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SEX AND GENDER ISSUES IN BEHAVIORAL HEALTH (CN EPPERSON AND L HANTSOO, SECTION EDITORS)

Sex Differences in Insomnia: from Epidemiology and Etiology to Intervention

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Abstract

Purpose of Review Insomnia is approximately 1.5 times more common in women than in men. To date, research has advanced our knowledge about why women report significantly more sleep problems than men despite not being reflected in objective sleep measures. Precisely understanding the symptomatology and pathological mechanisms underlying sex differences is important for prevention and providing appropriate interventions.

Recent Findings Sex differences found in insomnia goes beyond simple explanations and have been proven to be a complicated interplay of biological, psychological, and social factors that play different roles throughout the life span.

Summary This paper will review sex differences in insomnia based on risk factors, mechanisms, and consequences, as well as treatment response. In addition, we will also discuss treatment recommendations when working with female populations at different stages in the life span that may be more vulnerable to insomnia. Future studies utilizing prospective, longitudinal designs are needed to understand the interactions of various factors that can explain existing sex differences in insomnia.

Keywords Insomnia · Sex differences · Sleep · Sleep disorders · Sleep disparity · Cognitive-behavioral therapy for insomnia

Introduction

It has been widely published that sex differences exist across the sleep literature. Women, in general, report more somatic symptoms and mental distress compared to men in terms of number, intensity, and frequency [1]. Insomnia is not the exception. Insomnia is about 1.5 times more common in women than in men [2]. Precisely understanding the symptomatology and pathological mechanisms underlying sex differences is imperative for prevention, predicting outcomes, and providing appropriate interventions, in addition to meeting other individual and social needs in women and men with insomnia disorder. This paper will review sex differences in epidemiological studies, risk factors, physiological and psychological mechanisms, and treatment response. In addition, we will also discuss treatment recommendations when working with female populations across the life span.

Potential Artifacts Affecting Sex Differences of Insomnia Disorder

Several studies have suggested that sex differences found in insomnia may exist or be exaggerated due to potential artifacts associated with insomnia disorder.

Thresholds for Determination of Clinical Cases It should be noted that women have more complaints and distress associated with insomnia symptoms compared to men in the general population. Additionally, women are more likely to report somatic symptoms and daytime impairments compared to men [3]. In the absence of a clear endophenotype or objective maker to classify individuals with clinical levels of insomnia disorder, different symptom distributions in different sexes

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may lead to a higher tendency for women to meet the diagnostic criteria or severity threshold of insomnia disorder.

Help-Seeking Behaviors Despite having similar levels of disease severity as men, females are more likely to report somatic symptoms and seek medical help compared to males [1]. Some studies have suggested that females with insomnia symptoms have a 2-fold higher likelihood of seeking help from health care professionals than males with insomnia symptoms [4, 5]. This sex difference in help-seeking behaviors may be due to symptom severity and/or mental comorbidity.

Epidemiological Evidence of Sex Differences

Normal Sleep Architecture and Sex Differences Sex differences in insomnia are not likely to be explained by sex differences in sleep physiology and sleep architecture. It has generally been shown that women have better objective sleep quality than men [6]. Women display twice as many sleep spindles and more slow wave sleep, spend more time sleeping in a free running environment, and display slower decline of age-related delta activity compared to men [7]. A meta-analysis by Ohayon and colleagues further confirmed that women have shorter sleep onset latency and higher sleep efficiency, but longer wake after sleep onset compared to men, which indicates that sex differences in sleep parameters as measured by polysomnography (PSG) do not necessarily point to better objective sleep in men [8]. One study by a German group showed that all sleep continuity measures as indicated by sleep duration, sleep efficiency, arousal index, and wake, and slow wave or REM sleep did not demonstrate significant sex differences in both insomniacs and healthy controls [9]. These findings highlight that women at least do not objectively sleep worse than men in the general population, which is contradictory to the higher prevalence of insomnia in females.

Children and Adolescents It should be noted that most studies conducted with children did not find any sex differences in insomnia [10, 11]. Females even have longer sleep duration than males in both children and adult population [12]. As sex differences in insomnia have been widely reported in adolescents [13•], puberty appears to play a critical role in the sex differences of insomnia. Indeed, puberty is accompanied by a series of factors that may contribute to the development of insomnia, such as decreased homeostatic sleep drive and delayed circadian phase, which subsequently may lead to a mismatch with social schedules [14].

