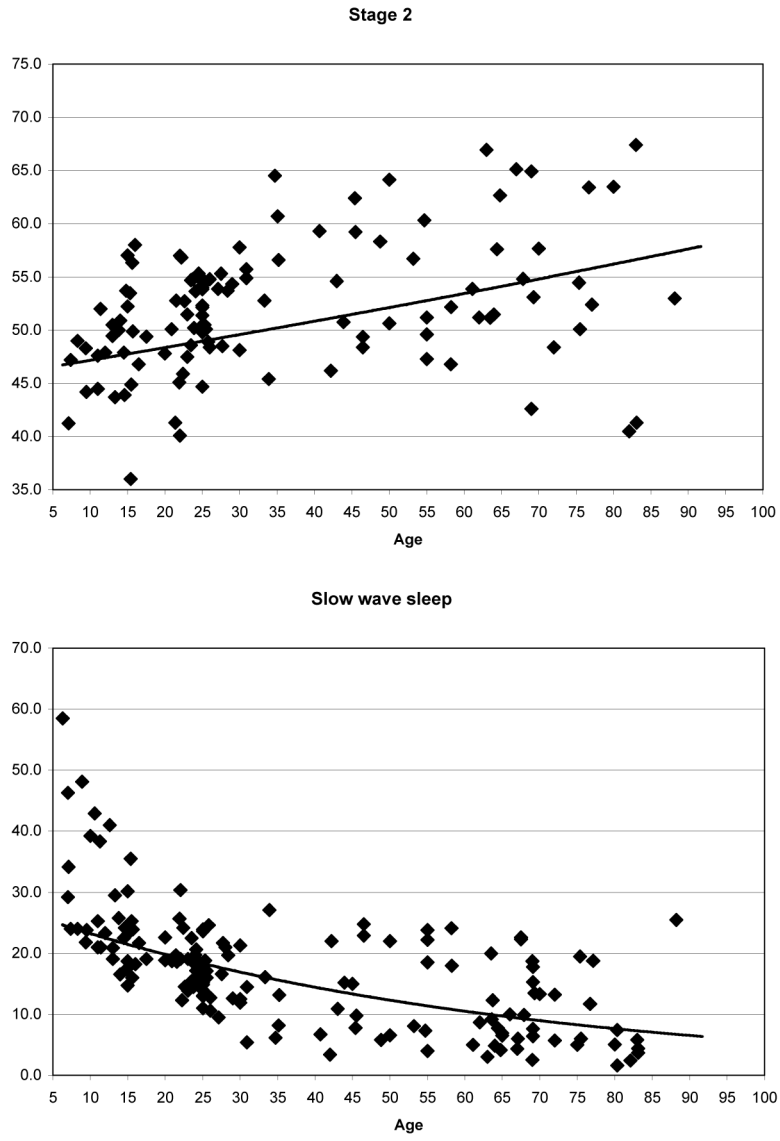


Figure 1c—Age-related trends for percentage of stage 2 sleep and percentage of slow wave sleep. Lines represent the exponential equations fitted for data from samples.

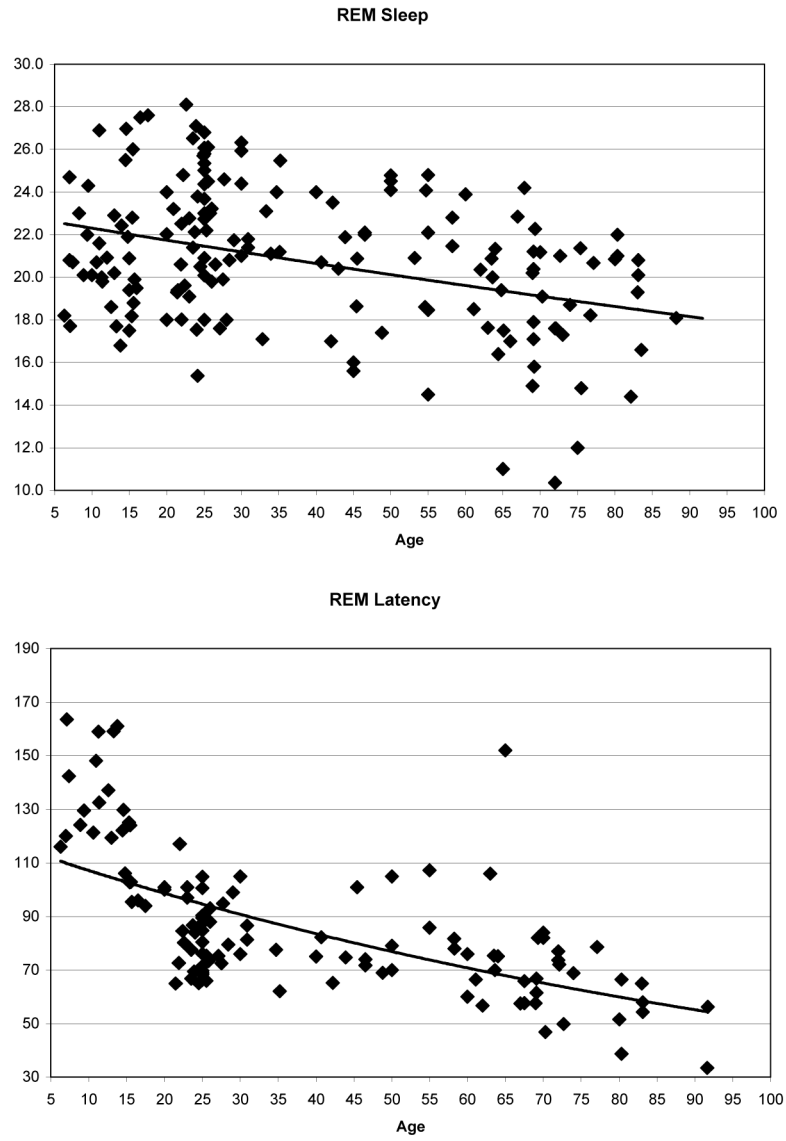


Figure 1d—Age-related trends for percentage of rapid eye movement (REM) sleep and REM sleep latency (minutes). Lines represent the exponential equations fitted for data from samples.

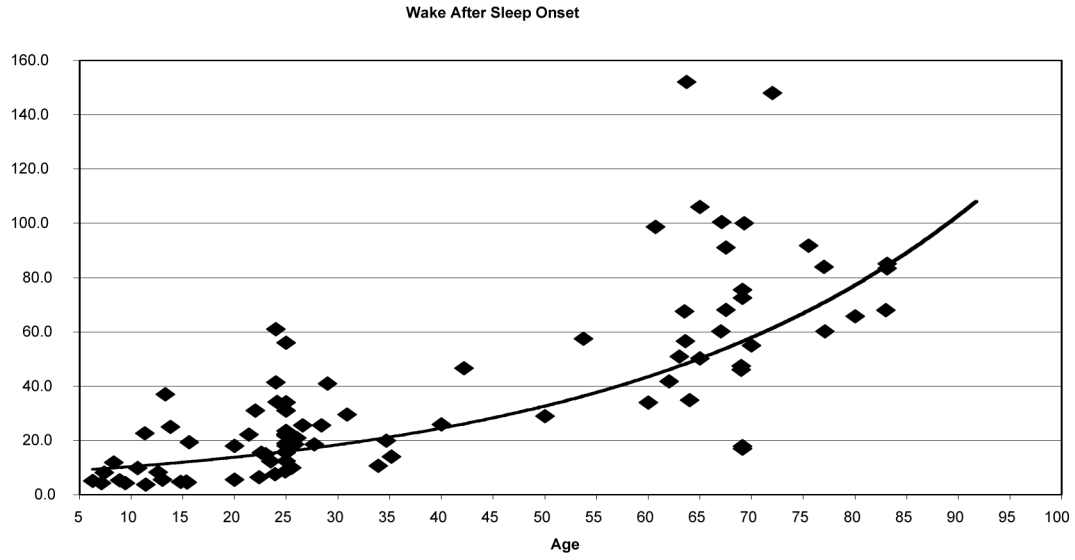


Figure 1e—Age-related trends for wake after sleep onset. Lines represent the exponential equations fitted for data from samples.

ies that used the habitual sleep patterns of the participants to set the PSG recording obtained larger effect sizes than did studies that imposed a fixed schedule for lights off and lights on (Table 8).

Percentage of SWS

In children and adolescents studies, moderator analyses showed a large effect size in studies performed on nonschool days and a small effect size for studies performed on school days.

In adults, as seen in Table 8, analyses of moderator variables did not produce different results: the exclusion or inclusion of participants with a mental disorder, physical illness, drug or alcohol use, sleep apnea, or other sleep disorders gave large effect sizes in all cases. However, it was noted that effect sizes were much larger when participants with a mental disorder, sleep apnea, or other sleep disorders were excluded. Furthermore, the use of habitual sleep patterns to set the PSG recording gave a larger size effect than in studies that imposed a fixed schedule for lights off and lights on (Table 8).

Effect sizes were similar in men and in women. When examining the sample composition, studies that included only elderly participants did not find changes in percentage of SWS.

Table 5—Effect Sizes and Homogeneity Statistics for Sleep Variables in Children and Adolescent Samples

	Effect sizes, no.	Studies, no.	Subjects, no.	Effect size (95% CI)	*Q*
Total sleep time					
All studies	37	15	1360	-0.48 (-0.59. -0.38)*	114.75 (27 *df*)*
Electroencephalogram	20	9	501	-0.65 (-0.82, -0.49)*	70.92 (19 *df*)*
Actigraphy	13	5	836	-0.33 (-0.49, -0.18)†	76.39 (12 *df*)*
School days	18	7	843	-0.57 (-0.72, -0.43)*	60.17 (17 *df*)*
Nonschool days	10	5	607	-0.04 (-0.23, 0.15)	11.75 (9 *df*)
Unknown	9	4	199	-1.05 (-1.32, -0.78)*	44.69 (8 *df*)*
Sleep latency	17	8	513	0.09 (-0.06, 0.25)	22.09 (16 *df*)
Sleep efficiency	21	9	653	0.01 (-0.13, 0.15)	32.74 (20 dif)†
Stage 1 %	17	8	455	-0.09 (-0.25, 0.08)	52.46 (17 *df*)*
Stage 2 %					
All studies	23	10	572	0.45 (0.30, 0.60)*	82.61 (22 *df*)†
School days	9	3	194	0.37 (0.13, 0.61)*	12.64 (8 *df*)
Nonschool days	6	3	164	0.44 (0.13, 0.74)‡	36.13 (5 *df*)
Unknown	8	4	214	0.55 (0.30, 0.80)*	32.80 (7 *df*)*
SWS %					
All studies	25	11	585	-0.57 (-0.71, -0.42)*	88.95 (24 *df*)*
School days	9	3	194	-0.37 (-0.60, -0.13)*	6.40 (8 *df*)
Nonschool days	6	3	164	-0.93 (-1.24, -0.61)*	29.36 (5 *df*)*
Unknown	10	5	227	-0.56 (-0.80, -0.32)*	45.34 (9 *df*)*
REM %	25	11	585	0.21 (0.07, 0.35)‡	30.49 (24 *df*)
REM latency	17	7	447	-0.68 (-0.86, -0.51)*	130.49 (16 *df*)*
WASO	12	5	318	-0.30 (-0.50, -0.11)*	36.64 (11 *df*)*

