Update on Energy Homeostasis and Insufficient Sleep

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Driven by the demands and opportunities of modern life, many people habitually sleep less than 6 h a night. In the sleep clinic, chronic sleep restriction is recognized by the diagnosis of insufficient sleep syndrome (ICSD-9, 307.49-4), which is receiving increased scrutiny as a potential risk to metabolic health. Its relevance for the practicing endocrinologist is highlighted by a stream of epidemiological data that show an association of insufficient sleep with increased incidence of obesity and related morbidities. A central theme of this update is the notion that sleep loss incurs additional metabolic cost, which triggers a set of neuroendocrine, metabolic, and behavioral adaptations aimed at increasing food intake and conserving energy. Although this coordinated response may have evolved to offset the metabolic demands of extended wakefulness in natural habitats with limited food availability, it can be maladaptive in the context of a modern environment that allows many to overeat while maintaining a sedentary lifestyle without sufficient sleep. Importantly, such sleep loss-related metabolic adaptation may undermine the success of behavioral interventions based on reduced caloric intake and increased physical activity to lower metabolic risk in obesity-prone individuals. This emerging perspective is based on data from recently published human interventional studies and requires further experimental support. Nevertheless, it now seems prudent to recommend that overweight and obese individuals attempting to reduce their caloric intake and maintain increased physical activity should obtain adequate sleep and, if needed, seek effective treatment for any coexisting sleep disorders. (***J Clin Endocrinol Metab* 97: 1792–1801, 2012**)

Multiple heritable and nonheritable factors including age, sex, race/ethnicity, physical and mental health, and socioeconomic conditions (*e.g.* poverty, shift work) contribute to the considerable interindividual variability in sleep (1–5). Brain networks involved in the regulation of feeding and locomotion also modulate the quantity and quality of mammalian sleep to allow optimal adaptation of the organism to a variety of environmental pressures and natural habitats.

Self-reported sleep in U.S. adults averages approximately 7.5 h/night (2), and laboratory experiments indicate that sleeping 7–8 h/night is needed to optimize human neurobehavioral performance (6). Driven by the demands and opportunities of modern life, a considerable number of people habitually sleep less than 6 h/night (2). In the sleep clinic, chronic sleep restriction is recognized by the diagnosis of insufficient sleep syndrome (ICSD-9, 307.49-4), which is receiving increased scrutiny as a potential risk to human health. Its relevance for practicing endocrinologists is highlighted by a stream of epidemiological data showing an association of insufficient sleep with increased incidence of obesity (7, 8). Additional concerns are raised by the even stronger association of short sleep with excess weight in children and adolescents (9, 10). Body adiposity is determined by the dynamic interaction of genetic, environmental, behavioral, and psychosocial factors. For any individual, energy balance can be achieved and maintained at different degrees of adiposity and with various levels of matching energy intake and expenditure. Under pressure from an environment that promotes overeating and physical inactivity, the control system of energy homeostasis sets the body weight of ap-

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Abbreviation: RQ, Respiratory quotient.

proximately two thirds of Americans above the recommended healthy range. The epidemiological association of inadequate sleep with obesity raises the question whether insufficient sleep can modify the defended level of individual adiposity.

Observational data alone cannot establish whether insufficient sleep should join overeating and physical inactivity as a modifiable risk factor that affects energy homeostasis and individual risk for obesity. To underscore this difficulty, our understanding of the relationship between sleep-wake behavior and the mechanisms that support fuel availability and metabolic survival indicates the presence of reciprocal links between energy balance and sleep (11). This is well illustrated by animal studies where weight gain in rodents kept in a safe environment with abundant supply of palatable food triggers increased amounts of sleep, whereas food deprivation results in increased vigilance and sleep loss, presumably to help maximize food finding and energetic survival (11). The last few years have brought increased understanding of the role of the hypocretin/orexin system in these processes (12, 13). On the other hand, experimental sleep deprivation in *ad libitum* fed rats leads to weight loss, consistent with a role of sleep in energy conservation (14). Human sleep and energy metabolism also share reciprocal connections (11). Recent data established an important link between epidemiological variation in sleep and a polymorphism in the human gene encoding a subunit of the ATP-sensitive potassium channel (SUR2) regulated by the level of cellular energy metabolism (3). The ability of such metabolic sensors to modify the amount of sleep of the organism has been confirmed by mutagenesis and knock-down experiments in *Drosophila* (3). Other observations (reviewed in Ref. 11) also argue that human sleep is influenced by changes in energy balance and metabolic fuel availability. But are there effects in the opposite direction? Can insufficient sleep cause changes in human energy homeostasis? This update is based on experimental sleep deprivation studies published during the last 24 months, which indicate that inadequate sleep can modify waking behaviors (*e.g.* feeding and daily activity) governing the balance between human energy intake and expenditure (Fig. 1). A recurring theme in this discussion will be the notion that loss of sleep carries higher metabolic cost (Fig. 2), which triggers a set of neuroendocrine, metabolic, and behavioral adaptations aimed at increasing food intake and conserving energy. Although this coordinated response may have evolved to offset the metabolic cost of extended wakefulness in natural habitats with limited food availability, it can become highly maladaptive in the context of a modern environment that allows many to overeat while maintaining a sedentary lifestyle without sufficient sleep

