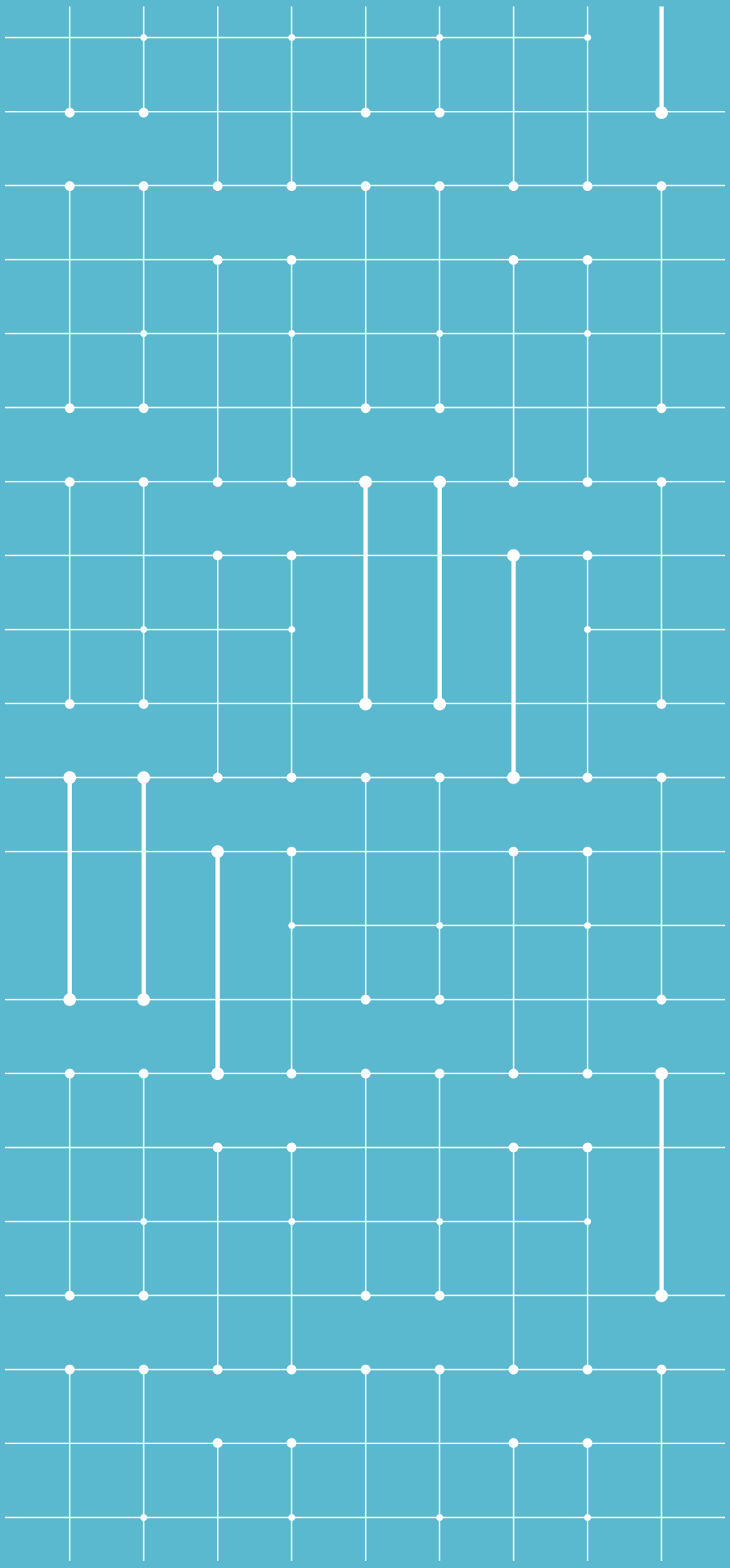
SWHR
INTERDISCIPLINARY
NETWORK ON SLEEP
2017

WOMEN & SLEEP

A Guide for Better Health

Society for
Women's Health
Research



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Dear Readers,

In the past decade, rapid advances have been made in our understanding of the science of sleep and circadian rhythms and their essential role in health, well-being, safety, and productivity. The game changer is the mounting evidence that sleep and circadian rhythms regulate nearly all biological and behavioral processes from molecules, single cells, and androgen systems to whole body physiology and functions. Thus, short sleep duration and circadian disruptions are linked to our modern society's major health problems such as obesity, cardiovascular disease, diabetes, stroke, cancer, mental illness, and dementia. The evidence is clear that poor sleep and circadian health can have deleterious effects on both mental and physical health.

Many biological, social, and environmental factors influence sleep, vary across the lifespan, and are impacted by sex and/or gender. Throughout this document, the word sex refers to the biological status female or male, whereas gender refers to attitudes, feelings, and behaviors that a given culture associates with a person's biological sex. Gender is rooted in biology and shaped by environment and experience. The distinct social and environmental experiences of women and men likely contribute to sleep differences. Therefore, women and men may have the same sleep problems, but present with different symptoms creating a need for unique screening, diagnosis, and treatments for both women and men. Unfortunately, many of these sex- and gender-specific needs, which could significantly improve sleep health, are lacking.

The primary aim of this guide is to bring attention to sleep health issues in women in order to improve diagnosis, treatment, and management of sleep and circadian rhythm sleep-wake disorders. It is divided into three sections: (I) Sleep Across the Lifespan; (II) Sleep and Circadian Rhythm Sleep-Wake Disorders; (III) Sleep and Circadian Rhythms in Health and Disease. Each topic within a section offers answers to a question about a sleep health issue and provides key clinical takeaways. We hope this guide will stimulate and enhance discussions between healthcare providers and their patients to better address women's sleep needs. We encourage you to share this document with healthcare providers, patients, and support groups so that we can improve sleep and circadian health for both women and men. If you have any questions or would like more information, please contact the Society for Women's Health Research at science@swhr.org or 202.223.8224.

Sincerely,

Society for Women's Health Research Interdisciplinary Network on Sleep

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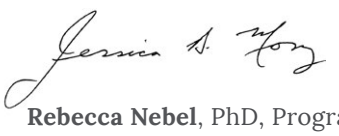

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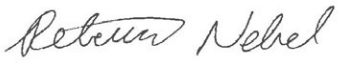

About the Society

Since 1990, the Society for Women's Health Research (SWHR®) has been the thought leader in promoting women's health and research on biological differences in disease. As a non-profit organization, SWHR is dedicated to improving women's health through science, advocacy, and education. Due to SWHR's advocacy efforts, women are now routinely included in most major medical research studies and scientists are required to consider sex and gender as variables in their research. Visit www.swhr.org for more information.

About SWHR's Interdisciplinary Networks

Throughout its history, SWHR has advocated for women's health and research on biological differences in disease through science, policy, and education. Over a decade ago, SWHR recognized the need to have researchers and clinicians across various disciplines with diverse perspectives, conceptual frameworks, and methods come together to discover new ideas in a particular health field. SWHR created the SWHR Interdisciplinary Networks to allow boundaries to be bridged and cross-cutting ideas to develop. SWHR Networks examine knowledge gaps and identify focused innovative directions for conditions that disproportionately, differently, or exclusively affect women.

The SWHR Interdisciplinary Network on Sleep is a collaborative model that brings together basic researchers and clinicians across sleep-related fields, including epidemiology, obstetrics/gynecology, neurology, pain, physiology, psychiatry, pulmonology, and sleep medicine. Launched in 2014, the Network aims to promote awareness, education, and research that highlights sex and gender differences in sleep and circadian rhythms, and their impact on health and well-being across the lifespan.

Acknowledgments

We extend our sincere thanks to the following individuals who have contributed to *Women & Sleep: A Guide for Better Health*:

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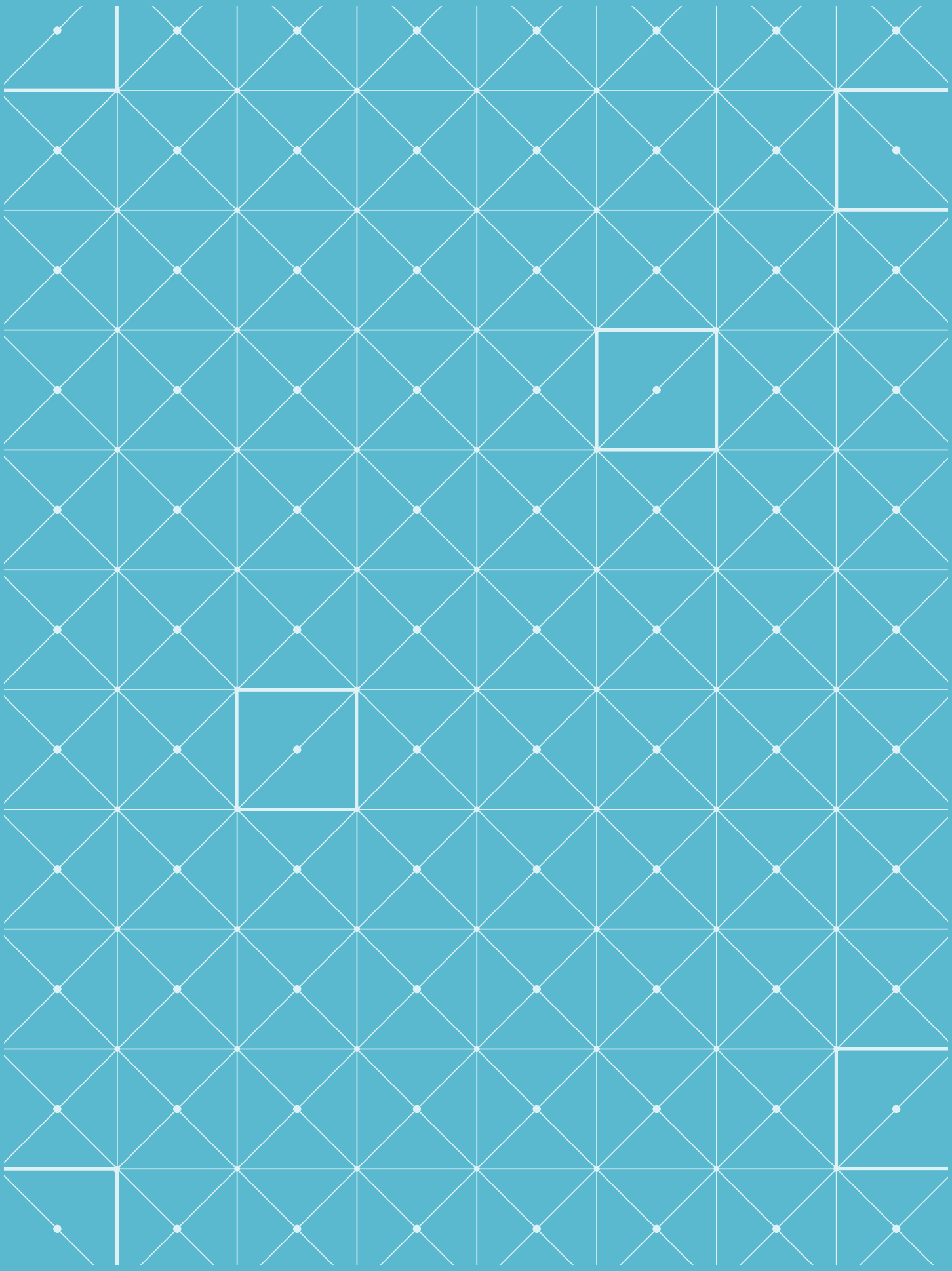
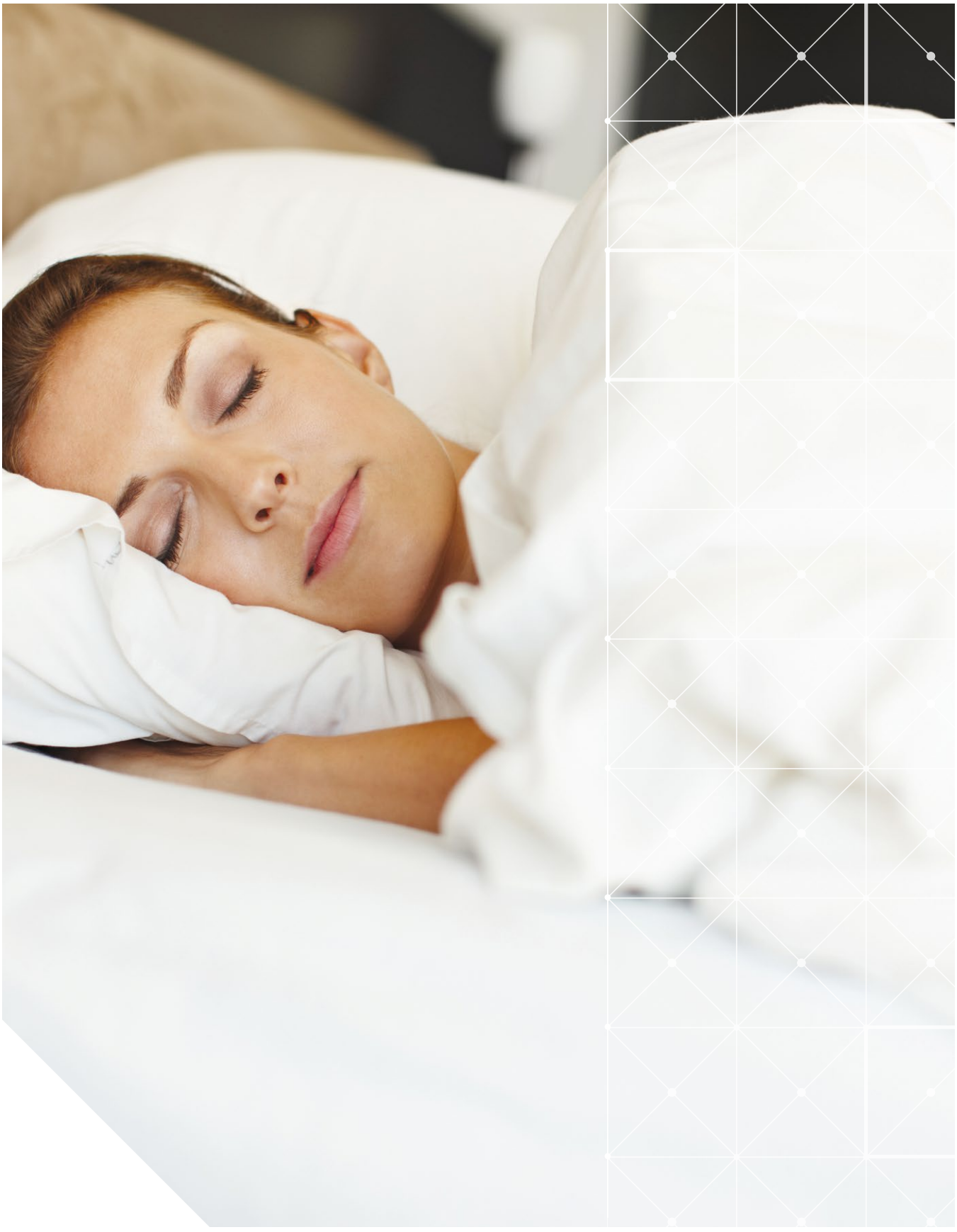


INTRODUCTION

SEX AND GENDER DIFFERENCES IN SLEEP AND CIRCADIAN RHYTHMS



WHY SHOULD YOU CARE?

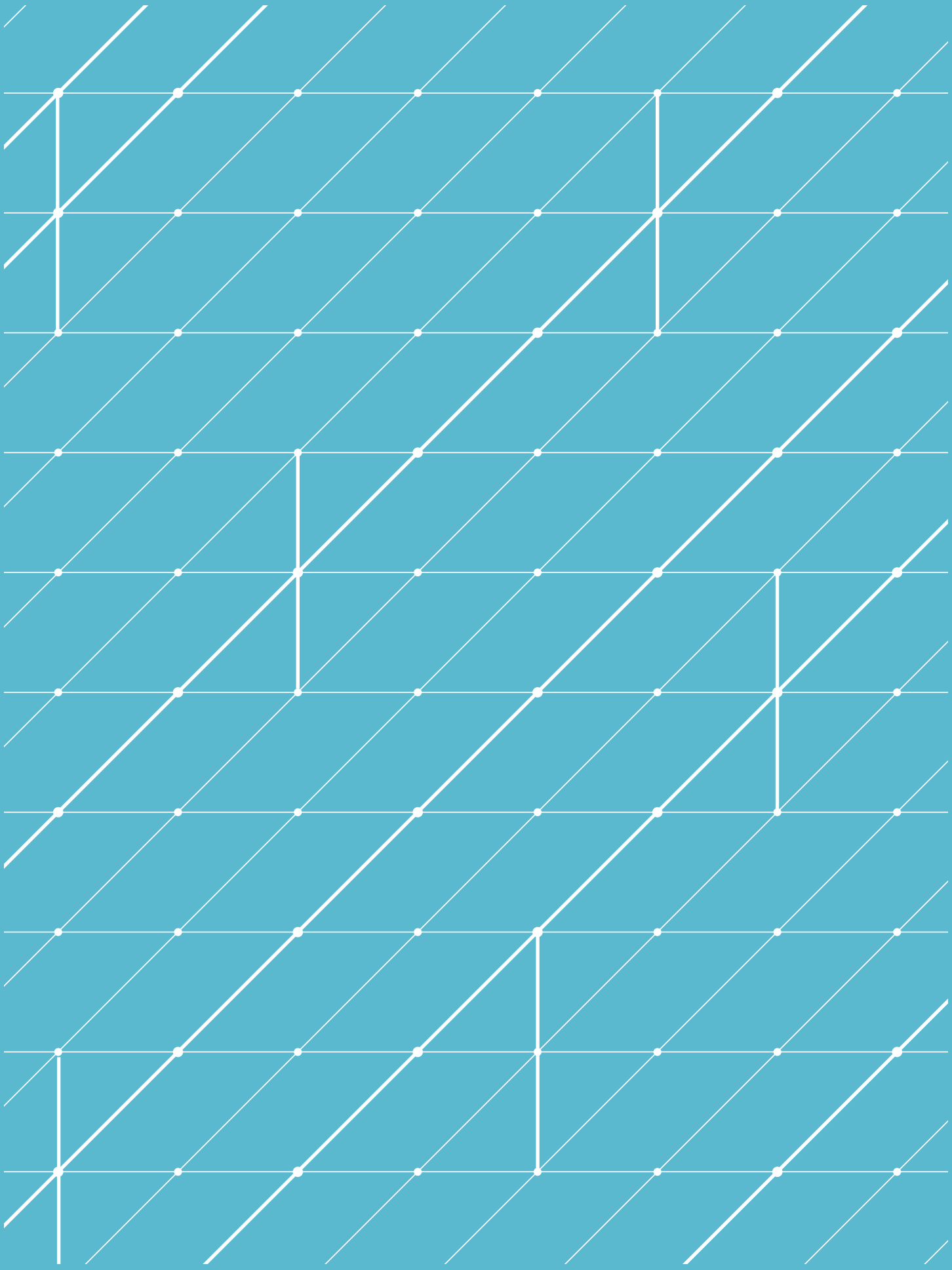
Women constitute more than 50% of the U.S. population. Promoting **sleep and circadian health** and prioritizing accurate diagnosis and effective treatment of sleep disorders that affect large numbers of women – such as **insomnia**, **sleep apnea**, **restless legs syndrome**, and **shift work sleep-wake disorder**[1-4] – are essential for women's well-being, and therefore the health of the entire population.