CI refers to confidence interval; SWS, slow-wave sleep; REM, rapid eye movement; WASO, wake after sleep onset.
*$P < .0001$
†$P < .05$
‡$P < .01$

Table 6—Effect Sizes Related to Age And Homogeneity Statistics for Sleep Variables in Adult Samples

	Effect sizes, no.	Studies, no.	Subjects, no.	Effect size (95% CI)	*Q*
Total sleep time	62	38	2009	-0.60 (-0.69, -0.51)*	343.63 (61 *df*)*
Sleep latency	42	27	1436	0.27 (0.17, 0.37)*	92.25 (41 *df*)*
Sleep efficiency	54	32	1738	-0.71 (-0.81, -0.61)*	372.28 (54 *df*)*
Stage 1%	37	21	1072	0.38 (0.26, 0.49)*	179.20 (36 *df*)*
Stage 2 %	40	24	1133	0.28 (0.17, 0.40)*	310.53 (39 *df*)*
SWS %	51	31	1544	-0.85 (-0.96, -0.75)*	406.03 (50 *df*)*
REM %	63	38	1986	-0.46 (-0.55, -0.37)*	234.88 (62 *df*)*
REM latency	32	21	933	-0.15 (-0.28, -0.03)†	56.85 (31 *df*)*
WASO	27	20	1012	0.89 (0.75, 1.202)*	177.07 (26 *df*)*

CI refers to confidence interval; SWS, slow-wave sleep; REM, rapid eye movement; WASO, wake after sleep onset.
*$P < .0001$
†$P < .05$

Percentage of REM Sleep

As seen with percentage of SWS, exclusion of participants with any of the moderator variables did not produce major changes in the effect sizes for mental disorder, drug or alcohol use, habitual sleep patterns, and sex. The most notable effect was observed in studies that excluded participants with other sleep disorders compared to those that kept them (Table 9). Once more, the effect size was not significant for studies that included only elderly individuals. Studies that compared young to elderly subjects and young to middle-aged subjects found greater effect sizes.

REM Latency

The relationship between REM latency and age was modified by the exclusion of subjects with sleep apnea or other sleep disorders (Table 9). In both cases, a negative association was observed between REM latency and age. Effect sizes were also larger in women than in men and in studies that kept the habitual sleep patterns of the participants. Similarly, studies that compared young to elderly participants obtained the largest effect sizes between REM latency and age; however, those studies that included only elderly participants or broader age ranges had nonsignificant effect sizes.

Wake After Sleep Onset

The exclusion of participants with a mental disorder, a physical illness, or sleep apnea or those using drugs or alcohol decreased the effect sizes, while the exclusion of participants with other sleep disorders increased the effect sizes (Table 9). This pattern indicates that when sleep disorders were possibly present, the association of WASO and age was weakened.

Sex Trends

Table 10 provides information about effect sizes and homogeneity tests calculated for comparisons between men and women. Negative effect sizes indicated that women had higher means than men on the sleep measures, while positive effect sizes indicated that men had higher means than women on the sleep measures. As can be seen, TST, sleep latency, percentage of SWS, percentage of REM sleep, and REM latency had negative effect sizes, indicating that men had higher means on these variables. On the other hand, percentage of stage 2 sleep and WASO

Table 7—Moderator Analyses for Total Sleep Time, Sleep Efficiency, Sleep Latency, and Age in Adult Samples

	Total sleep time		Sleep efficiency		Sleep latency	
Moderators & Levels	Effect size (95%CI)	*z* value	Effect size (95%CI)	*z* value	Effect size (95%CI)	*z* value
Mental disorders						
Included	-0.24 (-0.42, -0.06)	-2.66‡	-0.34 (-0.53, -0.14)	-3.38*	0.23 (-0.05, 0.40)	2.59‡
Excluded	-0.72 (-0.82, -0.62)	-13.78*	-0.83 (-0.94, -0.72)	-14.70*	0.29 (0.17, 0.41)	4.59*
Physical illness						
Included	-0.20 (-0.37, -0.03)	-2.34†	-0.32 (-0.50, -0.14)	-3.55*	0.15 (-0.05, 0.35)	1.45
Excluded	-0.75 (-0.86, -0.65)	-14.15*	-0.87 (-0.99, -0.76)	-14.94*	0.30 (0.19, 0.42)	5.19*
Drugs/alcohol						
Included	-0.46 (-0.60, -0.32)	-6.51*	-0.71 (-0.86, -0.56)	-9.18*	0.27 (0.12, 0.41)	3.63*
Excluded	-0.71 (-0.83, -0.59)	-8.18*	-0.71 (-0.83, -0.58)	-11.18*	0.27 (0.13, 0.41)	3.77*
Sleep apnea						
Included	-0.47 (-0.57, -0.37)	-9.26*	-0.68 (-0.78, -0.57)	-12.45*	0.29 (0.18, 0.40)	5.22*
Excluded	-1.17 (-1.38, -0.97)	-11.33*	-0.85 (-1.07, -0.63)	-7.50*	0.14 (-0.10, 0.38)	1.16
Other sleep disorders						
Included	-0.24 (-0.37, -0.11)	-3.55*	-0.35 (-0.49, -0.21)	-4.97*	0.12 (-0.03, 0.27)	1.55
Excluded	-0.91 (-1.03, -0.79)	-14.80*	-1.04 (-1.71, -0.91)	-15.30*	0.38 (0.24, 0.51)	5.59*
Habitual sleep time						
Unknown	-0.27 (-0.48, -0.06)	-2.49†	-0.44 (-0.67, -0.21)	-3.71*	0.22 (-0.02, 0.46)	1.78
No	-0.43 (-0.64, -0.22)	-4.08*	-0.86 (-1.07, -0.64)	-7.77*	0.33 (0.14, 0.52)	3.35*
Yes	-0.75 (-0.86, -0.64)	-13.16*	-0.74 (-0.86, -0.62)	-11.93*	0.25 (0.12, 0.39)	3.69*
Sex						
Both	-0.72 (-0.83, -060)	-11.82*	-0.92 (-1.04, -0.79)	-14.83*	0.36 (0.24, 0.48)	5.72*
Men	-0.37 (-0.51, -0.23)	-5.09*	-0.30 (-0.48, -0.13)	-3.45*	0.08 (-0.11, 0.26)	0.84
Women	-1.18 (-1.59, -0.77)	-5.73*	-0.64 (-1.04, -0.24)	-3.17*	0.16 (-0.30, 0.62)	0.70
Sample composition						
E	-0.13 (-0.35, 0.08)	-1.21	-0.41 (-0.63, -0.19)	-3.72*	0.10 (-0.20, 0.40)	0.67
YM	-0.77 (-1.01, -0.53)	-6.43*	-1.12 (-1.42, -0.82)	-7.41*	0.22 (-0.03, 0.46)	1.75
YME	-0.28 (-0.45, -0.10)	-3.13*	-0.20 (-0.38, -0.02)	-2.16†	0.19 (-0.01, 0.39)	1.87
YE	-0.60 (-0.69, -0.51)	-13.29*	-1.58 (-1.77, -1.40)	-16.47*	0.51 (0.34, 0.68)	5.85*

CI refers to confidence interval; Included, no screening for the condition; Excluded, exclusion of subjects with the condition; E, samples including groups of elderly only; YME, samples including groups of young, middle-aged, and elderly subjects; YE, samples including groups of young and elderly subjects.
*$P < .0001$
‡$P < .01$
†$P < .05$

had positive effect sizes, indicating higher means for women than for men. Effect sizes were in the small range for most variables (TST, sleep latency, percentage REM sleep, REM latency, and WASO), indicating that the differences between men and women on these variables were modest.

DISCUSSION

This study aimed to describe age-related changes in the macrostructure of sleep and to clarify the issues regarding earlier contradictory results regarding the evolution of sleep latency and percentages of stage 1, stage 2, and REM sleep. Indeed, about half of the studies that analyzed age-related changes for percentages of REM and stage 1 sleep reported that these parameters changed with age, while the other half found no change. Similarly, about 2 of 3 studies reported that sleep latency and percentage of stage 2 sleep did not change with age, while the others found that these 2 parameters increased with age. One of the problems was that these studies based their conclusions on a small number of subjects. Therefore, it is very difficult to identify age-related trends when the changes are subtle. To summarize all this information, we decided to perform meta-analyses on 65 studies, which represented 3,577 subjects aged 5 years or older. This method allowed quantifying conclusions, which cannot be done with traditional literature reviews. We also performed the analyses in relationship with several moderators that can have a significant impact on any potential associations between sleep and aging.

In relationship with the objectives of the study, the following conclusions can be drawn from our meta-analytic results.

(1) Sleep latency increases with age. Overall, it appeared that sleep latency modestly but significantly increased with age. However, the change is very subtle: when young adults were compared to middle-aged individuals, and middle-aged compared to elderly individuals, sleep latencies were comparable. The significant difference appeared only when very young adults were compared to elderly individuals. The overall increase in sleep latency between 20 and 80 years was less than 10 minutes.

(2) Percentage of stage 1 sleep increases with age. The significant increase in stage 1 sleep was found between young and middle-aged adults and between middle-aged and elderly individuals, which means that percentage of stage 1 sleep significantly increased across all adulthood.

(3) Percentage of stage 2 sleep increases with age. This increase was present across the full age range studied, from childhood (5 years and older) until age 60.

Table 8—Moderator Analyses for Stages 1, 2, and Slow-Wave Sleep and Age in Adult Samples.

