Sleep Medicine Reviews 75 (2024) 101926

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

Sex differences in sleep, circadian rhythms, and metabolism: Implications for precision medicine

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ARTICLE INFO

Handling Editor: M Vitello

Keywords:
Sex differences
Sleep
Circadian
Metabolism
Precision medicine

ABSTRACT

The number of individuals experiencing sleep loss has exponentially risen over the past decades. Extrapolation of laboratory findings to the real world suggests that females are more affected by extended wakefulness and circadian misalignment than males are. Therefore, long-term effects such as sleep and metabolic disorders are likely to be more prevalent in females than in males. Despite emerging evidence for sex differences in key aspects of sleep-wake and circadian regulation, much remains unknown, as females are often underrepresented in sleep and circadian research. This narrative review aims at highlighting 1) how sex differences systematically impinge on the sleep-wake and circadian regulation in humans, 2) how sex differences in sleep and circadian factors modulate metabolic control, and 3) the relevance of these differences for precision medicine. Ultimately, the findings justify factoring in sex differences when optimizing individually targeted sleep and circadian interventions in humans.

Glossary of terms

Actigraphy
The use of a wrist-worn device designed to gauge patterns of rest and activity.

Acrophase
Highest point of activity within a 24-hour period.

Core body temperature
The temperature of the body's internal organs.

Cortisol awakening response
The change in cortisol concentration in the first hour after waking up from sleep.

Circadian Rhythms
Natural rhythms with a cycle length of approximately 24 h, reoccurring even without fluctuations in light.

Circadian disruption
Disturbance of biological timing, which can occur at different organizational levels and/or between different organizational levels, ranging from molecular rhythms in individual cells to misalignment of behavioral cycles with environmental changes.

Circadian misalignment
Misalignment between the endogenous circadian system and 24-h environmental and behavioral cycles.

Cohen's D (d)
A statistical measure used to quantify the effect size of the difference between two groups in a research study.

Endogenous
Originating from within an organism.

Energy balance
The state achieved when the energy intake equals energy expenditure.

Epidemiology
The study (scientific, systematic, and data-driven) of the distribution (frequency, pattern) and determinants (causes, risk factors) of health-related states and events (not just diseases) in specified populations (neighborhood, school, city, state, country, global).

Forced desynchrony
An experimental design used in human circadian rhythm research to disentangle endogenous circadian rhythms from effects of homeostatic sleep pressure.

Ghrelin

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https://doi.org/10.1016/j.smrv.2024.101926
Received 11 November 2023; Received in revised form 16 February 2024; Accepted 18 March 2024
Available online 21 March 2024

Abbreviations

CAR	Cortisol Awakening Response
CBT	Core Body Temperature
fMRI	functional Magnetic Resonance Imaging
FSH	Follicle-Stimulating Hormone
ICD-10	International Classification of Diseases, Tenth Revision
IS	Interdaily Stability
IV	Intradaily Variability
LH	Luteinizing Hormone
NREM	Non-Rapid Eye Movement
OSA	Obstructive Sleep Apnoea
PSG	Polysomnography
REM	Rapid Eye Movement
RLS	Restless Legs Syndrome
SHBG	Sex Hormone Binding Globulin
TDM2	Type 2 Diabetes Mellitus

A hormone primarily produced in the stomach, often referred to as the "hunger hormone," as it plays a significant role in regulating appetite, hunger, and energy balance.

Glucose tolerance

The body's ability to regulate blood sugar (glucose) levels effectively after consuming a specific amount of glucose within a certain period.

Hedonic eating

The consumption of food for pleasure rather than for physiological hunger.

Insomnia

Difficulty falling asleep, staying asleep, or early morning awakenings more than three times per week for over three months.

Interdaily stability:

A measure of day-to-day stability or consistency of a rhythmic pattern over multiple days

Intradaily variation:

A measure of how consolidated the rest-activity rhythm is within a 24-hour period.

Jetlag

A temporary disorder that occurs when a person's internal biological clock is out of sync with the time zone they are in after traveling across multiple time zones.

Leptin

A hormone produced by fat cells (adipocytes) referred to as the "satiety hormone" because of its role in controlling hunger and appetite.

Melatonin

The nocturnal hormone secreted by the pineal gland during circadian evening *and* in the absence of external light information.

Menstrual cycle

A monthly hormonal cycle that prepares a woman's body for pregnancy.

Metabolic disease

A cluster of conditions that occur together, including hypertension, hyperglycemia, and cholesterol, increase the risk of heart disease, stroke, and type 2 diabetes.

Metabolism

The internal processes that convert nutrients from food and drinks into energy used for bodily functions.

Mesor

The average level of activity around which the daily rhythmic pattern fluctuates.

Obstructive sleep apnoea

A sleep-related breathing disorder involves a decrease or complete halt in airflow despite an ongoing effort to breathe.

Parasomnias

Unusual and undesirable physical events or experiences that can disrupt sleep.

Phase angle

The time difference between an internal circadian marker (such as the dim light melatonin onset) and a repetitive external event (such as the onset or offset of sleep).

Polysomnography

A diagnostic test that is conducted to evaluate and study sleep patterns and disorders, during which a patient is connected to various sensors and monitoring devices that measure brain activity, eye movements, muscle activity, heart rate, breathing patterns, and oxygen levels.

Pseudo-F

Used to assess the overall fit of the model to the observed rhythmic patterns in activity levels.

Restless legs syndrome

A neurological disorder characterized by uncomfortable sensations and the urge to move.

Sex differences

Sexually dimorphic traits.

Shift work

A work schedule that falls outside the typical 9 a.m. to 5 p.m. working hours.

Sleep

A condition of body and mind that typically recurs for several hours every night, in which the eyes are closed, the postural muscles relaxed, the activity of the brain altered, and consciousness of the surroundings practically suspended.

Sleep deprivation

The condition of not having enough sleep.

Sleep latency

The time it takes a person to fall asleep after intending to go to sleep.

Sleep quality

An individual's satisfaction with all aspects of the sleep experience. This can be assessed through either self-report or polysomnography.

Social jetlag

The misalignment between an individual's circadian rhythm and their socially imposed schedule occurs when people must shift their daily routines, such as waking up and going to bed, on workdays compared to non-workdays, leading to a kind of "jetlag" experienced not from traveling across time zones but from the inconsistency in sleep patterns.

Tau

The length of the intrinsic circadian period of an organism.

1. Introduction

Sleep is a crucial biological function for maintaining physical and mental health. According to the National Institutes of Health, 1 in 3 adults in the United States experience sleep deprivation, and 50 to 70 million Americans have chronic sleep disorders [1]. Historically, biomedical research has been biased against female and non-human female mammals. Justifications include the assumption that findings derived from male subjects are universally applicable or fearing that hormonal variations in females might add complexity to study designs and interpretation of results [2]. However, emerging studies have shed light on distinctive sleep patterns in males and females, including sleep quality, duration, latency, and architecture [3,4]. These variations may be rooted in differences in circadian rhythms, such as core body temperature and melatonin levels, which differ between the sexes [5,6].