Women generally show **longer sleep duration** and perhaps have a higher sleep need than men,[1] yet women may sacrifice sleep because they often are the primary caregiver for their families. Many women work atypical shifts, such as in the 24-7 service and healthcare industries, which increases the risk for adverse effects of circadian disruption and **chronic sleep loss**.[5] Single parents, especially women, who are the sole source of family income and child care, are also at higher risk for **short sleep duration** and insomnia. Women also tend to use more sleep medications than men,[6] yet little is known about **sex** differences in drug effectiveness and dosing.

Furthermore, there are important biological and hormonal differences across the lifespan that influence symptoms and consequences of sleep and circadian rhythm sleep-wake disorders in women.[1,2] Improving sleep health requires consideration of these differences. Across the lifespan, women may have distinct needs from men related to screening, diagnosis, treatment, and public health interventions. For example, women and men with sleep apnea often present with different symptoms, yet available screening tools may bias diagnosis towards symptoms seen more commonly in men. Socioeconomic and **gender** biases may negatively affect proper diagnosis and treatment for women with sleep and circadian rhythm sleep-wake disorders as well. Sex- and gender-specific symptomatology in sleep and circadian problems also needs to be examined in the context of other disorders with sex- and gender-specific symptomology. For instance, psychiatric disorders such as anxiety and depression, which are more prevalent in women, may put women at greater risk for comorbid insomnia and vice versa.

The high prevalence of sleep and circadian rhythm sleep-wake disorders in women identifies important targets for improving health and well-being. Furthermore, studying sex and gender differences in these disorders provides opportunities to better understand and integrate information on reproductive cycles, lifestyles, socioeconomics, cultural factors, and access to healthcare into prevention, screening, diagnosis, and management strategies aimed at improving sleep health, which benefits overall health and well-being. A sex- and gender-specific approach to sleep health is an exemplar initial step in moving towards a vision for "precision medicine."

NOTE: Bolded terms are located in the glossary.



SECTION 1

SLEEP ACROSS THE LIFESPAN

How much sleep do I need? Do I need less sleep as I get older? Across the lifespan, there are changes in **sleep duration**, patterns of **EEG** activity during sleep, and **circadian rhythms**.[7] These changes also vary by **sex**. Sleep duration gradually declines from over 16 hours per day in early infancy to 9 hours in adolescence, with a further gradual decline into early adulthood and later life. Women have a shorter (faster) **circadian cycle** than men and this is associated with earlier sleep times.[8-10]

PUBERTY /

Puberty is associated with a delayed circadian cycle (falling asleep later, waking up later) and a decrease in total sleep time. However, early school start times require adolescents to wake up earlier than they would be set by their biological clock.[11,12] This misalignment may cause significant sleep deprivation. With adolescence, circadian rhythms change causing later sleep times; this happens at a younger age for girls than for boys. Sleep deprivation may contribute to poor school performance, attention deficit disorder, obesity, and metabolic dysfunction.[12]

PREGNANCY /

Many hormonal and physiologic changes during pregnancy affect sleep and may contribute to poor **sleep quality** during pregnancy, which varies by trimester.[13] Pregnancy can exacerbate sleep disorders such as **sleep apnea** and **restless legs syndrome**. Pregnancy- and postpartum-associated sleep difficulties as well as **short sleep duration**, resulting from the demands of caring for infant children, can contribute to mood dysregulation, postpartum depression, and chronic illnesses, such as weight gain and glucose impairment.[14,15] These health issues can persist into later life and even contribute to premature mortality.

MENOPAUSE /

Menopause is associated with poor sleep quality and increased symptoms of **insomnia**,[16] which negatively affect daytime function and quality of life. In addition, waning sex hormones likely contribute to an increase in sleep apnea in menopausal women, which may contribute to increased risk of cardiometabolic diseases.

OLDER AGE /

More than 50% of individuals older than 65 report difficulty sleeping. For these individuals, poor sleep quality is due to a variety of factors including intrinsic changes in circadian rhythms and sleep, medical or psychiatric conditions, medications, and sleep disorders such as insomnia, **periodic limb movement disorder**, and sleep apnea[17] With age, there is reduced stage 3 sleep (**slow wave sleep-** felt to be the most restorative or deepest **non-REM sleep**) and an increase in frequency of **arousals** with awakenings and subsequently reduced sleep continuity. The reduction in stage 3 sleep, which is correlated with many neurological processes, may be a sensitive biomarker of aging and its decrease correlates with many health parameters.

01

HOW DO REPRODUCTIVE HORMONES AND SLEEP INTERACT TO INFLUENCE HEALTH?

- **Women who suffer from severe premenstrual syndrome and/or painful menstrual cramps may experience insomnia during the week prior to and first few days of menstruation. Sleep disruptions can often exacerbate their premenstrual/menstrual symptoms.**
- **Women with polycystic ovary syndrome are at high risk for sleep apnea and should be screened for sleep apnea and appropriately treated.**
- **Reproductive hormone levels are affected by sleep quality, and, in turn, exert an effect on sleep.**

Female reproductive hormones such as estrogen and progesterone, fluctuate across the menstrual cycle and influence the **sleep-wake cycle**.[18,19] Some women may experience more sleep disturbances during the premenstrual week and the first few days of menstruation, when hormone levels are declining, compared with other times of the menstrual cycle.[20,21] These effects appear to be more pronounced in older reproductive-aged women.[21] For a few days every month, women with severe premenstrual syndrome and/or menstrual pain may also experience more significant sleep disruption that occurs cyclically in association with their other premenstrual/menstrual symptoms.[20] Birth control pills impact some aspects of sleep stage distribution, but do not appear to affect **sleep quality**.[20]

Polycystic ovary syndrome (PCOS), a hormonal disorder, is associated with increased risk for **sleep apnea**,[22] even when controlling for obesity.[23] Preliminary evidence suggests that successful treatment with **continuous positive airway pressure** therapy in extremely obese women with PCOS leads to a modest improvement in insulin sensitivity.[24]

There is a two-way interaction between reproductive and sleep regulatory systems. **Sleep duration**, timing, and **quality** can influence the regulation of reproductive hormone release in women and men, with effects dependent on reproductive maturity.[25-27] Altered sleep patterns or duration, therefore, can influence reproductive function. Some studies show that women shift workers (in whom sleep is often disturbed) have impaired reproductive health, which could be a consequence of disrupted sleep and **circadian rhythms** and/or alterations in other factors such as diet.[28] However, findings are mixed and possibly point to increased sensitivity for a subset of women to the effects of shift work.

02

WHAT ARE COMMON SLEEP ISSUES IN INFANTS AND CHILDREN?

- **Sleep disturbances are very common in both girls and boys.**
- **Sudden infant death syndrome occurs in girls and boys, but is somewhat more common in boys (60% vs 40%).**
- **Children with mood disorders, which more commonly affect girls, are likely to encounter related sleep problems such as insomnia.**

Sleep duration decreases from the newborn period to the end of the school age period, with increases in sleep consolidation (e.g., reduced **night wakings**, increased **longest sleep period**).[29,30] Studies are limited regarding **gender** differences in sleep patterns, with the majority of the studies finding no differences. However, a few studies indicate that girls get more sleep than boys, have decreased night wakings, and fewer sleep problems in the first few years of life.[31] When children do not obtain sufficient sleep, there are numerous consequences impacting growth, development, cognitive functioning, performance, health, mood, and family functioning.[32]

Sleep problems are highly common, occurring in 25–40% of typically developing children. The most common sleep problems during infancy and childhood include problematic bedtime behaviors, night wakings, **sleep apnea**, and **parasomnias**. Sleep problems are equally experienced by girls and boys, with a few exceptions. For example, bedtime fears are more common in girls,[33] whereas bedwetting is two to three times more common in boys and persists longer than in girls.[34] Sudden infant death syndrome occurs in both girls and boys, but a higher proportion of victims are boys (60%) versus girls (40%).

Sleep problems are also highly prevalent in children with neurodevelopmental disorders and psychiatric issues.[35-37] Girls are more likely to experience anxiety and depressive disorders, and thus are more likely to experience associated sleep issues such as **insomnia**.[38] In contrast, boys with such conditions as ADHD or autism spectrum disorder are more likely to experience concomitant associated sleep disturbances, including difficulties falling/staying asleep, **restless legs syndrome**, and sleep apnea.

03

WHAT ARE COMMON SLEEP ISSUES IN ADOLESCENTS?

- Given that girls physically develop at a younger age than boys, they experience a circadian delay at a younger age too.
- Insomnia, more commonly experienced by girls, is an early predictor of depression and suicide risk, and should be evaluated and appropriately treated in adolescents.
- Weight gain in adolescence increases risk of sleep apnea.

Significant changes occur in sleep during adolescence. Across adolescence, bedtimes get later and total sleep time decreases. On a physiological level, both the occurrence of a **circadian delay** and the slower accumulation of **homeostatic sleep pressure** (sleep drive) contribute to these outcomes.[11] Since puberty begins earlier in girls, these physiological factors occur at an earlier age and result in less sleep throughout their adolescence. Increased risk for **insomnia** in girls emerges after puberty, an effect not completely explained by their increased risk for depression.[39] There are also multiple psychosocial factors that contribute to **shorter sleep duration**, including early high school start times, increased screen time and electronics use, reduction in parental limit-setting around bedtime, and increased social engagement and extracurricular activities.[40]

A number of sleep disorders are also common during adolescence. Insomnia is highly prevalent, affecting approximately 10% of adolescents.[41] The prevalence of insomnia symptoms increases across pubertal development, with the emergence of preponderance in young women at Tanner stage 4. Insomnia symptoms are highly associated with behavioral problems and poor mental health in both girls and boys, with girls more susceptible to emotional and behavioral difficulties. Studies indicate that insomnia can be an early predictor of depression and suicide risk.[42]

Other sleep disorders that typically emerge during the adolescent period include **narcolepsy** and **delayed sleep-wake phase disorder**. Studies indicate that as many as one-third of adult patients report the

onset of narcolepsy symptoms before age 15 and about 15% before age 10.[43] Narcolepsy is equally common in girls and boys. Approximately 1–16% of adolescents experience delayed sleep-wake phase disorder, which is associated with depression, anxiety, and poor school performance.[44-46] Weight gain during adolescence increases the risk of **sleep apnea**,[47] which can lead to behavioral, cognitive, metabolic, and cardiovascular problems.

04

WHAT IS THE ROLE OF SLEEP IN FERTILITY?

- **Shift workers are more likely to experience irregular menses and a longer time to achieve pregnancy.**
- **Women with polycystic ovary syndrome are 30 times more likely to have sleep apnea.**
- **Chronic insomnia is associated with alterations in stress hormones, predisposing individuals to anovulation.**

Infertility is prevalent in the United States, with rates reported between 7–15% among American women aged 15–44 years old.[48] Although studies on the role of sleep disorders in infertility are limited, existing studies highlight a complex interaction between sleep and sex hormones.

The bulk of studies have focused on women who are shift workers. Their irregular work schedules have been associated with irregular menstrual cycles, dysmenorrhea, and a longer time to achieve pregnancy.[49,50]

Polycystic ovary syndrome (PCOS) is marked by insulin resistance, decreased glucose tolerance, and hyperandrogenism. The sum of these changes can cause anovulation, which leads to infertility. Premenopausal women with PCOS are 30 times more likely to suffer from **sleep apnea** than women without PCOS.[51] There are currently no studies that directly measure the impact of sleep apnea on infertility, or the impact of treatment of sleep apnea on fertility.

Another area of concern for fertility is chronic **insomnia**. Women are disproportionately affected by insomnia. Among women with chronic insomnia, levels of stress hormones (cortisol and adrenocorticotropic hormones) are higher than in women who report normal sleep. These stress hormones can result in changes that affect fertility.[52]

Although the findings of existing studies are inconsistent, **short sleep duration**, poor **sleep quality**, and sleep apnea have been associated with elevated prolactin, testosterone, and estradiol.[53] Elevations of these hormones predispose a woman to anovulation and hence infertility.[52] Studies examining the role of naturally occurring melatonin have also shown conflicting results with reports of both decreased and increased melatonin being associated with sleep disturbance.[54] One study found an improvement in oocyte and embryo quality among women with sleep disturbances undergoing *in vitro* fertilization who were supplemented with melatonin.[55] This finding may indicate a role for treatment of sleep disorders among women undergoing treatment for infertility.

05

HOW DO SLEEP AND SLEEP DISORDERS CHANGE DURING PREGNANCY?

- **Women experience changes in their sleep during all three trimesters of pregnancy.**
- **Sleep apnea, insomnia, and restless legs syndrome are common in pregnancy and when left untreated are associated with worse outcomes for mothers and infants.**
- **Sleep problems during pregnancy are often overlooked by clinicians who do not recognize their clinical importance.**
- **Difficulty in falling asleep or maintaining sleep may be a sign of perinatal depression.**

Pregnancy is a time of rapid physiological and emotional changes for expectant mothers, and many women report altered sleep patterns and increased sleep disturbance during pregnancy. Pregnancy-related sleep changes begin during the first trimester, when women commonly report increased levels of sleepiness. Although the second trimester is often believed to be a time of enhanced well-being, most women continue to experience sleep disturbances throughout mid-pregnancy.[13,56] By the third trimester, approximately 75–84% of women report **daytime sleepiness** and/or difficulty sleeping at night. In addition to the sleep disorders discussed below, physical discomfort, increased nocturnal urination, anxiety, depression, and psychosocial factors (e.g., poverty, intimate partner violence) can all disturb sleep during pregnancy.[57]

Objective sleep measures such as laboratory **polysomnography** and wrist activity monitoring corroborate women's reports of disrupted sleep during pregnancy. Sleep recordings of pregnant women consistently show increased wakefulness at night and decreased **REM sleep**.

Women who start their pregnancy at a higher BMI are at higher risk for developing **sleep apnea**. Sleep apnea is associated with pregnancy-induced hypertension, preeclampsia, gestational diabetes, caesarean delivery, and small for gestational age infants. Snoring is also associated

◇ "Sleep problems during pregnancy are often overlooked by clinicians who do not recognize their clinical importance."

with adverse outcomes similar to those for sleep apnea. Sleep apnea during pregnancy is usually treated with auto-titrating **continuous positive airway pressure** machines, since the pressure to treat sleep apnea may change as the pregnancy progresses.

An estimated 12–26% of women experience **restless legs syndrome** (RLS) by the third trimester of pregnancy, compared to about 10% in the general population. This sleep disorder, also called **gestational RLS** when it occurs during pregnancy, may be more common during pregnancy because of the increased iron needs during gestation. Other phenomena associated with gestational RLS include decreased folate, gestational diabetes, and uremia. RLS symptoms have also been associated with hypertensive pregnancy disorders in expectant mothers as well as low birth weight and earlier gestational age at birth in infants.[58] Iron supplementation for serum ferritin <75 mcg/L is considered first line treatment in gestational RLS, whereas use of carbidopa/levodopa, clonazepam, or oxycodone are reserved for refractory cases.[59]

Insomnia is experienced by an estimated 20–60% of pregnant women.[60,61] Insomnia is reported more frequently by first-time mothers and women who are younger, smoke tobacco, are further along in their pregnancy, or have high blood pressure. Negative consequences of insomnia during pregnancy include preeclampsia, preterm labor, increased incidence of caesarean delivery, gestational diabetes, and perinatal depression.[59,62] **Cognitive behavioral therapy for insomnia** is a promising treatment during pregnancy,[63] and pharmacologic treatment may be indicated in pregnancy in circumstances where the benefits are expected to outweigh the risks.

20-60%

OF PREGNANT WOMEN EXPERIENCE INSOMNIA[59,60]

— Negative consequences of insomnia during pregnancy include —

PREECLAMPSIA / PRETERM LABOR / INCREASED INCIDENCE OF CAESAREAN DELIVERY / GESTATIONAL DIABETES / PERINATAL DEPRESSION

06

WHAT HAPPENS TO SLEEP IN NEW MOTHERS?

- **New mothers experience shortened and disrupted sleep.**
- **Current U.S. maternity and family leave policies do not adequately account for infant sleep patterns and the sleep disturbances that result from providing 24-hour infant care.**
- **Disturbed postpartum sleep is associated with chronic illness and poor mental health outcomes.**

A new mother's sleep is affected by the presence of an infant after childbirth or adoption.[64] Postpartum sleep disturbances are usually attributed to caring for the infant. However, while maternal and infant sleep are coupled tightly in the earliest postpartum weeks, later in the postpartum period, a mother's sleep continues to be disturbed despite improvements in infant sleep continuity.[65–68] Infant sleep is better in families who provide a regular bedtime routine and help their infants self-soothe.[69] Thus, good parenting practices around sleep may improve infant sleep, and reciprocally, maternal sleep.[70]

A first-time mother experiences more postpartum sleep disruption than an experienced mother, but the exact mechanisms responsible are not well understood.[71] A mother's sleep is influenced by many social and psychological factors in the family, including quality of partner support.[72] These varied factors should be considered when addressing sleep issues in a new mother.