	Stage 1 sleep, %		Stage 2 sleep, %		Slow-wave sleep, %	
Moderators & Levels	Effect size (95%CI)	*z* value	Effect size (95%CI)	*z* value	Effect size (95%CI)	*z* value
Mental disorders						
Included	0.30 (0.12, 0.48)	3.25*	0.15 (-0.02, 0.32)	1.74	-0.67 (-0.85, -0.50)	-7.60*
Excluded	0.43 (0.28, 0.58)	5.57*	0.40 (0.24, 0.56)	4.93*	-0.96 (-1.09, -0.83)	-14.25*
Physical illness						
Included	0.35 (0.13, 0.57)	3.10*	0.23 (0.02, 0.44)	2.17†	-0.85 (-1.06, -0.64)	-8.12*
Excluded	0.39 (0.25, 0.52)	5.56*	0.31 (0.17, 0.45)	4.31*	-0.86 (-0.98, -0.73)	-13.72*
Drugs/alcohol						
Included	0.05 (-0.14, 0.24)	0.55	0.01 (-0.17, 0.19)	0.10	-0.96 (-1.12, -0.80)	-11.55*
Excluded	0.57 (0.42, 0.72)	7.61*	0.49 (0.34, 0.64)	6.24*	-0.78 (-0.92, -0.64)	-11.12*
Sleep apnea						
Included	0.18 (0.04, 0.32)	2.46‡	0.07 (-0.07, 0.21)	1.01	-0.78 (-0.90, -0.66)	-12.76*
Excluded	0.77 (0.57, 0.97)	7.53*	0.83 (0.61, 1.05)	7.43*	-1.11 (-1.33, -0.89)	-9.91*
Other sleep disorders						
Included	0.23 (0.07, 0.39)	2.78‡	0.11 (-0.04, 0.27)	1.49	-0.55 (-0.70, -0.39)	-7.06*
Excluded	0.55 (0.38, 0.72)	6.34*	0.53 (0.34, 0.71)	5.69*	-1.14 (-1.29, -1.00)	-15.34*
Habitual sleep time						
Unknown	0.11 (-0.22, 0.45)	0.67	0.20 (-0.11, 0.52)	1.28	-0.62 (-0.85, -0.40)	-5.44*
No	0.35 (0.16, 0.55)	3.54*	0.11 (-0.08, 0.30)	1.12	-0.50 (-0.69, -0.31)	-5.07*
Yes	0.45 (0.29, 0.61)	5.55*	0.44 (0.27, 0.60)	5.17*	-1.17 (-1.32, -1.02)	-15.27*
Gender						
Both	0.44 (0.29, 0.59)	5.75*	0.25 (0.10, 0.40)	3.22*	-0.85 (-1.00, -0.70)	-11.20*
Men	0.23 (0.04, 0.43)	2.33†	0.31 (0.12, 0.51)	3.19*	-0.85 (-1.02, -0.69)	-10.37*
Women	0.60 (0.09, 1.10)	2.33†	0.45 (-0.06, 0.96)	1.77	-0.87 (-1.24, -0.50)	-4.60*
Sample composition						
E	0.15 (-0.20, 0.50)	0.85	0.02 (-0.31, 0.35)	0.12	-0.08 (-0.41, 0.25)	-0.48
YM	0.59 (0.36, 0.83)	4.96*	0.60 (0.35, 0.85)	4.66*	-0.69 (-0.90, -0.48)	-6.42*
YME	0.21 (0.02, 0.40)	2.12†	0.20 (0.01, 0.39)	2.11†	-0.61 (-0.80, -0.43)	-6.46*
YE	0.46 (0.18, 0.74)	3.28*	0.00 (-0.27, 0.26)	-0.03	-1.71 (-1.93, -1.48)	-14.96*

CI refers to confidence interval; Included, no screening for the condition; Excluded, exclusion of subjects with the condition; E, samples including groups of elderly only; YME, samples including groups of young, middle-aged, and elderly subjects; YE, samples including groups of young and elderly subjects.

*$P < .0001$

‡$P < .01$

†$P < .05$

(4) Percentage of REM sleep decreases with age in adults. Percentage of REM sleep first increased from childhood to adolescence, than decreased between young and middle-aged adults, and remained unchanged in subjects older than 60 years of age.

(5) In adults, the increase in the percentage of stage 2 sleep with age and the decrease of REM latency with age appeared to be very sensitive to psychiatric disorders, use of drugs or alcohol, sleep apnea, or other sleep disorders; failure to exclude individuals with these conditions resulted in the confounding of their significant associations with age.

(6) In children 5 years and older and in adolescents, the apparent decrease in TST with age appears to be related to environmental factors rather than to biologic changes. As we showed in Table 5, the studies analyzed indicated a significant decrease of TST with age but only when recordings were performed during school days.

(7) While almost all studies in children 5 years of age or older and adolescents did not find significant changes in REM sleep with age, it appeared that there actually is a modest but significant increase in the percentage of REM sleep from childhood to the end of adolescence. After that age, percentage of REM sleep remains relatively stable until 60 years of age, when it again begins to decrease.

Sleep in Children and Adolescents

Studies that examined the normal sleep in children aged 5 years or older and adolescents using PSG recordings are still scant, making it difficult to impossible to effectively perform moderator analyses and to analyze all the sleep variables examinable in the older population.

Results of the meta-analysis suggested that different recording techniques are likely to give different results. Although the conclusion for TST was the same for in-laboratory recordings and actigraphy, the association between TST and age was weaker with actigraphy (-0.33) than with in-laboratory recordings (-0.69). Furthermore, the discrepancy for TST between the different methods was large among the younger children: more than 60 minutes for children aged between 8 and 12 years.

Importantly, the timing of the recording influenced the age-related change for several sleep variables. Thus, the reduction in TST with age was significant only when recordings were made during school days; TST was unassociated with age when studied on nonschool days. This pattern suggests that, in children and adolescents, the decrease in TST is not related to maturation but to other factors such as school schedules. Several North American studies have reported the difficulties adolescents have

Table 9—Moderator Analyses for REM Sleep, REM Latency, Wake After Sleep Onset, and Age in Adult Samples

	REM%		REM latency		Wake after sleep onset	
Moderators & Levels	Effect size (95%CI)	*z* value	Effect size (95%CI)	*z* value	Effect size (95%CI)	*z* value
Mental disorders						
Included	-0.36 (-0.52, -0.19)	-4.30*	-0.09 (-0.51, 0.33)	-0.42	0.98 (0.64, 1.32)	5.69*
Excluded	-0.50 (-0.60, -0.40)	-9.54*	-0.16 (-0.29, -0.03)	-2.34†	0.87 (0.73, 1.01)	11.81*
Physical illness						
Included	-0.29 (-0.46, -0.12)	-3.32*	-0.22 (-0.63, 0.20)	-1.04	1.28 (0.55, 2.01)	3.54*
Excluded	-0.52 (-0.62, -0.42)	-10.08*	-0.15 (-0.28, -0.01)	-2.14†	0.87 (0.74, 1.01)	12.66*
Drugs or alcohol						
Included	-0.42 (-0.56, -0.29)	-6.07*	-0.19 (-0.41, 0.03)	-1.68	1.26 (1.03, 1.49)	10.96*
Excluded	-0.48 (-0.60, -0.37)	-8.42*	-0.13 (-0.29, 0.02)	-1.71	0.69 (0.52, 0.85)	8.22*
Sleep apnea						
Included	-0.40 (-0.50, -0.30)	-8.04*	-0.10 (-0.25, 0.05)	-1.34	0.92 (0.77, 1.07)	12.21*
Excluded	-0.69 (-0.88, -0.50)	-7.05*	-0.31 (-0.56, -0.05)	-2.39†	0.74 (0.44, 1.04)	4.85*
Other sleep disorders						
Included	-0.22 (-0.34, -0.09)	-3.45*	0.02 (-0.20, 0.23)	0.16	0.14 (-0.13, 0.42)	1.02
Excluded	-0.70 (-0.82, -0.57)	-11.16*	-0.25 (-0.41, -0.09)	-3.06*	1.12 (0.97, 1.27)	14.43*
Habitual sleep time						
Unknown	-0.16 (-0.36, 0.05)	-1.47	0.12 (-0.19, 0.43)	0.74	0.29 (0.05, 0.53)	2.34†
No	-0.50 (-0.69, -0.31)	-5.19*	-0.07 (-0.32, 0.18)	-0.55	0.89 (0.57, 1.20)	5.55*
Yes	-0.53 (-0.64, -0.42)	-9.40*	-0.27 (-0.44, -0.10)	-3.17*	1.24 (1.06, 1.43)	13.16*
Gender						
Both	-0.55 (-0.67, -0.43)	-8.92*	-0.12 (-0.28, 0.04)	-1.46	0.89 (0.74, 1.04)	11.68*
Men	-0.34 (-0.48, -0.21)	-4.91*	-0.14 (-0.39, 0.11)	-1.13	0.86 (0.54, 1.19)	5.26*
Women	-0.46 (-0.76, -0.15)	-2.92*	-0.44 (-0.87, -0.01)	-2.02†	0.87 (0.23, 1.51)	2.72‡
Sample composition						
E	-0.13 (-0.35, 0.08)	-1.21	-0.04 (-0.34, 0.27)	-0.24	-0.08 (-0.43, 0.27)	-0.46
YM	-0.52 (-0.71, -0.32)	-5.12*	-0.27 (-0.59, 0.05)	-1.68	0.39 (-0.02, 0.81)	1.87
YME	-0.17 (-0.34, -0.00)	-1.97†	0.06 (-0.31, 0.42)	0.31		
YE	-0.85 (-1.02, -0.69)	-9.95*	-0.35 (-0.57, -0.13)	-3.13*	1.52 (1.32, 1.71)	15.32*

REM refers to rapid eye movement; CI, confidence interval; Included, no screening for the condition; Excluded, exclusion of subjects with the condition; E, samples including groups of elderly only; YME, samples including groups of young, middle-aged, and elderly subjects; YE, samples including groups of young and elderly subjects.

*$P < .0001$

‡$P < .01$

†$P < .05$

in adjusting to early school days, which occurs for older rather than younger children.[76]

Sleep latency and sleep efficiency remained largely unchanged from childhood to adolescence, and none of the studies in the meta-analysis reported significant age-related changes for these 2 sleep parameters.

Percentage of stage 2 sleep was found to increase with age, while percentage of SWS decreased. These 2 results were also found individually in the 5 studies that examined these 2 parameters. Of note, however, is a very large difference between results using the ambulatory monitoring system and in-laboratory recording, which may be attributed to methodologic differences in the studies.

The results of the meta-analysis suggested that the percentage of REM sleep significantly (but modestly) increased with age, an unexpected finding since the studies that examined this parameter did not find this association.[26,49,52,53,58,59] Since the effect size is small, it would have been difficult to identify this association without the quantitative assessment provided by the meta-analysis.

Sleep in Adults

As expected, TST and sleep efficiency consistently decreased with age. WASO obtained the largest effect size, showing the important increase with age of time awake after sleep onset. Sleep latency and percentage of stage 2 sleep increased with age, but the associations were small (.27 and 0.28, respectively). Percentage of SWS and REM sleep both also decreased. In addition, small effect sizes were obtained for percentage of stage 1 sleep and REM latency; the first increasing with age, and the other decreasing with age. From the results of this meta-analysis, it is clear that all studied sleep parameters significantly change with age across the adult lifespan.

Roles of Moderator Variables

A great advantage of meta-analyses includes its potential to explore the role of different moderators on the association between aging and different sleep variables.

The analyses of potential moderators brought to light a number of noteworthy observations. Failure to exclude participants with a mental disorder had several significant consequences on the results: (1) it diminished the associations of TST and sleep efficiency with age, that is, the decreases observed in TST and sleep efficiency were less pronounced when participants were not screened for mental disorders; (2) it hid the age-related increase of percentage of stage 2 sleep; and (3) it hid the age-related diminution of REM latency.