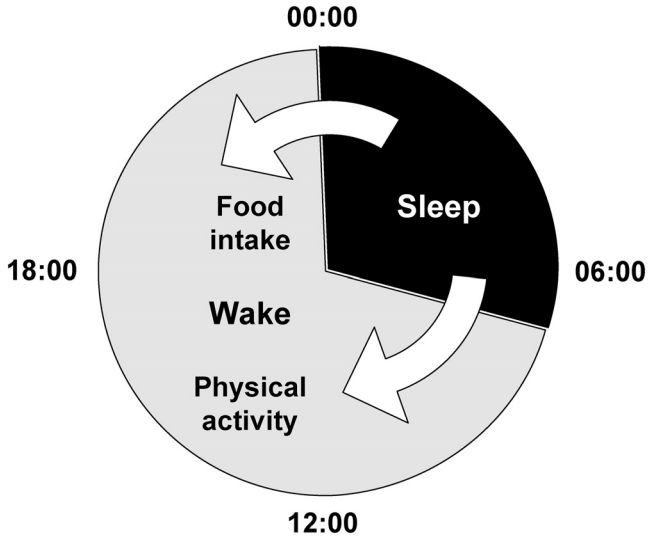

FIG. 1. The relationship between human sleep and metabolically relevant waking behaviors. This schematic drawing illustrates the concept that the amount, quality, and timing of human sleep can influence important waking behaviors (*e.g.* modify the amount, type, and frequency of food intake and physical activity) and thus modify the risk of metabolic morbidity in individuals who are prone to obesity. Multiple reciprocal interactions reflecting influences of diet and physical activity on human sleep have been omitted in this diagram to highlight the potential role of insufficient sleep as a causal factor in the pathogenesis of obesity and metabolic dysfunction.

(Fig. 3). In addition, such sleep-loss-related metabolic adaptation may undermine the success of behavioral interventions based on reduced caloric intake and increased physical activity to decrease metabolic risk in obesity-prone individuals. Finally, obstructive sleep apnea and insomnia will be used to discuss the possible implications of this emerging concept for the regulation of energy homeostasis in common sleep disorders and highlight important gaps, limitations, and controversies in our understanding of this topic. The role of excessively long sleep and circadian timing disorders for metabolic morbidity are growing areas of basic and clinical research that have been reviewed elsewhere and are beyond the scope of this update (1, 15).

The Paradox between Higher Risk of Obesity and the Metabolic Cost of Sleep Loss

Human energy expenditure can be divided into three principal components: 1) resting metabolic rate under basal conditions; 2) thermic effect of food—the energy cost of food assimilation equal to 5–10% of total energy expenditure; and 3) activity-related energy expenditure—the energy used for all spontaneous and volitional daily activities. Sleep is a state that requires the least amount of energy expenditure; normally absent nutrition and sleep-imposed immobility eliminate the cost of activity and food-related

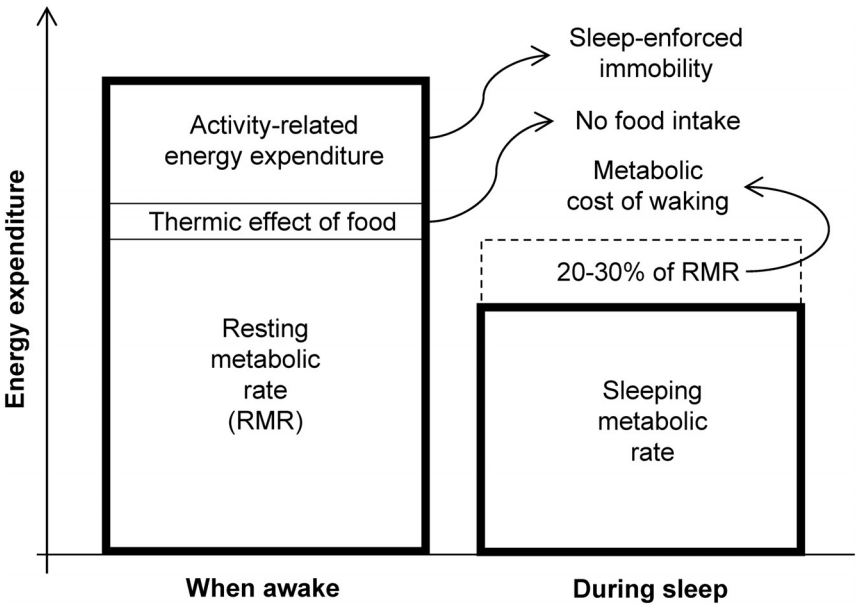

FIG. 2. Sleep as a state of maximally reduced energy expenditure. This is the result of sleep-imposed immobility and absent nutrition, which eliminates the energy cost of activity (activity-related energy expenditure) and food-related thermogenesis (thermic effect of food), and a 20–30% decrease in resting metabolic rate (RMR), because less energy is needed to support brain function, sympathetic activity, breathing, circulation, and core body temperature during sleep.

