Published in final edited form as:

Curr Obes Rep. 2017 December ; 6(4): 397–404. doi:10.1007/s13679-017-0290-7.

Role of Sex and the Environment in Moderating Weight Gain Due to Inadequate Sleep

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Abstract

Purpose of Review—The growing prevalence of obesity, inadequate sleep and sleep disorders together with the negative impact of lack of sleep on overall health highlights the need for therapies targeted towards weight gain due to sleep loss.

Recent Findings—Sex disparities in obesity and sleep disorders are present; yet, the role of sex is inadequately addressed and thus it is unclear whether sensitivity to sleep disruption differs between men and women. Like sex, environmental factors contribute to the development of obesity and poor sleep. The obesogenic environment is characterized by easy access to palatable foods and a low demand for energy expenditure in daily activities. These and other environmental factors are discussed, as they drive altered sleep or their interaction with food choice and intake can promote obesity.

Summary—We discuss data that suggest differences in sleep patterns and responses to sleep disruption influence sex disparities in weight gain, and that environmental disturbances alter sleep and interact with features of the obesogenic environment that together promote obesity.

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This article is part of the Topical Collection on *Metabolism*

Conflict of Interest Jamie E. Coborn, Monica M. Houser, Claudio E. Perez-Leighton, and Jennifer A. Teske declare they have no conflict of interest.

Human and Animal Rights and Informed Consent Although this article does not contain any studies conducted with human subjects performed by the authors, there is one study with animal subjects that has been disclosed by the authors.

Keywords

Obesity; Sleep deprivation; Sleep fragmentation; Brain; Estrogen

Introduction

While the rates of obesity have nearly doubled in > 70 countries since 1980 [1, 2], the amount of adequate sleep (i.e., 7 h of continuous sleep per night) obtained by adults has declined [3] and the incidence of physician-diagnosed sleep disorders has risen [4]. For example, 34.8% of respondents from the 2014 US Behavioral Risk Factor Surveillance System self-reported sleeping < 7 h per night in a 24-h period [5] and sleep-related visits to a physician increased by 29% between 1999 and 2010 [4]. The negative effects of inadequate sleep on overall health and well-being have been confirmed by a recent systemic review and meta-analysis which reported that inadequate sleep was associated with greater risk for obesity, waist circumference, mortality, and chronic diseases including diabetes mellitus, hypertension, cardiovascular and coronary heart disease [6, 7]. While obesity and poor sleep are pervasive in society, population-based studies consistently report that prevalence of obesity is greater in women compared to men both globally [8] and in the US [9]. Moreover, recent studies report poorer sleep quality among women [10, 11] and a negative association between sleep duration and quality with waist circumference and body mass index (BMI) in women but not men [12], although one study found no sex difference [13]. Also, the biological transition to menopause in women coincides with weight gain and a higher prevalence of insomnia [14]. Together, these data illustrate the influential role of sex on the relationship between disrupted sleep and risk of obesity. Like sex, environmental factors contribute to the development of obesity and poor sleep. Conceptually, the “obesogenic environment” describes all environmental factors that perpetuate a positive energy balance [15] but has become synonymous with easy access to palatable foods and a low demand for energy expenditure during daily activities. However, this standard definition does not consider environmental factors that drive altered sleep or their interaction with food choice and intake. Below, we discuss data which suggests (1) differences in sleep patterns and responses to sleep disruption influence sex disparities for weight gain and (2) environmental disturbances that lead to altered sleep interact with key aspects of the human obesogenic environment (easy access to a variety of palatable foods and preference-based food choice) to further promote obesity.

Do Sex Differences Modulate the Relationship Between Sleep and Obesity?

Clinical Studies that Reduce Sleep

Clinical studies demonstrate that sleep restriction increases weight gain and calorie intake alone or in parallel with either increased or reduced energy expenditure in adults [16–24]. Yet, it is unclear whether men and women respond differently to sleep restriction since the duration of sleep restriction differs between studies, weight gain is not always reported and men and women haven’t always been included in studies. For example, two studies determined the effect of acute sleep loss on energy expenditure but not weight gain in either men or women. While one night of total sleep deprivation (SD) significantly reduced resting

metabolic rate in men [23], two nights of sleep restriction (4-h time in bed; TIB) significantly increased total energy expenditure in women compared to habitual sleep (8-h TIB) [22]. Another study examined calorie intake, total energy expenditure with doubly labeled water and resting metabolic rate but not weight gain in normal-weight men and women in a cross-over design after six nights of sleep restriction (4-h TIB) and habitual sleep (8-h TIB) [21]. Despite that both sleep-restricted (SR) women and men non-significantly increased their calorie intake relative to the habitual sleep, only SR women significantly increased intake of total and saturated fat. This result suggests that sleep restriction may differentially affect macronutrient selection but not total calorie intake between men and women.