A similar pattern was observed with medical illness. Failure to

Table 10—Effect Sizes Related to Sex and Homogeneity Statistics for Sleep Variables in Adult Samples

	Effect sizes, no.	Studies, no.	Subjects, no.	Effect size (95% CI)	*Q*
Total sleep time	24	17	996	-0.26 (-0.39, -0.13)*	180.55 (23 *df*)*
Sleep latency	18	13	699	-0.35 (-0.51, -0.19)*	113.22 (17 *df*)*
Sleep efficiency	21	15	928	0.04 (-0.09, 0.17)	84.72 (20 *df*)*
Stage 1%	13	10	615	0.10 (-0.07, 0.26)	88.70 (12 *df*)*
Stage 2 %	13	10	615	0.43 (0.26, 0.60)*	74.69 (12 *df*)*
SWS %	23	16	1030	-0.49 (-0.63, -0.36)*	197.51 (22 *df*)*
REM %	24	16	1034	-0.16 (-0.28, -0.03)†	68.89 (23 *df*)*
REM latency	17	13	706	-0.30 (-0.46, -0.15)*	112.73 (16 *df*)*
WASO	13	8	487	0.38 (0.20, 0.57)*	28.92 (12 *df*)*

CI refers to confidence interval; SWS, slow-wave sleep; REM, rapid eye movement; WASO, wake after sleep onset
*$P < .0001$
†$P < .05$

Table 11—Summary of findings from the meta-analysis

	Direction of the Evaluation		
	C -> A	YA -> MA -> E	E -> OE
Total sleep time	⇔	⇓	⇔
Sleep latency	⇔	⇔	⇔
Sleep efficiency	⇔	⇓	⇓
Stage 1%	⇔	⇑	⇔
Stage 2 %	⇑	⇑	⇔
SWS %	⇓	⇓	⇔
REM %	⇑	⇓	⇔
REM latency	⇓	⇔	⇔
WASO	⇓	⇑	⇔

C refers to children (5-12 years old); A, adolescents (13-18 years old); YA, young adults (18-40 years old); MA, middle-aged adults (40-60 years old); E, elderly (60-70 years old); OE, old elderly (≥70 years old); SWS, slow-wave sleep; REM, rapid eye movement; WASO, wake after sleep onset;
⇔ Unchanged; ⇓ Decrease; ⇑ Increase

exclude participants with medical illness resulted in considerably diminished associations of TST and sleep efficiency with age and also obscured the relationship between aging and increased sleep latency.

Exclusion of participants with sleep apnea had important modifications on effect sizes for the TST; percentages of stage 1, stage 2, and REM sleep; and REM latency. Indeed, studies that did not screen participants for sleep apnea had smaller effect sizes on these variables, which indicated that age-related changes were less pronounced.

Using predetermined light off and light on time instead of the habitual sleep schedule of the participants also had consequences for the results: the observed decrease in TST with age was smaller and the significant increase of percentage of stage 2 sleep and the significant decrease in REM latency with age disappeared.

Why are the age effects less obvious with the inclusion of these disorders? There is no simple explanation for this fact. First, it is impossible to determine how many subjects were suffering from 1 or several of the diseases included in the moderator analyses. However, in small samples, the inclusion of some not perfectly healthy subjects creates a heterogeneous group, and it is enough to influence the results in unexpected ways. This is a very different situation than when the purpose of the research is to measure the effects of a disease on sleep architecture; in this case the subjects of the experimental group all have the disease, and some conclusions can be drawn. Second, the evolution of sleep architecture with age in specific diseases is not well known: studies usually used age-matched controls to measure the effect of the disease on sleep architecture—which is a methodologically sound; however, this does not provide information on the evolution of sleep architecture with age. Furthermore, participants in the studies included in the meta-analysis were all from nonclinical populations. It is unlikely that individuals with a severe mental disorder were included in the studies even when no screening was done to exclude mental disorders. It has been repeatedly demonstrated, however, that mild or moderate mental disorders such as anxiety or depression are often accompanied by sleep complaints. It is therefore reasonable to assume that the presence of such low-grade mental disorders may have adversely impacted sleep-age relationships. The same conjecture can be made about medical illnesses.

The sex analyses showed that the associations between sleep variables and aging were generally the same for both sexes; however, larger effect sizes were observed in women for TST, sleep efficiency, percentage of stage 1 sleep, and REM latency, indicating that the age effect on these variables were more important in women. On the other hand, effect sizes calculated for sex indicated that women have longer TST and sleep latency than similarly aged men. They also have less percentage of stage 2 sleep and greater percentage of SWS than age-matched men.

Interestingly, Figures 1c and 1d clearly illustrate that percentages of SWS and REM sleep that were based on in-laboratory studies decrease with age. The diminution in the percentage of SWS can be readily observed in childhood and continues steadily until old age. Conversely, for REM sleep, the overall data pattern (see Figure 1d) may explain disagreements among previous studies concerning the evolution of this sleep stage with age. Meta-analytic results indicated that the percentage of REM sleep decreased with age from young adulthood to late middle age, but the decrease is not significant in individuals over 60 years of age.

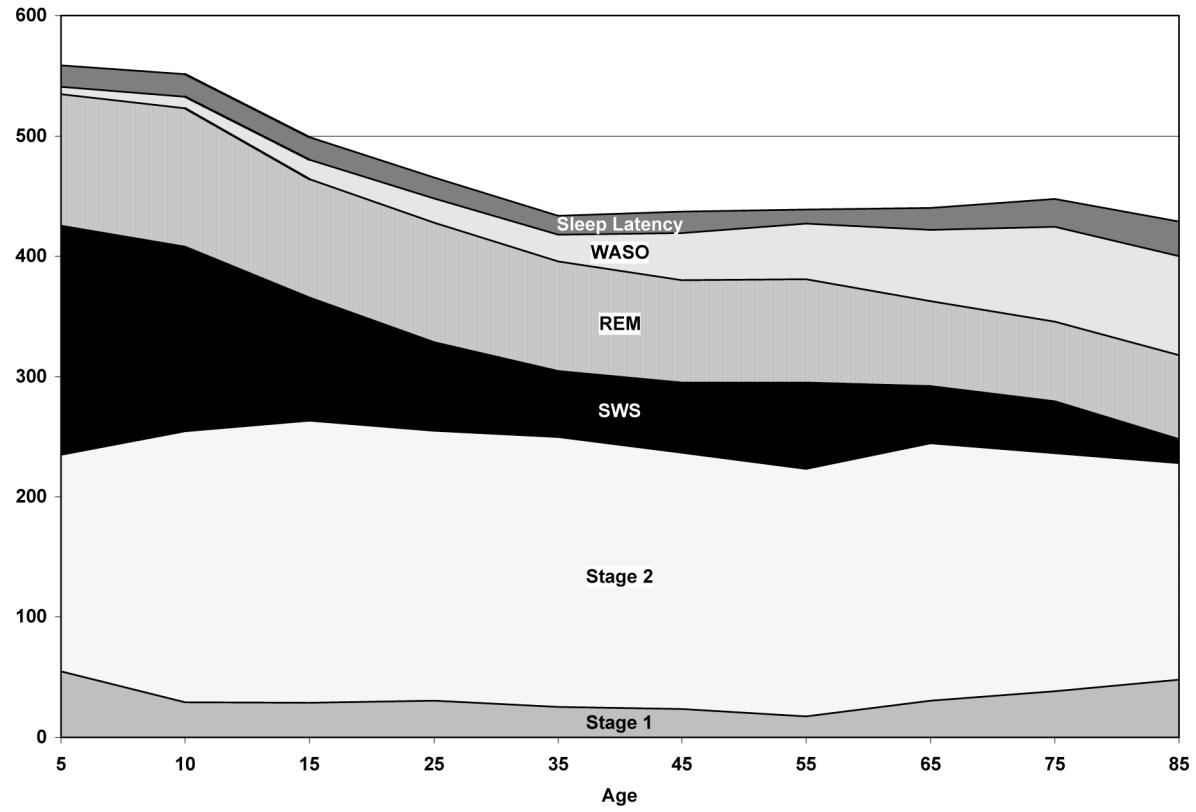


Figure 2—Age-related trends for stage 1 sleep, stage 2 sleep, slow wave sleep (SWS), rapid eye movement (REM) sleep, wake after sleep onset (WASO) and sleep latency (in minutes).

Limitations

This meta-analysis is not without limitations. For many studies, it was impossible to calculate effect sizes related to age and sex because no information was given in relation with the presence or absence of sex differences. Therefore, we had to discard several studies with otherwise usable data. Effect sizes can be calculated from different statistical information, but a minimum is needed. The same can be said for race. Most of the studies did not include information about the race composition of the sample. It was therefore impossible to include race as a moderator variable, as had been originally planned.

Several studies did not include middle-aged subjects. This is quite obvious in the Figures, where a concentration of information can be observed at both extremes: young adults and elderly participants. One of the consequences of this was to maximize the effect sizes related to age. In the sample composition moderator, we wanted to measure the effect size for the progression between young and middle-aged and between middle-aged and elderly subjects. This more-complex analysis showed that age progressions for all of the sleep variables were much more subtle than when a simple comparison of young to elderly subjects was made.

Another limitation may have come from our decision to limit our sample to peer-reviewed studies. It is known that, for clinical trials, the limitation to peer-reviewed reports might introduce a small bias on effect sizes because published studies often favor significant findings. On the other hand, this issue is less likely to have played a role in our study, since the reports used in the meta-analysis were mostly purely descriptive, aimed at describing age-related changes of sleep in the population.

Conclusions and Recommendations

Accurate normative data on the evolution of sleep architecture across the human life span are important to better understand exactly what type of changes in sleep patterns can be expected as individuals are aging. The main findings of this study are summarized in Table 11. The evolution with age of the different sleep stages, REM sleep, and WASO is shown in Figure 2. In summary, and in contrast to what was generally suggested in several small studies, the TST in children 5 years of age or older and adolescents did not really change with age. It appeared to be related to environmental factors rather than to biologic changes. There was a modest but significant increase in the percentage of REM sleep from childhood to the end of adolescence. After that age, percentage of REM sleep remained relatively stable until 60 years of age, when the percentage again began to decline. Sleep latency modestly but significantly increased with age. However, the change was very subtle and was apparent when very young adults were compared to elderly individuals. Percentage of stage 1 sleep increased with age through all adulthood. Percentage of stage 2 sleep increased with age from childhood (5 years and older) until old age. After 60 years of age, only sleep efficiency continued to significantly decrease, with all the other sleep parameters remaining unchanged.

The results of the meta-analysis clearly illustrated the importance of strict screening methods for the study of sleep parameters in healthy individuals, as it maximizes the emergence of age-related changes in sleep. As was demonstrated, inclusion of individuals with sleep, organic, or psychiatric disorders, as well as the modification of habitual sleep time, substantially obliterated the importance of changes in sleep patterns with aging.

There are several aspects of normal sleep that need to be further investigated: racial comparisons of sleep patterns are still poorly documented; polysomnographic data in healthy children and adolescents, and to a somewhat lesser degree in middle-aged adults, are still scant. Any future studies aimed at examining age-related changes in sleep should utilize carefully screened subjects and take into account subjects' habitual sleep schedules, as well as whether PSG recording occurs on weekday or weekend nights.

ACKNOWLEDGMENTS

This work was supported by a grant from the Sleep Medicine Education and Research Foundation

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Received: 1 March 2023 | Revised: 12 April 2023 | Accepted: 18 April 2023

DOI: 10.1002/hsr2.1250

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Perceived quality of sleep across the menopausal transition: A retrospective cohort study

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Abstract

Background and Aims: To compare sleep quality among naturally and surgically post-menopausal women, and to identify lifestyle factors that predict sleep quality in pre, peri, and postmenopausal women.

Methods: This is a retrospective cohort study of data collected from 429 women who participated in Fels Longitudinal Study data. Sleep quality, based on the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale, demographics, medical history, depression, quality of life, and physical activity levels were included in the analysis.