thermogenesis, and basal metabolic rate is reduced by 20–30% because less energy is needed to support brain function, sympathetic activity, breathing, circulation, and core body temperature (Fig. 2). Using a room calorimeter, Jung *et al.* (16) quantified the energy that is conserved by young nonobese adults during a day of indoor wakefulness with 8 h of nighttime sleep compared with a matching period of total sleep deprivation. Energy expenditure was 32% higher during the 8-h period without sleep, and the metabolic cost of sleep deprivation over 24 h averaged approximately 135 kcal (7% increase). If one extrapolates from these data (disregarding any homeostatic adaptation), a night with one third less sleep (*e.g.* 5.3 h instead of 8.0 h) would increase total energy expenditure by 45 kcal/d—a metabolic cost that can eliminate the positive "energy gap" and prevent weight gain in approximately 90% of the population in modernized societies (17, 18). Clearly, this simple arithmetic is not consistent with available epidemiological data and does not reflect the complexity of the relationship between sleep and energy homeostasis.

Humans have evolved a robust system of defenses that is activated when energy expenditure exceeds food intake and threatens the loss of stored fuel. The coordinated onset of multiple neuroendocrine, metabolic, and behavioral changes—including lower anorexigenic (leptin, insulin) and higher orexigenic (ghrelin) hormone concentrations to increase hunger, reduce satiety, and stimulate food intake, combined with decreased sympathetic tone, lower resting metabolic rate, and reduced activity to conserve energy—provides potent opposition to the loss of body weight (19, 20). This metabolic adaptation creates ideal conditions for efficient gain of fat in both lean and obese individuals who have lost weight and poses significant challenges to the success of behavioral attempts to reduce adiposity (19, 21). Remarkably, sleep deprivation experiments published during the last couple of years suggest that the changes in the regulation of energy homeostasis in response to insufficient sleep resemble the principles of human metabolic adaptation to negative energy balance (Fig. 3). This concept first emerged from crossover experiments in overweight and obese adults, each of whom completed two 14-d dietary weight loss treatments in random crossover fashion (22, 23). Interventions were carried out in laboratory settings with fixed time in bed of 5.5 *vs.* 8.5 h/night and restricted food intake (average daily deficit of ~680 kcal) to assess the effects of insufficient sleep on diet-induced changes in body weight and adiposity, energy expenditure, substrate utilization, and subjective hunger. Participants lost approximately 1.0 body mass index unit of body weight during each treatment, but the lack of sufficient sleep decreased the fraction of weight lost as fat by 55%. In other words, study participants defended their energy balance more vigorously (*i.e.* conserved energy-dense fat at the expense of 60% greater loss of less calorically dense and metabolically costly to maintain lean body mass) when they did not obtain enough sleep. Additional signs of enhanced neuroendocrine, metabolic, and behavioral responsiveness to diet-induced negative energy balance when sleep was curtailed included increased hunger accompanied by lower anorexigenic (insulin) and higher orexigenic (ghrelin) hormone concentrations, as well as decreased sympathetic activity (lower plasma epinephrine) and resting metabolic rate (independent of the loss of lean body mass) to conserve energy. Recent observations after a single night of total sleep deprivation also suggest that the additional energy cost of wakefulness can lead to compensatory declines in resting metabolic rate on the following morning (24) and energy expenditure during a subsequent night of recovery sleep (16). Compensation for increased activity-related energy expenditure due to experimental sleep fragmentation during the night was also present in respiratory chamber ex-

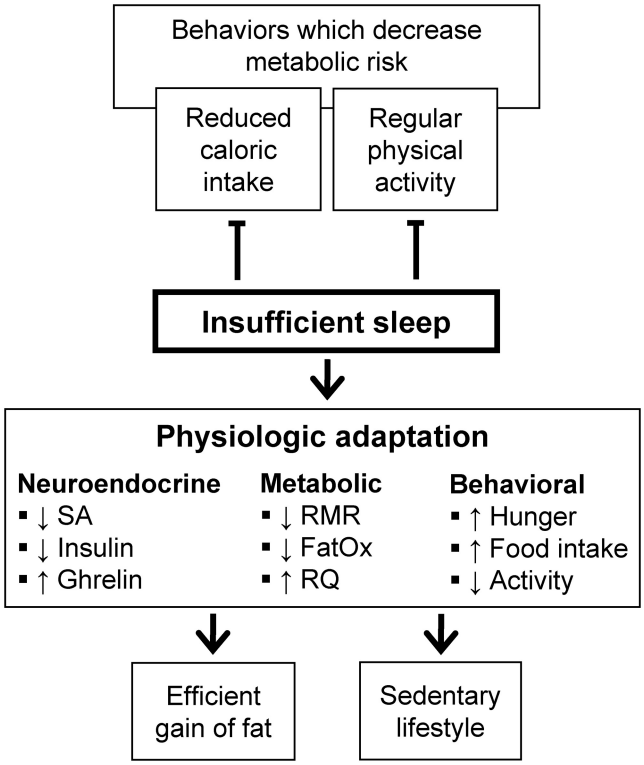

FIG. 3. An illustration of the concept that insufficient sleep triggers a set of neuroendocrine, metabolic, and behavioral adaptations aimed at increasing food intake and conserving energy. Although this coordinated response may have evolved to offset the metabolic cost of extended wakefulness in natural habitats with limited food availability, it can become highly maladaptive in the context of a modern environment that allows many to overeat while maintaining a sedentary lifestyle without sufficient sleep. SA, Sympathetic activity; RMR, resting metabolic rate under basal conditions; FatOx, fraction of energy derived from fat oxidation.