A sex difference in weight gain after sleep restriction has been directly examined, but with contradictory results. For example, in response to five consecutive nights of sleep restriction (5-h TIB) compared to adequate sleep (9-h TIB) [17], sleep restriction increased weight gain only in women despite total energy expenditure and daily calorie intake (including foods high in carbohydrates and intake during late night hours) was increased in both men and women. However, others report that men gain more weight compared to women in response to sleep restriction [17, 19], a difference that remained statistically significant after the data were analyzed by change in BMI or percent change in absolute weight gain from baseline (i.e., habitual or adequate sleep). This contrasts with a study reporting similar weight gain between SR men and women despite that calorie intake was significantly higher in SR men compared to SR women [24]. In this study, when men and women were combined, SR adults did not gain significantly more weight than controls after controlling for age, BMI, gender, and race despite that they consumed significantly more calories [24].

Clinical Studies that Improve Sleep

Given that reducing sleep increases weight gain, extending time spent sleeping would be expected to reduce weight gain, yet, it remains unclear if sleep extension reduces weight gain or whether there is a sex difference. In a home-based intervention study, Tasali and colleagues examined the effects of sleep extension on sleep duration, appetite, and desire for food with a crossover design in ten overweight young adults with habitual sleep patterns of < 6.5 h per night [25]. Participants completed 1 week of baseline measurements, followed by a 2-week intervention period designed to achieve 8.5 h of sleep per night. Sleep extension significantly increased sleep duration by 1.6-h per night and physical activity by 7% as indicated by wrist actigraphy and reduced overall ratings for appetite, sweet, and salty foods. A larger sleep extension study aimed to test whether extending sleep duration (i.e., up 7.5-h per night) would improve weight in 125 obese adults [26] that completed three consecutive visits (e.g., screening, randomization, and follow-up). Sleep, indicated by sleep diaries and wrist actigraphy, significantly increased between the screening and randomization visits among adults that were later randomized to the intervention group (sleep extension) relative to those that were randomized to the comparison group despite that weight gain was similar between groups. Thus, it is currently unclear if sleep extension would improve weight gain as the placebo and Hawthorne effects were present in this study since differences in sleep were observed between screening and randomization [26].

A separate line of research has focused on whether improving sleep with continuous positive airway pressure (CPAP) reduces weight gain among individuals with obstructive sleep apnea syndrome (OSA), a sleep disorder that increases weight gain [27]. A recent meta-analysis reported that CPAP treatment for OSA was associated with a modest but significant increase in BMI and weight gain [28]. However, it is unclear whether participants from the studies included in this meta-analysis achieved the recommended amount of sleep (e.g., seven continuous hours) by means of CPAP therapy during the interventions. While studies show that CPAP improves sleep efficiency, architecture and duration [29–32], few have reported the latter in conjunction with changes in weight. This is a key aspect since failure to achieve normal sleep would be expected to promote weight gain. Finally, it remains to be determined whether the reported increase in BMI and weight gain in response to CPAP [28] was due to elevated energy intake or reduced energy expenditure. Quantifying calorie intake and energy expenditure in CPAP studies would aid in determining whether the magnitude of improvement in sleep, weight gain, and anthropometric variables after CPAP differs between men and women who have OSA. Quan and colleagues addressed sex differences in weight gain during CPAP treatment. They reported that weight gain was significantly greater among participants in the CPAP-treated group compared to sham-CPAP group after a 6-month intervention, and this difference remained significant when adjusted for age, sex, race, baseline BMI, OSA severity or Epworth sleepiness scores [33]. Together, the current evidence is inconclusive as to whether there are sex differences in response to CPAP treatment, knowledge that is imperative given that sex disparities exist for OSA, sleep quality, and obesity [9, 11, 34].