Results: The four study groups did not differ on overall sleep quality with either scale ($p = 0.61$). Both Post-M groups were more likely to have a major sleep problem than the Peri-M and Pre-M groups ($p < 0.001$), and to have a history of restless leg syndrome ($p = 0.016$), but the two Post-M groups did not differ on these problems. Predictors of sleep quality included depression, bodily pain, vitality, and surgical menopause ($p<0.001$).

Conclusion: Menopause is associated with sleep disrupting conditions. This study did not find any significant differences in sleep quality among the three reproductive stages or for natural versus surgical menopause. Women may benefit from addressing other lifestyle factors associated with poor sleep quality including mental health factors.

KEYWORDS

perimenopause, postmenopause, quality of life, reproductive age, sleep quality

1 | BACKGROUND AND AIMS

The transition through menopause is associated with several physical and psychological changes. Decreased sleep quality is a frequent concern of peri- and postmenopausal women, although recent research suggests that various factors likely contribute to sleep disturbances during this time period.[1,2] Factors including physiological changes associated with aging, comorbid medical conditions (including underlying mental health disorders such as anxiety and depression), and various lifestyle factors such as decreased physical activity, and tobacco or alcohol consumption have all been demonstrated to have a profound impact on sleep quality.[3–8]

Subjective sleep quality, which encompasses waking after sleep onset, number of awakenings, sleep latency, and sleep efficiency, has been reported to decline in a linear fashion with increasing age.[1,4,5,9–12] Postmenopausal women are more likely to report sleep disorders than their premenopausal counterparts and among postmenopausal women, those with surgically induced menopause have worse sleep quality than those with naturally occurring menopause.[1,4,13,14] Data on the impact of hormone therapy (HT) on sleep quality during the menopausal transition are conflicting. While some data suggest that hormone changes may impact sleep quality at any age, other data suggest that HT only seems to improve sleep in women who experience hot flashes.[15–21]

Very few studies have addressed the key mechanisms accounting for sleep and health-related quality of life changes that women report before and during the menopausal transition, that is, while premenopausal or during peri-menopause.[22–24] In one study, sleep quality was shown to be worse for women who had undergone surgical menopause versus women who had undergone natural menopause, which the study authors argue that surgical menopause may result in a more rapid decline in hormones experienced by these individuals compared to women in the natural menopause group.[13] Given the existing literature, it is difficult to distinguish which components of the patient experience are related to hormonal changes of menopause and which are attributable to the myriad of other influences that are likely to be occurring simultaneously with menopausal changes.[18,25,26]

The purpose of this study is to examine sleep quality across the lifespan by investigating differences in sleep quality assessments in (1) pre-, (2) peri-, and (3) postmenopausal women. The postmenopausal group is further divided into subgroups based on natural menopause or surgical menopause. Second, we will examine health-related quality of life among the four study groups with follow up analyses comparing the two postmenopausal groups. Third, we will compare and analyze differences in various factors that are believed to impact sleep quality such as quality of life, physical activity levels, presence of depression, and presence of medical conditions associated with poor sleep quality across the study groups.

2 | METHODS

This is a retrospective cohort study utilizing data collected as part of the Fels Longitudinal Study (Fels) which began in 1929 and has been the longest running study of human growth, development, and body composition over the lifespan.[27] Data for the Fels study was actively being collected at the time of data extraction for this study, therefore, data for this study were selected by identifying the most recent study visit for each participant before the planned date of database extraction. Data collected at the identified visit were used for this study. This method ensured that each participant was counted only once in the extracted data set and that the most current data were used. Among the 1260 active Fels study participants at the time of data extraction, 429 participants qualified for inclusion in this study using the following criteria: (1) Females aged 18 years or older; (2) Individuals whose records contained data needed for classification using the Stages of Reproductive Aging Workshop (STRAW) criteria for menopausal status (i.e., age, Follicle Stimulating Hormone level [FSH], Last Menstrual Period [LMP], and oophorectomy with or without hysterectomy), and (3) Individuals who had completed key assessments needed for this study (described below). Participants provided informed consent when they signed consent for the Fels study which included consent for future secondary analyses. Data for the Fels study were collected by a combination of self-administered questionnaires including menstrual cycle and reproductive history and interviews by research team members. This study was approved by the Wright State University Institutional Review Board as a new analysis of existing data.

Study measures were as follows:

Demographic information included age, highest level of education, working status, marital status and number of individuals in the household by their age.

Menopausal state was determined using the Stages of Reproductive Aging Workshop (STRAW) criteria, a standardized menopause classification tool, in which premenopausal (Pre-M) women are those under the age of 40 and still having menstrual cycles, peri-menopausal (Peri-M) women are those with abnormal FSH (>25 mIU/mL) either with cycles or a last menstrual period (LMP) within 1 year before the visit date, and postmenopausal women are those who have not had a menstrual cycle for more than 1 year before the visit date and who also had an abnormal FSH (>25 mIU/mL) level at that visit. Surgical menopause was defined as history of oophorectomy, whereas natural menopause was defined as the absence of such a surgical history.[28]

Sleep quality assessments included the Pittsburgh Sleep Quality Index (PSQI) questionnaire in which higher scores represent poorer quality of sleep and the Epworth Sleepiness Scale (ESS) in which higher scores represent greater daytime sleepiness.[29,30] The PSQI consists of a global score and 7 subscales (sleep quality, latency, duration, efficiency, disturbance, medication, and dysfunction). The ESS has one total score.

Medical history information included participants' responses to questions worded as "Has a doctor ever told you that you have/had…" to record conditions that were diagnosed by a doctor. Medical conditions of interest for this study included diagnosed sleep disorders, hypertension, thyroid disease, high cholesterol, metabolic syndrome, and history of malignancy. Body mass index (BMI, kg/cm^2) was measured by following standard protocol. Additional information was recorded on study assessments by the research team and included nighttime urinary urgency/frequency and menopausal symptoms (e.g., hot flashes, vaginal dryness), sleep problems, such as restless leg syndrome, snoring, sleep apnea, and insomnia, and social history (e.g., alcohol and tobacco use). Alcohol use was measured as number of drinks per day using standard drink amounts. Smoking status was measured as being a current smoker, previous smoker or never a smoker.

Depression was assessed from participants' responses to the Patient Health Questionnaire (PHQ-9) with high scores representing greater severity of depression.[31]

Quality of Life assessments were determined using the Medical Outcomes Study 36-item Short Form Survey (SF-36). Eight health concepts are represented and include physical functioning ([PF] how does health affect regular physical functioning), role limitations due to physical health problems ([RP] how does health affect work or regular activities), bodily pain ([BP] how much does pain affect activities), general health perceptions ([GH] how healthy one perceives), vitality ([VT] feeling energetic versus worn out), social functioning ([SF] how health affects regular social activities), role limitations due to emotional problems ([RE] how emotional problems affect work or regular activities), and mental health ([MH] feeling happy, peaceful versus down). Lower scores on the SF-36 scales represent poorer functioning.[32,33]

Physical activity levels for work, leisure, and sports participation were determined from the Baecke Habitual Physical Activity questionnaire which is based on the Compendium of Physical Activities.[34] Responses to questions about activities at work, during leisure time, and during sports participation, including amount of time engaged for each category, were used to compute the metabolic equivalents (METs) for the activities. A MET is the ratio of the caloric consumption of an individual engaging in an activity compared to being at rest. Examples of METs include 1 (watching TV or sleeping), 5 (walking briskly), 10 (playing soccer), and 16 (competitive cycling).[35–37]

2.1 | Statistical analysis

ANOVA was used to test the null hypothesis that there are no differences in quality of sleep among the study groups. Post hoc Tukey tests were performed to identify whether differences in sleep quality scores exist between the Nat Post-M and Surg Post-M groups. Similarly, the study groups were compared using ANOVA to examine differences on quality of life measures, depression, and physical activity levels with post hoc Tukey tests to identify which groups differed and to specifically look at differences between the Nat Post-M and Surg Post-M groups.

χ^2 analyses were conducted to identify differences among the study groups on categorical variables such as having specific medical conditions (yes/no) or sleep behaviors such as going to the bathroom at night, taking sleep medications, and menopausal symptoms such as hot flashes and vaginal dryness.

Forward stepwise multiple regressions were conducted to identify predictors of sleep quality, that is, PSQI global score and Epworth sleepiness score. Menopausal state was characterized using dummy variables to denote group membership. Variables of interest for the regression analyses included menopausal group, depression, sleep disrupting conditions, quality of life scales, and physical activity levels. The Bonferroni inequality was used to reduce bias from multiple tests resulting in a $p < 0.005$ ($p < 0.05/10$ tests = $p < 0.005$) to be considered statistically significant. Tests were two sided. SPSS version 24 (IBM) was used for data analysis.

3 | RESULTS

Four hundred twenty-nine women completed a Fels study visit between 2008 and 2015 and had complete data for the variables of interest at the time of data extraction. Participants were classified into study groups based on STRAW criteria definitions, resulting in 163 premenopausal women (Pre-M), 49 perimenopausal women (Peri-M), 145 natural menopausal women (Nat Post-M), and 72 surgical menopausal women (Surg Post-M). The study groups differed on demographic variables as expected related to stage of life such as age, working status, marital status, and medical comorbidities (Table 1). However, no differences were noted on demographic variables or for medical comorbidities between the two post-menopause groups.

The study groups did not differ on sleep quality for the ESS score ($F = 0.18$; $p = 0.91$) or for the PSQI global score ($F = 0.60$; $p = 0.61$; Table 2). The Surg Post-M group had higher scores on the PSQI Sleep Medications scale (i.e., number of times taking sleep medications in a month) than the Pre-M group (0.4 ± 0.9 vs. 0.9 ± 1.3, respectively; Tukey post hoc $p = 0.006$). There were no differences among the study groups for average number of hours of sleep per night reported for the full week, including the comparison of the Nat Post-M and Surg Post-M groups.

Both Post-M groups were more likely to report having a major sleep problem (Surg Post-M = 22.2%; Nat Post-M = 16.7%) compared to the Peri-M and the Pre-M groups (Peri-M = 14.3%; Pre-M = 4.3%; $p < 0.001$), but the two Post-M groups did not differ from each other (Table 2). The Surg Post-M group was more likely to report sleep apnea than all other groups (Surg Post-M = 13.9%; Nat Post-M = 4.9%; Peri-M = 8.2%; Pre-M = 1.8% $p = 0.002$). The study groups did not differ on having a history of insomnia ($p = 0.25$) or using sleep medications three or more times a week ($p = 0.09$). Postmenopausal women were more likely to get up to use the bathroom three or more times a week than other groups (Surg Post-M = 58.3%; Nat Post-M = 55.6%; Peri-M = 32.7%; Pre-M = 17.9%; $p < 0.001$), but the two Post-M groups did not differ from each other ($p = 0.67$).

The Surg Post-M group had the lowest quality of life score for the impact of their health on physical role functioning, that is, their ability to perform physical activities related to work and daily life (RP scale, $p < 0.001$) although their scores were significantly different from only the Pre-M group (Table 3). The Surg-Post-M group also had the lowest quality of life scores for bodily pain affecting their ability to perform daily activities compared to the Pre-M group (BP scale, $p = 0.007$) although this was not considered significant due to our test criterion of $p < 0.005$. The study groups did not differ on smoking, alcohol use, or on physical activity for work, leisure, and sports participation (Table 3).