Several studies have explored the timing of when sex differences in insomnia emerge [15, 16]. One study found that the onset of menses was a major event that increased with risk of developing insomnia in adolescent girls, but pubertal maturation was not associated with increased prevalence of insomnia in adolescent boys [16]. In this study, the onset of menses was associated with 2.75-fold increased risk for insomnia. Zhang and colleagues found that the prevalence of insomnia symptoms progressively increased from 3.4 to 12.2% in girls (3.6-fold) and from 4.3 to 9.1% in boys following puberty (2.1-fold) [17••]. There was a significant interaction between sex and puberty in the prevalence of insomnia symptoms with the emergence of female preponderance at Tanner stage 4 even after controlling for age, family income, and school start time [17••]. Additionally, from a psychological perspective, Zhang and colleagues reported that girls with insomnia symptoms were more vulnerable in emotional and relationship problems compared to boys [10].

Taken together, previous studies have almost unanimously suggested that pubertal maturation plays a critical role in the onset of insomnia symptoms and the emergence of sex differences in insomnia. However, these studies have several limitations. First, none of these studies have used clinical ascertainment to confirm both pubertal status and insomnia diagnosis [18]. Further studies with clinician assessments on both pubertal status and insomnia may help to confirm the roles of pubertal maturation in sex differences in insomnia. Second, most of these studies have employed a cross-sectional study design, which does not allow for delineating the influences of sex and pubertal status on the longitudinal course of insomnia symptoms. In addition, it remains unknown whether the long-term impacts of insomnia symptoms on mental and physical health are also modulated by sex and pubertal status. In this regard, future studies are warranted to overcome these previous limitations to confirm the roles of puberty on sex differences in insomnia.

Adults Adulthood can be defined from early adulthood to midlife, consisting of a relatively broad time period. During adulthood, insomnia prevalence varied broadly based on the country and age range that was investigated, ranging from 10 to 40% [19]. Regardless of the variance of insomnia prevalence, women consistently reported higher insomnia prevalence compared to men despite various research sampling of age groups.

Sex differences found in the prevalence of insomnia may be driven by both physiological and psychological factors. Physiologically, women are reproductive during this period and reproductive hormones may influence women's sleep [20•]. Hormones such as luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone, and estrogen evoke changes in circadian rhythms and sleep architecture [21]. These hormones cause more sleep difficulties in women during the week before onset of menses [21]. Pregnancy and postpartum are also related with sleep disturbances, caused by drastic fluctuation of hormones with childbirth [22]. Menopause, a significant event for midlife women which is caused by reduced ovarian hormones and permanent cessation

of menstruation, evokes significantly more sleep disturbances in women compared to men and accelerates sex differences in insomnia prevalence in the midlife population [23]. With menopause, estrogen levels decrease and LH and FSH levels increase, which cause vasomotor symptoms (i.e., hot flashes and night sweating) which are known to disturb sleep [24]. Additionally, women who undergo menopause by surgical means (i.e., hysterectomy or bilateral oophorectomy) may experience a more acute drop in hormones, which may subsequently lead to sleep disturbance (Cho et al., under review).

Psychologically, women in the premenstrual period often report more depression, anxiety, and irritability, which are highly related with sleep disturbance [25]. During the postpartum period, role changes such as adjusting to the role of motherhood and caring for a newborn baby through the night may result in insufficient sleep and sleep deprivation, as well as increased negative emotions [21, 22]. Additionally, on a behavioral level, if women who undergo surgical menopause engage in more sleep-interfering behaviors, they may have higher levels of insomnia symptoms compared to women who undergo natural menopause (Cho et al., under review). An interaction of both physiological and psychological factors appears to contribute to sex differences in insomnia during adulthood.

Elderly It is well-known that the ability to sleep decreases with the aging process [26]. Many studies consistently show that the prevalence of insomnia is higher in the elder population compared to the younger populations [17••]. The prevalence of insomnia in elderly population ranges between 30 and 60% [27].