periments, where 24-h energy expenditure did not change despite the metabolic cost of multiple nighttime awakenings (25). Similarly, doubly labeled water measurements of 24-h energy expenditure under controlled laboratory conditions did not show any detectable increase in individuals exposed to longer periods of recurrent sleep restriction (22, 26, 27). As discussed next, this adaptation in 24-h energy expenditure to sleep loss raises the question whether changes in everyday activity may also help offset the metabolic cost of extended wakefulness.

Insufficient Sleep and Activity-Related Energy Expenditure

Physical activity is a complex behavior with an important role in the control of body weight and adiposity. Limited by the reliability of subjective recall and considerable differences in selected biological, psychosocial, and environmental variables, cross-sectional analyses of sleep and physical activity have given inconsistent results showing positive, negative, or no significant association (4, 10, 28). Only a handful of controlled experiments have tested the effect of sleep deprivation on the amount and intensity of everyday activity. Roehrs *et al.* (29) reported a higher percentage of daytime inactivity in laboratory settings after one night of total sleep deprivation. Schmid *et al.* (30) found that overnight sleep restriction results in less free-living activity, with a shift toward lower intensity on the next day. In contrast, Brondel *et al.* (31) reported that overnight sleep restriction was followed by a day with increased food intake and more movement, whereas Bosy-Westphal *et al.* (32) did not find effects of sleep restriction and increased food intake (2 d with time in bed of 6 h/night and 1 d with 4 h/night) on daily activity. Recently, St-Onge *et al.* (27) performed a crossover laboratory study of nine women and nine men exposed to five nights with time in bed of 4.0 *vs.* 9.0 h/night and inadvertent caloric restriction (average daily deficit of ~400 kcal) until night 4, followed by *ad libitum* food intake after that. The average recorded activity after the first, second, fourth, and fifth nights (night 3 was followed by repeated blood draws and reduced mobility) was not significantly different between the two sleep conditions (27). Interpreting these studies is difficult because they examined the effects of acute sleep deprivation only and did not control the food intake of the participants. The consequences of insufficient sleep are likely to change as participants adapt to recurrent exposure (33) and brief interventions may not capture the changes in daily activity of people who exercise a few times per week. In addition, both positive and negative energy balance can influence the amount of daily activity (19, 34).

Our laboratory started testing the hypothesis that reduced daily movement may contribute to the association of insufficient sleep with obesity and metabolic morbidity by examining the relationship between insufficient sleep and physical activity in healthy urban adults with parental history of type 2 diabetes (28). Study participants completed 2 wk of sleep and activity monitoring by wrist actigraphy and waist accelerometry while following their usual lifestyle at home. Daily activity counts and time spent in sedentary, light, and moderate plus vigorous intensity physical activities were compared between matching groups of participants with habitual sleep of less than 6 h *vs.* 6 or more h/night. Short sleepers had no sleep abnormalities and showed signs of increased sleep pressure consistent with a behavioral pattern of habitual sleep curtailment and chronic sleep insufficiency. Compared with participants who slept 6 or more h/night, short sleepers had 27% fewer daily activity counts, spent less time in moderate-plus-vigorous physical activity (−43 min/d), and were more sedentary (+69 min/d; Fig. 4).

To explore whether insufficient sleep could play a

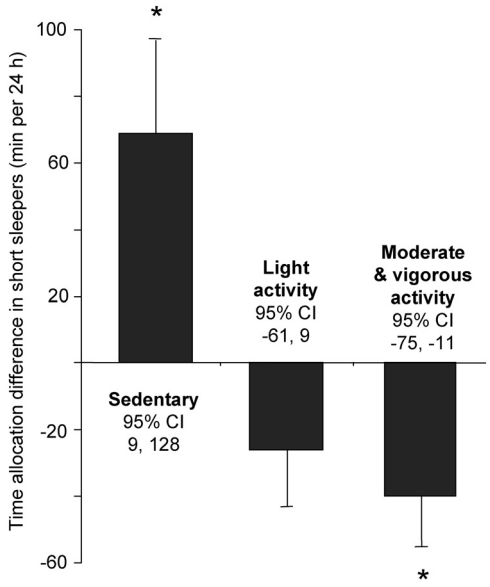

FIG. 4. Mean ± SE differences in daily time allocation to sedentary, light, and moderate plus vigorous physical activity in urban free-living adults with actigraphy-measured habitual sleep of less than 6 h/night compared with a similar group of subjects with average sleep of 6 or more h/night (n = 20 in each group). CI, Confidence interval. *, $P < 0.03$ (graph based on our own data; see Ref. 28 for details).