TABLE 1 Demographic and medical characteristics for four menopausal status groups.

	Pre-M (n = 163)	Peri-M (n = 49)	Nat Post-M (n = 145)	Surg Post-M (n = 72)	All groups p Value	Post-M groups p Value[a]
Age	31.3 (8.4)	50.4 (3.1)	65.7 (10.2)	66.5 (12.5)	<0.001	0.93
Highest education level completed[b]					0.34	0.71
HS/GED	24 (14.7%)	4 (8.2%)	25 (17.2%)	14 (19.7%)		
College or higher	139 (85.3%)	45 (91.8%)	120 (82.8%)	57 (80.3%)		
Currently working (full or part-time)	152 (93.3%)	40 (81.6%)	83 (57.2%)	28 (38.9%)	<0.001	0.01
Marital status (% married)	71 (43.6%)	34 (69.4%)	100 (69.4%)	44 (61.1%)	0.01	0.44
Gravida	2.1 (0.9)	3.7 (1.7)	3.2 (1.5)	3.1 (2.0)	<0.001	0.87
Parity	1.7 (0.9)	2.6 (1.1)	2.5 (1.2)	2.6 (1.6)	<0.001	0.97
# Residents >65-year-old	0.02 (0.14)	0.02 (0.14)	0.81 (0.84)	0.92 (0.88)	<0.001	0.59
Age menarche	12.5 (1.3)	13.3 (1.1)	12.7 (1.2)	12.6 (1.4)	0.008	0.91
Age first delivery	26.9 (5.5)	26.7 (5.8)	26.1 (5.8)	24.7 (4.2)	0.08	0.28
BMI (kg/m^2)	26.8 (6.4)	28.0 (8.3)	27.1 (5.6)	27.6 (4.9)	0.63	0.92
Thyroid disease	8 (4.9%)	5 (10.4%)	26 (17.9%)	17 (23.6%)	<0.001	0.37
Cancer history						
Breast cancer	1 (0.6%)	1 (2.0%)	2 (1.4%)	1 (1.4%)	0.89	>0.99
Ovarian	0	0	0	3 (4.2%)	0.002	0.04
Uterine	4 (2.5%)	0	5 (3.4%)	4 (5.6%)	0.34	0.48
Other	9 (5.5%)	3 (6.1%)	33 (22.8%)	22 (30.6%)	<0.001	0.25
CVD/stroke	2 (1.2%)	2 (4.1%)	27 (18.6%)	13 (18.1%)	<0.001	>0.99
Hypertension	17 (10.4%)	12 (24.5%)	81 (55.9%)	45 (62.5%)	<0.001	0.38
Diabetes	6 (3.7%)	3 (6.1%)	22 (15.2%)	14 (19.4%)	<0.001	0.44
High cholesterol	16 (9.8%)	9 (18.4%)	72 (49.7%)	47 (65.3%)	<0.001	0.03
Metabolic syndrome	12 (8.1%)	11 (25.6%)	27 (22.5%)	20 (31.3%)	<0.001	0.22
Menopausal symptoms						
Hot flashes	11 (7.3%)	29 (64.4%)	108 (82.4%)	51 (70.8%)	<0.001	0.07
Vaginal dryness	7 (4.7%)	16 (35.6%)	72 (55.0%)	34 (47.2%)	<0.001	0.31

Note: Data are presented as n (%) and mean (SD).

[a]Nat Post-M vs. Surg Post-M.

[b]Less than high school category is not included.

3.1 | Predicting sleep quality

Predictors of sleep quality (PSQI global score) included PHQ9 depression score ($\beta = 0.53$; $p < 0.001$), SF-36 bodily pain (BP) score ($\beta = -0.17$; $p < 0.001$), SF-36 vitality (VT) score ($\beta = -0.14$; $p = 0.004$), and being Surg Post-M ($\beta = 0.08$; $p = 0.03$) (Model $R = 0.73$; $R^2 = 0.53$; $p < 0.001$). When medical history, activity levels, and current health were allowed to enter the equation, variables in the regression model included depression score ($\beta = 0.46$; $p < 0.001$), history of insomnia ($\beta = 0.19$; $p < 0.001$), bodily pain (BP) score ($\beta = -0.14$; $p = 0.001$), vitality (VT) score ($\beta = -0.16$; $p = 0.001$), getting up to go to the bathroom ($\beta = 0.07$; $p = 0.05$), work activity index ($\beta = 0.09$; $p = 0.01$), and current hypertension ($\beta = 0.09$; $p = 0.01$) predicted PSQI sleep quality (Model $R = 0.76$; $R^2 = 0.58$; $p < 0.001$). So, having higher depression, having a history of insomnia, having poorer quality of life from bodily pain, getting up to go to the bathroom, greater work activity, and having current hypertension were related to worse quality of sleep.

Predictors of daytime sleepiness (Epworth score) included only the SF-36 vitality (VT) score ($\beta = -0.41$; $p < 0.001$) (Model $R = 0.41$; $R^2 = 0.17$; $p < 0.001$), that is, having low energy or feeling tired because of one's health, was associated with increased daytime sleepiness.

TABLE 2 Sleep quality, average hours of sleep, and sleep disrupting conditions among four menopausal status groups.

	Pre-M (*n* = 163)	Peri-M (*n* = 49)	Nat Post-M (*n* = 145)	Surg Post-M (*n* = 72)	All groups *p* Value	Post-M groups *p* Value[a]
Epworth Sleepiness Scale[b]	6.4 (3.9)	6.7 (4.9)	6.6 (3.8)	6.7 (4.0)	0.91	0.99
PSQI Global Score[c]	4.5 (3.0)	4.8 (3.1)	4.5 (3.0)	5.0 (2.9)	0.61	0.69
PSQI sleep quality	1.0 (0.7)	1.1 (0.8)	0.8 (0.8)	1.0 (0.7)	0.05	0.55
PSQI sleep latency	1.1 (1.0)	0.9 (1.0)	0.9 (0.9)	1.0 (1.0)	0.37	0.77
PSQI sleep duration	0.1 (0.5)	0.1 (0.5)	0.1 (0.4)	0.1 (0.4)	0.99	>0.99
PSQI sleep efficiency	0.02 (0.23)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.65	>0.99
PSQI sleep disturbance	1.2 (0.5)	1.3 (0.5)	1.3 (0.6)	1.3 (0.5)	0.52	0.92
PSQI sleep medication	0.4 (0.9)	0.5 (1.0)	0.6 (1.1)	0.9 (1.3)	0.01	0.28
PSQI day dysfunction	0.7 (0.8)	0.9 (0.8)	0.6 (0.7)	0.8 (0.7)	0.29	0.59
Average # sleep hours/night	8.4 (1.3)	8.1 (1.0)	8.1 (1.1)	8.4 (1.4)	0.09	0.21
Took sleep medications >3 times per week	14 (8.6%)	6 (12.2%)	23 (16%)	14 (19.4%)	0.09	0.57
Got up for bathroom ≥3 times per week	29 (17.9%)	16 (32.7%)	80 (55.6%)	42 (58.3%)	<0.001	0.67
Any major sleep problem	7 (4.3%)	7 (14.3%)	24 (16.7%)	16 (22.2%)	<0.001	0.35
Untreated sleep problem	13 (8%)	4 (8.2%)	18 (12.4%)	4 (5.6%)	0.35	0.15
History of sleep apnea	3 (1.8%)	4 (8.2%)	7 (4.9%)	10 (13.9%)	0.002	0.03

Note: Data are presented as *n* (%) and mean (SD).

[a]Nat Post-M vs. Surg Post-M.

[b]Higher scores represent greater daytime sleepiness (scores range from 0–24).

[c]Higher scores represent worse sleep (scale scores range from 0–3; global score ranges from 0–21).

4 | DISCUSSION

The four study groups did not differ on the primary sleep quality outcome measures. The women, regardless of menopausal status, reported similar average number of hours of sleep as well as similar physical activity levels for sports, work, and leisure in our study. Medical conditions differed as expected with increasing age, and the two Post-M groups did not differ from each other on demographic variables or medical conditions. Quality of life was worse for both the Nat Post-M and Surg Post-M women for health affecting daily physical functioning, and for only Surg Post-M women for health affecting work or role related activities. While the Surg Post-M group had lower health related quality of life for most scales, including bodily pain affecting daily activities, the Surg Post-M and Nat Post-M groups did not differ from each other. Regarding the predictors of poor sleep quality, our finding that depression score was the predominant predictor for poor (higher) sleep scale scores is consistent with some of the literature reporting lower mental health scores being associated with poor sleep quality in the general population.[38,39] We did not find higher depression scores in the Post-M groups as others have reported.[40]

Quality of life scales for bodily pain (BP) and vitality (VT) also entered the prediction equation, indicating that poorer function due to BP affecting regular activities was related to poorer sleep quality and that lower scores on VT, that is, feeling tired or worn out, were also associated with poor sleep quality. Bodily pain has been reported in the literature to affect sleep quality however, low vitality may be the result of poor sleep quality.[39,41–43] The literature on physical activity is mixed in that some studies have shown that high levels of physical activity may be related to poor sleep, for example, athletes with high levels of physical activity and fatigue had poorer sleep quality, while other studies suggest physical exercise, including meditative movements and yoga, decreased depression scores and improved sleep quality and quality of life.[41,44–47] One strength of this study is the well-characterized data set from the Fels study that included multiple validated and reliable assessments for the outcomes of interest. This study adds to the literature by extending our understanding of sleep and sleep related problems across three stages of reproductive life and between different groups of postmenopausal women. We did not find differences in sleep quality across the three reproductive stages, nor did we show differences between natural versus surgical menopausal women. We did not find a difference in history of insomnia between naturally menopausal women and surgically menopausal women that has previously been reported in the literature.[13] This study adds quality of life and physical activity, assessed with validated methods, to the conversation about factors affecting sleep, which provides an analysis of novel factors, not previously described in the same study.[38,39,41–45,48,49]

TABLE 3 Quality of life and lifestyle factors among four menopausal status groups.