It is not surprising that females show higher insomnia risk compared to males throughout all age groups, with the risk ratio increasing with age [17••]. A meta-analysis about the sex differences in insomnia indicated that females had a 1.28 times higher risk of having insomnia compared to males in the younger group (15–30 years), 1.46 times higher in midlife group (31–64 years), and 1.73 times higher in elderly group (> 64 years). This suggests that elderly women are the most vulnerable to insomnia and require special clinical attention preventing or managing the sleep problems.

According to Guidozzi's study with older men and women, steroid hormones and circadian rhythms influence sex differences of elderly insomnia [28]. Gonadal steroid hormones influence circadian rhythm by modulating suprachiasmatic nucleus (SCN) functions. In terms of circadian rhythms, although melatonin secretion is earlier in women than in men, there was no difference between men and women in sleep timing. This implies that women biologically spend longer time after melatonin secretion to fall asleep. These results could explain the complaints of elderly women reporting significantly longer time to fall asleep than men [29] as older females have significantly lower melatonin secretion compared to older men [30•].

Psychosocial activity and physical activity were the best predictors for circadian rhythm maintenance among elder dementia patients [31]. Engaging in psychosocial activities could prevent napping, resulting in improvements of nocturnal sleep quality and circadian sleep-wake rhythms [31]. However, study outcomes of sex differences in social activities in elder population are inconsistent [32, 33]. Future studies studying sex differences in insomnia should also consider the role of psychosocial activity among elder populations.

Sex Differences in Insomnia Persistence Recent longitudinal studies with two or more assessment points for insomnia have ascertained insomnia as a highly persistent condition [34, 35]. Sex differences may be due to high persistence of insomnia in females. Several prospective studies have shown that females have a higher persistence rate, but similar incidence rate of insomnia when compared with males [36, 37]. One prospective study followed 1282 non-depressed individuals over 6 years, with 4 assessments points spaced 2 years apart [37]. Individuals were divided into three groups: no insomnia, single-episode insomnia (insomnia at one time point), or persistent insomnia (insomnia at more than 2 time points). There was significantly higher proportion of women in the persistent insomnia group compared to the other two groups. However, inconsistent results have been reported. A longitudinal study by Ellis and colleagues [38] analyzed two community samples from the USA and UK, and found that females reported more sleep problems than men in first-onset acute insomnia and comorbid acute insomnia, although a recurrent episode of acute insomnia was slightly more prevalent in men.

This kind of observation implies that sex differences may exist in both the course and occurrence, and they may both account for the sex differences in the prevalence of insomnia as confirmed by most studies. Future studies are needed to investigate mechanisms underlying sex differences of insomnia through perpetuating factors, such as mental distress, and maladaptive sleep behaviors and lifestyle factors [36].

Risk Factors and Mechanisms Contributing to Sex Differences in Insomnia

Although the exact mechanisms underlying sex differences insomnia are still unclear, we propose some potential mechanisms underlying sex differences in insomnia.

Socioeconomic Risk Factors One explanation for sex differences is that females are more likely to be exposed to socioeconomic risk factors contributing to insomnia, such as lower education level and unemployment [10]. Despite these suggestions, studies have found that men also carry a heavier burden of other risk factors of insomnia, such as smoking,

snoring, and alcohol consumption [10, 39]. Additionally, sex differences in insomnia still persist after controlling for these risk factors, which suggests that these demographic and lifestyle risk factors are not major factors that contribute to sex differences [39]. In a large-scale study from Taiwan, Chen et al. showed that social role and socioeconomic status did not explain sex differences in insomnia [40]. In addition, it seems that these demographic factors have differential effects on insomnia symptoms depending on the sex [10, 39]. For example, it has been shown that marital status is associated with insomnia symptoms in women but not in men, while unemployment is associated with insomnia symptoms in men but not in women [10]. Nonetheless, there is a lack of data to systematically examine how much variance of sex differences in insomnia can be explained by the differences in the levels of exposed to these risk factors and in the strengths of the associations between these risk factors with insomnia.

