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Gender Differences in Sleep Structure and Circadian Rhythms: A Biological, Hormonal, and Genetic Perspective

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Abstract:

Sleep and circadian rhythms are fundamental biological processes crucial for maintaining physiological functions and overall health. Growing evidence indicates significant sex differences in the regulation of sleep structure and circadian rhythms, stemming from complex interactions among biological mechanisms. This review systematically analyzes sex-based variations in sleep parameters (including NREM-REM cycles, sleep efficiency, and fragmentation) and circadian traits (such as phase preference and clock gene expression). It delves into the specific mechanisms of neuroendocrine regulation involving the suprachiasmatic nucleus (SCN) and sex hormones (estrogen, progesterone, testosterone). The findings indicate that women often exhibit greater circadian robustness but report more subjective sleep complaints, while men show a higher risk of objective sleep fragmentation. Genetic factors, such as the PER3 VNTR and CLOCK 3111T/C polymorphisms, demonstrate differential distribution and effects between sexes, with epigenetic mechanisms further shaping sex-specific sleep patterns. This review underscores the necessity of integrating sex as a critical variable in sleep research and clinical practice. It provides a theoretical foundation for developing sex-specific interventions for sleep disorders, thereby enhancing the efficacy of chronotherapy and precision sleep medicine.

Keywords: Sleep Architecture; Circadian Rhythms; Sex Differences; Neural Regulation.

1. Introduction

Sleep and circadian rhythms are fundamental biological processes that underpin cognitive function, emotional stability, metabolic balance, and immune competence. In recent years, substantial evidence has revealed significant sex differences in the regulation of sleep structure and circadian rhythms, differences

that persist across the lifespan and have profound implications for health outcomes [1]. For instance, epidemiological surveys consistently show that women self-report a higher prevalence of sleep complaints (e.g., 51.1%) compared to men (45.9%), yet objective actigraphy data often reveal that women have longer total sleep time and higher sleep efficiency, creating a "subjective-objective paradox" [2]. Conversely, men, particularly from certain ethnic backgrounds, exhibit poorer objective sleep quality, with one study reporting a Sleep Fragmentation Index of 34.5% in African American men [3]. These disparities suggest influences beyond sociocultural factors, pointing to underlying biological mechanisms.

Research in this field has evolved from phenomenological descriptions to mechanistic explorations. Studies using animal models have confirmed that the suprachiasmatic nucleus (SCN), the master circadian pacemaker, exhibits sexual dimorphism in both structure and function [4]. Sex hormones act as key modulators, interacting with clock gene promoters via nuclear receptors to shape circadian phenotypes; for example, estrogen can enhance the amplitude of Bmal1 and Per2 expression, while testosterone may weaken rhythm stability [5]. Genetically, the association between polymorphisms like the PER3 VNTR and morning/evening preference shows sex-specific strength [6]. Emerging epigenetic research suggests that sleep duration during adolescence is linked to differential methylation patterns on the X and Y chromosomes, indicating that sex-specific epigenetic regulation may be a key mechanism [7].

Despite these advances, significant controversies and gaps remain. The causal direction of sleep-sex differences is unclear: do epigenetic changes drive sleep behaviors, or does sleep disruption trigger epigenetic adaptations? Mendelian randomization analyses have not fully resolved this question [8]. Furthermore, most studies focus on White and Black populations, leaving a scarcity of data on other groups, such as Mexican Americans. Research on hormonal mechanisms often relies on animal models, with limited clinical translational evidence, and genetic association studies frequently suffer from small sample sizes and poor reproducibility.

The motivation for this review is to systematically synthesize multi-level evidence on sex differences in sleep and circadian rhythms. From the perspectives of biological basis, neural regulation, hormonal modulation, and genetic factors, this review aims to dissect the mechanisms underlying sexual dimorphism. By integrating the latest research, it seeks to bridge the gap between basic science and clinical practice, providing a theoretical framework for developing sex-specific interventions for sleep disorders. This review will pay particular attention to dynamic changes across the lifespan (e.g., puberty, pregnancy, menopause/andropause) and discuss the integration of sex as a biological variable into precision sleep medicine.