	Pre-M (n = 163)	Peri-M (n = 49)	Nat Post-M (n = 145)	Surg Post-M (n = 72)	All groups p Value	Post-M groups p Value[a]
SF-36: Rated health as excellent	21 (12.9%)	13 (26.5%)	23 (16.1%)	8 (11.1%)	0.12	0.25
SF-36: Physical functioning	91.9 (14.4)	84.3 (20.8)	73.8 (26.0)	70.6 (25.8)	<0.001	0.73
SF-36: Role physical	89.9 (25.4)	88.8 (26.0)	75.8 (36.9)	63.5 (40.0)	<0.001	0.04
SF-36: Bodily pain	73.9 (21.9)	72.2 (21.3)	68.2 (21.6)	63.8 (23.7)	0.007	0.52
SF-36: General health	73.2 (17.5)	73.3 (20.4)	70.9 (18.1)	68.4 (19.0)	0.24	0.77
SF-36: Vitality	55.7 (19.1)	56.8 (20.6)	58.8 (20.9)	56.0 (21.9)	0.58	0.78
SF-36: Social function	84.1 (21.1)	82.7 (22.6)	83.9 (24.0)	83.2 (22.0)	0.07	>0.99
SF-36: Role emotional	84.0 (28.7)	85.0 (23.6)	81.5 (32.4)	84.0 (29.2)	0.29	0.93
SF-36: Mental health	74.3 (15.9)	76.2 (13.4)	78.8 (16.6)	79.8 (15.8)	0.05	0.91
PHQ9 (depression)	3.97 (4.5)	3.07 (3.8)	2.96 (4.3)	2.75 (3.1)	0.09	0.98
Current smoker	29 (17.8%)	11 (22.4%)	16 (11.0%)	10 (13.9%)	0.18	0.66
Average # drinks/day	0.4 (0.7)	0.5 (1.0)	0.5 (0.8)	0.3 (0.5)	0.20	0.25
Physical activity level						
Sports	2.2 (0.7)	2.2 (0.7)	2.1 (0.6)	2.1 (0.7)	0.24	>0.99
Work	2.7 (0.7)	2.7 (0.5)	2.7 (0.5)	2.7 (0.5)	0.80	>0.99
Leisure	2.6 (0.6)	2.6 (0.7)	2.4 (0.6)	2.4 (0.6)	0.09	0.98

Note: Data are presented as n (%) and mean (SD). On SF-36, lower scores represent poor function/greater disability; (weighted) scores range from 0–100. On PHQ9, higher scores represent greater severity of depression; depression severity is minimal for scores 0–4, mild for scores 5–9, moderate for scores 10–14, moderately severe for scores 15–19, and severe for scores 20–27. A MET is the ratio of the caloric consumption of an individual engaging in an activity compared to being at rest. Examples of METs include 1 (watching TV or sleeping), 5 (walking briskly), 10 (playing soccer), and 16 (competitive cycling).

[a]Nat Post-M vs. Surg Post-M.

Additionally, our use of the STRAW criteria to categorize women into menopausal groups ensured that hormonal changes, such as changes in FSH and removal of ovaries, regardless of age, were considered. In addition, the data used in this secondary data analysis were gathered in a large longitudinal study minimizing the impact of participant response bias for sleep related assessments.

The limitations of our study include an acknowledgment that given this was a cross-sectional study of sleep quality, health status, quality of life and physical activity levels, we are only able to assess for association not causation. We acknowledge the potential for a circular relationship between quality of life, mental health, and physical activity with sleep quality, each having the potential to affect sleep quality and be affected by it. This study is further limited to the population of participants of a large longitudinal study who have participated over their lifetime. This population is predominantly Caucasian, living in the Midwest, and may not be representative of other population segments. However, the sleep quality scores and quality of life scores in the Pre-M group are consistent with scores reported by van Dammen et al.[22] and Celikhisar et al.[50] for reproductive aged women suggesting that our results may be applicable to other populations.

Additional research is needed to understand the multifactorial influences of reproductive stage, lifestyle, activity level and physical health, including quality of life, on sleep quality. Our study noted little difference across the different stages of reproductive life suggesting that the impact of hormones on sleep quality is minimal. The variations among studies on how variables are defined results in challenges in synthesizing this literature.

5 | CONCLUSIONS

Stage of reproductive life was not associated with sleep quality for women across the lifespan. Postmenopausal groups, that is, natural and surgical onset of menopause, had lower quality of life for general physical functioning and physical function for their role, but the two post-menopausal groups did not differ from each other. Poor sleep quality was associated with having depression, lower quality of life due to bodily pain, lower quality of life due to decreased vitality, and a surgical onset for menopause.

AUTHOR CONTRIBUTIONS

Rose A. Maxwell: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; software; supervision; validation; writing—original draft; writing—review & editing.

Keith M. Reisinger-Kindle: Conceptualization; validation; writing—original draft; writing—review & editing. **Traci M. Rackett**: Conceptualization; project administration; resources; writing—review & editing. **Jerome L. Yaklic**: Conceptualization; investigation; methodology; project administration; writing—original draft; writing—review & editing. **Stefan A. Czerwinski**: Conceptualization; Data curation; formal analysis; investigation; methodology; writing—original draft; writing—review & editing. **Miryoung Lee**: Conceptualization; formal analysis; investigation; methodology; validation; writing—original draft; writing—review & editing.

CONFLICT OF INTEREST STATEMENT

Keith M. Reisinger-Kindle is an Editorial Board member of Health Science Reports and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data will be available upon request.

TRANSPARENCY STATEMENT

The lead author Rose A. Maxwell affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Maxwell RA, Reisinger-Kindle KM, Rackett TM, Yaklic JL, Czerwinski SA, Lee M. Perceived quality of sleep across the menopausal transition: a retrospective cohort study. *Health Sci Rep*. 2023;6:e1250. doi:10.1002/hsr2.1250

Unique Aspects of Sleep in Women

by Navina Mehta, MD, Fariha Shafi, MD & Abid Bhat, MD

While many aspects of sleep are similar in men and women, there are a number of important differences that need to be identified and confirmed by the health care provider. This article reviews the unique aspects of sleep in women.

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Abstract

Sleep in women differs in many respects from that of men. In general, women appear to report a greater need for sleep and more subjective complaints of non-refreshing sleep than men. Sleep in women is affected at least partially by hormonal factors, with women typically suffering from sleep disturbance in connection with the menstrual cycle, pregnancy, and menopause. Menstrual cycles are associated with prominent changes in reproductive hormones that may influence sleep. Sleep apnea and restless legs syndrome may be aggravated by pregnancy. Women may also develop insomnia during pregnancy, childbirth and menopause.

Introduction

Different phases of the life cycle in female population are associated with unique features of sleep disruption. Changes in sleep patterns are often linked to hormonal factors leading to disturbed sleep in connection with the menstrual cycle, pregnancy and menopause (See Figure 1). It has also been shown there may be a long interval between the onset of symptoms and the correct diagnosis of some sleep disorders.[1, 2]

In general, women tend to have slightly more slow wave sleep than men (13% vs 9%) and less stage 1 sleep (8% vs 11%).[3] Women also report having a greater sleep need and report poor or insufficient sleep than men.[4] Since most studies on sleep and sleep loss have been conducted in males, it is still unclear what factors contribute most to the sleep disturbances in women. It is also clear more research is required to fully elucidate the impact of life cycle on sleep parameters in women. This article will summarize what is presently known about different aspects of sleep and sleep disorders in women in relation to various lifespan stages.

Sleep during Adolescence

The transition to puberty brings with it a myriad of changes both physical and mental. These changes are influenced by age, developmental status, as well as changes in sleep schedule. In studies using actigraphy, adolescent boys were noted to sleep less, have less sleep efficiency, and awaken earlier than girls in the same age group.[5] The onset of menses may also be linked to an increased risk of insomnia. This increased risk of insomnia corresponds with an increased risk of depression, which in turn is a risk factor for insomnia.[6]

In adolescence, a striking feature in the polysomnographic data is the steep decline in the slow wave (delta) activity of non-REM sleep, by almost 50% between the ages of 10 and 20 years.[7,8] This decline in delta activity may be a component of widespread brain reorganization, of which other manifestations include

reduction in brain metabolic rate, decreased plasticity, and the emergence of adult cognitive capacity.[9] Studies have also indicated that adolescent girls undergo the steep drop in the slow wave activity earlier than boys in the corresponding age.[10]

Sleep During the Menstrual Cycle

Female reproductive hormones, specifically estrogen and progesterone, not only regulate reproductive tissue function during menstrual cycle, but also influence other physiologic principles, including sleep and circadian rhythms. Conventionally, in a normal menstrual cycle of 28 days, day 1 is identified as the first day of bleeding (menses). Ovulation usually occurs during day 14, dividing the cycle into two phases: a preovulatory follicular phase and a postovulatory luteal phase. The follicular phase is when estrogen is the predominant hormone. After ovulation, the luteal phase lasts 14-16 days and is when concentrations of estrogen and progesterone are high, and body temperature is elevated by about 0.4 degree Celsius when compared to the follicular phase. This rise in temperature is attributed to the rise in progesterone levels. Many women of reproductive age have recurrent emotional and physical symptoms in association with the menstrual cycle, particularly during the late luteal (premenstrual) and menstrual phases. These symptoms may interfere with social and occupational functioning, as well as with sleep; women who have menstrual-related problems are between two and three times more likely than other women to report insomnia and excessive sleepiness.[11]

Approximately 60% of women experience mild symptoms of premenstrual syndrome (PMS), and an estimated 20% have moderate PMS that they feel requires treatment. For 3-8% of women, the cyclical pattern of symptoms is severe and labelled as premenstrual dysmorphic disorder (PMDD). [12] Most common complaints include irritability, mood swings, depression, fatigue, headaches, bloating and cramping. Sharkey and colleagues studied twenty-seven healthy women to determine the relationship between sleep fragmentation and different points in the menstrual cycle.[13] Hormone levels were measured at two time points during a single menstrual cycle: the follicular phase and the peri-ovulatory to mid-luteal phase. A single night of home polysomnography (PSG) was recorded on the day of the peri-ovulatory/mid-luteal-phase blood draw. The study determined that the rise in progesterone level in the peri-ovulatory through mid-luteal phase resulted in an increase in the wake after sleep onset resulting in an increase in sleep fragmentation.

Figure 1
Changes in women's sleep patterns are often linked to hormonal factors leading to disturbed sleep in connection with the menstrual cycle, pregnancy and menopause.

It is surprising to note that limited research has been done on the effects of oral contraceptives (OCs) on sleep since OCs are so frequently used by women. Ho compared the sleep of three women (ages 24-34) with regular ovulatory menstrual cycles to three females taking fixed dose OCs. There was an increase in slow wave sleep (SWS) in the premenstrual phase in the cycling group, compared to the OC group in which SWS declined.[14] Another study described the sleep of three women at the follicular and luteal phases who were taking OCs. REM sleep latency was shorter in women taking OCs compared to 13 women with ovulatory cycles.[15] It is obvious that no clear link can be made about the effects of OCs on sleep, and additional research is therefore required.

Women also have more difficulty adapting to shift work than men.[16] Shift work, particularly at night, is problematic for the worker. It represents a serious risk factor for sleep disorders, such as insomnia and daytime sleepiness.[17] The frequency of sleep complaints in this population is twofold higher than in the general population. These problems are mainly due to a disruption of the normal sleep/wake pattern

but also involve other factors such as age, gender, stress at work, health problems and social and family factors.