Physiological Factors Sleep is regulated by various internal mechanisms involving neurotransmitters, hormones, and peptides. However, it is unclear whether sleep is regulated in the same way by both sexes as many of these mechanisms are sexually dimorphic, and are also associated with sex hormones [41]. Female reproductive hormones such as progesterone and estrogen affect sleep in women, which is observed by changes in sleep during the menstrual cycle. The women's menstrual cycle can be divided into the follicular phase and luteal phase, which is distinguished by timing of ovulation. Estrogen increases during the follicular phase, and a complex process involving FSH and LH leads to ovulation. After ovulation, estrogen and progesterone increase for the first 7 days followed by a sharp decrease preceding the onset of menses. Several animal and human studies have indicated that progesterone reduces arousal and can have a sedative effect [42], while estrogen increases the turnover of the neurotransmitter norepinephrine and subsequently increases time spent in REM sleep and decreases REM latency [41]. Many women have increased sleep complaints during the luteal phase compared to the follicular phase, with one study reporting reduced sleep quality in the luteal phase compared to the follicular phase, but not sleep continuity [43]. Additionally, many women report increased insomnia symptoms during the menopause transition, which is characterized by a precipitous drop in luteal phase progesterone [44]. Decreases in female reproductive hormones are associated with decreased melatonin synthesis and secretion, which may subsequently affect sleep [45].

Hyperarousal is an overarching pathophysiological condition in insomnia, which includes increased somatic, cognitive, and cortical overactivation over the 24-h period [46]. Some of these physiological parameters related to hyperarousal have been shown to have sex differences. First, hypothalamic–pituitary–adrenal (HPA) axis dysfunction has been shown to be a key phenomenon supporting the hyperarousal hypothesis for insomnia. There are significant sex differences in cortisol levels upon awakening or in response to a stressor [47], and these sex differences become more robust after pubertal maturation [48]. In addition, women with insomnia show a higher cortisol awakening response compared to men with insomnia [49••]. These data indicate that sex differences in HPA axis reactivity to stressors or awakening may play a key role in explaining sex differences in insomnia.

Differences in sleep-wake regulation may also explain underlying mechanisms of sex differences in insomnia. Sleep-wake regulation is controlled by the two-process model, which includes circadian process and homoeostatic process [50]. The circadian process is determined by an internal clock located in the suprachiasmatic nuclei, while the homoeostatic process is mainly determined by prior cumulative wakefulness duration [50]. Late chronotype has generally been associated with a higher risk of insomnia [51], indicated by a later average dim light melatonin onset (DLMO) in insomnia patients compared to healthy controls [52]. These findings highlight the circadian etiology for patients with a diagnosis of insomnia. Reports on sex differences in regard to circadian typology have indicated that women have an earlier DLMO phase and earlier chronotype compared to men [53], which should be considered as a protective factor for insomnia [51]. In this regard, there are likely other factors aside from circadian rhythm control that contribute to the sex differences in insomnia, and suggest the contributing factors to be more complex [54].

Another potential explanation related to sleep-wake regulation is that women have lower homeostatic drive than men. Electroencephalographic (EEG) slow-wave activity during NREM sleep, an indicator of homeostatic drive of sleep need, shows women present with more slow-wave activity than men both at baseline and after sleep deprivation [55]. This observation is consistent with those findings from objective measures that women objectively sleep better than men, which is contradictory to the female predominance in the risk of insomnia.

Psychological Factors Patients with insomnia present with more signs of negative personality traits, such as neuroticism, internalization, anxious concerns, and perfectionism [56], and some of these personality traits (such as neuroticism) are more commonly found in females [57]. It should be noted that the timing for the emergence of sex differences in neuroticism [58] is very similar to that in insomnia [17••]. However, the roles of neuroticism on the sex differences warrant further studies. Edinger and colleagues found that patients with insomnia who responded to behavioral treatment had a higher "neurotic" profile as measured by the MMPI [59]. Nonetheless, it is still unclear whether personality differences may explain the sex differences in clinical course and treatment outcomes of insomnia.