causal role for the reduced physical activity in short sleepers, a similar group of 18 nonobese adults with parental history of type 2 diabetes completed 1 wk of experimental sleep restriction in the laboratory (time in bed, 5.5 h/night) and a matching period with 8.5-h nighttime sleep opportunity in randomized crossover fashion (35). Subjects received a controlled weight-maintenance diet (the average body weight variability during the study was 0.6%), and those who exercised regularly at home could follow their usual exercise routines. Study participants had 31% fewer daily activity counts, spent 24% less time engaged in moderate plus vigorous intensity physical activity, and became more sedentary when their sleep was curtailed. Individuals with regular exercise habits had more total counts and were responsible for most of the decrease in physical activity during the 5.5-h time-in-bed condition (−39% *vs.* −4% decline in exercisers *vs.* nonexercisers); on average they reallocated 30 min of daily moderate plus vigorous intensity activity to less intense light and sedentary behaviors when their sleep was curtailed. Preliminary estimates of energy balance in ongoing crossover studies of habitual exercisers exposed to 2 wk of sleep restriction (time in bed, 5.5 h/night) suggest that insufficient sleep is accompanied by a combined reduction in resting and activity-related energy expenditure of approximately 250 kcal/d—an amount equivalent to 1 h of moderate physical activity at 3.6 metabolic equivalent for the average participant weighing 70 kg. Such reduction in energy expenditure is clinically important, given existing recommendations for 60 min of daily moderate-intensity activity to minimize long-term weight gain (36). Based on estimates of energy balance derived from changes in body composition, overweight and obese adults placed on a 2-wk hypocaloric diet seemed to exhibit similar large sleep loss-related reductions in resting and activity-related energy expenditure (22). Taken together, these observations support the hypothesis that the lack of sufficient sleep can reduce the amount and intensity of everyday physical activity and contribute to the metabolic risk of obesity-prone individuals.

Insufficient Sleep and Control of Energy Intake

Influential early experiments found lower plasma leptin and higher ghrelin concentrations in association with increased hunger and appetite in young men exposed to two nights of insufficient sleep and restricted caloric intake (1500 kcal/d for the average 75-kg study participant) at the time of sampling (37). Decreased leptin concentrations were also seen during a period of sleep restriction in young men whose caloric intake was reduced by approximately 30% the day before sampling (10 kcal/kg breakfast replaced by 1.2 kcal/kg bolus of iv glucose) (38). Supported by data from some observational studies (39, 40), but not others (41, 42), these reports have given rise to the popular notion that insufficient sleep triggers hormonal signals of "famine in the midst of plenty" to cause excessive food intake and weight gain. In reality, only recently have human volunteers been exposed to experimental sleep restriction while truly in the midst of plenty (*i.e.* given access to adequate or excess amounts of self-selected calories). These reports found either stimulatory (mostly in women) (32, 43–45) or no independent effects of acute sleep loss on plasma leptin concentrations (30). Experiments combining 2 wk of sleep restriction with over- or underfeeding also showed that sleep insufficiency did not affect the corresponding rise and fall in leptin, whereas ghrelin increased only in the presence of negative, but not positive, energy balance (22, 26). Acute sleep deprivation may increase ghrelin concentrations in the early morning hours, possibly in response to increased energy expenditure during the night while fasting is maintained (24, 46), and some but not other reports have noted increased food intake at breakfast (31, 47). These observations suggest that the early reports of lower leptin and higher ghrelin concentrations during experimental sleep restriction (37, 38) were not signals of famine in the midst of plenty, but were a reflection of the ability of sleep loss to amplify the human neuroendocrine response to acute caloric restriction (11). If so, sleep-deprived humans will be likely to defend their

energy balance more vigorously against voluntary or involuntary reductions in habitual food intake (Fig. 3) (22). This hypothesis was inadvertently tested by St-Onge *et al.* (27), who exposed healthy men and women to 4 d with sleep opportunity of 4.0 *vs.* 9.0 h/night and unintended caloric restriction (average daily deficit of ~400 kcal) in randomized crossover fashion. Indeed, when participants did not obtain sufficient sleep during the 4-d period of caloric restriction, their *ad libitum* energy intake on d 5 was increased by approximately 300 kcal compared with that after caloric restriction with adequate sleep. If operational under longer-term, free-living conditions, this enhanced response to caloric restriction may undermine the success of dietary weight loss therapy in individuals with insufficient sleep (5, 21, 48)—an important possibility that awaits further testing.

In addition to energy, sleep also conserves carbohydrate. Higher respiratory quotient (RQ) measurements after sleep restriction (32) and repeated disruption of sleep (25) suggest that partial sleep loss is associated with the use of a greater proportion of energy from carbohydrate. Some studies have found that such higher RQ may predict future weight gain (49). Insufficient sleep also caused a shift in substrate utilization toward oxidation of relatively more carbohydrate in overweight and obese adults placed on a 2-wk hypocaloric diet (22). In fact, the modest decline in fasting blood glucose and improved insulin economy in this setting (23) resembled the human metabolic adaptation to reduced carbohydrate availability. Knutson *et al.* (50) reported a similar reduction in fasting insulin concentrations in lean adults with difficulty sleeping. These findings raise the possibility that increased use of carbohydrate in individuals with insufficient sleep may stimulate hunger and food intake at times of diminishing glucose availability at night and during the late postprandial period. Indeed, Chaput *et al.* (51) observed that self-reported short sleepers have more relative hypoglycemia at the end of an oral glucose tolerance test, which predicted future weight gain in the Quebec Family Study (52). In accordance with these possibilities, epidemiological data indicate that insufficient sleep is accompanied by irregular eating habits, more snacking between meals, and late-night eating (10, 49, 53, 54).