2. Biological Basis and Neural Regulation

2.1 Sex Differences in Sleep Architecture

Sleep architecture, encompassing the distribution of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep and the structure of sleep cycles, demonstrates significant differences between males and females. Numerous studies indicate that women generally exhibit superior objective sleep quality, characterized by longer total sleep time (on average 0.3 hours longer than men) and higher sleep efficiency (ratio of total sleep time to time in bed) [2]. An actigraphy study of 838 adults over 50 revealed that non-Hispanic white women had a sleep efficiency of 91.2%, compared to 87.2% in African American men [3]. Paradoxically, despite better objective metrics, women self-report a higher prevalence of sleep problems (51.1%) than men (45.9%). This "subjective-objective paradox" highlights the need to consider sex-specific factors in sleep quality assessment.

Sex differences in sleep architecture evolve dynamically across the lifespan. During adolescence, differences become pronounced and complex. Epigenetic studies have found that female adolescents exhibit a unique hypomethylation pattern in X-chromosome inactivation (XCI) regions, while males show sleep duration-dependent CpG island methylation fluctuations in the male-specific region (MSY) of the Y chromosome [7]. These epigenetic variations may contribute to the differential vulnerability to sleep disorders observed between sexes during this developmental stage (Table 1).

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Table 1. Key Sex Differences in Sleep Parameters (Adulthood) [7]

Sleep Parameter	Typical Pattern in Females	Typical Pattern in Male	Notes
Total Sleep Time (TST)	Generally longer	Generally shorter	Difference is more consistent in objective (actigraphy) vs. subjective (self-report) measures.
Sleep Efficiency (SE)	Higher	Lower	Women often maintain higher SE into older age, though the gap may narrow.
Slow-Wave Sleep (SWS)	Percentage may be higher or similar in young adulthood; declines steeply after menopause.	Percentage may be lower; more gradual age-related decline.	Strongly influenced by hormonal status.
REM Sleep	Some studies suggest slightly higher percentage, particularly in younger women.	Slightly lower percentage.	May be more sensitive to hormonal fluctuations across the menstrual cycle.
Sleep Latency	Similar or slightly longer	Similar or slightly shorter	Subjective reports of sleep initiation problems are more frequent in women.
Sleep Fragmentation	Lower objective fragmentation, but higher subjective feeling of unrefreshing sleep.	Higher objective fragmentation, especially in older age and certain ethnic groups.	Links to different health risks (e.g., cardiovascular disease in men).
Sleep Parameter	Typical Pattern in Females	Typical Pattern in Males	Notes

2.2 Sexual Dimorphism in Circadian Rhythms

The core circadian clock, governed by a transcriptional-translational feedback loop of clock genes (e.g., CLOCK, BMAL1, PER, CRY), also exhibits sex differences. Research indicates that women tend to have an earlier endogenous circadian phase compared to men, meaning their internal clock runs at a slightly faster pace [9]. This manifests as a stronger tendency for morningness (being a "morning lark"), whereas men more frequently exhibit eveningness ("night owl") preferences [6]. This phase advance in women is observable in the timing of melatonin and core body temperature rhythms, which peak and decline earlier relative to clock time.

At the molecular level, the expression of core clock genes shows sex-specific patterns. In animal models, the amplitude of rhythmic expression for genes like Bmal1 and Per2 is often higher in females, an effect modulated by estrogen [5]. Genetic variations in these genes can also have disparate effects. For example, the CLOCK 3111T/C polymorphism has been linked to eveningness and greater sleep disruption, with some studies suggesting this association is stronger in women [10].

2.3 Neural Substrates: The Suprachiasmatic Nucleus (SCN)

The SCN is the central pacemaker of the circadian system, and its structure and function are not identical between sexes. Anatomically, the SCN has been found to contain a greater number of vasopressin-expressing neurons and to be larger in volume in males compared to females in some species, including humans [4]. Functionally, the SCN's response to phase-resetting stimuli, such as light, may differ. Evidence suggests that the female SCN might be more sensitive to the phase-shifting effects of light, particularly during specific hormonal states, which could contribute to the differences in circadian phase alignment.

The SCN is richly endowed with receptors for sex hormones, providing a direct pathway for hormonal modulation of circadian timing. The interaction between the SCN, sex hormones, and sleep-regulating nuclei (like the VLPO) creates a complex neural network that generates the observed sex differences in sleep-wake patterns. The differential wiring of this network is a primary focus of current research.

3. Hormonal and Genetic Modulation

3.1 The Role of Sex Hormones Across the Lifespan

Sex hormones (estrogen, progesterone, testosterone) are potent modulators of sleep and circadian rhythms, and their fluctuating levels throughout life contribute significantly to sex-specific patterns. Puberty: The surge of sex hormones during puberty amplifies sleep-circadian differences. The phase-delaying tendency of adolescence is often more pronounced in boys, aligning with their higher prevalence of eveningness.