The implications of these sex disparities in sleep and circadian biology are profound and extend to overall health. For instance, short-term sleep deprivation heightens the brain's response to pleasurable food stimuli, particularly in females, who exhibit 1.5 times higher limbic region activity in response to sweet foods than males [7]. Additionally, when individuals experience circadian misalignment, sex differences in metabolism become more pronounced, such that males engaged in shift

work have a higher risk of Type 2 Diabetes Mellitus (T2DM) than females [8,9]. As society moves towards a more personalized approach to healthcare, embracing technological advancements and evidence-based practices makes understanding these sex-based differences pivotal.

In this narrative review, we discuss the profound influence of biological sex on sleep, sleep disorders, circadian regulation, and their relevance to metabolic control in humans. Due to the limited research on this research topic, though it is expanding and holds high translational relevance, there are currently minimal evidence-based approaches applicable to precision medicine. This is the reason for conducting an unstructured narrative review instead of a systematic review, given the scarcity of randomized controlled trials on this central research topic. Our narrative review thus explores these differences and highlights their potential implications for crafting personalized interventions based on sex, leading the path toward precision medicine.

2. What are sex and gender differences?

Sex pertains to the biological and physical attributes that commonly differentiate males from females. It is determined by a combination of factors, including reproductive anatomy (such as genitals and reproductive organs), chromosomes (XX for females and XY for males in most cases), and hormones (such as estrogen and testosterone). Traditionally, sex has been categorized as male or female, but some individuals are born intersex, displaying variations in their sex characteristics that do not align with typical male or female definitions. In contrast, gender refers to the social, cultural, and psychological aspects of being male or female [10]. It encompasses the roles, behaviors, activities, and expectations a specific society deems appropriate for males and females. Unlike sex, which is primarily rooted in biological factors, gender is a social construct that varies across cultures and societies [10]. This narrative review focuses on sex-based differences between (pre-menopausal) females and males.

3. The menstrual phase

Females undergo hormonal changes over an average monthly cycle lasting approximately 26–30 days, while hormonal concentrations in males remain relatively constant [11]. The female menstrual cycle comprises four phases marked by shifts in reproductive hormones, including estrogen and progesterone, which influence mood, cognition, and other physiological processes that can introduce variability in the responses to experimental intervention [12]. Hormonal contraceptives, on the other hand, ranging from oral contraceptives to intrauterine devices, can impact hormonal profiles and thereby also influence study outcomes. Considering these factors is imperative as they can confound research findings, leading to misinterpretations or oversights in sex-specific effects. While recognizing the significance of considering menstrual phase and contraceptive use in sex-difference research, this narrative review does not delve into their intricacies. Instead, our focus is on acknowledging their importance and assessing whether the cited studies reported and controlled for these factors.

4. Sex differences in sleep

4.1. Self-reported sleep quality

In field and epidemiological studies, evaluating sleep quality is commonly achieved through self-report [13], utilizing questionnaires (such as the Pittsburgh Sleep Quality Index), or sleep-wake diaries. The perceived sleep quality is influenced by sex, such that females generally rate their sleep quality as lower than males [14], independent of differences in socio-demographical and/or lifestyle factors [15] (Fig. 1). Females are approximately twice as likely to develop anxiety disorders, which are associated with lower sleep quality [16]. While self-reported sleep quality does not correlate well with objective measures of sleep (with N2 sleep being the highest predictor of perceived sleep quality but merely explaining 7% of the variance [13]), the relationship between these measures tends to be better in males than in females [14]. Females report more monthly fluctuations in self-reported sleep quality, such that more sleep disturbances, including insomnia, frequent awakenings, non-restorative sleep, unpleasant dreams or nightmares, are reported during the premenstrual week and the first days of menstruation compared to other menstrual phases [17].

4.2. Objective sleep quality - Polysomnography

Sex-based differences in sleep as measured by polysomnography (PSG) have important implications for personalized sleep medicine and treatment approaches. PSG is currently considered the gold standard for measuring sleep in laboratories or clinics [18].

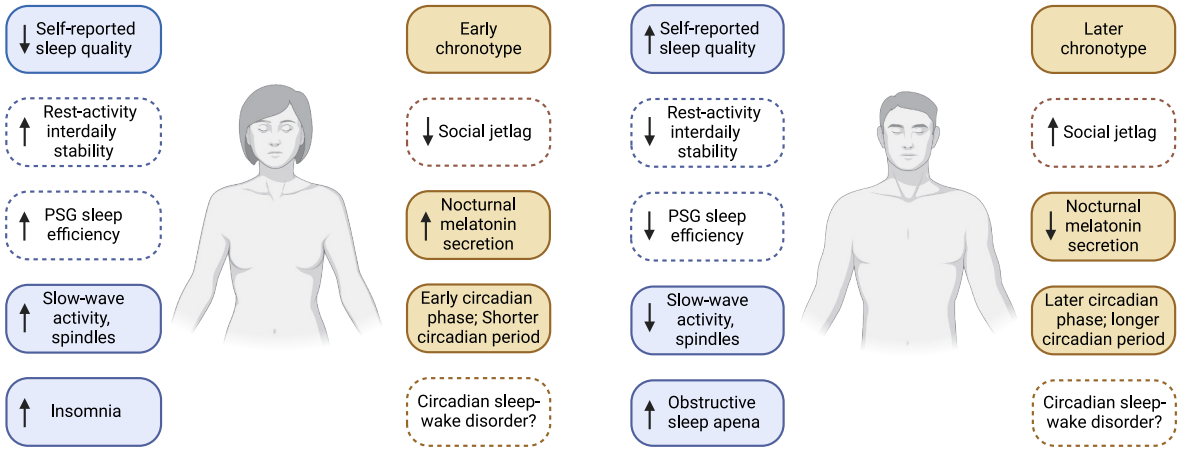

Fig. 1. Conceptual framework of sex differences in sleep and circadian rhythms. This schematic diagram encapsulates the current understanding of sex-based differences in self-reported sleep quality [13–16], rest-activity sleep-related parameters derived from wrist-worn wearables [86], laboratory-assessed sleep architecture and EEG activity [18–29,31–36], as well as the risk of sleep disorders (blue boxes) [4,37–48,51,53–56,145]. Likewise, it summarizes the current evidence on sex differences in self-reported circadian proxies as chronotype, social jetlag, laboratory-assessed melatonin secretion [6,69,70] [67] and circadian phase and period estimates [83–85], as well as circadian sleep-wake disorders (orange boxes). Bold-lined boxes (blue: sleep, orange: circadian) indicate robust evidence, whereas dashed-lines boxes (blue dashed lines: sleep, orange dashed lines: circadian) indicate preliminary evidence. Abbreviations: PSG: polysomnography; EEG: electroencephalography. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4.2.1. NREM sleep

In a laboratory-based study with 13 males and 15 females, variations in the duration of non-REM (NREM) sleep were observed, indicating slightly longer (~8 min) durations of NREM sleep in females [19], and 50% more delta frequencies during NREM sleep. While for 6 of the females, the exact menstrual phase was unknown, no recordings were made during menses, and the other nine females used oral contraceptives. These inconsistencies may have affected the reported findings. Due to differences in the experimental protocols, not all nights were terminated spontaneously. Therefore, total sleep time could not be compared between the sexes. A retrospective analysis of 6064 polysomnographically recorded sleep cycles revealed a minor sex-related difference [20]. In this study, the second NREM cycle was slightly longer for females at various menstrual cycle phases than for males (~10 min) [20]. Considering that the percentage of time spent asleep is higher in females (refer to 4.2.3 Sleep efficiency), it is probable that this time is dedicated to NREM sleep [21]. While the total amount of NREM sleep decreases with age, significant declines are reported in (40–80 years) older males than in females [22,23]. This may, in part, be influenced by changes in testosterone production, which progressively decreases at an average rate of 1–2% per year in males, starting at the age of 40 [24]. Compared to males with high testosterone levels, males with lower concentrations have a ~3% lower sleep efficiency, increased occurrence of nocturnal awakenings (±13 min), higher apnoea-hypopnea index (2.78 more apnoea and hypopnea events), and more sleep time (±14.5 min) with O2 saturation levels below 90% [25]. Currently, there is a lack of human studies documenting the influence of estrogen on PSG-recorded sleep, which \warrants consideration in future research.