Increased availability of dietary carbohydrate in the setting of negative energy balance limits the loss of body protein. In contrast, insufficient sleep increased the loss of lean body mass in overweight and obese adults placed on a 2-wk hypocaloric diet (22). The shift toward oxidation of more carbohydrate when sleep was curtailed raises the possibility that this loss of lean body mass was related to increased use of protein to support the extended metabolic needs of glucose-dependent tissues. Whether chronic sleep insufficiency places similar catabolic pressures on the protein balance of free-living individuals with *ad libitum* food intake remains unknown. If so, this may be one of the factors that contribute to the association of insufficient sleep with increased consumption of protein from meat and other food items (which commonly contain high amounts of fat) (10, 54, 55), because nutritionally relevant amino acids can stimulate the activity of hypothalamic orexin/hypocretin neurons (56) and participate in the central control of macronutrient balance and energy homeostasis (57). Insufficient sleep may also increase snacking and energy consumption from fat and carbohydrate as a result of more prolonged exposure to environmental stimuli that promote overeating, as well as changes in reward-seeking behavior (13, 26).

Current Areas of Concern and Uncertainty

Most of the research on the relationship between insufficient sleep and energy homeostasis remains observational in nature. Many of these studies are limited by incomplete assessments of sleep quantity and quality, reliance on subjective measures of sleep that harbor various systemic biases, and lack of control for relevant confounders such as physical activity, physical and mental health, socioeconomic stress, coexisting sleep disorders, *etc.* (58). The vexing inconsistency between self-reported sleep and that measured by polysomnography (which can modify the usual sleep pattern of individuals at home or in the laboratory) or free-living actigraphy (which uses immobility as a behavioral surrogate for sleep) makes it difficult to assess the true quantity and quality of habitual sleep and can result in different conclusions depending on which measure is used for analysis. The reliance of many studies on a single question about sleep is equally problematic because the answer can be influenced by comorbid depression, anxiety, sleep disorder, or other health problems and reflect one or more aspects of a participant's usual time in bed, perceived sleep duration, or subjective sleep quality. For instance, psychological distress and complaints of poor sleep were the main predictors of self-reported short sleep among obese participants in the Penn State cohort (59). A similar association between self-reported short sleep, sleeping problems, and emotional distress was found in the MONICA/KORA study (60). Thus, emotional distress, anxiety, or depression with concomitant difficulty sleeping, changes in eating patterns, and adoption of other unhealthy behaviors may be important factors for the association of insufficient sleep with obesity and metabolic morbidity (58, 61, 62). On the other hand, primary insomnia characterized by central hyperarousal,

adrenal and sympathetic hyperactivity, elevated brain glucose metabolism, and resting energy expenditure (63) may represent failure to recruit the full spectrum of the already discussed metabolic adaptations to reduced sleep (this is consistent with the historically lean phenotype of most insomniacs in the older clinical literature), leaving disproportionally increased food intake and reduced daily activity made possible by the modern way of living as potential enhancers of metabolic risk in obesity-prone individuals.

Obstructive sleep apnea can also confound the association of insufficient sleep with obesity. Besides loss of slow-wave and rapid-eye-movement sleep, this disorder involves recurrent hypoxia, frequent arousals, and nighttime hyperactivity of adrenal and sympathetic stress-response mechanisms with higher metabolic cost, which may lead to compensatory changes in daytime energy intake and physical activity (64) and facilitate the retention of stored fat in affected individuals (Fig. 3). However, the study of energy homeostasis in patients with sleep disorders has been rather limited, and available clinical reports lack comprehensive assessments of energy balance and substrate metabolism. Additional research is also needed to characterize the effects of insufficient sleep on the sensitivity of central and peripheral regulatory mechanisms to key metabolic signals in various sleep disorders.

Sleep deprivation experiments in the laboratory have their own limitations (65). The presence of considerable interindividual differences in response to sleep deprivation, weight loss, or overfeeding is well established. Unfortunately, the limited sample size of most laboratory studies and their artificial setting makes it difficult to identify subgroups with differential vulnerability to the metabolic consequences of sleep loss. For example, individuals with regular exercise habits were more susceptible to the inhibitory effect of insufficient sleep on physical activity (35). However, study participants were exposed to highly sedentary conditions that minimized the activity of nonexercisers irrespective of the presence or absence of sleep loss, and it is possible that these subjects may exhibit more pronounced sleep loss-related declines in activity under free-living conditions. The absence of changes in daytime activity in respiratory-chamber studies of total sleep deprivation could be due to a similar "floor effect" (16, 25).