Some postpartum sleep difficulties may occur because the body's internal clock does not stay stable across the perinatal period due to altered **sleep-wake cycles** and exposure to light at night.[73] Studies have shown that mothers' sleep is more fragmented at night than fathers, reflecting the fact that they perform most of the nighttime child care.[74] Increased paternal involvement in nighttime care improves infant sleep, even in breastfeeding families.[75,76]

The effects of providing round-the-clock infant care and the ensuing sleep loss have important implications for maternity and family leave policies. In the United States, the average maternity leave is 10.3 weeks, but most infants do not sleep through the night consistently until 4 to 6 months of age. This lack of infant sleep continuity creates chronic restricted and/or interrupted sleep for new parents.

Disturbed postpartum sleep may contribute to the development of chronic illnesses such as obesity or diabetes in later life.[14,15] Shortened and disturbed postpartum sleep is also a risk factor for postpartum mood disorders in mothers who have given birth and in adoptive mothers. Postpartum psychosis is a psychiatric emergency that can be triggered by postpartum sleep deprivation.[77] Furthermore, infant sleep problems are associated with depressed mood in postpartum women. **Cognitive behavioral therapy for insomnia** has been used with success in women with postpartum depression.[78] Women who experience **insomnia** in the postpartum period should be evaluated and appropriately treated.

07

WHAT IS THE ROLE OF MENOPAUSE IN SLEEP DISTURBANCES IN MIDLIFE WOMEN?

- **The prevalence of sleep problems increases significantly in midlife women and is linked with changes in mood and other psychosocial factors.**
- **Sleep difficulties in midlife women are often caused by hot flashes. Strategies to treat sleep disruptions should consider this unique instigating factor.**
- **Midlife women have an increased risk of sleep apnea compared to younger women, particularly post-menopause. Midlife women with symptoms of sleep apnea should be screened and appropriately treated.**

The transition to menopause, which occurs around 51 years of age, is associated with a stark increase in sleep problems, particularly more frequent **night wakings**. Sleep problems are one of the most bothersome symptoms that impact quality of life in many women going through the menopausal transition.[16] The increase in sleep problems is attributed to several factors, including menopausal hormone changes, hot flashes and night sweats, depressed mood and psychosocial factors (e.g., life stress), as well as comorbid conditions like **sleep apnea**.[16,79-83] Although all women go through the hormonal changes of menopause, not all experience sleep difficulties and other menopausal symptoms, suggesting that some women may be more vulnerable to the effects of hormonal fluctuations than others.

A unique factor that contributes to sleep troubles during the menopausal transition is hot flashes, and these symptoms are linked with **insomnia**.[84] Most women transitioning through menopause experience hot flashes but to different degrees of frequency, severity, and duration, with the median duration of hot flashes lasting 7.4 years.[85] Hormone therapy is an effective treatment for hot flashes and associated sleep disturbances.[83] Non-hormonal pharmacological treatments, such as selective serotonin reuptake inhibitors and gabapentin, are also effective.[16,86] **Cognitive behavioral therapy for insomnia** has clear benefits with no significant adverse effects for treating insomnia in the general population, including in midlife and older women, and should be considered as a treatment option for insomnia associated with menopause.[86] A healthy lifestyle that includes high-intensity exercise is also recommended,[86] and may help women with menopausal symptoms.

Although hot flashes may be a primary cause of sleep problems in peri- and post-menopausal women, other conditions like sleep apnea can contribute as well.[16] While the overall incidence of sleep apnea is higher in men than women, the **gender** gap narrows as women age, particularly after menopause. Sleep problems that develop in the context of the menopausal transition should be addressed because of the impact that **short sleep duration** and disrupted sleep have on other health outcomes, safety, performance, and quality of life.

Women who undergo surgical menopause (particularly when the procedure includes bilateral oophorectomy) have the highest prevalence of sleep difficulties among midlife women,[87] possibly because of the severe hot flashes and abrupt hormonal changes that can occur. Hormone therapy improves sleep in women with severe symptoms associated with surgical menopause.[83]

08

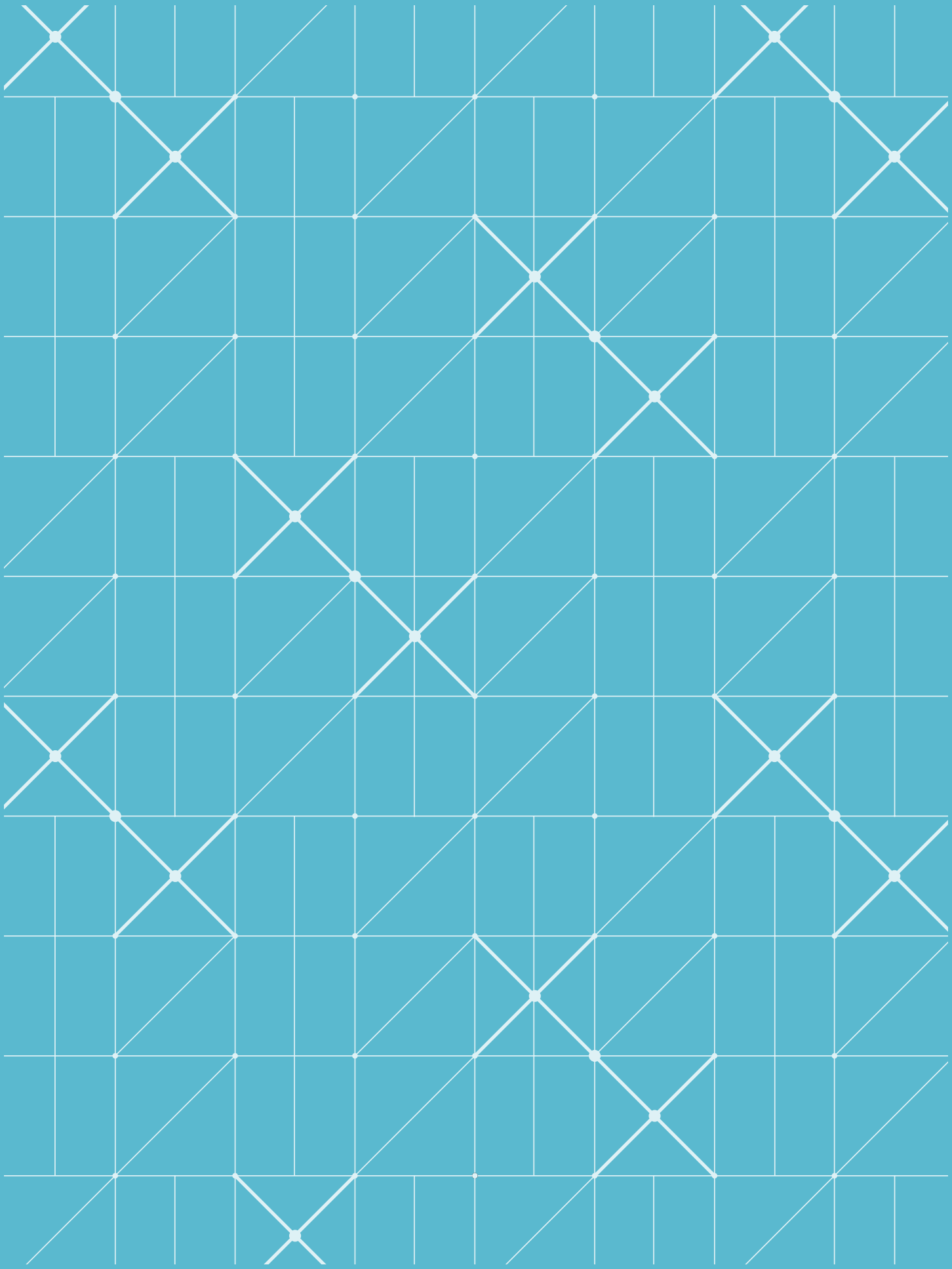
WHY IS SLEEP IMPORTANT FOR SUCCESSFUL AGING?

- **Older adults are at risk for sleep disturbances, and women are at higher risk for insomnia than men.**
- **Good sleep quality is a marker of successful aging.**
- **Poor sleep quality is associated with many diseases and health conditions, such as cardiovascular disease, metabolic disorders, and cognitive impairment.**

Successful aging is characterized by high physical, psychological, and cognitive functioning, and active engagement with life. Although sleep disturbances and sleep disorders – such as **insomnia**, **sleep apnea**, and **circadian rhythm sleep-wake disorders** – are common in older adults, they are not inevitable consequences of healthy aging.[88] Most sleep disturbances are associated with poor mental and physical health, as well as poor overall quality of life. In addition, age-associated changes in sleep regulation, such as decline in stage 3 **(slow wave) sleep**, and alterations in **circadian rhythms**, such as earlier timing of sleep, can increase the vulnerability to sleep disturbances.[89,90]

As people age, complaints of sleep disturbances become more prevalent. In a study of 9,000 women and men aged 65 years and older, over 50% of the participants reported at least one chronic sleep complaint.[91] In the elderly, symptoms of sleep problems include difficulty falling asleep and maintaining sleep, early morning awakening, and excessive **daytime sleepiness**. Although women across all ages are at a higher risk for developing insomnia compared to men, elderly women are at the highest risk.[92,93] Good sleep hygiene is important across the lifespan, and recent findings suggest good sleep habits, such as maintaining a regular sleep-wake schedule, may be particularly important for successful aging.

The relationship between sleep and aging is bidirectional. Poor sleep can increase the risk of common chronic age-related disorders – such as cardiovascular disease, metabolic disorders, and cognitive impairments – and in turn, these conditions can contribute to poor sleep. Hence, maintaining good **sleep quality** is crucial for successful aging.



SECTION 2

SLEEP AND CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

Intrinsic biological factors such as sex hormones (particularly during times of hormonal change like puberty, pregnancy, and menopause), as well as environmental factors that interact with **sex** and **gender** can all influence risk, development, and treatment of sleep and **circadian rhythm sleep-wake disorders**.[86,94-96] Despite clear sex and gender differences, diagnostic tools, treatment, and general awareness of these disorders may be biased towards one sex or gender, which can result in misdiagnosis and mistreatment and impact future research.

Disorders such as **insomnia** and **restless legs syndrome** are more prevalent in women.[97,98] On the other hand, sleep disorders that are more common in men, such as **sleep apnea** and **REM sleep behavior disorder**, often go undiagnosed in women because women may present with "atypical" symptoms of these disorders or clinicians are less vigilant in screening for these conditions in women.[99] Furthermore, lifestyle and social factors – such as caring for children and the elderly – can negatively impact **sleep quality** in women, who are often the primary caregiver. It is important to recognize these disparities in order to create better diagnostic and treatment options for women.

The treatment for sleep and circadian rhythm sleep-wake disorders may work differently in women compared to men. For instance, zolpidem, a sedative hypnotic used to treat insomnia, is metabolized differently in women and men. As a result, the recommended dosage for women was lowered in 2013.[100] For treatment of sleep apnea, women require lower **continuous positive airway pressure (CPAP)** than men and may require CPAP masks specifically designed to fit a woman's face.[101] Other life events such as pregnancy, breastfeeding, and menopause as well as medications like birth control pills and other hormone therapies must be taken into consideration when choosing the right treatment options for sleep and circadian rhythm sleep-wake disorders in women.

09

WHAT IS RESTLESS LEGS SYNDROME AND HOW DOES IT AFFECT WOMEN?

- **Restless legs syndrome is prevalent in pregnancy, especially among women with a family history of the disorder or a personal history of growing pains during adolescence.**
- **Gestational restless legs syndrome can have adverse pregnancy and birth-related outcomes.**
- **Ferritin level should be increased to >75 mcg/L in women with gestational restless legs syndrome to help manage symptoms.**
- **Restless legs syndrome is often misdiagnosed as leg cramps, peripheral neuropathy, or anxiety.**

Restless legs syndrome (RLS), or **Willis Ekbom disease**, is a well-established neurological disorder that can cause significant sleep disruptions and subsequent fatigue. Pathophysiology of RLS is most likely due to brain iron metabolism and secondary dopaminergic dysfunction.[102] The prevalence of RLS varies depending on ethnicity and geographic area but ranges from 0.3–8%. However, its preponderance in women remains constant.[98] RLS is twice as prevalent in women compared to men and is primarily due to increased incidence of RLS with pregnancy, estimated to be 12–26%.[103] Women who experience **gestational RLS (gRLS)** are at fourfold increased risk of RLS later in life and threefold risk of gRLS with subsequent pregnancies.[104] Risk factors for gRLS include a personal history of growing pains as an adolescent and a family history of RLS.[105] gRLS is associated with preterm birth, small for gestational age infants, and pregnancy-related hypertensive disorders.[58,106]

There is a strong genetic component to RLS, with one-third of cases showing strong familial tendencies. Several candidate genes have been identified. Pattern of inheritance is autosomal dominant with both variable penetrance and evidence of genetic anticipation.[107]

To date, there are no well-studied and safe pharmacologic treatments for gRLS. Most medications used to treat RLS have some teratogenic potential.[108] As a first line treatment for gRLS, non-pharmacological methods include a workup for and treatment of other comorbid sleep disorders, dietary changes, massage, and oral iron to increase serum ferritin to >75 mcg/L.[59] A last resort for treatment is using medications such as carbidopa/ levodopa, clonazepam, and opiates, of which the latter two have significant risk of dependence.[59]

Although the diagnosis of RLS can be made in a clinical setting without the need of a **polysomnography (PSG)**, a PSG may be needed to rule out coexisting sleep disorders in patients who do not respond to treatment or have symptoms of other disorders. Common disorders that need to be ruled out are **periodic limb movement disorder** and **sleep apnea**, both of which can have overlapping symptoms with RLS.[109] RLS is also commonly misdiagnosed as arthritic pain, anxiety, depression, leg cramps due to nutritional deficiencies,[110] and peripheral neuropathy.[111]

10

WHY ARE PARASOMNIAS IMPORTANT FOR WOMEN'S HEALTH?

- **Sleep related eating disorder, a parasomnia more common in women, can be caused by commonly prescribed sedative hypnotics such as zolpidem. Since women have a higher prevalence of insomnia, they may be prescribed these sedative hypnotics more often.**
- **REM sleep behavior disorder is under-recognized in women because women's dreams have less violent contents and their dream enactment is less physical.**

Parasomnias are abnormal behaviors during sleep and are generally classified based on the type of sleep from which they arise: **non-REM sleep** or **REM sleep**.

In the **non-REM parasomnia** known as **sleep related eating disorder (SRED)**, there is complete or partial loss of awareness and eating of unusual food combinations and even of non-food substances during sleep, which may lead to injury and harm. Overall prevalence of SRED ranges from 0.5–4.7% and the ratio of women to men with SRED ranges from 1.5:1 to 4:1.[112] SRED is associated with depression and daytime eating disorders. Management includes addressing other exacerbating sleep disorders, stopping zolpidem and other sedative hypnotics, and low dose topiramate or low dose pramipexole.[113] Sedative hypnotics, particularly zolpidem, have been associated with automatic behaviors in sleep including sleep walking and SRED.[114] SRED and the related condition **nocturnal eating syndrome** may potentially be associated with disturbances of **circadian rhythms** of metabolic pathways.[115]

The **REM parasomnia** known as **REM sleep behavior disorder (RBD)** is strongly associated with the risk of neurodegeneration, particularly Parkinson's disease and other α-synucleinopathies. Initially thought to be a predominantly male disease, later studies have demonstrated that ratio of women to men with RBD is actually about 1:1.62.[116] The initial impression of it being primarily a man's disease is because women tend to have less violence-themed dreams and their dream enactment tends to be less physical. Women with RBD tend to present with more vocalizations and verbal arguments while dreaming than actual violent physical movements.[116]

◇ "REM sleep behavior disorder is under-recognized in women."

11

HOW DOES SLEEP APNEA AFFECT WOMEN?

- Approximately 90% of cases of sleep apnea in women are undiagnosed.
- Women with sleep apnea may report symptoms of insomnia, mood disturbances, and fatigue rather than sleepiness.
- Sleep apnea may be exacerbated at key points across the woman's lifespan, such as during pregnancy and after menopause.
- Sleep apnea increases risk of poor pregnancy outcomes and a myriad of chronic health conditions.
- Home sleep apnea tests may miss the diagnosis of sleep apnea in women since women may present with shorter apneas associated with arousals rather than hypoxemia.

Sleep apnea, characterized by repetitive pauses in breathing during sleep, leads to fragmented sleep, hypoxemia, sleepiness, and cognitive deficits; and increases the risk for vehicle crashes, hypertension, cardiovascular disease, stroke, and diabetes.[117] Factors associated with sleep apnea risk include high BMI, advancing age, a family history of sleep apnea, a small jaw or narrow upper airway, and sedative, alcohol, or opioid use.

Although early reports identified a large male predominance, community studies indicate that the ratio of women to men with sleep apnea is only 1:3.[118] Approximately 90% of women with severe sleep apnea are undiagnosed.[119] This lack of proper diagnosis in women may be because sleep apnea risk factors and presenting symptoms differ by **sex.** Sleep apnea screening instruments may not be sufficiently sensitive in women due to their focus on symptoms more predominant in men such as sleepiness, **apneas**, and snoring rather than on symptoms commonly reported in women such as fatigue, **insomnia**, and depressed mood.[120,121]

During pregnancy, sleep apnea may first appear, or become exacerbated, due to nasal mucosal edema, fluid shifts, and weight gain. Sleep apnea can increase risk for pregnancy-related health problems, including gestational diabetes and hypertension, as well as increase risk for adverse delivery and perinatal outcomes such as preterm birth, neonatal intensive care admission, and maternal in-hospital death.[122,123] Sleep apnea during pregnancy can be challenging to identify because some existing screening and diagnostic instruments do not measure **arousals** occurring with apneas and because women may have worse sleep apnea in **REM sleep**, which may not be fully recorded with home sleep apnea tests. Although snoring, observed apneas, obesity, and enlarged neck size are associated with an increased sleep apnea risk, additional symptoms to consider in pregnant women include fatigue, insomnia, depression, and cognitive problems.[124]

Because female sex hormones are protective for sleep apnea, severity increases following menopause. Sleep apnea during this life stage may contribute to

increased cardiovascular disease risk in women at later stages of life.