Pre-clinical Studies that Reduce Sleep

Discrepancies between population-based and clinical studies underscores the significance of developing animal models to investigate mechanisms contributing to sex differences in sleep loss-induced weight gain. Similar to humans, sleep differs between male and female rodents with females spending significantly more time awake and less time in non-rapid eye movement sleep (NREM) sleep [35, 36]. Compared to males, females also spend significantly less time in rapid eye movement sleep (REM) sleep across the light/dark cycle [35, 37] despite that one study reported no sex differences in REM sleep across 24-h [36]. Gonadectomy eliminates sleep disparities between males and females [36], highlighting the influence of sex hormones on differences in sleep between male and female rodents (reviewed by [38•]). Early studies in female rodents reported differences in sleep and locomotor activity across the four phases of the estrous cycle (e.g., proestrus, estrus, metestrus/diestrus one, and diestrus two); yet, this outcome appears species-dependent. While one study reported that sleep and locomotor activity were similar across phases of the estrous cycle in three different strains of mice [39], another reported that female Sprague-Dawley rats spend significantly more time awake and less time in both NREM and REM sleep and have greater locomotor activity during the dark cycle in proestrus (e.g., high estradiol and progesterone levels) relative to all other phases [40]. Our analysis of 24-h weight gain and food intake corrected for uneaten food particles in female Sprague-Dawley rats across the estrous cycle indicates that weight gain and food intake are also significantly lower during proestrus relative to the other phases (Fig. 1). These data demonstrate that sex hormones influence sleep, locomotor activity, calorie intake, and weight gain within intact

female rats. Thus, accounting for differences in these parameters throughout the estrous cycle would be imperative for studies seeking to examine whether sex moderates the effect of sleep loss on weight gain between males and females.

Like humans, rodents show sex differences in response to sleep disruption; however, limited research has addressed the extent to which sleep disruption alters sleep parameters and outcomes related to weight gain between male and female rodents while controlling for the effect of the estrous cycle on these outcomes. Early studies did not validate whether methods that had been shown to disrupt sleep in male rodents were effective in females but instead focused on the recovery period after exposure to gentle handling [40] or SD during REM [41]. One study reported that the time required to recover from sleep disruption was similar between female rats that were subjected to sleep loss during proestrus and estrus [40]. This contrasts with data that showed the time required to return to baseline sleep after SD during REM differed between phases of the estrous cycle as well as between males and intact females [41]. Finally, sleep disruption (during non-REM and REM for > 3 h) has yet to be validated within intact female rats across each phase of the estrous cycle despite that one abstract reported that the disk-over-water method completely abolished REM sleep during a 3-h time period of SD during REM in pregnant and non-pregnant female rats [42].

Sex differences in sleep and wake parameters after sleep disruption have also been examined in mice. Kohel and colleagues showed a similar change in NREM and REM sleep between males and females in response to 6-h sleep disruption by the multiple platform method plus gentle handling as well as during the recovery period [35]. These data contrast results from Paul and colleagues who reported that 6-h of sleep disruption by gentle handling reduced sleep more so in male compared to female mice [36]. This same study showed that sleep during the recovery period was greater in females compared to males when expressed as a percentage of baseline sleep, which suggests that females were more sensitive to sleep disruption. Thus far sleep disruption by gentle handling or SD during REM reliably reduces sleep in male rats [43, 44] and mice [45], but this has yet to be validated in intact female rodents [40, 41]. Furthermore, these methods of sleep disruption cause weight loss in rodents [43, 46–50], which contrasts sleep disruption-induced weight gain in humans [19]. Recently, one study increased sleep fragmentation with no effect on time spent asleep for days 14–19 of gestation in pregnant dams by utilizing a motorized mechanical sweeper and examined weight outcomes in male and female offspring [51•]. They reported that sleep fragmentation only affected male offspring, which was indicated by an increase in their absolute bodyweight, food intake (g/day), visceral fat and subcutaneous fat compared to males who were not subjected to sleep fragmentation during gestation. While these data suggest that male offspring may be more sensitive to sleep fragmentation during gestation, it remains unknown whether a differential response to sleep fragmentation between male and female juvenile or adult rodents exists.