An important problem in the interpretation of many sleep deprivation experiments has been their lack of attention to the fact that caloric restriction can alter the metabolic impact of insufficient sleep. Future investigation will require meticulous attention to the nutritional state of the study participants. In addition, more work is needed to understand the impact of insufficient sleep on human substrate metabolism. The catabolic state in response to recurrent sleep loss in rats is characterized by the breakdown of skeletal muscle, whereas lean tissue in vital organs remains surprisingly well preserved (14). Overweight and obese dieters also lose more fat-free mass when their sleep is curtailed, which raises the possibility that the lack of sufficient sleep during periods of voluntary weight loss may have catabolic effects on whole-body and skeletal muscle protein (22).

Finally, most laboratory interventions are relatively brief and capture only the acute (<1 wk) and subacute (<1 month) effects of sleep loss, instead of its long-term consequences, which are likely to differ both qualitatively and quantitatively (*e.g.* insulin signaling may be reduced via acute declines in β-cell function or increased insulin resistance due to increased adiposity over time; sympathetic activity may rise in response to acute metabolic stress followed by down-regulation during more extended caloric restriction, *etc.*). Failure to recognize this can lead to erroneous long-term extrapolations based on data from brief interventions (33). Most definitive answers about the effect of chronic sleep insufficiency on human energy and substrate metabolism will rely on future trials combining extended behavioral and pharmacological interventions with free-living monitoring, functional imaging, *in vivo* and *in vitro* metabolic testing, and well-defined clinical outcomes.

Conclusion and Perspectives

Mammalian evolution has resulted in reciprocal connections between sleep and energy homeostasis. Driven by the demands and opportunities of modern life, many people sleep less than 6 h/night, and such short sleep has been associated with obesity and related metabolic morbidity. Some have argued that the relatively modest increase in risk seen in epidemiological studies should not cause any concern (66). However, if causal, a modest effect of inadequate sleep on the incidence of obesity will have considerable impact on public health given the high prevalence of insufficient sleep and sleep problems in the general population (2). Work published during the last few years supports the concept that loss of sleep in an environment with limited food availability incurs additional metabolic cost, which can trigger a set of neuroendocrine, metabolic, and behavioral changes aimed at increasing food intake and conserving energy. This coordinated response includes increased hunger and reduced satiety, decreased resting energy expenditure, reduced amount and intensity of physical activity, and more sedentary behavior, all of which can become maladaptive in the context of a modern environ-

ment that allows many to overeat while maintaining a sedentary lifestyle without sufficient sleep.

Based on the assumption that the weight gain related to a 2-h reduction in daily sleep from 7 to 5 h/night "could be worked off in very much shorter periods of brisk walking," it has been suggested that people should not worry about obtaining adequate sleep and instead focus on "more effective methods for weight reduction, such as comparatively brief periods of exercise" (66). Decreased caloric intake and increased physical activity can indeed have considerable health benefits in obese individuals (67). However, the advice to engage in more physical activity while ignoring the presence of insufficient sleep may be easier given than followed (68). Compared with urban adults who sleep at least 6 h/night, those who habitually curtail their sleep were more sedentary, had decreased amounts of daily movement, and spent less time in activities with moderate and vigorous intensity (Fig. 4) (28). A similar behavioral pattern was produced by experimental sleep restriction to 5.5 h/night (35), suggesting that insufficient sleep can undermine the maintenance of adequate physical activity and its health benefits. Furthermore, treatment with a hypocaloric diet resulted in reduced energy expenditure, decreased loss of fat, and more hunger when time in bed was restricted to 5.5 h/night (22), and sleep-deprived individuals ate more when *ad libitum* food intake resumed after a few days of caloric restriction (27). Thus, the latest evidence suggests that insufficient sleep can undermine the success of behavioral interventions based on decreased food intake and increased physical activity to reduce metabolic risk in obesity-prone individuals (Fig. 3). This emerging perspective is based on human interventional studies published during the last couple of years and requires further experimental support (5, 48, 68). Nevertheless, it now seems prudent to recommend that overweight and obese individuals attempting to reduce their caloric intake and maintain increased physical activity should obtain adequate sleep and, if needed, seek effective treatment for any coexisting sleep disorders.