The Menstrual Cycle, Pregnancy, and Menopause: In women, hormonal fluctuations have clear effects. During the luteal phase of the menstrual cycle, increased progesterone and estrogen can lead to poorer sleep quality and increased awakenings. Pregnancy is associated with significant sleep disruption due to physical and hormonal changes. Menopause, marked by a sharp decline in estrogen and progesterone, is a critical period where women's risk of developing sleep disorders (e.g., insomnia, OSA) increases dramatically, often linked to vasomotor symptoms (hot flashes) and circadian rhythm changes [1].

Andropause (in Men): In men, the gradual age-related decline in testosterone is associated with changes in sleep structure, including reduced slow-wave sleep and increased sleep fragmentation. While the changes are more gradual than in female menopause, they significantly impact sleep quality in older men (Table 2).

Table 2. Impact of Sex Hormones on Sleep and Circadian Parameters

Hormone	General Effect on Sleep	General Effect on Circadian Rhythms	Key Notes
Estrogen	Promotes wakefulness; tends to improve sleep quality (e.g., higher SWS).	Acts as a circadian *amplifier*; promotes phase advance.	Effects are complex and dose-dependent. The loss of estrogen at menopause is a major driver of sleep deterioration.
Progesterone	Has sedative and hypnotic properties; can promote sleep onset.	May have mild phase-advancing effects.	Its metabolite allopregnanolone is a potent GABA-A receptor agonist. Levels drop precipitously after menopause.
Testosterone	Associated with SWS percentage; decline linked to increased fragmentation.	May promote phase delay; associated with eveningness preference.	Administering testosterone to hypogonadal men can improve sleep, but its use as a supplement is complex.
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3.2 Genetic and Epigenetic Influences

Beyond the core clock genes, other genetic polymorphisms contribute to sex differences. A well-studied example is the variable number tandem repeat (VNTR) in the PER3 gene. The 5-repeat allele is linked to morningness, while the 4-repeat allele is associated with eveningness and greater sleep homeostatic pressure. Crucially, the association between PER3 VNTR and diurnal preference appears to be stronger in women than in men [6].

Epigenetics, which involves modifications like DNA methylation that regulate gene expression without changing the DNA sequence, provides a mechanism by which environment and behavior can interact with sex-specific biology. As mentioned earlier, sleep patterns in adolescence are linked to sex-chromosome-specific methylation patterns [7]. This suggests that social and behavioral factors (e.g., school start times, social activities) may leave different epigenetic marks on the genome in males and females, potentially having long-term consequences for sleep health (Table 3).

Table 3. Examples of Genetic Polymorphisms with Sex-Differentiated Effects on Sleep/Circadian Rhythms

Gene/Polymorphism	Function	Sex-Differentiated Effect	Gene/Polymorphism
PER3 VNTR	Involved in sleep homeostasis and circadian period.	Association with morningness/eveningness is stronger in females [6].	*PER3* VNTR
CLOCK 3111T/C	Core component of the positive circadian feedback loop.	Association with eveningness and sleep disruption may be more pronounced in females [10].	*CLOCK* 3111T/C
ABCC9	A gene associated with sleep duration.	A common variant has been shown to influence sleep duration in women but not in men.	ABCC9

4. Conclusion

This review consolidates evidence that sex is a fundamental biological variable shaping sleep structure and circadian rhythms. Key conclusions are that women often exhibit a phase-advanced, more robust circadian rhythm and better objective sleep efficiency, yet report more sleep complaints, particularly during periods of hormonal flux. Men are more prone to eveningness and objective sleep fragmentation. These differences arise from a complex interplay of neuroanatomical dimorphism in the SCN, the lifelong modulatory effects of sex hormones, and sex-specific genetic and epigenetic influences.

Future research should prioritize several avenues. First, longitudinal studies are needed to track the dynamic changes in sleep and circadian rhythms across the entire lifespan, capturing key hormonal transitions. Second, integrating multi-omics approaches (genomics, epigenomics, transcriptomics, metabolomics) in large, diverse cohorts will help unravel the precise biological pathways. Third, there is a critical need for clinical trials to test the efficacy of sex-specific interventions, such as hormone replacement therapy timed according to circadian principles or gender-tailored cognitive-behavioral therapy for insomnia. Ultimately, incorporating the concept of sex differences into the core of sleep medicine is essential for advancing both scientific understanding and clinical care, paving the way for true precision sleep medicine.

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