Treating sleep apnea in women requires both consideration of the different device pressure needs compared to men and the high prevalence of insomnia symptoms in women. The presence of insomnia symptoms may lead to exclusive focus on these symptoms at the expense of evaluating sleep apnea. **Continuous positive airway pressure (CPAP)** machines, the most common sleep apnea treatment, have been developed to provide pressure support that targets aspects of sleep apnea particularly relevant to women: REM-dependency, short apnea duration, and airflow limitation. In addition, addressing insomnia symptoms such as prolonged **sleep onset latency** or reduced **sleep maintenance** is particularly important in women to help reach CPAP use goals and to achieve adequate **sleep duration**.

◇ "Sleep apnea leads to fragmented sleep, hypoxemia, sleepiness, and cognitive deficits."

1:3

THE RATIO OF WOMEN TO MEN WITH SLEEP APNEA.[118]

90%

OF WOMEN WITH SEVERE SLEEP APNEA ARE UNDIAGNOSED.[119]

12

HOW DOES INSOMNIA AFFECT WOMEN?

- **Insomnia is 40–70% more common in women compared to men, with higher rates occurring with advancing age.**
- **The rate of metabolism of some hypnotic medications is slower in women than men. The FDA recommends using a zolpidem dosage for women that is half the recommended dosage for men.**

Insomnia, characterized by an inability to fall or stay sleep, can cause daytime impairment such as sleepiness and problems concentrating. Chronic insomnia lasts for at least three months, occurs at least three times per week, and can be associated with psychiatric disorders, suicidality, and cardiometabolic disorders.[125-127] Insomnia is more prevalent in women than men, with a ratio of approximately 1.5 to 1.[127,128] **Sex** differences in insomnia begin as early as adolescence.[128] The onset of first menses is associated with a 2.75-fold increased risk for insomnia.[128] In contrast, puberty has not been associated with insomnia in boys, which suggests that female sex hormones associated with puberty and menarche may play a role in insomnia.

Across the lifespan, women continue to report more difficulties with falling asleep, staying asleep, and non-restorative sleep than men.[128] In contrast to subjective experiences, when sleep is measured using **polysomnography**, results show that men have more objective sleep disruption than women. During midlife, women have about a 40% increased risk of insomnia than men, and this gap widens with aging such that women over the age of 65 have more than a 70% increased risk of insomnia compared to men. One reason for the large difference in insomnia prevalence between women and men may be that illnesses that are frequently comorbid with insomnia – such as affective disorders and pain syndromes that can interfere with normal sleep – are more common in women than in men.[129]

The gold-standard therapy for insomnia, **cognitive behavioral therapy for insomnia (CBT-I)**, has been shown to improve sleep for both women and men. However, preliminary studies are beginning to show some **gender** differences in how CBT-I treatment improves sleep quality (e.g., decreased sleep latency and fatigue in women versus decreased sleep disturbances in men) when treating insomnia comorbid with other conditions.[130] In addition, human and animal studies indicate that some hypnotic medications are metabolized differently in females and males and there may be different pharmacologic activity in female versus male brains.[131-134] Because of slower metabolism, the U.S. Food and Drug Administration (FDA) recommends that zolpidem doses be halved for women compared with the dosage recommended for men.[100] Taken together, these studies suggest that further research is need to better target insomnia treatment in women.

13

HOW DOES NARCOLEPSY AND DAYTIME SLEEPINESS AFFECT WOMEN?

- **The diagnosis of narcolepsy is often missed or delayed for women, and the duration from symptom onset to diagnosis is longer in women than in men.**
- **The burden of disease for women with narcolepsy is high and is associated with lower health-related quality of life.**
- **Women with narcolepsy are likely to be older and have a higher BMI when they get pregnant. Narcolepsy is associated with adverse pregnancy outcomes.**

While women tend to report more sleepiness and state that they need more sleep than men, the gold-standard objective measure of **daytime sleepiness**, the **multiple sleep latency test (MSLT)**, does not show compelling differences between women and men in a community setting.[135] Historically, **narcolepsy** – a **hypersomnia** characterized by excessive daytime sleepiness, cataplexy, and disrupted **sleep-wake cycles** – was reported to be more common among men than women. However, current epidemiologic evidence indicates that narcolepsy affects genders equally. Women with narcolepsy are reported to have earlier onset of symptoms than men, yet a recent study showed no **gender** difference in the age of onset but a significant delay in proper diagnosis: 16 years from the onset of symptoms in men and 28 years in women.[136] Women with narcolepsy are sleepier on the MSLT than men,[136] and in the Doberman canine model of narcolepsy, female dogs have more severe cataplexy than males.[137]

Women report more impact from the disease in everyday life, which can include effects on reproductive decision-making and career development. For instance, a study of pregnancies from nearly 250 women with narcolepsy found that narcolepsy patients were older at the beginning of pregnancy compared to controls. Furthermore, narcolepsy patients were more likely to have anemia, impaired glucose tolerance, and excess weight gain during pregnancy and had a higher C-section rate.[138] A large survey of practice patterns during pregnancy indicated that most physicians and patients discontinue medications during pregnancy.[139] Although patient-led advocacy groups (e.g., Narcolepsy Network) provide strong grassroots support for patients with narcolepsy, data are lacking to assist women with narcolepsy in deciding whether to take their medications while pregnant and breastfeeding.

Idiopathic hypersomnia is a syndrome characterized primarily by excessive daytime sleepiness. Some case series of this rare disorder suggest an increased preponderance in women,[138] whereas other series show equal distribution between both genders.[140] As more research appears in the literature on hypersomnia, it will be important to assess whether more robust **sex** and gender differences emerge or serve to distinguish different hypersomnia subtypes.

14

HOW DO CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS AFFECT WOMEN'S HEALTH?

- Circadian rhythm sleep-wake disorders and disturbed circadian rhythms increase the risk of health problems such as obesity, diabetes, substance abuse, mood disorders, and cancer.
- Women show higher levels of sleepiness during the biological night and shorter sleep duration during the biological day, which combined with social and familial obligations may put them at greater risk than men for shift work sleep-wake disorder.

Circadian rhythm sleep-wake disorders (CRSWDs) are defined by a mismatch between the timing of the internal clock and the external environment/social-school-work schedule or by a disrupted/broken internal clock.[141-143] Mismatches can occur due to a clock that is timed too early or too late, shift work, jet lag, or a failure to synchronize the internal clock to the light-dark cycle. If the clock is disrupted/broken, 24-hour rhythms can be lost. CRSWDs and disturbed **circadian rhythms** are associated with health problems such as obesity, diabetes, substance abuse, mood disorders, and cancer.

ABBREVIATIONS

CRSWDS
circadian rhythm sleep-wake disorders

SWSWD
shift work sleep-wake disorder

ASWPD
advanced sleep-wake phase disorder

DSWPD
delayed sleep-wake phase disorder

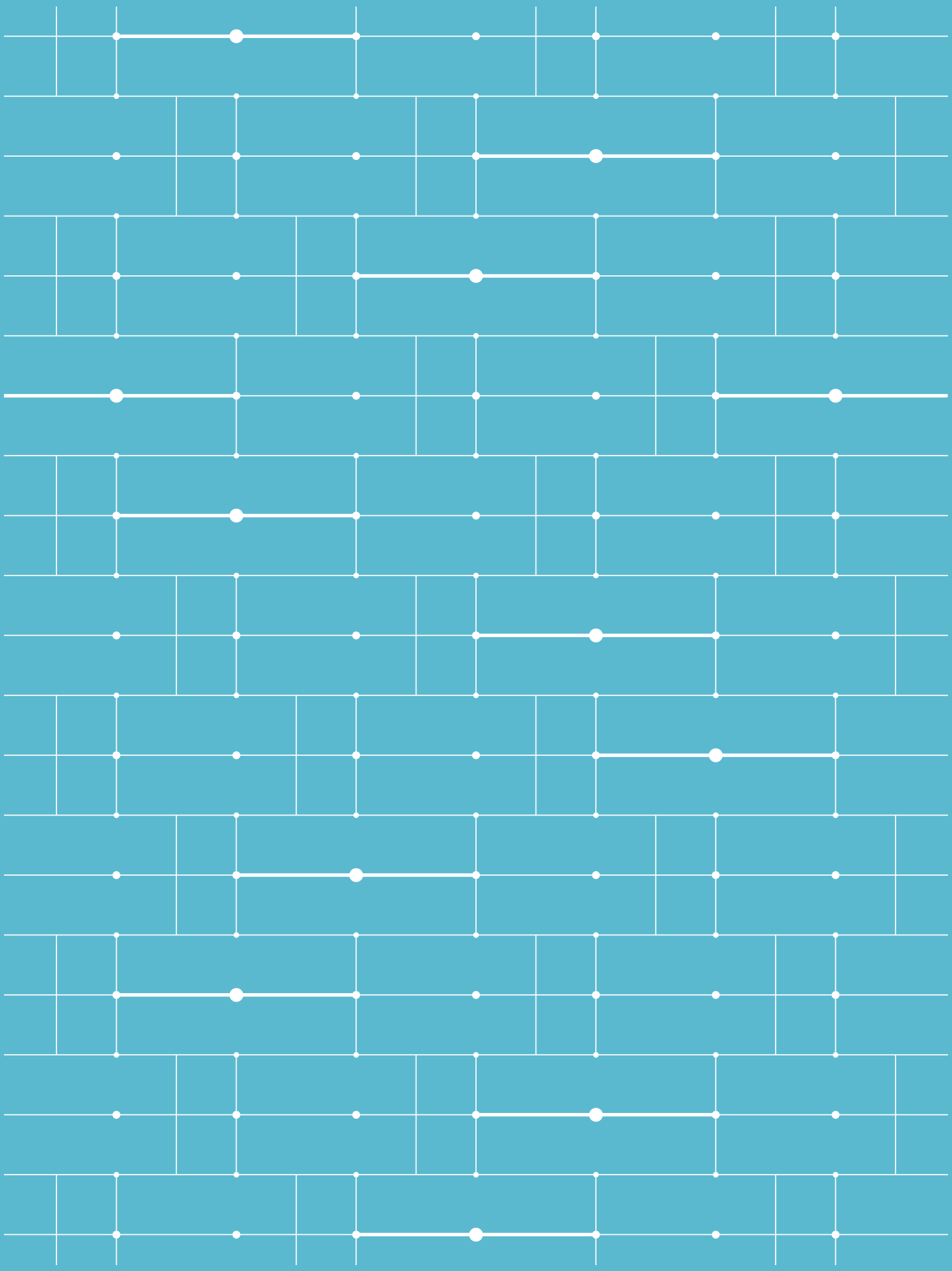
ISWRD
irregular sleep-wake rhythm disorder

CRSWDs such as **advanced sleep-wake phase disorder (ASWPD)**, **delayed sleep-wake phase disorder (DSWPD)**, and **shift work sleep-wake disorder (SWSWD)** are commonly due to misalignment between the internal circadian rhythms and the required timing of school, work, or social activities. For example, approximately 10–40% of shift workers meet the diagnostic criteria for SWSWD, which is characterized by clinically relevant excessive sleepiness and/or sleep disturbance associated with work schedules outside typical daytime hours. Obligations outside of work (e.g., child care) may exacerbate **short sleep duration** in shift working women.[144] Women show higher levels of sleepiness during the biological night and shorter sleep duration during the biological day, which may contribute to SWSWD risk.[10,18]

In general, little research has been done to examine **sex** and **gender** differences in CRSWDs. ASWPD is characterized by earlier circadian rhythms and sleep timing in relation to the desired or required sleep and wake-up times, while DSWPD is characterized by later circadian rhythms and/or sleep timing of the major sleep episode. On average, women show shorter **circadian cycles** and men show longer ones,[145] which may increase the risk for these disorders in a sex-dependent manner. Specifically, men might be expected to be at higher risk for DSWPD compared to women. **Irregular sleep-wake rhythm disorder (ISWRD)** is characterized by a loss in the circadian rhythm of sleep timing and loss of consolidated nighttime sleep with shorter sleep bouts distributed across the 24-hour day. ISWRD is common in patients with Alzheimer's disease, a disease more prevalent in women. However, gender differences in the prevalence of ISWRD are unknown.

Treatment for CRSWDs is focused on stabilizing the **circadian clock** and sleep by maintaining scheduled and appropriately timed light exposure (e.g., increased morning exposure to light and reduced evening exposure to electrical lighting to treat DSWPD).[141-143] Treatment of SWSWD is focused on improving appropriate **sleep duration** and increasing alertness on the work shift and the commute to and from work.

◇ "CRSWDs are commonly due to misalignment between the internal circadian rhythms and the required timing of school, work, or social activities."



SECTION 3

SLEEP AND CIRCADIAN RHYTHMS IN HEALTH AND DISEASE

In general, not getting good **sleep quality** adversely affects quality of life, school and work performance, safety, and increases the risk for numerous chronic health disorders. Changes in sleep impact numerous physiological systems, including those important for weight, cardiopulmonary function, metabolism, learning and memory, mood regulation, and immune and inflammatory functions.[5,146-150] For example, sleep difficulties such as **insomnia** are very prevalent in depression, a condition that disproportionately affects women. Additionally, evidence indicates that sleep problems are not only be a symptom of psychiatric conditions but can also increase risk in the development of them as well.[151]

Changes in sleep and circadian rhythms may also influence age-dependent diseases as well as susceptibility to chronic diseases such as obesity, diabetes, vascular disease, depression, neurological disease, and cancer.[152,153] Individuals with Alzheimer's disease often have sleeping difficulties. Meanwhile, research suggests an important role for poor sleep in the development of the disease. Sleep and circadian disturbances are also associated with increased risk for cardiovascular conditions such as hypertension, coronary heart disease, and stroke.[5,154-158]

Short or long sleep duration, sleep apnea, and disruptions in circadian rhythms (such as disruptions caused by shift work) are associated with increased cancer risk.[159,160] Meanwhile, both cancer and cancer treatment can lead to poor sleep and in turn, poor quality of life. Sleep can also play a role in treatment and prognosis of disease. Poor sleep is associated with a poorer prognosis and response to cancer treatments like chemotherapy.[161]

15

HOW DOES SLEEP AFFECT WOMEN'S MENTAL HEALTH?

- **Insomnia is more common in women than in men, and is a risk factor for developing depression and anxiety disorders.**
- **Sleep disturbance is associated with more severe psychiatric illness and poorer response to treatment.**
- **Women are at greater risk for developing psychiatric conditions, which may relate to their increased risk of having sleep problems.**

Sleep problems and psychiatric disorders have a bidirectional relationship.[162,163] Nearly all patients with depression or mania experience some type of sleep disturbance, and sleep problems are also extremely common in individuals with anxiety disorders, schizophrenia, and substance use disorders.[164-166] It was long believed that the sleep difficulties in those with psychiatric disorders were symptoms of the psychiatric disorders, but several studies now show that treating comorbid **insomnia** can improve the course of treatment for psychiatric illness.[167]

Sleep problems appear to be risk factors for a number of psychiatric conditions and impact the course and treatment of these conditions. For example, those with insomnia are roughly 10 times as likely to have major depression compared to those without sleep problems.[168] Conversely, insomnia is a significant risk factor for developing depression and anxiety disorders.[169,170] People with insomnia have approximately double the risk of developing anxiety disorders than those without sleep problems.[171] In addition, the existence of a sleep disturbance is associated with poorer outcomes and response to treatments.[172]

Women are at greater risk for developing psychiatric conditions, which may in part relate to their increased risk of having sleep difficulties.[129] If they do develop psychiatric problems, women are more likely to have more severe courses of illness. Alterations in sleep that occur premenstrually, during pregnancy, during the postpartum period, and during menopause may contribute to psychiatric diseases or may adversely affect the course of these conditions.[173] For instance, perinatal sleep disturbances may be a contributor to the development of postpartum depression and perimenopausal sleep disturbances are commonly associated with mood disorders.

16

WHAT ARE THE CONSEQUENCES OF SLEEP AND CIRCADIAN DISRUPTION ON CARDIOMETABOLIC HEALTH?

- **Women with sleep apnea, periodic limb movement disorder, restless legs syndrome, shift work sleep-wake disorder, insomnia, or short sleep duration are at increased risk for cardiovascular and metabolic diseases.**
- **Short sleep duration increases the risk of weight gain, obesity, and metabolic problems. This risk can be compounded by circadian disruption.**
- **Women with a long duration of untreated sleep apnea are at increased risk for heart failure and mortality compared to men.**

Sleep and **circadian rhythms** influence multiple physiological pathways involved in cardiovascular and metabolic function including the hypothalamic-pituitary-adrenal axis, the autonomic nervous system, the immune system, pro-inflammatory hormone release, glucose homeostasis, endothelial function, and vascular control. Sleep and circadian disruptions can alter these pathways, resulting in abnormalities in blood pressure, inflammation, lipid and glucose metabolism, and weight gain; and thus are associated with increased risk for developing hypertension, diabetes, coronary heart disease, heart failure, cardiac arrhythmias, and stroke.[5,153,174-176]

While **sleep apnea**, **periodic limb movement disorder**, **restless legs syndrome**, **shift work sleep-wake disorder**, **insomnia**, and **short sleep duration** are each associated with cardiometabolic disease, individuals with more than one sleep disorder may be particularly at risk for developing diabetes or cardiovascular disease. For example, individuals with both short sleep duration and insomnia have higher rates of hypertension and stroke than individuals with only one of these sleep problems.[177] Short sleep duration and shift work (causing disruption of circadian rhythms) can each lead to weight gain and subsequent metabolic problems such as diabetes; the occurrence of both short sleep and circadian disruption together may be a double hit in their impact on metabolism.