The finding that neurons in the suprachiasmatic nucleus (the circadian clock) contain receptors for estrogen and progesterone indicates a functional interaction between the circadian system and the menstrual cycle.[18] Female shift workers experience several menstrual cycle irregularities.[19] Compared with all other fixed schedules (including nights only), rotating nurses reported lengthened menstrual cycles, visited the clinic more often with menstrual associated complaints, and experienced more "tension, nervousness, weakness, and sickness at menstruation." Shift work may also increase the risk of some forms of cancer in women. One proposed explanation is the exposure to light at night suppresses melatonin production which has potential oncostatic action. The risk of breast cancer is higher among women who frequently do not sleep at night, with an increased risk among subjects working in the bright places.[20] Another study indicated that working a rotating night shift at least three nights per month for 15 or more years increased the risk of colorectal cancer in women.[21]

Sleep During Pregnancy

Pregnancy is not free from its share of sleep-related issues. Many factors contribute to sleep disruption during pregnancy, including increased progesterone and prolactin levels, diaphragmatic elevation, fetal movement, bladder distension, temperature fluctuation and gastrointestinal discomfort. Anatomical changes during pregnancy, such as weight gain, decreased respiratory functional reserve capacity and nasopharyngeal edema (due to estrogen), and hyperventilation with increased sensitivity to carbon dioxide may predispose women to developing sleep disordered breathing (snoring, obstructive and central sleep apnea).[22,23,24,25] Despite the physiological changes conducive to the development of sleep apnea during pregnancy, a number of other physiologic adaptations may provide protection against sleep apnea. [26] For example, elevated progesterone levels during pregnancy increase the pharyngeal muscle tone. Reduction in REM sleep duration during pregnancy may also protect against sleep apnea. During late pregnancy, there is also a greater tendency for women to sleep on sides as opposed to laying supine, thereby reducing the tendency to manifest severe sleep apnea. Hedman and colleagues surveyed 325 pregnant women with a series of five questionnaires to assess the effects of pregnancy on sleep.[27] The questionnaires were asked before becoming pregnant, once during each trimester, and a final questionnaire three months post-partum. The total hours of sleep increased during the first trimester, lessened during the second trimester, and further decreased during the third trimester.

Emerging evidence suggests an increased incidence of sleep disordered breathing (SDB) during pregnancy and exacerbation of pre-existing SDB, particularly during the later stages of pregnancy. A longitudinal questionnaire study of symptoms of SDB found cumulative increase in apnea symptom scores from 14 weeks until delivery. Although 1.3% of participants in the study reported witnessed apneas on at least three nights per weeks at 14 weeks gestation, by 28 to 29 week's gestation, the figure had increased to 15% of the cohort.[28] The prevalence of obstructive sleep apnea (OSA) is approximately 5% in nonpregnant women of reproductive age.[29] The risk for OSA in women who are obese pre-pregnancy was shown to be significantly higher than in those who are non-obese. Maasilta and colleagues found that patients who were obese pre-pregnant had 1.7 events per hour versus 0.2 events per hour in the nonobese group ($P < 0.05$), and 5.3 events per hour of 4% oxygen desaturation versus 0.2 events per hour ($P < 0.005$). [30] The obese women snored 32% of the time, whereas the non-obese group snored only 1% of the time. OSA may also contribute to a higher risk of hypertension during pregnancy.[31] Women with pre-eclampsia have upper airway narrowing in both upright and supine postures.[32] These changes could contribute to the upper airway resistance episodes during sleep in patients with pre-eclampsia, which may further increase their blood pressure. Pregnant women with apnea symptoms have a higher likelihood of gestational hypertensive disorders, gestational diabetes, and unplanned Caesarian sections.[33] Treatment for OSA in pregnant patients remains to be continuous positive airway pressure (CPAP), which has been shown to be safe during pregnancy.[34] Mild OSA may respond to the use of an oral appliance or conservative measures such as sleeping on one's side.

Restless leg syndrome (Willis-Ekbom disease) is a common complaint among pregnant women. Restless leg syndrome (RLS) is defined as an irresistible desire to move the legs in response to uncomfortable sensations in the legs and is relieved by movement. RLS is two to three times more prevalent during pregnancy than in the general population, affecting 15 to 25% of pregnant women in western countries.[35,36,37] The previous three studies also noted a peak in the number of women affected by RLS in the third trimester and resolution of symptoms for many by one month after delivery. Preexisting RLS also predicts greater severity during pregnancy.[38] The exact pathophysiology is not completely understood. A study determining the relationship between estradiol and RLS

Figure 2
Women whose insomnia is apparently related to mood symptoms benefit from hormone therapy as do some women with insomnia but without vasomotor symptoms.

found that pregnant women who reported RLS had higher levels of this hormone.[39] Iron and folate deficiencies are well-recognized factors associated with RLS in pregnancy. Levels of hemoglobin, ferritin, and Vitamin B12 start to fall in the second half of pregnancy, regardless of taking iron and vitamin supplementation, due to fetal growth and hemodilution.[40,41]

The management of RLS includes behavior modification in addition to medical management. Any underlying condition should be excluded. Pregnant women suffer from leg cramps, particularly in the second part of the pregnancy. Sleep related leg cramps is reported as a primary reason for sleep disruption during pregnancy.[42] These symptoms should be carefully assessed and differentiated from RLS. Avoiding anything that can worsen RLS is beneficial. This includes smoking, certain antidepressants, and caffeine. If medication is needed for RLS, pharmacological treatment (Ropinirole, Pramipaxole, Carbidopa) should be used only during the third trimester and at the lowest effective dose owing to their possible teratogenic effects.[43] Iron supplementation is an option for pregnant women with iron deficiency. Additionally, Folate supplementation should be considered.

Postpartum blues, or baby blues, is a transient form of moodiness experienced by up to 85% of new mothers three to four days after delivery, which usually dissipates within a week.[44] A smaller but notable percentage of mothers experience a major perinatal depressive disorder during pregnancy (up to 20%) or the postpartum period (about 12%-16%).[45] Several psychosocial factors have been shown to increase the risk for perinatal mood disturbances, including antenatal anxiety and depressive symptoms, the presence of psychiatric history, stressful life events, marital conflict and lack of social support.[46] Although postpartum blues is generally considered a normal event that does not impair functioning, perinatal depression is a psychiatric condition that requires clinical attention. Breast feeding, compared with bottle feeding, has been found to influence sleep, with marked increase in slow wave sleep that may be attributed to increased levels of circulating prolactin levels.[47]

Sleep During Menopause and Post-Menopause

Menopause is defined as permanent amenorrhea for a period of twelve months. The age range for natural menopause is from 45 to 55 years with a mean age of 51 to 52 years.[48] During the climacterium, or menopausal transition, women are at increased susceptibility for several symptoms that significantly reduce their quality of life. The hallmark symptoms during the climacterium comprise hot flashes and sweating (Vasomotor symptoms).[49] Hot flashes are described as a sudden onset of redness and intense feeling of warmth or hot resulting in perspiration. Hot flashes may be the result of decrease in the levels of estrogen.

Approximately, 75% of postmenopausal women and 40% of perimenopausal women suffer from vasomotor symptoms.[50,51] The vasomotor symptoms usually last for 1 to 2 years, but about 25% of women report them for 5 years and 9% may have it all their lifetime after menopause.[52,53] When present during the night, these symptoms often disturb sleep and may result in somatic, mental, and cognitive problems.[54,55] Insomnia was reported by 25% of the women and severe insomnia by 15% of the women between 50 and 64 years of age.[56] The clinical picture of menopausal insomnia is no different from common insomnia, which manifests itself as difficulty in falling asleep, frequent awakenings or awakening too early in the morning.[57] Although vasomotor symptoms correlate strongly with sleep complaints, insomnia may occur in the absence of

vasomotor symptoms and can be the exclusive climacteric symptom.[58] During the climacterium, other symptoms including palpitations, headaches, dizziness, numbness, dry eyes and mouth, and reduced skin elasticity are commonly noted. Vaginal dryness, nocturia, and other urinary tract symptoms also get worse after menopause.[59] Mental symptoms, including anxiety, depression, a decline in libido, loss of concentration, and memory impairment commonly occur, and may in fact surpass the severity of vasomotor symptoms.

Sleep disruption associated with hot flashes can impact the quality of life and therefore may require treatment. Hormone replacement therapy (HRT) has historically been the standard treatment. Hormone therapy is as an effective therapy for reducing climacteric vasomotor symptoms and related secondary insomnia.[60,61] Women whose insomnia is apparently related to mood symptoms benefit from hormone therapy as do some women with insomnia but without vasomotor symptoms.[62] (See Figure 2.) The results of the Women's Health Initiative results showing increased risk of breast cancer, stroke, heart disease, and vascular dementia in individuals who were on HRT regimen for one to seven years suddenly changed this common practice.[63] Women are counseled to use HRT for only a short period of time to alleviate extreme form of hot flashes and other vasomotor symptoms. Those with history of breast cancer or stroke should be excluded. In women who seek treatment but prefer to avoid hormonal therapy, or for whom hormone therapy is contraindicated, other options exist. A large body of literature suggests that noradrenaline and serotonin have a central role in the pathophysiology of hot flashes.[64] Thus Clonidine (an α_2 adrenergic agonist) or serotonin-reuptake inhibitors have been found to alleviate climacterial symptoms, and accordingly, related sleep problems. Gabapentin has also shown to be beneficial although the adverse events such as dizziness, rash, or weight again, often result in discontinuation of the treatment. Good sleep hygiene can also be useful to promote good quality sleep. If a woman has vasomotor symptoms, low ambient temperature is often helpful; and lightweight bed clothes may be more comfortable. Caffeinated beverages, smoking and alcohol intake close to the bedtime can also cause sleep disruption.

Sleep disordered breathing may also contribute to sleep disturbance during menopause. The Wisconsin Sleep Cohort Data suggest that apnea hypopnea scores of 5 or higher were more prevalent among women who were 50 to 60 years old than among younger women.[65] Another study found that 3.9% of post-menopausal women had OSA defined as apnea-hypopnea index of at least 15 per hour of sleep.[66] This number was statistically greater than that found in pre-menopausal women (0.6%). However, in post-menopausal women taking hormonal replacement therapy, the prevalence of sleep apnea was not statistically different from the pre-menopausal group, although this group may have included some peri-menopausal subjects. Proposed mechanisms for this apparent rise in sleep breathing disorders have included a change in the distribution of body fat and a decrease in progesterone.[67,68] With menopause, body fat composition changes, leading in particular to increases in the waist-hip ratio and neck circumference. The decrease in female sex hormones, particularly progesterone, may partly be responsible for sleep breathing disorders. Progesterone has respiratory stimulant properties and affects genioglossus muscle tone.[69] The most effective therapy for obstructive sleep apnea is continuous positive airway pressure. Other options include positional therapy, surgery and oral appliances. The therapeutic role of hormonal therapy for sleep apnea in menopausal patients has been considered, with conflicting outcomes. Improvement of nocturnal breathing, especially reduced AHI, with hormone therapy has been found in some but not all studies.[70,71,72] Progestin has been shown to decrease the duration of apneas as well as improvement in ventilation.[73] However, because the data is limited and conflicting, no definite recommendation of hormone therapy as an option for sleep-disordered breathing can be made.

Conclusion

While many aspects of sleep are similar in men and women, there are a number of important differences that need to be identified and confirmed by the health care provider.

It is also important to recognize there are clinically unique differences in the sleep of women at different stages of life. The risk of developing sleep disruption and disorders, including insomnia, sleep disordered breathing and restless legs syndrome is also higher during key phases, including menstrual cycle, pregnancy, postpartum period and menopause. As most basic and clinical studies have been performed in male subjects, more research is needed to clarify the influence of the life cycle on sleep framework in women.

References

References exceeded space. For listing, email bhata@umkc.edu.

Disclosure

None reported. **MM**