4.2.2. REM sleep

The timing of REM sleep is earlier in females than males, particularly during the luteal phase of the ovulatory menstrual cycle (±16.3 min) [26]. Additionally, during the follicular phase, females tend to experience a rise in the percentage of time spent in REM sleep, increasing from approximately 25.2% (± 4.0%) compared to the luteal phase (20.5 ± 4.7%). This corresponds with elevated body temperature levels observed during the luteal phase [27].

4.2.3. Sleep efficiency

The percentage of time spent asleep is higher in females (76.8 ± 0.5%) than in males (74.0 ± 0.6%), when given a similar time in bed (477.0 ± 0.6 min in females and 475.4 ± 0.7 min in males) [21] (Fig. 1). These effects were evaluated without considering the menstrual phase or oral contraception usage. A comparable pattern is observed in female children (84.9 ± 6.0%) compared to male children (83.2 ± 5.7%) [28]. However, as individuals age (>58 years), differences in total sleep time and sleep efficiency based on sex diminish [29]. While there are statistically significant differences in sleep efficiency based on sex, their clinical relevance is yet to be determined. Females tend to have a marginally lower sleep efficiency during the premenstrual phase (96 ± 0.6%) compared to other menstrual phases (97 ± 0.4%) [30].

4.2.4. Sleep characteristics

Compared to males, females in the follicular phase of their menstrual cycle reportedly have higher slow wave sleep amplitude (5 μV), larger slow wave slopes (20 μV/s), and frequencies (0.05 Hz difference), possibly due to a greater neural slow wave sleep synchronization [31] (Fig. 1). Overall, females tend to have higher power densities during NREM (225 μV2) over a wide frequency range (0.25–11.0 Hz) [19], but these effects were assessed in a mixed population, with approximately half of the females using oral contraception and the others experiencing natural cycling. Although no recordings were conducted during menses, the authors did not provide information on the menstrual phase of the participants. Females also tend to have higher spindle density (7.25 more spindle responses/minute in N3 stage sleep) [32] and higher peak frequencies of both slow (11–13 HZ) and fast (13–15 HZ) spindles [33]. The menstrual phase at which measurements took place or the usage of oral contraception by participants were not reported in either study. The frequency of sleep spindle activity appears to correlate with variations in core body temperature, with the highest spindle frequency occurring during the luteal phase [34].

Sex-based differences in PSG might not be due to differences in brain waves per se. Differences between the sexes in skull structure, subscapular skin fold thickness [35], or skin conductance [36] influence PSG measurements and outcomes. Consequently, the reported disparities could be attributed to these factors rather than inherent sex-based differences in brain waves.

4.3. Epidemiology of sex differences in sleep disorders

4.3.1. Insomnia

Insomnia is associated with low self-reported sleep quality and more daytime dysfunction (American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). Washington, DC: American Psychiatric Pub; (2013). Insomnia is a major health challenge in the general population, and sex differences have been well-studied [37]. A large body of evidence shows that females are more often diagnosed with insomnia than males are (odds ratio [OR] = 1.58) [38, 39]. This could, in part, be due to many contributing factors to insomnia that are more prevalent in females than males (Fig. 1). For example, insomnia is strongly associated with major depressive disorder (OR = 2.83) and anxiety disorders (OR = 3.23) [40–42], which are also more prevalent in females [43]. Since females are more likely to report symptoms of insomnia, they are also twice as likely to report these to their physician [44], increasing the number of insomnia diagnoses [45, 46].

4.3.2. Obstructive sleep apnoea (OSA)

The diagnosis of OSA is almost three times more common in males than in females [47]. This difference may be attributed to the distinct manifestation of OSA symptoms in females, who tend to report more issues with insomnia and fatigue, while males often complain about excessive daytime sleepiness [47]. Factors contributing to the higher occurrence of OSA in males involve physiological variances in upper airway composition [47] and differences in neuromuscular reflexes to upper airway collapse [48]. In females, upper airway resistance is affected by the menstrual phase, with lower resistance observed in the luteal phase (5.69 ± 3.88 cm H2O/L per second) compared to the follicular phase (7.68 ± 4.68 cm H2O/L per second) [49]. OSA may, therefore, be overlooked in a diagnostic study conducted in the luteal phase.

The presence of OSA in females is associated with a heightened risk of heart failure, which is not observed in males (OR: 1.25 [1.02–1.52] for females, and 0.98 [0.84–1.14] for males) [50]. In a follow-up conducted 13 years later within the same study, it was observed that females had a greater occurrence of mortality compared to males (HR: 1.26 [1.05–1.50] for females and 1.12 [0.98–1.29] for males) [50]. Notably, fat mass distribution can pose a risk factor for OSA in both sexes, with visceral adiposity as a risk factor for OSA in males, while in females, fat around the upper airway contributes to OSA [49]. Despite persistent assumption, testosterone levels most likely play a minor role in exacerbating or inducing changes in OSA [51]. The occurrence of OSA in females increases two-fold following menopause, regardless of age and body mass index. Of note, the highest prevalence is observed at 65 years, 10 years later than in males [52].

4.3.3. Restless legs syndrome (RLS)

RLS is primarily attributed to fluctuations in dopamine levels, and females have a 25–50% higher likelihood of developing RLS than males due to these fluctuations [53]. Estrogen, a hormone that suppresses dopamine release [54], is also believed to play a role in the risk of RLS

[55].

4.3.4. Parasomnias

Sleep-related eating disorder, a prevalent parasomnia characterized by repetitive eating episodes during sleep, occurs 1.5 to 4 times more frequently in females [56]. There is limited evidence suggesting increased premenstrual sleep terrors and sleepwalking [57].

4. 4. Summary

- Self-reported sleep quality is influenced by sex differences, such that females tend to rate their sleep quality as lower than males.
- PSG measures highlight marginal but statistically significant variations between males and females in NREM and REM sleep.
- Females exhibit a higher prevalence of insomnia, RSL, and parasomnias, whereas males demonstrate a higher prevalence of OSA.