Some research suggests that short sleep duration may have a larger negative impact on cardiometabolic health in women compared to men.[178] Although some studies reported that sleep apnea is a stronger cardiovascular disease risk factor in men compared to women, recent studies with long term follow-up of older women indicate the opposite and that over time, sleep apnea leads to an increased risk of developing heart failure and death in that is most evident in women.[179]

17

DOES SLEEP AFFECT COGNITIVE DECLINE IN WOMEN?

- **Sleep apnea and sleep and circadian disruptions are important risk factors for dementia and cognitive decline in older adults.**
- **Recent clinical findings show that treatment of sleep apnea with continuous positive airway pressure delayed the onset of the cognitive dysfunction.**
- **Short sleep duration and poor sleep quality may increase accumulation of toxic brain metabolites such as amyloid-β deposits.**

Sleep has been shown to play an important role in memory consolidation, and poor **sleep quality** and **short sleep duration** can disrupt cognitive functioning in all age groups.[180] Older adults are at particular risk for sleep-related cognitive decline. Although age itself is a risk factor for cognitive impairment, age-related reduction in stage 3 **(slow-wave) sleep**,[90] circadian disruptions, and a higher prevalence of sleep disorders likely contribute to cognitive decline.[181] Sleep disturbances may also preferentially affect cognition in young children, during times of developmental plasticity.[182] Data are not yet available to indicate potential sex differences in vulnerability.

Weaker **circadian rhythms** are associated with poorer cognition (executive functioning) in older women without dementia.[183] **Sleep apnea**, which is common in menopausal women, is another risk factor for the onset and/or exacerbation of cognitive decline. A recent longitudinal 5-year study found that people with sleep apnea showed signs of cognitive decline significantly earlier than people without sleep apnea.[184] Treatment of sleep apnea with **continuous positive airway pressure** delayed the onset of the cognitive dysfunction.[184]

Changes in sleep and circadian rhythms are even more prominent in dementia. Alzheimer's disease (AD) is the most common form of dementia and characterized by the progressive loss of cognitive function, including memory, social skills, and normal emotional reactivity. AD patients often exhibit disturbances in circadian rhythms (e.g., disrupted day–night activity patterns and mistimed sleep), fragmented sleep, and excessive **daytime sleepiness**. Although the exact mechanisms linking sleep-wake regulation and cognitive aging are poorly understood, emerging evidence suggests that short sleep duration and poor sleep quality may increase aggregation and accumulation of amyloid-β (Aβ) deposits in the brain, which is a hallmark of AD. Recent neuroimaging studies in cognitively normal older adults report an association between short sleep duration and an increase in Aβ burden, suggesting

◇ "Poor sleep quality and short sleep duration can disrupt cognitive functioning in all age groups."

that sleep quality and/or duration may impact the development of AD.[185,186]

Circadian rhythm disturbances are common in neurodegenerative disorders such as dementia and have been thought to be a consequence of AD. However, emerging evidence suggests that circadian disruptions may precede the onset of AD symptoms.[187] As the circadian system is a critical regulator of sleep, the possibility exists that circadian disruptions could impact sleep quality and thus the risk for Aβ pathology and AD. Therefore, it is plausible that sleep may represent a modifiable risk factor for cognitive decline in populations at risk for cognitive impairment, such as older adults, patients with traumatic brain injury, and individuals with neurodegenerative disorders. Although there is no cure for dementia or AD, accumulating evidence suggests that therapies targeted towards improving sleep quality and circadian rhythms could make a significant impact on slowing the rate of age-related cognitive decline.[184,188,189]

18

DO SLEEP AND CIRCADIAN DISRUPTIONS AFFECT CANCER RISK AND OUTCOMES IN WOMEN?

- **Short sleep duration can lead to obesity and insulin resistance and, in turn, increase risk of cancer.**
- **In women, shift work increases the risk of breast and endometrial cancers.**
- **Breast cancer treatments, especially endocrine therapy, can significantly impact sleep and quality of life.**

Short sleep duration, **sleep apnea**, and circadian disruptions can directly increase cancer risk or lead to other comorbidities, which in turn can promote cancer incidence or progression.[190-195]

Meanwhile, both cancer and cancer treatment can lead to poor sleep and, consequentially, poor quality of life.[196-199]

Short sleep duration increases the risk of certain cancers primarily by negatively impacting metabolic functions, which can result in obesity and insulin resistance. Obesity triples the risk for endometrial cancer, doubles breast cancer risk, and significantly increases risk for ovarian and colon cancers.[191-194]

Shift-working women are at significantly increased risk for both breast and endometrial cancers.[195] Shift work is often accompanied by sleep deficits and circadian disruptions, which

can lead to inflammation, insulin resistance, and obesity. In addition, shift work suppresses melatonin, which can affect neoplastic processes.[200] Consistent with these reports, genetic removal of **circadian clocks** in animal models has been associated with increased cancer susceptibility.[201]

Additionally, large cohort studies have shown an increase in overall cancer incidence and mortality in association with sleep apnea.[202] It is suggested that the fragmented sleep and low levels of oxygen in the blood from sleep apnea activate angiogenic and inflammatory pathways, which could increase the propensity for tumor growth and metastasis.[202]

Sleep and circadian problems can also impact cancer treatment and prognosis. For example, poor subjective sleep is associated with increased mortality, poorer response to chemotherapy, and more aggressive cancer progression.[196-198] Delivery of anticancer medications that coordinates well with circadian sleep-wake patterns (chronotherapy) can improve the ability of patients to tolerate them by 2- to 10-fold. It also improves efficacy due to inherently poor circadian entrainment of tumors as opposed to healthy tissues.[199]

Sleep complaints, which are a contributor to cancer-related poor quality of life, are common in women with breast cancer, affecting around 70% of women with the disease.[203,204] Some sleep impairment is directly related to the cancer itself, but other factors, such as treatments, play a role as well. For example, **insomnia** is emerging as one of the most troublesome symptoms experienced by women on endocrine therapy (ET) such as tamoxifen.[205] Although psychological distress may be linked to the increased prevalence of insomnia in breast cancer patients being treated with ET, emerging evidence suggests that ET-associated insomnia may actually be related to the occurrence of menopausal climacteric symptoms (e.g., disrupted sleep, hot flashes, mood changes) that this therapy induces.[206-208]

70%

OF WOMEN WITH BREAST CANCER HAVE SLEEP COMPLAINTS—WHICH ARE A CONTRIBUTOR TO CANCER-RELATED POOR QUALITY OF LIFE.[203,204]

19

HOW DOES PAIN AFFECT SLEEP IN WOMEN?

- **Sleep problems are common in people with chronic pain. The relationship between short sleep duration and pain is bidirectional.**
- **Insomnia, which is more common in women, may result from chronic pain as well as contribute to chronic pain.**
- **Interventions aimed at improving sleep quality may be beneficial in mitigating chronic pain syndromes and associated opioid use.**

Over one million women and men suffer from chronic pain. Chronic pain contributes to impaired quality of life, disability, and high healthcare costs. Poor **sleep quality** and pain commonly co-occur, indicating opportunities to address both conditions. Tackling comorbid pain and sleep conditions is particularly important in women. There is a higher frequency of pain conditions (e.g., migraines, fibromyalgia, rheumatoid arthritis) as well as **insomnia** in women compared to men.[209] A national survey reported that almost 25% of women reported that pain or physical discomfort commonly interrupted their sleep.[210-212]

The associations between **short sleep duration** and pain are bidirectional.[213] Pain can disrupt sleep and lead to insomnia. In addition, short sleep duration and sleep disturbances can initiate pain as well as amplify pain by negatively affecting endogenous pain modulation, mood, and pain-related coping mechanisms.[213,214] Sleep disorders such as insomnia, **sleep apnea**, and **restless legs syndrome** can amplify pain by directly disturbing sleep quality and duration through effects on sensory neural pathways, mood, and stress. Patients with sleep apnea, for example, report higher levels of general pain as well as pain syndromes, such as temporomandibular disorder.[215] Fibromyalgia is associated with both pain and disturbed sleep. Thus, addressing sleep quality and treating sleep disorders hold promise for pain management.

Some pain treatments may negatively impact sleep. In particular, opioids can alter respiratory rhythms during sleep and lead to sleep apnea.[216] Addressing sleep quality and pain jointly may lead to improved pain management and decrease opioid toxicity. In addition, patients using opioids should be considered at increased risk for sleep apnea, and potentially may need specific treatment such as an **adaptive servo-ventilation**.

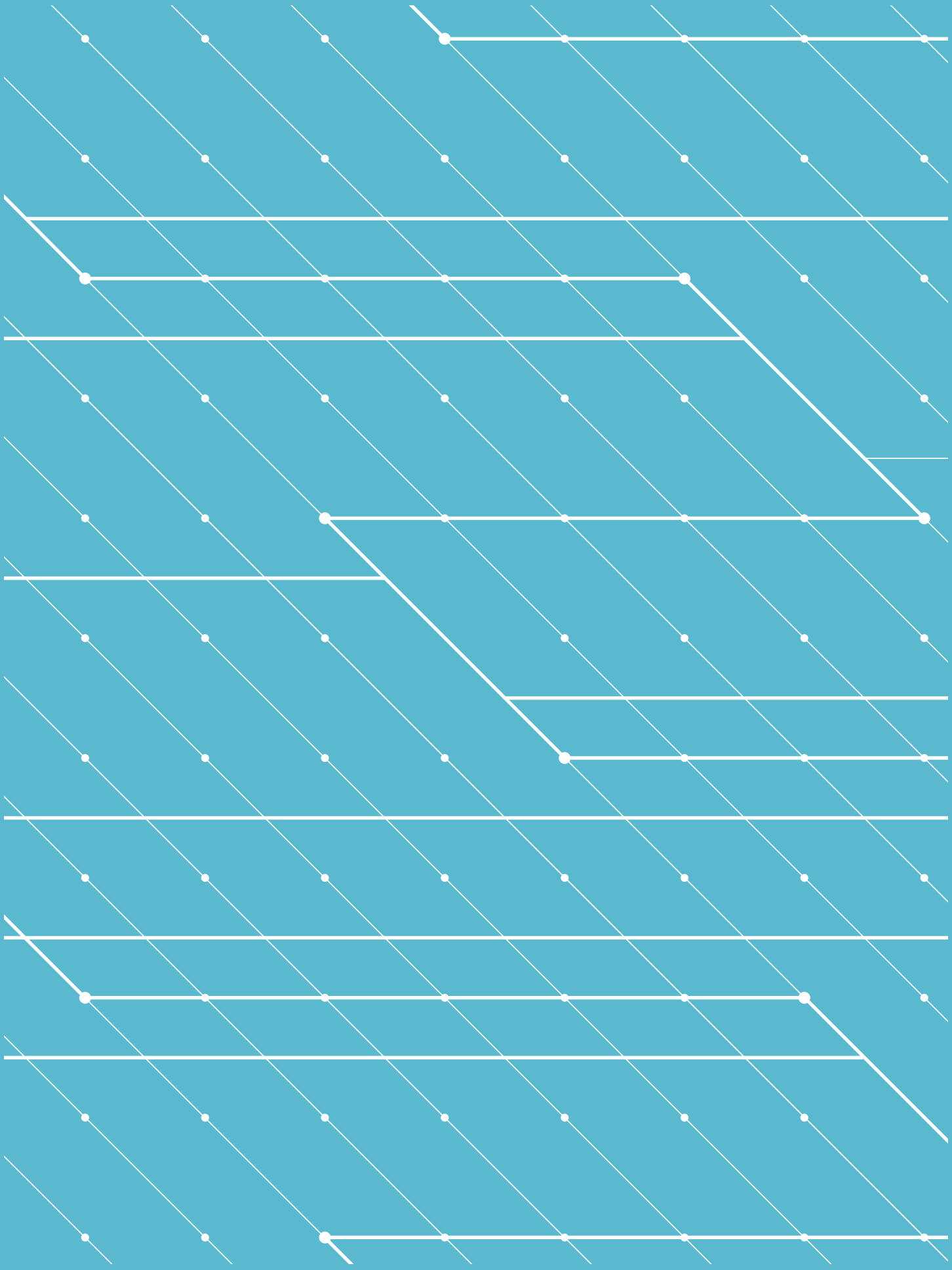
20

DOES URINATING FREQUENTLY AT NIGHT AFFECT WOMEN'S SLEEP?

- **The prevalence of nocturia is higher in women <40 years old than in similarly aged men, and increases across genders with age.**
- **Poor sleep quality and decreased daytime productivity is associated with frequent urination at night.**
- **Nocturia is common in sleep disorders such as sleep apnea and insomnia.**

In a national survey of over 1,400 U.S. women and men, the most common cause of sleep disturbance was **nocturia**, which was reported by over 50% of respondents.[217] Nocturia prevalence rises with increasing age across populations and **gender**.[218] While younger women (age <40 years) have more nocturia episodes than same aged men, the prevalence of nocturia is equally common in women and men in older age groups.[219,220] There are three broad categories of etiologies for significant nocturia: nocturnal polyuria (making too much urine at night), low nocturnal bladder capacity (low bladder volume at night), and mixed nocturia (a combination of both).

Most of the health effects of nocturia occur when sleep is disturbed two or more times in a night. Getting up at night to urinate ≥2 times is directly and indirectly associated with decreased quality of life in many countries and patient populations.[221] For instance, ≥2 nocturia episodes a night is a predictor of poor **sleep quality** and is associated with **daytime sleepiness** and decreased vitality and energy.[217,219,222,223] Sleep fragmentation and cumulative sleep loss are likely factors for the daytime fatigue associated with nocturia.[221] Nocturia also has a significant negative impact on daytime activity and work productivity due to associated sleep loss.[222] In addition, for elderly populations, the risk of falls is much higher with ≥2 nocturia episodes per night leading to increased hospitalization and medical care costs.[224,225] Nocturia is also prevalent in sleep disorders such as **sleep apnea** and **insomnia**. Treatment targeting sleep disorders may help reduce episodes of nocturia in these individuals, although research thus far is limited.[226]



TIPS

BEST PRACTICES FOR SLEEP HEALTH

Effective treatments are available for sleep and circadian rhythm sleep-wake disorders and some are discussed in the sections above. Further, there are good sleep behaviors that can help people with and without sleep problems to promote better sleep and circadian health.

Environmental stimuli can disrupt sleep and can also increase heart activity/blood pressure without full awakenings, which could have implications for heart health. Furthermore, brief arousals may contribute to daytime sleepiness, impaired cognition/mood, and poor metabolic health. Common environmental factors that disturb sleep include light in the bedroom, urban/traffic noises, music or TV in the bedroom/environment, a too hot and humid or too cold sleeping environment, pets, and bedpartners. Bedrooms can be darkened and quieted with blackout shades and drapes, with double/triple-pane windows, and by turning off electronics in the bedroom. Other options to improve one's sleep environment include ear plugs, white noise, moving the bed away from a noisy street, eye masks, and the removal of phones, personal electronic devices, and TVs from the bedroom. However, the ability to still hear sounds in case of an emergency, like a fire alarm, must be considered. The bedroom can be cooled by using AC in the summer and turning the heat down at night in the winter. Bedpartners who like the room warmer can wear more clothes to bed. Pets should sleep outside of the bedroom and untreated sleep problems in bedpartners should be addressed.

Environmental sleep disturbances are especially of concern in low socioeconomic status neighborhoods.[227,228] A possible higher sensitivity to noise in women and more hearing loss in older men may make women more susceptible to environmental sleep disturbances.[229] Job requirements and demands, such as long work hours and shift work, likely increase the impact of environmental sleep disruptors. For example, caffeine is more disruptive to sleep when taken prior to a daytime versus nighttime sleep.[230,231] Both stress and insomnia, which can be mediated by anxiety and depression, are causes of short-term sleep difficulties that are more common in women.[232,233] Women's sleep may also be more impacted than men's sleep by bedpartners and the need to care for others such as a newborn or a sick loved one. Avoiding smoking and alcohol prior to bedtime and stopping intake of caffeine and other stimulants for many hours before bed or completely can help improve sleep as well.

TAKEAWAYS /

- Environmental factors and poor health behaviors contribute to sleep disturbance.
- Removing electronic devices and installing heavy drapes in the bedroom are ways to create a quieter sleep environment.

GLOSSARY

Adaptive servo-ventilation · a machine used to help treat sleep apnea. The machine creates changes in air pressure based on an individual's breathing patterns to keep breathing airways open.

Advanced sleep-wake phase disorder (ASWPD) · a disorder characterized by earlier circadian rhythms and sleep timing in relation to desired or required sleep and wake times.

Apnea · a temporary suspension of breathing. An apnea lasts ≥10 seconds and airflow is reduced by 90% during this time.

Arousal · the sudden change from a deeper to a lighter stage of sleep lasting 3–15 seconds. Individuals are not completely woken out of sleep during these events.

Chronic sleep loss · prolonged periods of not getting enough sleep for optimal functioning and health.

Circadian clock · an "internal body clock" that regulates circadian rhythms.

Circadian cycle · the near 24-hour cycle period that circadian rhythms follow.

Circadian delay · a shift in circadian rhythms causing later sleep onset and wake times. These circadian shifts commonly occur during puberty in response to biological and environmental factors.

Circadian rhythm sleep-wake disorders (CRSWDs) · a group of disorders characterized by a mismatch between the timing of the internal clock that regulates 24-hour rhythms in physiology and behavior and the external environment/social-school-work schedule; or by a disrupted/broken internal clock.

Circadian rhythms · physical, mental, and behavioral changes that follow a near 24-hour cycle that are driven by an "internal body clock." Circadian rhythms help regulate sleeping and feeding times and can be modified by external factors such as light.

Cognitive behavioral therapy for insomnia (CBT-I) · a nonpharmacological treatment for insomnia that aims to change sleep habits and misconceptions about sleep with the aid of a healthcare professional.

Continuous positive airway pressure (CPAP) · a machine used to help treat sleep apnea. The machine provides air pressure to keep breathing airways open.