Future Directions to Address the Contribution of Sex to Sleep and Obesity

The discrepancies in weight gain after sleep restriction between men and women [17, 19], the inability of sleep restriction to increase weight gain among men in one study [17], limitations in the sleep extension studies, and the unexpected effect of CPAP on weight gain

suggest that additional variables need to be considered when comparing sex differences within interventions that reduce or improve sleep. First, despite its inherent complexity, quantifying weight gain over longer periods of sleep restriction (i.e., weeks or months) and reporting weight gain as percent gain of baseline bodyweight would be beneficial to gauge the clinical significance of sleep disruption-induced weight gain. The latter may be necessary to address whether sex modulates the effect of sleep restriction on weight gain since absolute bodyweight, energy intake, energy expenditure, and weight gain trajectories differ between men and women. For example, a 3.5 and 4.5-kg weight gain represents a 5% weight gain for a woman and man with an initial bodyweight of 70 and 90-kg, respectively, which is a clinically relevant change in weight in a 3-month period [52, 53]. Thus, is it correct to conclude that weight gain was the same between the women and man since both had a 5% weight gain from their initial body weight? Furthermore, using change in percent body fat or waist circumference in response to sleep restriction may better illustrate whether sleep restriction differentially alters risk for metabolic disease between men and women or augments fat distribution. Second, as hormones alter energy balance, controlling for hormonal differences across the menstrual phase and completing measurements during the same phase of the menstrual cycle at baseline and during sleep restriction in premenopausal women could reduce variability in results for body weight, physical activity, sleep, calorie intake, and energy expenditure. Third, it is also unclear whether sleep restriction has lasting effects on weight gain and metabolism. Hence, quantifying changes in these parameters after sleep restriction when individuals obtain adequate sleep would address maladaptive mechanisms that may further promote weight gain after sleep restriction has subsided. Finally, analysis of sex differences in weight gain due to sleep restriction requires that studies be appropriately powered to substantiate the conclusion that there are no significant differences between men and women.

Since energy intake increases energy expenditure due to diet-induced thermogenesis and plausibly weight gain if overall energy expenditure remains unchanged, standardizing methods for measuring energy intake and energy expenditure would aid in determining plausible mechanisms contributing to potential sex differences in weight gain due to sleep restriction. For example, providing free access to food during studies allows one to test whether sleep restriction does indeed increase calorie intake from specific macronutrients or at different times of the day. As with weight gain, it would be ideal to compare the percent change in energy intake and energy expenditure relative to baseline calorie intake between SR men and women to account for inherent differences in calorie intake and energy expenditure between men and women during adequate sleep. Reporting not only total energy expenditure but its components (diet-induced thermogenesis, energy expenditure due to rest, sleep, and physical activity) would allow one to design more effective behavioral interventions to prevent weight gain due to inadequate sleep. Finally, it is unknown whether sleep restriction augments volitional physical activity in free-living conditions based on studies conducted in whole room calorimeters since the latter limits volitional physical activity and is not recapitulated by involuntary sessions of physical activity during interventions. Collectively, implementing the aforementioned measures and types of analyses in future clinical studies may provide more conclusive evidence as to whether

women or men are more sensitive to weight gain in response to sleep restriction while also providing more congruency between population-based and clinical studies.

Given that sleep disruption and fragmentation increase obesity risk in men and women, it is important to develop animal models that mirror the human condition. We have previously shown that acute (12-h) and chronic (8 h/d for 9d during the light cycle) exposure to pre-recorded environmental noise reduces sleep time and quality [54, 55•, 56] and energy expenditure due to physical activity and increases weight gain and feeding in male rats [54, 55•]. Validating this method of sleep disruption and its effects on weight gain within intact female rats throughout the estrous cycle would provide a model with face validity to examine sex disparities in sleep and obesity and the mechanisms contributing to potential sex differences in the latter. Determining calorie intake and energy expenditure would also be imperative to ascertain mechanisms contributing to the change in weight after sleep disruption since no study to date has measured how sleep disruption alters energy intake or energy expenditure within intact females.

Does the Environment Modulate the Relationship Between Sleep and Obesity?

A fundamental aspect of the obesogenic environment is the easy and constant access to several novel and palatable food options since increasing food variety and access can increase calorie intake in humans and animal models in the absence of altered sleep [57]. This aspect of the obesogenic environment might explain in part the effect of inadequate sleep on weight gain, as epidemiological and experimental data in humans shows that decreasing either sleep time or quality increases hedonic food intake due to altered neuronal reward processing [58]. In particular, reducing sleep time and quality increases selection of energy-dense foods and larger portion sizes compared to undisturbed sleep [17, 59–62], yet whether there are sex differences remains to be determined. Therefore, we propose that having access to a variety of palatable foods could be a key factor modulating the effects of sleep disruption on food selection, which could consequently impact both calorie intake and weight gain. However, testing this hypothesis and from a broader perspective, understanding the interaction between sleep disruption, food availability and choice, requires use of appropriate experimental approaches. Most animal studies use diets enriched in a single macronutrient (i.e., high-fat or high-sucrose diets) as a single option, which is an excellent tool to cause obesity. However, these diets do not model the access to a variety of palatable foods, nor do they allow animals to express individual preference for specific foods [63], which mirrors human behavior [64]. The cafeteria-style diets [65•] provides animals with access to a variety of energy-dense foods made for human consumption [66] and thus models the variety and high accessibility of palatable foods present in the obesogenic environment. The cafeteria-style diet causes obesity in mice and rats [63, 65, 67] and its composition can be adjusted relative to individual preference to explore how availability of food drives the development of obesity [63]. Therefore, introducing the cafeteria-style diet in experimental models of sleep disruption, such as noise-induced sleep disruption [54, 55•] provides a model to understand how the food environment and sleep behavior interact to control food choice, intake, and obesity. Thus, the cafeteria-style diet is one approach that