5. Sex differences in circadian rhythms

Circadian rhythms are physical, mental, and behavioral changes that follow a 24-h cycle and are sustained in the absence of external time cues. These natural processes respond primarily to the light-dark cycle and affect most living organisms, including humans, animals, plants, and microbes. Female reproductive physiology in humans is under robust circadian control [58,59]. A recent meta-analysis of 16 cohorts (n = 123,403) showed that females engaged in shift work (which can disrupt circadian rhythms) have increased odds of menstrual cycle disruption and infertility by ~22% and ~30%, respectively, compared with females not engaged in shift work [60]. Hormones related to these functional outcomes have been reported to exhibit 24-h rhythms under normal sleep-wake, meal, and lighting conditions [61]. Under stringently controlled circadian laboratory protocols, endogenous circadian regulation of plasma estradiol, progesterone, Follicle-stimulating hormone (FSH), Luteinizing Hormone (LH), and sex hormone binding globulin (SHBG) exhibited robust circadian ~24-h rhythms during the follicular phase. In contrast, only FSH and SHBG were rhythmic during the luteal phase [58].

Male reproductive physiology also follows circadian, weekly, monthly, and annual rhythms, with the circadian rhythm being the most extensively studied aspect [62]. Testosterone secretion in males shows diurnal fluctuations, with the highest levels (750–800 ng/dL, 26–28 nmol/L) around awakening, followed by a decline throughout the day, with the nadir occurring in the late afternoon (with concentrations of 500 ng/mL, 17 nmol/L). Such fluctuations are due to changes in testicular testosterone secretion rather than changes in metabolic clearance [62]. A recent study showed that males engaged in shift work had statistically significantly lower total and free testosterone (effect size (Cohen's d) = 0.75). However, this study had a small sample size (n = 8 shift workers and n = 4 day workers) [63] that warrants therefore replication in larger cohorts. Other studies show that shift work in males associates with decreased fertility, low sperm count (OR = 2.11) [64], and other parameters of low semen quality [65]. Currently, there is a lack of established evidence regarding potential sex differences in circadian sleep-wake disorders, such as shift work disorder and advanced/delayed sleep phase disorder.

In humans, biomarkers indicating central circadian rhythms include the timing of melatonin production onset, cortisol peak production, core body temperature minimum in both females and males, and testosterone secretion, specifically in males [66]. Systematic sex differences in biomarkers of peripheral rhythms, including cardiovascular, metabolic (glucose and insulin), endocrine, and immune system rhythms, are yet to be described.

5.1. Melatonin

The timing, nocturnal peak, and suppression of the melatonin signal have been measured in humans. In a study where age, habitual bedtime, and wake time were standardized across sexes, melatonin secretion follows circadian rhythms, with females showing an earlier timing (22:49 ± 1.45 h) compared to males (23:28 ± 1.27 h) [6](Fig. 1). Phase angle (i.e., the relationship between the timing of the circadian clock and the timing of an external time cue) did occur at a later circadian phase for females (1.34 ± 0.96 h) than males (0.75 ± 0.83 h), despite being at the same external clock time [6]. However, in this study, menstrual cycle was not controlled.

Under real-world conditions, on average, males tend to be later chronotypes (i.e., prefer to go to bed and wake up later) [67]. Consequently, this predisposition leads to a higher incidence of social jetlag, characterized by a greater misalignment between their natural circadian rhythm and the schedule imposed by societal demands [67]. Females exhibit a nocturnal peak in the melatonin rhythm that is 38%–41% higher than males [6,68]. However, neither study controlled for the menstrual cycle, thus, outcomes may have been influenced by the menstrual phase. Nevertheless, the suppression of melatonin production, triggered by exposure to bright light *after* melatonin production has begun, does not appear to be influenced differently by sex [69,70].

5.2. Cortisol awakening response (CAR)

Cortisol can serve as a circadian marker; however, demonstrating an endogenous circadian rhythm requires highly controlled laboratory studies. Only a limited number of studies have employed such approaches, and not all of them have reported sex differences, as endogenous circadian melatonin and CBT rhythms often take precedence as primary circadian endpoints in these studies. The few studies that did measure CAR levels report mixed results, with some suggesting a more robust and sustained (~25 min) increase in cortisol levels after waking in females [71–74], while other studies do not observe these differences [75,76]. Crucially, studies noting sex differences in the CAR indicate minimal effect sizes, with sex accounting for only 1–3% of the observed variability [71,72,77]. While previous studies suggested an increased CAR during ovulation or an attenuated CAR during menses, more recent ones indicated no effect of the menstrual phase on the CAR [78–80].

5.3. Core body temperature (CBT)

Typical CBT fluctuates between 36.5 and 37.4 °C, reaching its highest ;evel before sleep onset and its lowest level a few hours before waking up. The hypothalamus regulates this thermoregulatory setpoint and is governed by circadian rhythms [81], but CBT is also under the influence of menstrual cycle, such that CBT is 0.3 °C–0.7 °C higher in the post-ovulatory luteal phase compared with the pre-ovulatory follicular phase [82]. In terms of the timing of CBT, consistent with the onset of melatonin production, the nadir of CBT is also earlier in females (04:46 ± 1.93 h) than in males (06:11 ± 1.32 h) [5,6], with an overall dampened amplitude of the rhythm in females (0.43 ± 0.13 °C) compared to males (0.55 ± 0.16 °C), when not controlling for menstrual phase [6].

5.4. Circadian period length (tau)

Research findings reveal slightly shorter intrinsic circadian periods in females (24.09 ± 0.2 h) compared to males (24.19 ± 0.2 h) [6], a difference equivalent to ~10% of the total range of interindividual variations in human tau, which averages ~24.2 h [83]. This variance corresponds with the earlier timing observed in melatonin, cortisol, and CBT rhythms (Fig. 1). Despite seemingly minor, this disparity translates into an approximately five times larger circadian phase angle difference between the central clock and the sleep/wake cycle [84]. It is thought that the higher occurrence of sleep disorders, such as insomnia, might be related to this difference in period length [85].

5.5. Circadian metrics derived from actigraphy

Standard methods used to analyze actigraphy data include extended cosinor and non-parametric analyses. Extended cosinor analysis show that females typically exhibit a slightly later acrophase (14:47 h) than males (14:36 h) [86]. The pseudo-F statistic, indicating the similarity of the rest-activity signal to a sine wave, shows a better sine fit for females (271.62 ± 6.51) than males (205.97 ± 4.50). Notably, no significant differences are reported in the amplitude of the rest-activity rhythm (14.01 ± 0.11 Monitor-Independent Movement Summary (MIMS)/min in females and 13.67 ± 0.15 MIMS/min in males) or the mesor (8.17 ± 0.05 MIMS/min in females and 8.01 ± 0.08 MIMS/min in males) [86]. Non-parametric analysis of the rest-activity signal also reveals sex-specific distinctions. Females tend to maintain a more consistent rest-activity schedule, as indicated by marginally higher interdaily stability (0.37 ± 0.002) compared to males (0.36 ± 0.002) [86]. Additionally, females experience lower levels of sleep-wake fragmentation, with an intradaily variation of 0.42 ± 0.001 in females, compared to 0.45 ± 0.002 in males [86]. While these reported differences are statistically significant, it has to be noted that they are marginal, possibly stemming from a lack of correction for the menstrual phase, and that the utility of such differences remains to be determined.

5.6. Summary

- Circadian rhythms play an important role in regulating most reproductive hormones in females, and disruption of circadian rhythms (as potentially experienced in shift work) may increase the the odds of menstrual cycle disruptions and infertility.
- Circadian rhythms influence testosterone secretion, and shift work has been associated with lower testosterone levels, decreased fertility, and low semen quality.
- Circadian biomarkers, such as melatonin, cortisol, and core body temperature, show an earlier timing in females and a shorter circadian period length. These differences may contribute to sex-specific sleep disorders, such as insomnia.