Daytime sleepiness · feeling drowsy or sleepy with consequences for work, school, driving, or social activities.

Delayed sleep-wake phase disorder (DSWPD) · a disorder characterized by later circadian rhythms and/or sleep timing of the major sleep episode.

EEG · a method used to record the brain's electrical activity. Each stage of sleep has a specific and distinct EEG pattern.

Gender · a person's self-representation as female or male, or how that person is responded to by social institutions based on the individual's gender presentation. Gender is rooted in biology and shaped by environment and experience.[234]

Gestational restless legs syndrome (gRLS) · RLS that develops during pregnancy. See restless legs syndrome entry for full definition.

Homeostatic sleep pressure · increased drive for sleep that becomes greater with more time spent awake.

Hypersomnia · a group of disorders characterized primarily by excessive daytime sleepiness and prolonged nighttime sleep.

Idiopathic hypersomnia · a syndrome of excessive daytime sleepiness that is not associated with the distinctive features of narcolepsy (e.g., cataplexy and disrupted sleep-wake cycles).

Insomnia · a disorder characterized by difficulty falling asleep, difficulty maintaining sleep, and/or frequent early morning awakenings.

Irregular sleep-wake rhythm disorder (ISWRD) · a disorder characterized by a loss in the circadian rhythm of sleep timing and loss of consolidated nighttime sleep, with shorter sleep bouts distributed across the day.

Long sleep duration · more sleep per night than needed. This amount is typically ≥9 hours per night.[235]

Longest sleep period · the longest stretch of sleep in a 24-hour cycle.

Multiple sleep latency test (MSLT) · a diagnostic tool that measures the time it takes an individual to transition from wakefulness to sleep multiple times across the day. It is typically used to evaluate excessive daytime sleepiness.

Narcolepsy · a disorder characterized by excessive daytime sleepiness, cataplexy, and disrupted sleep-wake cycles due to involuntary REM sleep during wakefulness.

Night waking · being roused awake during nighttime sleep.

Nocturia · awakening at night one or more times to void.

Nocturnal eating syndrome (NES) · an eating disorder caused by a delay in the circadian rhythm of food intake. Food consumption is low during the first half of the day and significantly increases in the second half. Sleep is disrupted to consume food and individuals are fully awake during this time.

Non-REM parasomnias · a group of disorders characterized by abnormal behaviors that occur during stage 3 of sleep. Examples include sleep related eating disorder, sleep walking, and night terrors.

Non-REM sleep · sleep stages 1–3. Each stage has distinct EEG characteristics.

Parasomnias · a group of disorders characterized by abnormal behaviors during sleep that occur due to the inappropriate activation of cognitive processes or physiological systems.

Periodic limb movement disorder · a disorder characterized by the involuntary movement of limbs that recurs every 5 to 90 seconds, which disturbs sleep.

Polysomnography (PSG) · a sleep study used to diagnose sleep disorders by measuring EEG, eye movements, oxygen levels in the blood, heart rate, breathing, and movement.

REM parasomnias · a group of disorders characterized by abnormal behaviors that occur during REM sleep. Examples include REM sleep behavior disorder and nightmares.

REM sleep · the stage of sleep characterized by rapid eye movements, dreaming, muscle paralysis, and rapid breathing and heart rate. Adults typically spend 2025% of total sleep time in REM sleep.

REM sleep behavior disorder (RBD) · a disorder in which individuals act out their dreams during REM sleep due to the loss of muscle atonia.

Restless legs syndrome (RLS) or Willis Ekbom disease (WED) · a neurological disorder defined by the presence of four cardinal clinical features: urge to move legs associated with uncomfortable sensations, temporary improvement of urge/sensations with movement, symptoms occur prominently in the evening or at night, urge/sensations occur while sedentary and get worse the longer one is sedentary.

Sex · the classification of living things, generally as female or male, according to their reproductive organs and functions assigned by chromosomal complement.[234]

Shift work sleep-wake disorder (SWSWD) · a disorder characterized by clinically relevant excessive sleepiness and/or sleep disturbance associated with work schedules outside typical daytime hours.

Short sleep duration · less sleep per night than needed. This amount is typically ≤6 hours per night.[236]

Sleep and circadian health · a practice of sleep-wakefulness that promotes physical and mental well-being.[237]

Sleep apnea · a disorder characterized by repetitive pauses in breathing during sleep, which leads to interrupted sleep.

Sleep duration · total sleep time.

Sleep maintenance · staying asleep during the night.

Sleep onset latency · the length of time to transition from wakefulness to sleep.

Sleep quality · how well an individual sleeps. It is often measured by a number of nighttime and daytime factors including ease of falling asleep, number of night wakings, total sleep time, restlessness during sleep, tiredness upon waking up, motivation to get up in the morning, and alertness after sleep.[238]

Sleep related eating disorder (SRED) · a disorder characterized by repeated episodes of eating during sleep. There is complete or partial loss of awareness and eating of unusual food combinations and even toxic substances.

Sleep-wake cycle · the 24-hour pattern of alternating nocturnal sleep (approximately 8 hours) and daytime wakefulness (approximately 16 hours).

Slow wave sleep · occurs during stage 3 of sleep. Slow wave sleep is often called deep sleep. EEG activity during slow wave sleep shows synchronized, slow waves.

Willis Ekbom disease (WED) · see restless legs syndrome.

REFERENCES

1. Krishnan V, Collop NA. Gender differences in sleep disorders. Current Opinion in Pulmonary Medicine. 2006; 12 (6): 383-389.
2. Mong JA, Cusmano DM. Sex differences in sleep: impact of biological sex and sex steroids. Philosophical Transactions of the Royal Society of London Series B, Biological Sciences. 2016; 371 (1688): 20150110.
3. Pavlova M, Sheikh LS. Sleep in women. Seminars in Neurology. 2011; 31 (4): 397-403.
4. Sack R, Auckley D, Auger R, Carskadon M, Wright K, Vitiello M, Zhdanova IV. Circadian rhythm sleep disorders: part I, basic principles, shift work and jet lag disorders. Sleep. 2007; 30 (11): 1460-1483.
5. Depner CM, Stothard ER, Wright Jr KP. Metabolic consequences of sleep and circadian disorders. Current Diabetes Reports. 2014; 14 (7): 1-9.
6. Chong Y, Fryer CD, Gu Q. Prescription sleep aid use among adults: United States, 2005-2010. NCHS Data Brief. 2013; (127): 1-8.
7. Dijk DJ, Duffy JF, Riel E, Shanahan TL, Czeisler CA. Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. The Journal of Physiology. 1999; 516 (2): 611-627.
8. Duffy JF, Cain SW, Chang A-M, et al. Sex difference in the near-24-hour intrinsic period of the human circadian timing system. Proceedings of the National Academy of Sciences. 2011; 108 (Supplement 3): 15602-15608.
9. Roenneberg T, Kuehnle T, Pramstaller PP, et al. A marker for the end of adolescence. Current Biology. 2004; 14 (24): R1038-R1039.
10. Santhi N, Lazar AS, McCabe PJ, Lo JC, Groeger JA, Dijk DJ. Sex differences in the circadian regulation of sleep and waking cognition in humans. Proceedings of the National Academy of Sciences. 2016; 113 (19): E2730-E2739.
11. Carskadon MA. Sleep in adolescents: the perfect storm. Pediatric Clinics of North America. 2011; 58 (3): 637-647.
12. Owens J, Adolescent Sleep Working Group, and Committee on Adolescence. Insufficient sleep in adolescents and young adults: an update on causes and consequences. Pediatrics. 2014; 134 (3): e921-e932.
13. Tsai S-Y, Lee P-L, Lin J-W, Lee C-N. Cross-sectional and longitudinal associations between sleep and health-related quality of life in pregnant women: a prospective observational study. International Journal of Nursing Studies. 2016; 56: 45-53.
14. IOM (Institute of Medicine) and NRC (National Research Council). *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, DC: The National Academies Press; 2009.
15. Sharkey K, Boni G, Quattrucci J, Blatch S, Carr S. Women with postpartum weight retention have delayed wake times and decreased sleep efficiency during the perinatal period: a brief report. Sleep Health. 2016; 2 (3): 225-228.
16. Joffe H, Massler A, Sharkey KM. Evaluation and management of sleep disturbance during the menopause transition. Seminars in Reproductive Medicine. 2010; 28 (5): 404-421.
17. Zdanys KF, Steffens DC. Sleep disturbances in the elderly. Psychiatric Clinics of North America. 2015; 38 (4): 723-741.
18. Boivin DB, Shechter A, Boudreau P, Begum EA, Ying-Kin NMKN. Diurnal and circadian variation of sleep and alertness in men vs. naturally cycling women. Proceedings of the National Academy of Sciences. 2016; 113 (39): 10980-10985.
19. Mong JA, Baker FC, Mahoney MM, et al. Sleep, rhythms, and the endocrine brain: influence of sex and gonadal hormones. The Journal of Neuroscience. 2011; 31 (45): 16107-16116.
20. Baker FC, Driver HS. Circadian rhythms, sleep, and the menstrual cycle. Sleep Medicine. 2007; 8 (6): 613-622.
21. de Zambotti M, Willoughby AR, Sassoon SA, Colrain IM, Baker FC. Menstrual cycle-related variation in physiological sleep in women in the early menopausal transition. The Journal of Clinical Endocrinology & Metabolism. 2015; 100 (8): 2918-2926.
22. Bixler EO, Vgontzas AN, Lin H-M, et al. Prevalence of sleep-disordered breathing in women: effects of gender. American Journal of Respiratory and Critical Care Medicine. 2001; 163 (3): 608-613.
23. Tasali E, Van Cauter E, Ehrmann DA. Polycystic ovary syndrome and obstructive sleep apnea. Sleep Medicine Clinics. 2008; 3 (1): 37-46.
24. Tasali E, Chapotot F, Leproult R, Whitmore H, Ehrmann DA. Treatment of obstructive sleep apnea improves cardiometabolic function in young obese women with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 2010; 96 (2): 365-374.
25. Boyar R, Finkelstein J, Roffwarg H, Kapen S, Weitzman E, Hellman L. Synchronization of augmented luteinizing hormone secretion with sleep during puberty. New England Journal of Medicine. 1972; 287 (12): 582-586.
26. Hall JE, Sullivan JP, Richardson GS. Brief wake episodes modulate sleep-inhibited luteinizing hormone secretion in the early follicular phase. The Journal of Clinical Endocrinology & Metabolism. 2005; 90 (4): 2050-2055.
27. Shaw N, Butler J, McKinney S, Nelson S, Ellenbogen J, Hall J. Insights into puberty: the relationship between sleep stages and pulsatile LH secretion. The Journal of Clinical Endocrinology & Metabolism. 2012; 97 (11): E2055-E2062.
28. Simonneaux V, Bahougne T. A multi-oscillatory circadian system times female reproduction. Frontiers in Endocrinology. 2015; 6: 157.
29. Blair PS, Humphreys JS, Gringras P, et al. Childhood sleep duration and associated demographic characteristics in an English cohort. Sleep. 2012; 35 (3): 353-360.

30. Mindell JA, Meltzer LJ, Carskadon MA, Chervin RD. Developmental aspects of sleep hygiene: findings from the 2004 National Sleep Foundation sleep in america poll. Sleep Medicine. 2009; 10 (7): 771-779.
31. Plancoulaine S, Lioret S, Regnault N, Heude B, Charles MA. Gender-specific factors associated with shorter sleep duration at age 3 years. Journal of Sleep Research. 2015; 24 (6): 610-620.
32. Beebe DW. Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescents. Pediatric Clinics of North America. 2011; 58 (3): 649-665.
33. Gordon J, King N, Gullone E, Muris P, Ollendick TH. Nighttime fears of children and adolescents: frequency, content, severity, harm expectations, disclosure, and coping behaviours. Behaviour Research and Therapy. 2007; 45 (10): 2464-2472.
34. Erdogan A, Akkurt H, Boettjer NK, Yurtseven E, Can G, Kiran S. Prevalence and behavioural correlates of enuresis in young children. Journal of Paediatrics and Child Health. 2008; 44 (5): 297-301.
35. Corkum P, Davidson FD, Tan-MacNeill K, Weiss SK. Sleep in children with neurodevelopmental disorders. Sleep Medicine Clinics. 2014; 9 (2): 149-168.
36. Gregory AM, Sadeh A. Annual Research Review: Sleep problems in childhood psychiatric disorders–a review of the latest science. Journal of Child Psychology and Psychiatry. 2016; 57 (3): 296-317.
37. Willis TA, Gregory AM. Anxiety disorders and sleep in children and adolescents. Sleep Medicine Clinics. 2015; 10 (2): 125-131.
38. Calhoun SL, Fernandez-Mendoza J, Vgontzas AN, Liao D, Bixler EO. Prevalence of insomnia symptoms in a general population sample of young children and preadolescents: gender effects. Sleep Medicine. 2014; 15 (1): 91-95.
39. Zhang J, Chan NY, Lam SP, et al. Emergence of sex differences in insomnia symptoms in adolescents: a large-scale school-based study. Sleep. 2016; 39 (8): 1563-1570.
40. Owens J, Au R, Carskadon M, et al. Insufficient sleep in adolescents and young adults: an update on causes and consequences. Pediatrics. 2014; 134 (3): e921-e932.
41. Dohnt H, Gradisar M, Short MA. Insomnia and its symptoms in adolescents: comparing DSM-IV and ICSD-II diagnostic criteria. Journal of Clinical Sleep Medicine. 2012; 8 (3): 295-299.
42. Clarke G, McGlinchey EL, Hein K, et al. Cognitive-behavioral treatment of insomnia and depression in adolescents: a pilot randomized trial. Behaviour Research and Therapy. 2015; 69: 111-118.
43. Mindell JA, Owens JA. *A Clinical Guide to Pediatric Sleep: Diagnosis and Management of Sleep Problems.* Lippincott Williams & Wilkins; 2015.
44. Danielsson K, Markström A, Broman J-E, von Knorring L, Jansson-Fröjmark M. Delayed sleep phase disorder in a Swedish cohort of adolescents and young adults: prevalence and associated factors. Chronobiology International. 2016; 33 (10): 1331-1339.
45. Lovato N, Gradisar M, Short M, Dohnt H, Micic G. Delayed sleep phase disorder in an Australian school-based sample of adolescents. Journal of Clinical Sleep Medicine. 2013; 9 (9): 939-944.
46. Sivertsen B, Pallesen S, Stormark KM, Bøe T, Lundervold AJ, Hysing M. Delayed sleep phase syndrome in adolescents: prevalence and correlates in a large population based study. BMC Public Health. 2013; 13 (1): 1.
47. Spilsbury JC, Storfer-Isser A, Rosen CL, Redline S. Remission and incidence of obstructive sleep apnea from middle childhood to late adolescence. Sleep. 2015; 38 (1): 23.
48. Thoma ME, McLain AC, Louis JF, et al. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. Fertility and Sterility. 2013; 99 (5): 1324-1331.e1.
49. Bisanti L, Olsen J, Basso O, Thonneau P, Karmaus W. Shift work and subfecundity: a European multicenter study. Journal of Occupational and Environmental Medicine. 1996; 38 (4): 352-358.
50. Labyak S, Lava S, Turek F, Zee P. Effects of shiftwork on sleep and menstrual function in nurses. Health Care for Women International. 2002; 23 (6-7): 703-714.
51. Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance 1. The Journal of Clinical Endocrinology & Metabolism. 2001; 86 (2): 517-520.
52. Vgontzas AN, Bixler EO, Lin H-M, et al. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. The Journal of Clinical Endocrinology & Metabolism. 2001; 86 (8): 3787-3794.
53. Kloss JD, Perlis ML, Zamzow JA, Culnan EJ, Gracia CR. Sleep, sleep disturbance, and fertility in women. Sleep Medicine Reviews. 2015; 22: 78-87.
54. Tamura H, Nakamura Y, Korkmaz A, et al. Melatonin and the ovary: physiological and pathophysiological implications. Fertility and Sterility. 2009; 92 (1): 328-343.
55. Eryilmaz OG, Devran A, Sarikaya E, Aksakal FN, Mollamahmutoğlu L, Cicek N. Melatonin improves the oocyte and the embryo in IVF patients with sleep disturbances, but does not improve the sleeping problems. Journal of Assisted Reproduction and Genetics. 2011; 28 (9): 815-820.
56. Okun ML, Buysse DJ, Hall MH. Identifying insomnia in early pregnancy: validation of the insomnia symptoms questionnaire (ISQ) in pregnant women. Journal of Clinical Sleep Medicine. 2015; 11 (6): 645-654.