could be used to model the obesogenic food environment in rodent studies and address its influence on weight gain due to sleep disruption.

The relationship between sleep duration and intake is an example of the bi-directional relationship between circadian control and feeding behavior [68]. Thus, it is not surprising that along with sleep duration and quality, other aspects of sleep behavior can also alter food intake. These include circadian misalignments due to advanced wake-time or delayed bedtime (e.g., social jet-lag), which increases carbohydrate intake and liking for foods high in fat [69, 70]. In particular, social jet-lag describes the circadian misalignment due to delayed bedtime between weekend and weekdays, which is associated with increased prevalence of obesity [71–73]. From the perspective of the obesogenic environment, social-jet lag can be understood as a behavioral adaptation to a cultural pressure, as it might be caused by social activities that occur at night during weekends, thus pushing later bedtimes compared to weekdays. Social jet-lag has also been associated with higher risk-taking behavior and a negative emotional state [74, 75], which may also increase hedonic eating [76]. Therefore, we speculate that social jet-lag combines circadian misalignment with the opportunity for intake of energy-dense foods in social settings, factors that can independently promote hedonic food intake [57, 76]. Following this idea, social jet-lag promotes altered sleep patterns that drive food intake in an obesogenic environment, which further promotes disrupted sleep and functions as a positive feedback loop to drive excessive caloric intake and facilitate obesity. Pre-clinical research to provide the mechanistic evidence for this idea is lacking; yet, recent studies suggest that exposing rats to a free selection of high-fat and sugar snacks alters circadian clocks in several brain sites [77] and a rodent study shows that circadian misalignment can potentiate obesity caused by consumption of a cafeteria diet [78]. Overall, these data highlight the necessity of understanding the consequences of social jet-lag and its interaction with inadequate sleep during exposure to multiple palatable and highly accessible foods and the context in which the opportunity for intake occurs.

In summary, the current data shows that altering sleep duration, quality, or timing are related to obesity; all of which occurs in an environment that facilitates access to multiple palatable foods, allowing the constant option of choosing foods that match individual preference. This favors hedonic intake, which can alter circadian control; thus creating a vicious cycle that drives obesity. We propose it is necessary to include these concepts into our standard definition of an obesogenic environment and develop adequate animal studies to understand the neuronal mechanisms that drive our behavior in this complex environment.

Conclusion

Sex and the built obesogenic environment, specifically access to highly palatable foods mediate the relationship between insufficient sleep and weight gain. Yet, their precise mechanisms remain unknown. Studies with diets that model the obesogenic environment which investigate basic mechanisms contributing to weight gain during sleep restriction and the differential response between men and women are essential for understanding whether women or men are more sensitive to weight gain after sleep loss in an obesogenic environment. The development of sex- and environment-specific therapies to treat disordered

sleep and the high of prevalence of obesity may be more effective than the one-size-fits all approach.

Acknowledgements

Funding for the publication was supported by the National Institutes of Health NS099468-01A1 (JAT), FONDECYT REGULAR 1150274 (CEPL), and the United States Department of Agriculture ARZT-1372540-R23-131 (JAT) and the National Needs Fellowship 2014-38420-21799 (JEC).

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Fig. 1.

a Twenty-four-hour bodyweight gain and **b** food intake (g) corrected for uneaten food in female Sprague-Dawley rats during the four phases of the estrous cycle including proestrus (P), estrus (E), diestrus 1 (D1), and diestrus 2 (D2) were significantly lower during proestrus compared to any other phase ($P < 0.05$ for all comparisons). Data are expressed as mean $\pm$ SEM; $N = 4$. Brackets indicate bars that are significantly different from each other ($*P < 0.05$). Note different scaling on y-axes