6. Sex differences in sleep and circadian factors affect metabolic control

6.1. Sleep disturbances and metabolic control

The global increase in obesity is primarily linked to excessive calorie consumption triggered by constant food cues and the widespread availability of energy-dense foods [87]. Food desirability regulated in the human frontal and insular cortex is influenced by sleep deprivation [88]. Over 30% of adults aged 30–64, both males and females, report sleeping less than 6 hours per night, which may be a key contributor to the inrease in obesity [89].

6.1.1. Hedonic eating

Hedonic eating is often driven by cravings for food high in sugar, salt, and/or fat, which can activate reward centers in the brain, leading to feelings of pleasure and satisfaction. Acute sleep loss enhances hedonic stimulus processing in the brain underlying the drive to consume food, a potential mechanism to restore energy in the brain [90,91]. Growing evidence indicates dramatic sex differences in hedonic eating and underlying brain activity [92,93]. For instance, brain networks associated with cognitive/affective processes (within e.g., orbitofrontal cortex, amygdala, insula) had a two-fold higher activation during exposure to pictures of food stimuli in females than in males [93] (Fig. 2).

Moreover, females demonstrate 1.5 times higher activation in the limbic region in response to sweet food stimuli compared to males [94]. Collectively, these findings suggest that females display heightened brain activation in response to food stimuli, and estrogen maybe implicated in such motivational and reward processes [95]. However, neither study assessed menstrual phase, thus a definitive relationship between estrogen and hedonic eating cannot be determined. Conversely, when measuring food intake as opposed to parameters of brain activation, males tend to overeat to a greater degree than females in response to sleep loss, with a greater increase in caloric intake (d = 0.62) and higher consumption of a more significant percentage of daily calories during late-night hours (d = 0.78) [96]. In males only, more sleep fragmentation, longer sleep onset latency, and lower sleep efficiency associate with more hunger (β = 0.115 ± 0.037; β = 0.169 ± 0.07; β = −0.150 ± 0.055, respectively) [97]. Females using oral contraceptives were excluded from this study, but the menstrual phase was not assessed.

6.1.2. Glucose tolerance

Lack of sleep can disrupt various physiological processes essential for glucose tolerance, such as insulin sensitivity, hormonal balance, stress responses, and inflammation. Research has demonstrated that after five days of sleep restriction, glucose clearance rate slowed by almost 40% (1.45 ± 0.31 percentage glucose clearance per minute), in contrast to well-rested conditions (2.40 ± 0.41 percentage glucose clearance per minute). This suggests a significant decrease in glucose tolerance under sleep-deprived conditions [98] (Fig. 2). Other experimental studies have shown that sleep restriction (typically 4–5.5 h of sleep per night for 5 to 14 nights) decreases insulin sensitivity by 18–24% without concurrent increases in insulin levels, leading to diminished glucose tolerance [7]. Although the evidence linking sleep deprivation to changes in glucose tolerance and insulin sensitivity is compelling, most of these studies have only involved male participants.

6.1.3. Appetite-Stimulating hormones

Leptin, which is a long-term mediator for satiety, and ghrelin, a fast-acting hormone that increases hunger, are hormones that control energy balance and caloric intake. Studies suggest that recurrent partial sleep deprivation and chronic short sleep lead to a statistically significant decrease in leptin levels (from 2.5 ± 0.6 to 2.0 ± 0.5 ng/ml) and an increase in ghrelin levels (from 2.5 ± 0.2 to 3.0 ± 0.2 ng/ml) [7,99] (Fig. 2). Nevertheless, conflicting results persist; certain studies demonstrate no sleep-deprivation-related effects on leptin concentrations, and a comprehensive meta-analysis found no consistent impact of sleep restriction on ghrelin [99,100]. However, significant variability was observed across studies. Sex differences could be a potential source of this variation, but the lack of research in this area, owing to insufficient representation of both sexes, hampers definitive conclusions.

6.1.4. Metabolic disorders

Numerous studies have explored the relationship between sleep duration, obesity, and T2DM. In a systematic review, shorter sleep duration (less than 6 h) has been linked to higher odds of obesity (OR = 1.55, 95% CI: 1.43–1.68) [101]. Paradoxically, longer sleep duration (more than 8 h, based on self-report) in older individuals (57–97 years) has also been associated with obesity, showing a 193% increased relative risk [102]. However, some studies conducted in a similar age population (51–72 years) and using self-reported methods for assessing sleep duration do not validate these outcomes [103] (Fig. 2). In adolescents, longer self-reported sleep duration has been linked to a higher risk of T2DM (OR 1.52, 95% CI: 1.05, 2.20) [7]. While reports on sex-related differences in sleep duration are limited, there is significant variation in self-reported sleep quality, with females frequently rating their sleep quality lower [refer to section 2.2 Self-reported sleep quality]. Inadequate sleep quality is associated with a heightened risk of metabolic syndrome. An in-laboratory study (n = 200, 57% males) show that a 2.6-point increase in the Pittsburgh Sleep Quality Index, indicating lower self-reported sleep quality, was associated with a 1.44-fold increase in the likelihood of having metabolic syndrome [104].