57. Balserak BI, Lee K. Sleep and sleep disorders associated with pregnancy. In: Kryger MH, Roth T, Dement WC, editors. *Principles and Practice of Sleep Medicine*. 6th ed. Saunders/Elsevier; 2011; Chapter 156: 1525-1539.
58. Oyieng'o DO, Kirwa K, Tong I, Martin S, Rojas-suarez JA, Bourjeily G. Restless legs symptoms and pregnancy and neonatal outcomes. Clinical Therapeutics. 2016; 38 (2): 256-264.
59. Picchietti DL, Hensley JG, Bainbridge JL, et al. Consensus clinical practice guidelines for the diagnosis and treatment of restless legs syndrome/Willis-Ekbom disease during pregnancy and lactation. Sleep Medicine Reviews. 2015; 22: 64-77.
60. Dorheim SK, Bjorvatn B, Eberhard-Gran M. Insomnia and depressive symptoms in late pregnancy: a population-based study. Behavioral Sleep Medicine. 2012; 10 (3): 152-166.
61. Mindell JA, Jacobson BJ. Sleep disturbances during pregnancy. Journal of Obstetric, Gynecologic, & Neonatal Nursing. 2000; 29 (6): 590-597.
62. Lee KA, Gay CL. Sleep in late pregnancy predicts length of labor and type of delivery. American Journal of Obstetrics and Gynecology. 2004; 191 (6): 2041-2046.
63. Tomfohr-Madsen LM, Clayborne ZM, Rouleau CR, Campbell TS. Sleeping for two: an open-pilot study of cognitive behavioral therapy for insomnia in pregnancy. Behavioral Sleep Medicine. 2016 Apr 28: 1-17.
64. Mott SL, Schiller CE, Richards JG, O'Hara MW, Stuart S. Depression and anxiety among postpartum and adoptive mothers. Archives of Women's Mental Health. 2011; 14 (4): 335-343.
65. Doering JJ. The physical and social environment of sleep in socioeconomically disadvantaged postpartum women. Journal of Obstetric, Gynecologic, & Neonatal Nursing. 2013; 42 (1): E33-E43.
66. Montgomery-Downs HE, Insana SP, Clegg-Kraynok MM, Mancini LM. Normative longitudinal maternal sleep: the first 4 postpartum months. American Journal of Obstetrics and Gynecology. 2010; 203 (5): 465.e1-465.e7.
67. Sharkey KM, Iko IN, Machan JT, Thompson-Westra J, Pearlstein TB. Infant sleep and feeding patterns are associated with maternal sleep, stress, and depressed mood in women with a history of major depressive disorder (MDD). Archives of Women's Mental Health. 2016; 19 (2): 209-218.
68. Zambrano DN, Mindell JA, Reyes NR, Hart CN, Herring SJ. "It's not all about my baby's sleep": a qualitative study of factors influencing low-income african american mothers' sleep quality. Behavioral Sleep Medicine. 2016; 14 (5): 489-500.
69. Sadeh A, Mindell JA, Luedtke K, Wiegand B. Sleep and sleep ecology in the first 3 years: a web-based study. Journal of Sleep Research. 2009; 18 (1): 60-73.
70. Moore M, Mindell JA. The impact of behavioral interventions for sleep problems on secondary outcomes in young children and their families. In: Wolfson A, Montgomery-Downs, H, editors. *The Oxford Handbook of Infant, Child, and Adolescent Sleep and Behavior.* Oxford University Press; 2013; Chapter 37: 547-558.
71. Lee KA, Zaffke ME, McEnany G. Parity and sleep patterns during and after pregnancy. Obstetrics & Gynecology. 2000; 95 (1): 14-18.
72. Troxel WM, Buysse DJ, Hall M, Matthews KA. Marital happiness and sleep disturbances in a multi-ethnic sample of middle-aged women. Behavioral Sleep Medicine. 2009; 7 (1): 2-19.
73. Sharkey KM, Pearlstein TB, Carskadon MA. Circadian phase shifts and mood across the perinatal period in women with a history of major depressive disorder: a preliminary communication. Journal of Affective Disorders. 2013; 150 (3): 1103-1108.
74. Insana SP, Garfield CF, Montgomery-Downs HE. A mixed-method examination of maternal and paternal nocturnal caregiving. Journal of Pediatric Health Care. 2014; 28 (4): 313-321.
75. Gay CL, Lee KA, Lee S-Y. Sleep patterns and fatigue in new mothers and fathers. Biological Research for Nursing. 2004; 5 (4): 311-318.
76. Tikotzky L, Sadeh A, Glickman-Gavrieli T. Infant sleep and paternal involvement in infant caregiving during the first 6 months of life. Journal of Pediatric Psychology. 2011; 36 (1): 36-46.
77. Sharma V, Mazmanian D. Sleep loss and postpartum psychosis. Bipolar Disorders. 2003; 5 (2): 98-105.
78. Swanson LM, Flynn H, Adams-Mundy JD, Armitage R, Arnedt JT. An open pilot of cognitive-behavioral therapy for insomnia in women with postpartum depression. Behavioral Sleep Medicine. 2013; 11 (4): 297-307.
79. de Zambotti M, Colrain IM, Baker FC. Interaction between reproductive hormones and physiological sleep in women. The Journal of Clinical Endocrinology & Metabolism. 2015; 100 (4): 1426-1433.
80. Kravitz H, Zhao X, Bromberger J, et al. Sleep disturbance during the menopausal transition in a multi-ethnic community sample of women. Sleep. 2008; 31 (7): 979-990.
81. Kravitz HM, Janssen I, Santoro N, et al. Relationship of day-to-day reproductive hormone levels to sleep in midlife women. Archives of Internal Medicine. 2005; 165 (20): 2370-2376.
82. Nowakowski S, Meliska CJ, Martinez LF, Parry BL. Sleep and menopause. Current Neurology and Neuroscience Reports. 2009; 9 (2): 165-172.
83. Polo-Kantola P. Sleep problems in midlife and beyond. Maturitas. 2011; 68 (3): 224-232.
84. Baker FC, Willoughby AR, Sassoon SA, Colrain IM, de Zambotti M. Insomnia in women approaching menopause: beyond perception. Psychoneuroendocrinology. 2015; 60: 96-104.
85. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Internal Medicine. 2015; 175 (4): 531-539.

86. Attarian H, Hachul H, Guttuso T, Phillips B. Treatment of chronic insomnia disorder in menopause: evaluation of literature. Menopause. 2015; 22 (6): 674-684.
87. Kravitz HM, Ganz PA, Bromberger J, Powell LH, Sutton-Tyrrell K, Meyer PM. Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. Menopause. 2003; 10 (1): 19-28.
88. Fung CH, Vitiello MV, Alessi CA, Kuchel GA. Report and research agenda of the American Geriatrics Society and National Institute on Aging bedside- to- bench conference on sleep, circadian rhythms, and aging: new avenues for improving brain health, physical health, and functioning. Journal of the American Geriatrics Society. 2016; 64 (12): e238-e247.
89. Mattis J, Sehgal A. Circadian rhythms, sleep, and disorders of aging. Trends in Endocrinology & Metabolism. 2016; 27 (4): 192-203.
90. 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: 1255-1274.
91. Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. Sleep. 1995; 18 (6): 425-432.
92. Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation sleep in america survey. Journal of Psychosomatic Research. 2004; 56 (5): 497-502.
93. Zhang B, Wing Y. Sex differences in insomnia: a meta-analysis. Sleep. 2006; 29 (1): 85.
94. Abbott SM, Attarian H, Zee PC. Sleep disorders in perinatal women. Best Practice & Research Clinical Obstetrics & Gynaecology. 2014; 28 (1): 159-168.
95. Dzaja A, Arber S, Hislop J, et al. Women's sleep in health and disease. Journal of Psychiatric Research. 2005; 39 (1): 55-76.
96. Mindell JA, Cook RA, Nikolovski J. Sleep patterns and sleep disturbances across pregnancy. Sleep Medicine. 2015; 16 (4): 483-488.
97. Krystal AD. Insomnia in women. Clinical Cornerstone. 2003; 5 (3): 41-50.
98. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: a synthesis of the literature. Sleep Medicine Reviews. 2012; 16 (4): 283-295.
99. Mirer AG, Young T, Palta M, Benca RM, Rasmuson A, Peppard PE. Sleep-disordered breathing and the menopausal transition among participants in the sleep in midlife women study. Menopause. 2017; 24 (2): 157-162.
100. U.S. Food and Drug Administration. Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). FDA Drug Safety Communication. 2013 Jan 10.
101. Won C, Guilleminault C. Gender differences in sleep disordered breathing: implications for therapy. Expert Review of Respiratory Medicine. 2015; 9 (2): 221-231.
102. Pedroso JL, Bor-Seng-Shu E, Felicio AC, et al. Severity of restless legs syndrome is inversely correlated with echogenicity of the substantia nigra in different neurodegenerative movement disorders. A preliminary observation. Journal of the Neurological Sciences. 2012; 319 (1): 59-62.
103. Hübner A, Krafft A, Gadient S, Werth E, Zimmermann R, Bassetti CL. Characteristics and determinants of restless legs syndrome in pregnancy: a prospective study. Neurology. 2013; 80 (8): 738-742.
104. Cesnik E, Casetta I, Turri M, et al. Transient RLS during pregnancy is a risk factor for the chronic idiopathic form. Neurology. 2010; 75 (23): 2117-2120.
105. Balendran J, Champion D, Jaaniste T, Welsh A. A common sleep disorder in pregnancy: restless legs syndrome and its predictors. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2011; 51 (3): 262-264.
106. Meharaban Z, Yahya S, Sadegniiat K. Restless legs syndrome during pregnancy and preterm birth in women referred to health centers of Ardabil. Iranian Red Crescent Medical Journal. 2015; 17 (12): e24438.
107. Lazzarini A, Walters AS, Hickey K, et al. Studies of penetrance and anticipation in five autosomal-dominant restless legs syndrome pedigrees. Movement Disorders. 1999; 14 (1): 111-116.
108. Dostal M, Weber- Schoendorfer C, Sobesky J, Schaefer C. Pregnancy outcome following use of levodopa, pramipexole, ropinirole, and rotigotine for restless legs syndrome during pregnancy: a case series. European Journal of Neurology. 2013; 20 (9): 1241-1246.
109. Bianchi M, Goparaju B, Moro M. Sleep apnea in patients reporting insomnia or restless legs symptoms. Acta Neurologica Scandinavica. 2016; 133 (1): 61-67.
110. Gupta R, Lahan V, Goel D. Restless legs syndrome: a common disorder, but rarely diagnosed and barely treated-an Indian experience. Sleep Medicine. 2012; 13 (7): 838-841.
111. Nineb A, Rosso C, Dumurgier J, Nordine T, Lefaucheur JP, Creange A. Restless legs syndrome is frequently overlooked in patients being evaluated for polyneuropathies. European Journal of Neurology. 2007; 14 (7): 788-792.
112. Schenck CH, Hurwitz TD, Bundlie SR, Mahowald MW. Sleep-related eating disorders: polysomnographic correlates of a heterogeneous syndrome distinct from daytime eating disorders. Sleep. 1991; 14 (5): 419-431.
113. Chiaro G, Caletti MT, Provini F. Treatment of sleep-related eating disorder. Current Treatment Options in Neurology. 2015; 17 (8): 1-11.
114. Hoque R, Chesson Jr AL. Zolpidem-induced sleepwalking, sleep related eating disorder, and sleep-driving: fluorine-18-flourodeoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem. Journal of Clinical Sleep Medicine. 2009; 5 (5): 471.

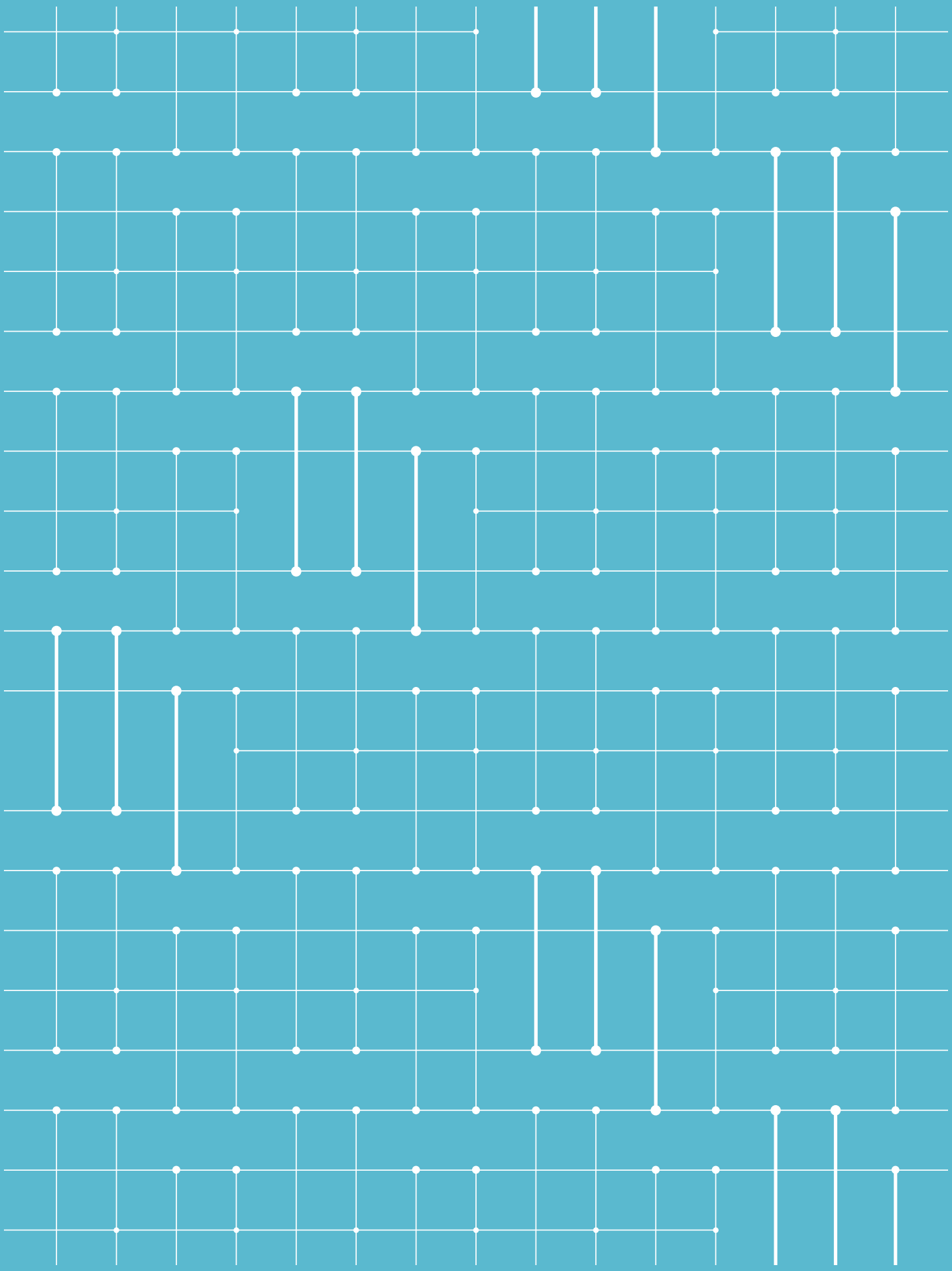
115. Inoue Y. Sleep- related eating disorder and its associated conditions. Psychiatry and Clinical Neurosciences. 2015; 69 (6): 309-320.
116. Bjørnarå KA, Dietrichs E, Toft M. REM sleep behavior disorder in Parkinson's disease–is there a gender difference? Parkinsonism & Related Disorders. 2013; 19 (1): 120-122.
117. Jackson CL, Redline S, Emmons KM. Sleep as a potential fundamental contributor to disparities in cardiovascular health. Annual Review of Public Health. 2015; 36: 417-440.
118. Redline S, Kump K, Tishler PV, Browner I, Ferrette V. Gender differences in sleep disordered breathing in a community-based sample. American Journal of Respiratory and Critical Care Medicine. 1994; 149 (3): 722-726.
119. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep. 1997; 20 (9): 705-706.
120. Kump K, Whalen C, Tishler PV, et al. Assessment of the validity and utility of a sleep-symptom questionnaire. American Journal of Respiratory and Critical Care Medicine. 1994; 150 (3): 735-741.
121. Valipour A, Lothaller H, Rauscher H, Zwick H, Burghuber OC, Lavie P. Gender-related differences in symptoms of patients with suspected breathing disorders in sleep: a clinical population study using the sleep disorders questionnaire. Sleep. 2007; 30 (3): 312.
122. Louis J, Auckley D, Miladinovic B, et al. Perinatal outcomes associated with obstructive sleep apnea in obese pregnant women. Obstetrics & Gynecology. 2012; 120 (5): 1085-1092.
123. Louis JM, Mogos MF, Salemi JL, Redline S, Salihu HM. Obstructive sleep apnea and severe maternal-infant morbidity/mortality in the United States, 1998-2009. Sleep. 2014; 37 (5): 843.
124. Lockhart EM, Abdallah AB, Tuuli MG, Leighton BL. Obstructive sleep apnea in pregnancy: assessment of current screening tools. Obstetrics & Gynecology. 2015; 126 (1): 93-102.
125. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. 5th ed. American Psychiatric Publishing, Inc.; 2013.
126. American Academy of Sleep Medicine. *International Classification of Sleep Disorders—Third Edition (ICSD-3).* AASM Resource Library. 2014.
127. Morin CM, Drake CL, Harvey AG, et al. Insomnia disorder. Nature Reviews Disease Primers. 2015; 1: 15026.
128. Johnson EO, Roth T, Schultz L, Breslau N. Epidemiology of DSM-IV insomnia in adolescence: lifetime prevalence, chronicity, and an emergent gender difference. Pediatrics. 2006; 117 (2): e247-e256.
129. Krystal AD. Depression and insomnia in women. Clinical Cornerstone. 2004; 6 (1): S19-S28.
130. Lami MJ, Martínez MP, Sánchez AI, et al. Gender differences in patients with fibromyalgia undergoing cognitive-behavioral therapy for insomnia: preliminary data. Pain Practice. 2016; 16 (2): E23-E34.
131. Greenblatt DJ, Harmatz JS, von Moltke LL, et al. Comparative kinetics and response to the benzodiazepine agonists triazolam and zolpidem: evaluation of sex-dependent differences. Journal of Pharmacology and Experimental Therapeutics. 2000; 293 (2): 435-443.
132. Krystal A, Attarian H. Sleep medications and women: a review of issues to consider for optimizing the care of women with sleep disorders. Current Sleep Medicine Reports. 2016; 2 (4): 218-222.
133. Peer CJ, Strope JD, Beedie S, et al. Alcohol and aldehyde dehydrogenases contribute to sex-related differences in clearance of zolpidem in rats. Frontiers in Pharmacology. 2016; 7.
134. Verster JC, Roth T. Gender differences in highway driving performance after administration of sleep medication: a review of the literature. Traffic Injury Prevention. 2012; 13 (3): 286-292.
135. Roehrs T, Kapke A, Roth T, Breslau N. Sex differences in the polysomnographic sleep of young adults: a community-based study. Sleep Medicine. 2006; 7 (1): 49-53.
136. Won C, Mahmoudi M, Qin L, Purvis T, Mathur A, Mohsenin V. The impact of gender on timeliness of narcolepsy diagnosis. Journal of Clinical Sleep Medicine. 2014; 10 (1): 89-95.
137. Riehl J, Nishino S, Cederberg R, Dement WC, Mignot E. Development of cataplexy in genetically narcoleptic Dobermans. Experimental Neurology. 1998; 152 (2): 292-302.
138. Maurovich-Horvat E, Kemlink D, Högl B, et al. Narcolepsy and pregnancy: a retrospective European evaluation of 249 pregnancies. Journal of Sleep Research. 2013; 22 (5): 496-512.
139. Thorpy M, Zhao CG, Dauvilliers Y. Management of narcolepsy during pregnancy. Sleep Medicine. 2013; 14 (4): 367-376.
140. Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. Sleep. 2007; 30 (10): 1274.
141. Abbott SM, Reid KJ, Zee PC. Circadian rhythm sleep-wake disorders. Psychiatric Clinics of North America. 2015; 38 (4): 805-823.
142. Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). An update for 2015: an American Academy of Sleep Medicine clinical practice guideline. Journal of Clinical Sleep Medicine. 2015; 11 (10): 1199-1236.