Another important factor is the occurrence of major life events and reactivity to these stressful life events. According to Spielman's 3P model for the explanation of the development of chronic insomnia, stressful life events are considered important precipitating factors that initiate the onset of insomnia symptoms [46]. A high level of stressful life events contributes not only to the incidence of insomnia, but also to the persistence of insomnia [36]. There is no doubt that stressful life events are a substantial cause of the development of insomnia. In this regard, it is reasonable to speculate that higher female prevalence of insomnia may be due to higher vulnerability to stressful life events in females than males, especially in adolescents [60]. Women are also more likely to perceive stressful life events as more distressing than men [61]. Previous studies have indicated that women demonstrate higher stress reactivity and more depressive symptoms than men even when experiencing similar levels of stress [62]. In this regard, future studies should investigate how sex differences in stress levels and psychological reactivity to stressors contribute to the sex differences in insomnia.

Sex Differences in Insomnia Comorbidity and Consequences

Psychiatric Comorbidity Previous studies on the relationship between insomnia and psychiatric disorders have established that having insomnia increases the risk of having future psychiatric disorders [63, 64]. Among psychiatric disorders, both depression and anxiety disorders are more likely to affect females. In the past two decades, an increasing number of studies have suggested that insomnia is merely a secondary symptom of depression or anxiety disorders. However, it is being more widely accepted that insomnia shall be treated as a distinct diagnostic entity when it coexists with depression and anxiety disorders [65]. One study by Buysse et al. [66] found primary insomnia and major depression had distinct quantitative EEG profiles, with distinct patterns for each sex.

Previous studies have confirmed that there is a bidirectional association between insomnia and depression [67]. Indeed, mental illnesses, such as depression and anxiety, are considered as one of the most robust perpetuating factors of chronic insomnia [46]. Prospective studies [35] have also supported that depression is a strong risk factor for the persistence of insomnia. While higher prevalence of psychiatric disorders in women compared to men can partially explain sex differences in insomnia, further studies are needed that examine directionality and role of comorbid depression and anxiety disorders on the sex differences in insomnia.

Comorbidity of Other Sleep Disorders Insomnia is frequently comorbid with obstructive sleep apnea, although both are considered different clinical conditions with some opposing features, such as vigilance and sleepiness [68]. Nonetheless, OSA and insomnia also share some common symptoms, such as non-restorative sleep and daytime function impairments [68]. Thus, a large proportion of patients with insomnia also have an apnea-hypopnea index meeting the diagnostic criteria for OSA [69]. On the other hand, over 50% of patients with OSA also suffer from clinically significant insomnia [70], leading to more severe consequences and difficulties in management [71]. Muscle relaxation effects of benzodiazepines in treating insomnia symptoms exacerbate sleep apnea events [72]. OSA is a male-dominated disease. Li et al. have shown that among patients with insomnia, the prevalence of sleep apnea by using different criteria (AHI > 5, > 15, and > 30) was much higher in males than females under the age of 55 years old. However, the prevalence of OSA was very similar for those patients with insomnia aged over 55 years [73]. It is unclear whether there are sex differences in the consequences and management of the comorbid conditions between insomnia and OSA.

Restless leg syndrome (RLS) is characterized by an urge to move the legs, usually accompanied by uncomfortable sensations and sleep disturbances. Females are about 1.5–2-fold more likely to develop RLS than males in the general population [74]. It has been found that pregnancy is a specific behavioral risk factor for RLS and may account for the sex differences in RLS [74]. However, a recent study by Zhang and colleagues has shown that sex differences in RLS symptoms emerge in late adolescence [75], which is very close to the timing of emergence of sex differences in insomnia [17••]. However, the role that RLS plays in the sex differences in insomnia in terms of epidemiology and management are largely unknown.

Cognitive Outcomes Surprisingly, insomnia or sleep deprivation-related cognitive decline is remarkable in men rather than women, even though sleep disturbance is more prevalent in women through almost all age groups [76]. In Cricco's longitudinal study, men who had chronic insomnia showed higher risk for cognitive decline among age 65 and older. In contrast, there was no association between insomnia and cognitive decline in women. The authors speculated that sex differences in cognitive outcomes for insomnia symptoms may be due to a higher threshold toward sleep complaints in men. Thus, men with insomnia who report sleep complaints may experience more severe symptoms of insomnia, and result in more cognitive impairments compared to women [76].