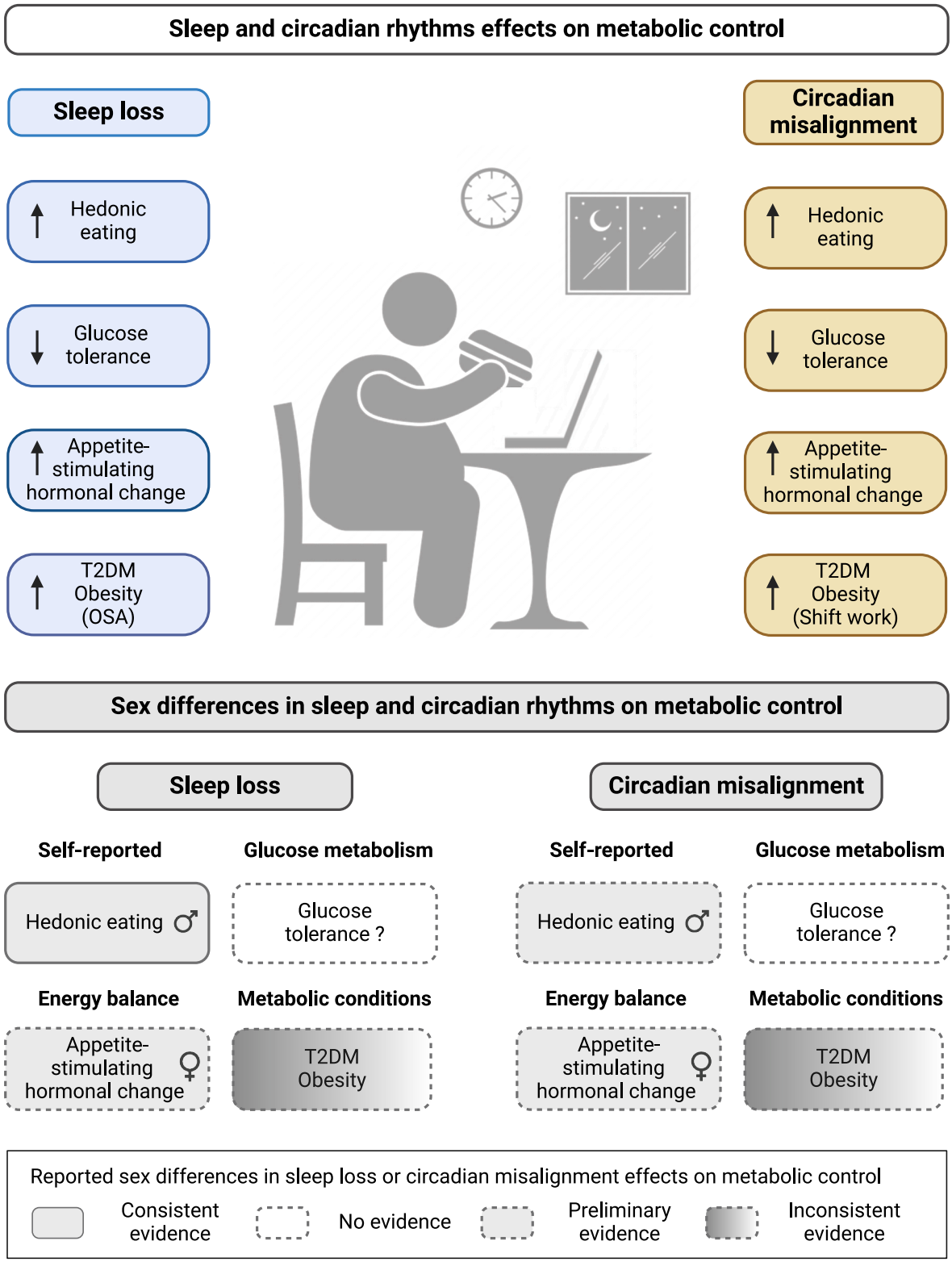

Fig. 2. Research landscape of sex differences in sleep and circadian rhythms implicated in metabolic control. The upper section of this schematic diagram encapsulates the current understanding of sleep loss effects on self-reported hedonic eating [90–96], laboratory-assessed glucose tolerance (e.g., glucose levels, insulin sensitivity) [7,98], and appetite-stimulating hormonal change (e.g., leptin and ghrelin levels) [99,100], as well as the risk of metabolic diseases (upper left panel, blue boxes) [101–104]. The lower section of the figure depicts sex differences in circadian phase and circadian misalignment effects on self-reported hedonic eating [108,109], laboratory-assessed glucose tolerance [110,111], and appetite-stimulating hormonal change [111–115], and the risk of metabolic diseases (upper right panel, orange boxes) [8,9,116,117]. Lastly, it illustrates the shifting landscape of potential sex differences in sleep and circadian rhythms effects on metabolic control, highlighting knowledge gaps in the field. Abbreviations: T2DM, type 2 diabetes mellitus. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

6.2. Circadian rhythms and metabolic control

The circadian clock regulates the timing and synchronization of various metabolic processes, including glucose tolerance, lipid balance, olfactory sensitivity and acuity, and energy usage [105,106]. Consequently, circadian phase significantly influences most of these metabolic parameters. This influence is evident in studies demonstrating circadian misalignment's independent effects on metabolic measures, as well as the impact of behavioral cycles and circadian phase [107].

6.2.1. Hedonic eating

The circadian clock regulates the hedonic aspect of eating [108]. Dysregulation of central structures in the metabolic and hedonic eating pathways is primarily linked to physiological and pathophysiological eating behaviors, including compulsive eating, obesity, and diabetes [108]. Of those working night shifts, exhacerbated emotional eating occurred in 66.4% of the females, but their menstrual phase or choice of contraception was not assessed [109] (Fig. 2). Albeit speculative, such sex differences in sleep and circadian factors underlying hedonic eating might also contribute to sex-specific risks for cardiometabolic disorders through different eating behaviors in males and females.

6.2.2. Glucose tolerance

In healthy humans, glucose tolerance has a robust time-of-day variation, with a peak in the morning and a trough in the evening and night. The extent of the daily fluctuation in glucose tolerance is remarkable: individuals with standard glucose tolerance in the morning exhibit metabolic levels akin to those with prediabetes in the evening [110]. Crucially, disturbances in circadian rhythms adversely affect metabolic control and contribute to the development of metabolic disorders. Circadian misalignment induced by shift work, jetlag, night lifestyles, etc., resulting from inappropriate exposure to light, irregular sleep patterns, or mistimed meals can significantly deteriorate glycaemic control in humans [107]. Even a short exposure to circadian misalignment can elevate postprandial glucose levels by 11–21% [111] (Fig. 2). Currently, there is a lack of human studies examining sex-based differences in the effects of circadian misalignment on glucose tolerance.

6.2.3. Appetite-stimulating hormones

Some research has suggested a circadian influence on leptin levels, with a 21% difference between its peak during the biological night and trough during the biological morning [112]. However, a recent forced desynchrony study revealed that leptin levels are not subject to circadian modulation but were instead influenced by meal timing [111]. Likewise, there is some evidence that the levels of the hormone ghrelin are not dependent on time of day but are influenced by sleep patterns, regular mealtimes, and postprandial glucose levels [113]. Conversely, some studies report circadian fluctuations in ghrelin fasting levels. Typically, these levels reach their lowest level in the morning (109.20 $\pm$ 22.45 pg/ml) and with a peak in the evening (123.30 $\pm$ 23.98 pg/ml) [114]. In a recentl within-subject laboratory protocol, acute exposure to circadian misalignment had a differential effect on the energy balance between females and males, such that females had decreased 24-h average levels of leptin (7%) and increased wake levels of ghrelin (6%) [115]. Conversely, males had increased leptin levels (11%) but no change in ghrelin, suggesting they may be less likely to overeat under circadian misalignment (Fig. 2). Although females were enrolled in the protocol at various menstrual phases (two in the follicular phase and four in the luteal phase), they were admitted during the same menstrual phase for both visits.

6.2.4. Metabolic disorders

Irregular meal patterns and nocturnal eating, common in individuals with disrupted circadian rhythms or those engaged in shift work, can disrupt the synchronization between the central circadian clock and peripheral clocks. This state of internal desynchronization is hypothesized to increase the risk of developing obesity and T2DM. Epidemiological studies on sex differences in the metabolic consequences in adults engaged in shift work report conflicting findings. While there might be a higher risk of T2DM in males engaged in shift work (OR = 1.37, 95% CI 1.20 to 1.56) compared to females (OR = 1.09, 95% CI 1.04 to 1.14) [8], other studies report that females engaged in shift work may have higher T2DM risk (OR = 1.42, 95% CI 1.39–1.45) than males in shift work (OR = 1.06, 95% CI = 1.04–1.01) [9] (Fig. 2). Regardless, both females and males working night shifts have a higher likelihood of developing T2DM compared to those not working shifts (OR = 0.96, 95% CI 0.94 to 0.99 for females, and OR = 0.99, 95% CI 0.98 to 1.01 for males) [9]. Epidemiological data from a large Swedish working sample revealed similar odds of obesity for males (OR, 95% CI: 1.44, 1.27–1.64) and females (OR, 95% CI: 1.39, 1.25–1.55) engaged in shift work after accounting for age and socioeconomic status [116], but not menstrual phase. Others, however, have indicated that females working 1–2 night shifts per week were 1.46 times more likely to be overweight or obese than those working day shifts. At the same time, no such association is observed in males [117].