143. Sack R, Auckley D, Auger R, Carskadon M, Wright Jr K, Vitiello M, Zhdanova, IV. Circadian rhythm sleep disorders: part II, advanced sleep phase disorder, free-running disorder, and irregular sleep-wake rhythm. Sleep. 2007; 30 (11): 1484-1501.
144. Chung SA, Wolf TK, Shapiro CM. Sleep and health consequences of shift work in women. Journal of Women's Health. 2009; 18 (7): 965-977.
145. Duffy J, Cain S, Chang A, et al. Sex difference in intrinsic circadian period in humans. In: Proceedings from the Associated Professional Sleep Societies (APSS) The 25th Annual Meeting. 2011.
146. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. Journal of Clinical Sleep Medicine. 2007; 3 (5): 519-528.
147. Besedovsky L, Lange T, Born J. Sleep and immune function. Pflügers Archiv-European Journal of Physiology. 2012; 463 (1): 121-137.
148. Monahan K, Redline S. Role of obstructive sleep apnea in cardiovascular disease. Current Opinion in Cardiology. 2011; 26 (6): 541.
149. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. Progress in Cardiovascular Diseases. 2009; 51 (4): 294-302.
150. Watling J, Pawlik B, Scott K, Booth S, Short MA. Sleep loss and affective functioning: more than just mood. Behavioral Sleep Medicine. 2016 May 9: 1-16.
151. Buysse DJ. Insomnia, depression and aging. Assessing sleep and mood interactions in older adults. Geriatrics. 2004; 59 (2): 47-51; quiz 52.
152. Nagy AD, Reddy AB. Time dictates: emerging clinical analyses of the impact of circadian rhythms on diagnosis, prognosis and treatment of disease. Clinical Medicine. 2015; 15 (Suppl 6): s50-s53.
153. Videnovic A, Zee PC. Consequences of circadian disruption on neurologic health. Sleep Medicine Clinics. 2015; 10 (4): 469-480.
154. Bansil P, Kuklina EV, Merritt RK, Yoon PW. Associations between sleep disorders, sleep duration, quality of sleep, and hypertension: results from the national health and nutrition examination survey, 2005 to 2008. The Journal of Clinical Hypertension. 2011; 13 (10): 739-743.
155. Haupt CM, Alte D, Dörr M, et al. The relation of exposure to shift work with atherosclerosis and myocardial infarction in a general population. Atherosclerosis. 2008; 201 (1): 205-211.
156. Knutsson A, Jonsson B, Akerstedt T, Orth-Gomer K. Increased risk of ischaemic heart disease in shift workers. The Lancet. 1986; 328 (8498): 89-92.
157. Sabanayagam C, Shankar A. Sleep duration and cardiovascular disease: results from the national health interview survey. Sleep. 2010; 33 (8): 1037-1042.
158. Vyas MV, Garg AX, Iansavichus AV, et al. Shift work and vascular events: systematic review and meta-analysis. BMJ. 2012; 345: e4800.
159. Gozal D, Farré R, Nieto FJ. Obstructive sleep apnea and cancer: epidemiologic links and theoretical biological constructs. Sleep Medicine Reviews. 2016; 27: 43-55.
160. Lin X, Chen W, Wei F, Ying M, Wei W, Xie X. Night-shift work increases morbidity of breast cancer and all-cause mortality: a meta-analysis of 16 prospective cohort studies. Sleep Medicine. 2015; 16 (11): 1381-1387.
161. Ortiz-Tudela E, Innominato PF, Rol MA, Lévi F, Madrid JA. Relevance of internal time and circadian robustness for cancer patients. BMC Cancer. 2016; 16 (1): 285.
162. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biological Psychiatry. 1996; 39 (6): 411-418.
163. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA. 1989; 262 (11): 1479-1484.
164. Center for Behavioral Health Statistics and Quality. *Behavioral health trends in the United States: results from the 2014 National Survey on Drug Use and Health*. 2015. (HHS Publication No. SMA 15-4927, NSDUH Series H-50)
165. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Archives of General Psychiatry. 2005; 62 (6): 593-602.
166. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. Archives of General Psychiatry. 2005; 62 (6): 617-627.
167. Smith MT, Huang MI, Manber R. Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders. Clinical Psychology Review. 2005; 25 (5): 559-592.
168. Krystal AD. Psychiatric disorders and sleep. Neurologic Clinics. 2012; 30 (4): 1389-1413.
169. Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression: the Johns Hopkins precursors study. American Journal of Epidemiology. 1997; 146 (2): 105-114.
170. Livingston G, Blizard B, Mann A. Does sleep disturbance predict depression in elderly people? A study in inner London. The British Journal of General Practice. 1993 Nov; 43 (376): 445-448.
171. Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. Journal of Psychiatric Research. 2003; 37 (1): 9-15.
172. Weissman MM, Greenwald S, Niño-Murcia G, Dement WC. The morbidity of insomnia uncomplicated by psychiatric disorders. General Hospital Psychiatry. 1997; 19 (4): 245-250.

173. Okun ML. Sleep and postpartum depression. Current Opinion in Psychiatry. 2015; 28 (6): 490-496.
174. Arble DM, Bass J, Behn CD, et al. Impact of sleep and circadian disruption on energy balance and diabetes: a summary of workshop discussions. Sleep. 2015; 38 (12): 1849.
175. Morris CJ, Purvis TE, Hu K, Scheer FA. Circadian misalignment increases cardiovascular disease risk factors in humans. Proceedings of the National Academy of Sciences. 2016; 113 (10): E1402-E1411.
176. Spiegel K, Tasali E, Leproult R, Van Cauter E. Effects of poor and short sleep on glucose metabolism and obesity risk. Nature Reviews Endocrinology. 2009; 5 (5): 253-261.
177. Fernandez-Mendoza J, Vgontzas AN, Liao D, et al. Insomnia with objective short sleep duration and incident hypertension. Hypertension. 2012; 60 (4): 929-935.
178. Cappuccio FP, Taggart FM, Kandala N, et al. Meta-analysis of short sleep duration and obesity in children and adults. Sleep. 2008; 31 (5): 619.
179. Roca GQ, Redline S, Claggett B, et al. Sex-specific association of sleep apnea severity with subclinical myocardial injury, ventricular hypertrophy, and heart failure risk in a community- dwelling cohort: the atherosclerosis risk in communities-sleep heart health study. Circulation. 2015; 132 (14): 1329-1337.
180. Born J, Rasch B, Gais S. Sleep to remember. The Neuroscientist. 2006; 12 (5): 410-424.
181. Bliwise DL. Sleep in normal aging and dementia. Sleep. 1993; 16 (1): 40-81.
182. Philby MF, Macey PM, Ma RA, Kumar R, Gozal D, Kheirandish-Gozal L. Reduced Regional Grey Matter Volumes in Pediatric Obstructive Sleep Apnea. Scientific Reports. 2017; 7: 44566.
183. Walsh CM, Blackwell T, Tranah GJ, et al. Weaker circadian activity rhythms are associated with poorer executive function in older women. Sleep. 2014; 37 (12): 2009.
184. Osorio RS, Gumb T, Pirraglia E, et al. Sleep-disordered breathing advances cognitive decline in the elderly. Neurology. 2015; 84 (19): 1964-1971.
185. Spira AP, Gamaldo AA, An Y, et al. Self-reported sleep and β-amyloid deposition in community-dwelling older adults. JAMA Neurology. 2013; 70 (12): 1537-1543.
186. Virta JJ, Heikkilä K, Perola M, et al. Midlife sleep characteristics associated with late life cognitive function. Sleep. 2013; 36 (10): 1533.
187. Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. Sleep. 2013; 36 (7): 1027.
188. Ferini-Strambi L, Baietto C, Di Gioia M, et al. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). Brain Research Bulletin. 2003; 61 (1): 87-92.
189. Pallier PN, Morton AJ. Management of sleep/wake cycles improves cognitive function in a transgenic mouse model of Huntington's disease. Brain Research. 2009; 1279: 90-98.
190. Chen X, Wang R, Zee P, et al. Racial/ethnic differences in sleep disturbances: the multi-ethnic study of atherosclerosis (MESA). Sleep. 2015; 38 (6): 877-888.
191. Frezza EE, Wachtel MS, Chiriva-Internati M. Influence of obesity on the risk of developing colon cancer. Gut. 2006; 55 (2): 285-291.
192. Goday A, Barneto I, García-Almeida J, et al. Obesity as a risk factor in cancer: a national consensus of the Spanish Society for the Study of Obesity and the Spanish Society of Medical Oncology. Clinical and Translational Oncology. 2015; 17 (10): 763-771.
193. Li H-T, Han X-H, Liu Y-X, Leng K-M, Dong G-M. Relationship between body mass index and incidence of breast cancer. International Journal of Clinical and Experimental Medicine. 2015; 8 (7): 11549.
194. Montazeri A, Sadighi J, Farzadi F, et al. Weight, height, body mass index and risk of breast cancer in postmenopausal women: a case-control study. BMC Cancer. 2008; 8 (1): 278.
195. Viswanathan AN, Schernhammer ES. Circulating melatonin and the risk of breast and endometrial cancer in women. Cancer Letters. 2009; 281 (1): 1-7.
196. Cash E, Sephton S, Chagpar A, et al. Circadian disruption and biomarkers of tumor progression in breast cancer patients awaiting surgery. Brain, Behavior, and Immunity. 2015; 48: 102-114.
197. Innominato PF, Spiegel D, Ulusakarya A, et al. Subjective sleep and overall survival in chemotherapy-naïve patients with metastatic colorectal cancer. Sleep Medicine. 2015; 16 (3): 391-398.
198. Lévi F, Dugué P-A, Innominato P, et al. Wrist actimetry circadian rhythm as a robust predictor of colorectal cancer patients survival. Chronobiology International. 2014; 31 (8): 891-900.
199. Lévi F, Okyar A, Dulong S, Innominato PF, Clairambault J. Circadian timing in cancer treatments. Annual Review of Pharmacology and Toxicology. 2010; 50: 377-421.
200. Davis S, Mirick DK, Chen C, Stanczyk FZ. Night shift work and hormone levels in women. Cancer Epidemiology and Prevention Biomarkers. 2012; 21 (4): 609-618.
201. Fu L, Lee CC. The circadian clock: pacemaker and tumour suppressor. Nature Reviews Cancer. 2003; 3 (5): 350-361.
202. Cao J, Feng J, Li L, Chen B. Obstructive sleep apnea promotes cancer development and progression: a concise review. Sleep and Breathing. 2015; 19 (2): 453-457.
203. Costa AR, Fontes F, Pereira S, Gonçalves M, Azevedo A, Lunet N. Impact of breast cancer treatments on sleep disturbances–a systematic review. The Breast. 2014; 23 (6): 697-709.

204. Palesh O, Aldridge-Gerry A, Ulusakarya A, Ortiz-Tudela E, Capuron L, Innominato PF. Sleep disruption in breast cancer patients and survivors. Journal of the National Comprehensive Cancer Network. 2013; 11 (12): 1523-1530.
205. Van Nes J, Fontein D, Hille E, et al. Quality of life in relation to tamoxifen or exemestane treatment in postmenopausal breast cancer patients: a tamoxifen exemestane adjuvant multinational (TEAM) trial side study. Breast Cancer Research and Treatment. 2012; 134 (1): 267-276.
206. Azim Jr H, Davidson N, Ruddy K. Challenges in treating premenopausal women with endocrine-sensitive breast cancer. American Society of Clinical Oncology Educational Book. 2016; 36: 23-32.
207. Carpenter JS, Elam JL, Ridner SH, Carney PH, Cherry GJ, Cucullu HL. Sleep, fatigue, and depressive symptoms in breast cancer survivors and matched healthy women experiencing hot flashes. Oncology Nursing Forum. 2004; 31 (3): 591-598.
208. Knobf MT. The influence of endocrine effects of adjuvant therapy on quality of life outcomes in younger breast cancer survivors. The Oncologist. 2006; 11 (2): 96-110.
209. Ohayon MM. Relationship between chronic painful physical condition and insomnia. Journal of Psychiatric Research. 2005; 39 (2): 151-159.
210. National Sleep Foundation. Women & Sleep. https://sleepfoundation.org/sleep-topics/women-and-sleep. Accessed February 2016.
211. Fries JF. Aging, natural death, and the compression of morbidity. The New England Journal of Medicine. 1980; 303 (3): 130-135.
212. Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: The National Academies Press; 2011.
213. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. Sleep Medicine Reviews. 2004; 8 (2): 119-132.
214. Edwards RR, Almeida DM, Klick B, Haythornthwaite JA, Smith MT. Duration of sleep contributes to next-day pain report in the general population. Pain. 2008; 137 (1): 202-207.
215. Sanders AE, Akinkugbe AA, Bair E, et al. Subjective sleep quality deteriorates before development of painful temporomandibular disorder. The Journal of Pain. 2016; 17 (6): 669-677.
216. Van Ryswyk E, Antic NA. Opioids and sleep-disordered breathing. Chest. 2016; 150 (4): 934-944.
217. Bliwise DL, Foley DJ, Vitiello MV, Ansari FP, Ancoli-Israel S, Walsh JK. Nocturia and disturbed sleep in the elderly. Sleep Medicine. 2009; 10 (5): 540-548.
218. Bosch JR, Weiss JP. The prevalence and causes of nocturia. The Journal of Urology. 2010; 184 (2): 440-446.
219. Kupelian V, Wei JT, O'Leary MP, Norgaard JP, Rosen RC, McKinlay JB. Nocturia and quality of life: results from the Boston area community health survey. European Urology. 2012; 61 (1): 78-84.
220. Yu HJ, Chen FY, Huang PC, Chen TH, Chie WC, Liu CY. Impact of nocturia on symptom-specific quality of life among community-dwelling adults aged 40 years and older. Urology. 2006; 67 (4): 713-718.
221. Rosen RC, Holm-Larsen T, Kupelian V. Consequences of nocturia. Postgraduate Medicine. 2013; 125 (4): 38-46.
222. Kobelt G, Borgström F, Mattiasson A. Productivity, vitality and utility in a group of healthy professionally active individuals with nocturia. BJU International. 2003; 91 (3): 190-195.
223. Tikkinen KA, Johnson TM, Tammela TL, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. European Urology. 2010; 57 (3): 488-498.
224. Nakagawa H, Ikeda Y, Kaiho Y, et al. Impact of nocturia on medical care use and its costs in an elderly population: 30 month prospective observation of national health insurance beneficiaries in Japan. Neurourology and Urodynamics Special Issue: 39th Annual Meeting of the International Continence Society San Francisco, USA 29 September - 3 October, 2009. 2009; 28 (7): 930-931.
225. Stewart RB, Moore MT, May FE, Marks RG, Hale WE. Nocturia: a risk factor for falls in the elderly. Journal of the American Geriatrics Society. 1992; 40 (12): 1217-1220.
226. Ancoli-Israel S, Bliwise DL, Nørgaard JP. The effect of nocturia on sleep. Sleep Medicine Reviews. 2011; 15 (2): 91-97.
227. Bagley EJ, Kelly RJ, Buckhalt JA, El-Sheikh M. What keeps low-SES children from sleeping well: the role of presleep worries and sleep environment. Sleep Medicine. 2015; 16 (4): 496-502.
228. Stringhini S, Haba-Rubio J, Marques-Vidal P, et al. Association of socioeconomic status with sleep disturbances in the Swiss population-based CoLaus study. Sleep Medicine. 2015; 16 (4): 469-476.
229. Helzner EP, Cauley JA, Pratt SR, et al. Race and sex differences in age-related hearing loss: the health, aging and body composition study. Journal of the American Geriatrics Society. 2005; 53 (12): 2119-2127.
230. Carrier J, Fernandez-Bolanos M, Robillard R, et al. Effects of caffeine are more marked on daytime recovery sleep than on nocturnal sleep. Neuropsychopharmacology. 2007; 32 (4): 964-972.
231. McHill AW, Smith BJ, Wright KP. Effects of caffeine on skin and core temperatures, alertness, and recovery sleep during circadian misalignment. Journal of Biological Rhythms. 2014; 29 (2): 131-143.
232. Drake CL, Pillai V, Roth T. Stress and sleep reactivity: a prospective investigation of the stress-diathesis model of insomnia. Sleep. 2014; 37 (8): 1295-1304.
233. Vargas I, Friedman NP, Drake CL. Vulnerability to stress-related sleep disturbance and insomnia: investigating the link with comorbid depressive symptoms. Translational Issues in Psychological Science. 2015; 1 (1): 57.
234. Institute of Medicine. *Exploring the Biological Contributions to Human Health: Does Sex Matter?* Washington, DC: The National Academies Press; 2001.

235. Patel SR, Malhotra A, Gottlieb DJ, White DP, Hu FB. Correlates of long sleep duration. Sleep. 2006; 29 (7): 881.
236. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Archives of General Psychiatry. 2002; 59 (2): 131-136.
237. Buysse DJ. Sleep health: can we define it? Does it matter. Sleep. 2014; 37 (1): 9-17.
238. Harvey AG, Stinson K, Whitaker KL, Moskovitz D, Virk H. The subjective meaning of sleep quality: a comparison of individuals with and without insomnia. Sleep. 2008; 31 (3): 383.



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