In contrast, studies investigating sex differences in cognitive functioning associated with insomnia found out that there was no significant sex differences in total cognitive scores measured by the Mini-Mental Status Exam [77]. Sex differences in cognitive functions as an outcome of insomnia are equivocal and understudied. Future studies exploring specific cognitive domains utilizing various neuropsychological

measurements to further investigate sex differences in cognitive impairments resulting from insomnia are needed.

Behavioral and Mental Health Outcomes Insomnia is a robust risk factor for many behavioral problems and mental disorders, and the management of insomnia may also benefit the outcomes of these consequences. However, there is limited evidence of the sex differences in the consequences of insomnia in terms of these outcomes. One previous study has shown that insomnia was associated with more significant HPA axis dysfunction in females than males [49••], which suggests that insomnia may lead to more mental health and behavioral consequences than men.

Sex differences in behavioral outcomes should also be taken into consideration. For example, adolescent boys with insomnia have more maladaptive lifestyles (smoking, alcohol, and energy drinks), whereas adolescent girls with insomnia are more vulnerable to emotional and relationship difficulties [17••]. Nonetheless, studies with prospective design are needed to delineate the sex differences in mental health outcomes.

Pain and somatic symptoms As mentioned above, insomnia, pain, and somatic symptoms are all more prevalent in the female population [1]. There is a bidirectional association between insomnia and pain in both the short-term and long-term [34]. In addition, management of insomnia also improves pain symptoms in patients with both conditions [78••], although inconsistent findings have been also reported [79]. In view of the close relationship, it is reasonable to speculate that sex may modulate this complex relationship. One previous study has shown that sex is a key modulating factor for the associations of insomnia with pain and somatic symptoms [3]. In addition, this modulation effect of sex seems to be more prominent in adults than in adolescents, which provides additional evidence that sex differences appear to emerge after puberty. Evidence from experimental studies also support that women are more vulnerable to pain perception after sleep deprivation [80]. By using a Forced Awakening protocol, a condition mimicking sleep fragmentation in insomnia, Smith et al. showed that continuity disturbance per se, rather than simple sleep restriction by using delayed bedtime, impairs endogenous pain-inhibitory function and increases spontaneous pain in women [81]. However, a lack of men as controls was noted as a limitation of this study to investigate the potential sex differences in pain perception under the condition of insomnia or fragmented sleep.

Chronic Medical Conditions Both descriptive community and experimental studies have shown that the associations of sleep loss with inflammatory markers are stronger in females than males [82, 83]. This suggests that females might be more vulnerable to poor cardiovascular outcomes in the context of sleep loss or insomnia. Indeed, stronger associations of short sleep duration with hypertension in females have been shown in two large-scale epidemiological studies [84, 85]. However, sex differences in the associations of insomnia with chronic medications are not consistent. A study in Sweden found that men who complained of difficulty maintaining sleep had a higher risk of developing diabetes after a 12-year follow-up but this observation was not replicated in women [86].

Sex Differences in Treatment Response

Pharmacological Treatment Although previous studies have shown that there are significant sex differences in help-seeking behaviors [4, 5], no such differences were found for prescribing profile, frequency of taking medication, or length of use between women and men with insomnia [87]. Nonetheless, concerning the sex differences in the pharmacokinetics in hypnotics with higher concentration and slower clearance in women [88], one may argue that there might be sex differences in the efficacy and safety in hypnotics for patients with insomnia. Indeed, the Food and Drug Administration (FDA) revised zolpidem-containing products to lower doses in 2013, particular for women, in view of the sex difference observed with the sublingual low-dose product (Intermezzo) [89]. A later study by Roehrs and Roth showed that chronic nightly use of zolpidem had similar efficacy and safety between men and women [90••].

Other studies have investigated potential sex differences in response to hypnotics and medication with sedative effects in healthy subjects and patients with insomnia. Among healthy volunteers, women have an increase while men have a decrease in slow wave sleep during nighttime after a single dose of olanzapine in the morning [91]. In a clinical model of transient insomnia by using phase-advance approach, women seem to have larger increases in delta and theta activity in NREM and REM sleep after the administration of gaboxadol. Administration of zolpidem leads to the increase in sleep spindle activity in women than men [92]. Suvorexant, an orexin receptor antagonist that is used as a hypnotic, has shown similar efficacy in treating insomnia symptoms in both sexes. However, women seem to have more adverse events than men [93]. In summary, sex differences in treatment responses to hypnotics are still largely variable and unknown.