6.3. Summary

- Following sleep deprivation, females exhibit greater activation in motivational and reward processes in response to food, but males tend to overeat to a greater degree.
- The limited research on sex-specific differences in glucose tolerance, leptin and ghrelin concentrations, and the prevalence of metabolic disorders under conditions of sleep deprivation, emphasizes the necessity for thorough and comprehensive investigations.
- Among individuals engaged in shift work, females often exhibit overeating, decreased levels of leptin, and increased levels of ghrelin, whereas males experience increased leptin levels without changes in ghrelin. Research data on metabolic disorders indicates an elevated risk of T2DM in both males and females due to shift work compared to those not working shifts, with additional correlations to obesity observed specifically in females. There is a lack of human studies examining sex-based differences in the effects of circadian misalignment on glucose tolerance

Exploring sex differences in sleep and circadian factors affecting metabolic control reveals a multi-faceted landscape. Understanding this complexity is not only essential but also transformative, serving as a cornerstone for the future of personalized sleep and circadian medicine.

7. Moving towards precision medicine: Potential sex differences in promising interventions

As technology advances and more evidence emerges regarding its efficacy, our society is shifting away from a standardized approach to healthcare. Instead, we are embracing a more precise and personalized system that enhances the likelihood of positive outcomes while minimizing the potential for adverse effects. This movement towards precision medicine recognizes the potential influence of sex differences, particularly in pharmacokinetics, necessitating distinct approaches for females and males [118]. In the upcoming sections, we discuss treatment options that can help alleviate symptoms related to sleep or circadian rhythm disturbances while also considering their ramifications on metabolic health. Most of these interventions represent a newly emerging field where research is beginning to explore sex-based differences. The findings are frequently derived from retrospective, underpowered, and primarily proof-of-concept studies.

7.1. Sex differences in sleep disorder interventions

7.1.1. Insomnia

Cognitive Behavioural Treatment for insomnia (CBT-I) is considered

the first-line treatment for insomnia and consists of a multicomponent psychological intervention often delivered by a psychologist [119]. Until now, no sex differences exist in CBT-I success rate or adherence, despite a higher enrollment of females compared to males [44]. This trend may stem from differences in insomnia diagnoses based on sex [38], sex-based acceptability to CBT-I [120], including the higher likelihood of females seeking healthcare services and therapy, and their increased comfort in seeking treatment. This highlights the need for future research to enhance insomnia diagnosis in males and promote the adoption of CBT-I in males.

Differences in pharmacokinetics between males and females are notable in various treatments. For instance, zolpidem, a non-benzodiazepine hypnotic that improves sleep quality in those with insomnia or OSA, exhibits significant sex-based variations. In a four-way crossover study, healthy female and male participants were administered an equal zolpidem dosage. However, females exhibited a higher maximum concentration (77 ± 24 ng/mL in females, compared to 53 ± 14 ng/mL in males) and a considerably slower clearance (179 ± 66 mL/min for females and 307 ± 250 mL/min for males). These findings suggest that females prescribed zolpidem may require a significantly lower dosage than their male counterparts [121]. If prescribed a similar dosage, females may face an increased risk of impaired next-morning driving and activities requiring full alertness due to lingering sleepiness. Further investigation is needed to determine if the menstrual phase influences pharmacokinetics in this context.

7.1.2. OSA

OSA is twice as common in people who are overweight or obese [122]. Yet, in a recent observational cohort study comprising 79 males and 79 females of similar ages at baseline, all undergoing weight loss management through bariatric procedures (69 gastric bypass and 10 sleeve gastrectomy each), it was observed that weight loss proved to be a more successful treatment for females with OSA. Although there were no statistically significant differences between males and females in the mean percentage of excess BMI loss, a higher rate of females (90%) discontinued CPAP treatment than males (77.5%) [123]. To some extent, this difference might result from sex-based variations in fat mass distribution [49].

7.2. Sex differences in circadian interventions

7.2.1. Light

Light is the main entrainer of the circadian system and can be used to enhance the entrainment process when working rotating night shifts or traveling over time zones [124]. It is also a standard treatment method to change the phase angle of entrainment in late chronotypes or other ICD-10 classified disorders, including delayed or advanced sleep phase syndrome, free-running disorder, shift work disorder, and jetlag. Some studies suggest that males are more sensitive to lower light intensities, such that males perceive the same light as significantly brighter (mean ± SEM: 85.6 ± 4.5 on a Visual Analogue Scale) compared to females (mean ± SEM: 67.8 ± 4.8) [125]. A recent review suggests that our understanding of the underlying mechanisms of individual differences in light sensitivity is still in its infancy, indicating much more to discover in this field [126]. However, a recent randomized controlled trial suggests that females exhibit higher melatonin suppression than males when exposed to the same light intensity (at 400 lux: 93.7 ± 9.6% suppression in females and 83.2 ± 18.7% suppression in males; at 2000 lux: 99.5 ± 1.0% suppression in females vs. 96.9 ± 4.3% suppression in males). Sex-based differences disappear under lower-intensity lighting (10–200 lux) and remain independent of the menstrual phase or sex-hormone concentration, implying that females are more sensitive to high-intensity lighting across the menstrual cycle [127].

7.2.2. Melatonin

The circadian system can be synchronized through the strategic use of external melatonin adminstration, a method frequently utilized to align phase angle of entrainment. For instance, when aiming to correct a late circadian phase in those experiencing Delayed Sleep-Wake Syndrome, melatonin is typically administered around 5 h before DLMO [128]. Some studies indicate that, following a nocturnal intravenously (i.v.) 20 μg melatonin infusion (from 21:00 to 01:00 h), melatonin levels were 1.4–3 times higher in females compared to males [129], suggesting enhanced bioavailability of exogenous melatonin in females. However, when administered at midday with a dose of 23 μg, there were no observed sex-based differences [130]. Neither study considered the menstrual phase. The impact of these differences in bioavailability on circadian clock entrainment remains to be investigated.

7.3. Sex differences in chrono-metabolic interventions

7.3.1. Chrono-nutrition

Dietary advice for metabolic health is primarily aimed at the quantity and quality of nutrition. As evidence is emerging that the circadian system can interact with nutrients to influence bodily function, there is a growing awareness of the importance of nutrient timing. Experimental studies in humans have demonstrated that the timing of nutrient ingestion during the day can have diverse effects on energy utilization, hunger and appetite, and glucose control [110,131]. This may contribute to the association of misalignment between mealtime and the circadian system (i.e., late eating, night eating) with higher obesity risk [132]. Recent dietary intervention trials incorporating nutrient timing broadly encompass three approaches: 1) time-restricted eating (TRE), defined as eating within a consistent time window and fasting for the rest of the day; 2) early meal schedule by advancing meals to earlier in the daytime without changing fasting duration and energy intake; 3) early calorie loading by shifting distribution of calorie intake to morning (large breakfast, small dinner) without changing the timing of each meal. Among them, TRE is the most studied, and a recent meta-analysis reported that TRE moderately reduces body weight by −1.60 kg (95% CI −2.27 to −0.93) [133]. In particular, early TRE rather than later TRE also benefits glycemic control and blood pressure [134]. Proof-of-principle clinical trials have demonstrated that early meal schedules and calorie loading lower appetite and hunger, with early meal schedules also increasing daytime energy expenditure [135,136]. These studies indicated that modifying nutrient timing could be an alternative and feasible dietary intervention for metabolic health. It is worth noting that sex-dimorphic responses to dietary intervention and nutrient metabolism are well-recognized [137]. Thus, there may also be sex differences in chrono-nutrition. However, there is very limited data to address this question.

7.3.2. Exercise timing

Current exercise and physical activity guidelines focus on intensity, duration, frequency, and modality. The potential influences of exercise *timing* have started to surface recently. Some human studies demonstrated that afternoon/evening exercise is more efficacious than morning exercise in improving glucose metabolism [138–140]. Accumulating observational studies reported associations between the timing of objectively measured physical activity and cardiovascular health, including sex-dependent association with cardiovascular risk [141]. Given the prominent sex differences in exercise physiology [142], it is possible that the impact of exercise timing differs by sex. As females may have an earlier circadian phase than males (refer to section 5), future research on the timing of exercise and nutrition may need to factor in such potential sex differences to achieve maximal benefit.

7.4. Summary

- Insomnia Interventions: CBT-I success rates and adherence show no sex differences, but higher female enrollment may be influenced by factors like insomnia diagnoses and treatment acceptability.

- OSA Interventions: Weight loss is more successful in treating OSA in females, and sex-based variations in drug metabolism, such as Zolpidem, pose distinct risks for females, impacting treatment outcomes.
- Circadian Interventions: Light sensitivity varies between sexes, with subjective ratings of light intensity suggesting that males are more sensitive, although physiological responses indicate that females might be. Melatonin bioavailability exhibits sex-based differences, with higher concentrations in females. Sex-based differences in chrono-nutrition and exercise timing remain to be investigated.

8. Conclusions & future directions

The role of sex-based differences in sleep and circadian effects on metabolic control and its implication for precision medicine is an emerging area of research with far-reaching consequences. Collectively, the data reported in this review highlight that we need to adopt multifaceted approaches to address such a knowledge gap.

The first is a broader general consideration of sex differences in research per se, ranging from participant recruitment and selection of study designs to statistical robustness. For instance, many studies do not have an equal distribution of females and males, do not distinguish the (social construct) gender from the (biological construct) sex, and do not factor in the interplay of intersectional identities (i.e., interaction with age, race, and socioeconomic class). Moreover, virtually all studies to date are retrospective, not adequately powered, and/or not designed to test sex as an a priori independent variable of interest. This is a concern that has only recently been recognized and addressed by grant funding agencies, such as the National Institute of Health in the United States [143]. There is a need for more rigorous study designs, including human experimental studies, to investigate the underlying mechanisms and causal relationships between sleep, circadian biology, and metabolic outcomes in both males and females. To some degree, such studies can separate gender and sex-specific contributions. By experimentally controlling external factors, the systemic differences in environment and behaviors between males and females resulting from social construct (e.g., socioeconomic status, household responsibility, types of shift work) can be limited.

Furthermore, it is also worth mentioning that considering the menstrual phase and changes in sex hormone concentrations in study designs should become standard practice. The few studies that a priori investigate sex-based differences often do not correct for the usage of (oral) contraception or the menstrual phase at which effects were assessed. This is imperative because 1) changes in sex hormones can influence self-reported sleep quality, and sleep architecture [17,26,60]; 2) hormonal changes associated with the menstrual phase are known to affect appetite control and energy metabolism [144]; 3) vulnerability to circadian/sleep disruption may vary by menstrual phase [59]. By incorporating the above approaches, we will gain a better insight into sex-based differences in sleep, circadian system, and metabolism. Such knowledge is essential for developing targeted interventions and precision medicine approaches. On the other hand, understanding the differential response to treatment strategies, such as weight loss in patients with obstructive sleep apnea, emphasizes the need to consider sex-based differences in clinical management.

In conclusion, investigating sex-based differences in sleep and circadian factors implicated in metabolism and precision medicine represents a crucial and dynamic field. Future research must be thoughtfully designed, rigorously conducted, and transparently reported to deepen our understanding of the complex interplay between sleep, the circadian system, and sex-based variations. Recognizing and comprehending sex differences in sleep and circadian rhythms is essential for tailoring approaches to sleep medicine and optimizing treatment strategies for sleep disorders. By addressing limitations in study design, incorporating sex-based considerations into clinical practice, utilizing clear and consistent terminology, and embracing precision medicine principles, we can advance our knowledge of sex-specific responses to sleep interventions and ultimately enhance the health outcomes.

Practice points

1. Sleep, circadian, and metabolic sciences must consider the crucial role of sex as a pivotal determinant.
2. Biological sex may have modest effects on sleep as assessed by PSG, but it significantly influences self-reported sleep quality and the prevalence of sleep disorders.
3. Females exhibit an earlier circadian clock phase than males, emphasizing sex as a crucial biological variable in chronobiology research.
4. Differences in hedonic eating and hunger patterns resulting from sleep deprivation may elevate the risk of obesity and T2DM, especially among males.
5. Personalized medicine and treatment approaches must consider sex differences to optimize outcomes and enhance patient care.

Research agenda

1. Conducting well-designed, adequately powered studies that ensure equal statistical power for both female and male participants is essential to effectively explore the impact of sex on circadian, sleep, and metabolic factors.
2. Considering menstrual phases and information on oral contraceptives in research involving female participants is crucial to prevent potential confounding variables, enhancing the quality and validity of study results.
3. Further investigation into the disparate effects of shift work and internal desynchronization on peripheral oscillators in males and females is necessary to deepen our understanding of sex-related influences on chronobiology.
4. Achieving personalized medicine requires well-powered studies mapping sex-specific responses to intervention strategies and treatment methods.
5. Achieving a consensus on the terminology employed in sex and gender research is vital for clear and precise communication. It is imperative to differentiate between sex as a biological determinant and gender as a social construct. Funding bodies should initiate workshops and endeavors to establish such a consensus.
6. Specific funding initiatives targeted towards female health are required to expedite the translation of evidence into clinical practice.

Funding

S.L.C. is funded by the Alexander Von Humboldt Foundation. R.L. is supported by the U.S. Department of Defense (W81XWH-16-1-0223). J. Q. is supported by NIH R00HL148500.

Author contributions

Conceptualization, R.L., J.Q., S.L.C. Writing – original draft preparation, R.L., Writing – review and editing, J.Q., S.L.C. Visualization, S.L.C. All authors have read and agreed to the published version of the manuscript.

Citation diversity statement

Recent work in several fields of science has identified a bias in citation practices, such as papers from women and other minority scholars being under-cited relative to the number of such papers in the field. Here, we sought to proactively consider choosing references that reflect the diversity of the field in thought, form of contribution, gender, race, ethnicity, and other factors. First, we obtained the predicted

gender of each reference's first and last author by using databases that store the probability of a first name being carried by a woman. By this measure and excluding self-citations to the first and last authors of our current paper), our references contain 11.54% woman (first)/woman (last), 20.36% man/woman, 24.28% woman/man, and 43.82% man/man. By this measure (and excluding self-citations), our references contain 12.55% author of color (first)/author of color (last), 16.03% white author/author of color, 17.39% author of color/white author, and 54.03% white author/white author.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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