Psychological Treatment While many studies have investigated the efficacy and effectiveness of psychological treatment, especially cognitive-behavioral therapy for insomnia (CBTI), there have been few studies that have reported on sex differences to treatment response (Table 1). Out of the 10 studies (9 original articles, 1 meta-analysis) that we found, only one reported sex differences in treatment response [94–103]. Lami et al. reported that after 9 sessions of CBTI, women reported longer sleep onset latency and more general fatigue compared to men [101]. In contrast, men reported higher

Table 1 Studies investigating sex differences with cognitive-behavioral therapy for insomnia

Name	Sample size/females	Treatment	Gender effects
Cincotta et al. [94]	*N* = 70, 38 female 54.1%	MBSR, 8 weeks	X/ Gender did not significantly predict treatment outcome
Currie et al. [95]	*N* = 51, 27 female 52.9%	CBTI, 7 sessions	X/ Gender did not significantly predict treatment outcome
Espie et al. [96]	*N* = 190, 78 female 72%	CBTI, 6 sessions	X/ Gender did not significantly predict treatment outcome
Espie et al. [97]	*N* = 139, 95 female 68%	CBTI, 6 sessions	X/ Gender did not significantly predict treatment outcome
Gagne et al. [98]	*N* = 54, 35 female 64.8%	CBTI, 8 sessions	X/ Gender did not significantly predict treatment outcome
Garland et al. [99]	*N* = 40, 32 female 79%	CBTI, 8 sessions MBSR, 8 sessions	X/ There were no significant differences in treatment effect by sex
Houdenhove et al. [100]	*N* = 138, 93 female 67%	CBTI, 6 sessions	X/ Gender did not significantly predict treatment outcome
Lami et al. [101]	*N* = 28, 15 female 53.6%	CBTI, 9 sessions	Δ / - Both responded well in total sleep (difference was not significant in total sleep) - Women > men: sleep latency, general fatigue - Men > women: sleep disturbances (subscale of PSQI)
Morin et al. [102]	*N* = 2102, female 59.9% (meta-analysis)	(Meta-analysis)	X/ (Meta-analysis) Gender was not significantly related with treatment outcome
Verbeek et al. [103]	*N* = 86, 56 female 65.1%	CBTI, 4 sessions	X/ Gender did not significantly predict treatment outcome

CBTI cognitive-behavioral therapy for insomnia, *MBSR* mindfulness-based stress reduction

scores on the Pittsburgh Sleep Quality Index compared to men after treatment. Five other studies did not report any gender differences, and a meta-analysis by Morin and colleagues reported in a meta-analysis that sex was not significantly associated with treatment outcome based on 2102 individuals [102]. Overall, evidence to date indicates that men and women benefit equally from CBTI.

Special Treatment Considerations for Women

Puberty Puberty is considered a critical period in that it marks the divergence of insomnia prevalence between sexes, as sex differences were not found in children in many studies [10, 11, 15]. Many studies have reported that girls start experiencing more sleep disturbance than boys with the onset of puberty [10, 15].

Clinicians who treat insomnia in female adolescents should be mindful of physical changes as well as exploring psychological problems such as peer relations and affective status. Additionally, developmental changes in circadian and sleep characteristics occur during puberty, such as a gradual change toward eveningness tendencies due to biological factors as well as a behavioral preference for delayed bedtime, and delayed weekend wake-up time compared to weekdays should be taken into consideration during treatment [104]. Adolescents may prefer to engage in a range of behaviors that delay sleep onset, such as engaging in social interactions on the internet or using electronic media, all of which increase arousal levels before bedtime [105]. Thus, morning light exposure and reducing the variability of weekday-weekend sleep schedules may be important to address when treating adolescent girls. Structuring sleep-wake schedules by utilizing behavior modification principles may be helpful in preventing delayed bedtime as well as addressing issues in puberty.

Pregnancy and Birth Many women report sleep disturbance during pregnancy, with prevalence ranging from 14 to 27% [106]. Sleep in pregnancy may differ based on trimester, with risk of insomnia being 2.03 times higher later in the pregnancy compared to that in early pregnancy [107]. Sleep disturbance in the later stages of pregnancy is most likely associated with hormonal changes and body discomfort. While reductions in sleep quality in pregnant women may be expected, it is important to be attentive of pregnant women who meet clinical criteria for insomnia and require intervention. Some pregnant women who already have a history of insomnia may be particularly worried about sleep deprivation after childbirth, and may catastrophize the consequences of their sleep problems and extend to worries about being able to take care of a newborn. Thus, it is important to tailor existing treatments to accommodate pregnant women while they adapt to their new maternal role.

While there are various treatment options for pregnant women who experience sleep disturbance, a recent study has reported that pregnant women preferred CBTI compared to pharmacotherapy and acupuncture for treatment of insomnia

during pregnancy [108]. An open trial of CBTI in pregnant women found significant reductions in insomnia symptoms and increases in subjective sleep quality post-treatment, with secondary treatment effects shown for depressive symptoms, pregnancy-specific anxiety, and fatigue [109•]. In addition to traditional CBTI, it may be helpful to add sleep education about infant sleep and what to expect after childbirth, and acquiring skills to optimize infant sleep. Other adaptations such as adding scheduled naps, which is usually discouraged for traditional CBTI, may be helpful after sleep fragmentation due to nighttime feedings. Finally, clinicians who use cognitive restructuring should also explore cognitive distortions that also apply to their infants' sleep [110].

Menopause Menopause-related sleep problems are common in midlife women. Prevalence rates of sleep disturbance in menopausal women were 40 to 56% [111]. It is important for the clinician treating menopausal women to understand that many of the menopausal symptoms (e.g., hot flashes, night sweating) are precipitating factors for insomnia. Depression and vasomotor symptoms were associated with high frequency of poor sleep in menopausal women [112•]. Especially, hot flashes are one of the most typical menopausal symptoms, and are highly associated with awakenings of perimenopausal women [113]. Baker measured hot flashes objectively using skin conductance and PSG, and reported that women with insomnia reported more hot flashes, which subsequently predicted the number of awakenings captured by PSG [24]. Repeated exposure of menopausal symptoms that cause wakefulness at night may perpetuate insomnia symptoms through conditioned arousal. A combination of hormonal replacement therapy or hormonal medications while receiving CBTI may be useful in decreasing sleep-related physiological symptoms [114, 115]. Additional assessment for other sleep disorders, especially obstructive sleep apnea, should also be considered.

Psychologically, personal beliefs and cognitive representations toward menopause and symptoms have been shown to mediate the relationship between attentional detection and hot flashes or night sweats [116]. If menopausal women focus intensely on their internal physical symptoms and detect every trivial sensation and then attribute these sensations to menopause, it is likely they may report more hot flashes or night sweating than those who pay less attention to their physical sensations. Thus, distraction from body sensations could be helpful in alleviating sleep disturbance.

When treating women experiencing menopausal symptoms, clinicians should be attentive to temperature-related behaviors, such as suggesting sleeping with a light blanket, and managing a comfortable bedroom temperature. It may also be helpful to suggest limiting caffeinated beverages or alcoholic drinks close to bedtime as they may worsen menopausal symptoms. Additionally, psychoeducation about what to expect during the menopausal transition may be helpful for the patient to establish an accepting stance toward their attitude about menopause. Finally, relaxation techniques such as diaphragmatic breathing and progressive muscle relaxation may help alleviate vasomotor symptoms.

Conclusion

To date, there have been numerous basic and clinical studies that have advanced our understanding of why sleep disparities among men and women exist. The conundrum of why women report significantly more sleep problems than men despite not being reflected in objective sleep measures goes beyond simple explanations and has been proven to be a complicated interplay of biological, psychological, and social factors that play different roles throughout the life span. Future studies utilizing prospective study designs that focus on the interaction of these factors are needed to understand relative contributions to sex differences in sleep. Further understanding of these mechanisms will help advance treatments that may be better tailored to specific genders across developmental stages.

Compliance with Ethical Standards

Conflict of Interest Sooyeon Suh, Nayoung Cho, and Jihui Zhang declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
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