Acknowledgments

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References

1. **Grandner MA, Drummond SP** 2007 Who are the long sleepers? Towards an understanding of the mortality relationship. Sleep Med Rev 11:341–360
2. **Krueger PM, Friedman EM** 2009 Sleep duration in the United States: a cross-sectional population-based study. Am J Epidemiol 169: 1052–1063
3. **Allebrandt KV, Amin N, Muller-Myhsok B, Esko T, Teder-Laving M, Azevedo RV, Hayward C, van Mill J, Vogelzangs N, Green EW, Melville SA, Lichtner P, Wichmann HE, Oostra BA, Janssens AC, Campbell H, Wilson JF, Hicks AA, Pramstaller PP, Dogas Z, Rudan I, Merrow M, Penninx B, Kyriacou CP, Metspalu A, van Duijn CM, Meitinger T, Roenneberg T** 22 November 2011 A K(ATP) channel gene effect on sleep duration: from genome-wide association studies to function in *Drosophila*. Mol Psychiatry 10.1038/mp.2011.142
4. **Evans DS, Snitker S, Wu SH, Mody A, Njajou OT, Perlis ML, Gehrman PR, Shuldiner AR, Hsueh WC** 2011 Habitual sleep/wake patterns in the Old Order Amish: heritability and association with non-genetic factors. Sleep 34:661–669
5. **Garaulet M, Sánchez-Moreno C, Smith CE, Lee YC, Nicolás F, Ordovás JM** 2011 Ghrelin, sleep reduction and evening preference: relationships to CLOCK 3111 T/C SNP and weight loss. PLoS One 6:e17435
6. **Van Dongen HP, Maislin G, Mullington JM, Dinges DF** 2003 The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 26:117–126
7. **Bo S, Ciccone G, Durazzo M, Ghinamo L, Villois P, Canil S, Gambino R, Cassader M, Gentile L, Cavallo-Perin P** 2011 Contributors to the obesity and hyperglycemia epidemics. A prospective study in a population-based cohort. Int J Obes (Lond) 35:1442–1449
8. **Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB** 2011 Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 364:2392–2404
9. **Carter PJ, Taylor BJ, Williams SM, Taylor RW** 2011 Longitudinal analysis of sleep in relation to BMI and body fat in children: the FLAME study. BMJ 342:d2712
10. **Garaulet M, Ortega FB, Ruiz JR, Rey-López JP, Béghin L, Manios Y, Cuenca-García M, Plada M, Diethelm K, Kafatos A, Molnár D, Al-Tahan J, Moreno LA** 2011 Short sleep duration is associated with increased obesity markers in European adolescents: effect of physical activity and dietary habits. The HELENA study. Int J Obes (Lond) 35:1308–1317
11. **Penev PD** 2007 Sleep deprivation and energy metabolism: to sleep, perchance to eat? Curr Opin Endocrinol Diabetes Obes 14:374–381
12. **Carter ME, Borg JS, de Lecea L** 2009 The brain hypocretins and their receptors: mediators of allostatic arousal. Curr Opin Pharmacol 9:39–45
13. **Tsujino N, Sakurai T** 2009 Orexin/hypocretin: a neuropeptide at the interface of sleep, energy homeostasis, and reward system. Pharmacol Rev 61:162–176
14. **Everson CA, Szabo A** 2011 Repeated exposure to severely limited sleep results in distinctive and persistent physiological imbalances in rats. PLoS One 6:e22987
15. **Bass J, Takahashi JS** 2010 Circadian integration of metabolism and energetics. Science 330:1349–1354
16. **Jung CM, Melanson EL, Frydendall EJ, Perreault L, Eckel RH, Wright KP** 2011 Energy expenditure during sleep, sleep deprivation and sleep following sleep deprivation in adult humans. J Physiol 589:235–244
17. **Hill JO, Wyatt HR, Reed GW, Peters JC** 2003 Obesity and the environment: where do we go from here? Science 299:853–855
18. **Zhai F, Wang H, Wang Z, Popkin BM, Chen C** 2008 Closing the energy gap to prevent weight gain in China. Obes Rev 9(Suppl 1): 107–112

19. **Rosenbaum M, Leibel RL** 2010 Adaptive thermogenesis in humans. Int J Obes (Lond) 34(Suppl 1):S47–S55
20. **Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, Proietto J** 2011 Long-term persistence of hormonal adaptations to weight loss. N Engl J Med 365:1597–1604
21. **Dulloo AG, Jacquet J, Montani JP** 2002 Pathways from weight fluctuations to metabolic diseases: focus on maladaptive thermogenesis during catch-up fat. Int J Obes Relat Metab Disord 26(Suppl 2): S46–S57
22. **Nedeltcheva AV, Kilkus JM, Imperial J, Schoeller DA, Penev PD** 2010 Insufficient sleep undermines dietary efforts to reduce adiposity. Ann Intern Med 153:435–441
23. **Nedeltcheva A, Zhou M, Imperial J, Benyavkaya Y, Penev P** 2010 Effects of sleep restriction on glucose regulation during diet-induced weight loss. Sleep 33(Suppl):A22
24. **Benedict C, Hallschmid M, Lassen A, Mahnke C, Schultes B, Schiöth HB, Born J, Lange T** 2011 Acute sleep deprivation reduces energy expenditure in healthy men. Am J Clin Nutr 93:1229–1236
25. **Hursel R, Rutters F, Gonnissen HK, Martens EA, Westerterp-Plantenga MS** 2011 Effects of sleep fragmentation in healthy men on energy expenditure, substrate oxidation, physical activity, and exhaustion measured over 48 h in a respiratory chamber. Am J Clin Nutr 94:804–808
26. **Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD** 2009 Sleep curtailment is accompanied by increased intake of calories from snacks. Am J Clin Nutr 89:126–133
27. **St-Onge MP, Roberts AL, Chen J, Kelleman M, O'Keeffe M, Roy-Choudhury A, Jones PJ** 2011 Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals. Am J Clin Nutr 94:410–416
28. **Booth JN, Bromley LE, Darukhanavala AP, Whitmore HR, Imperial JG, Penev PD** 2012 Reduced physical activity in adults at risk for type 2 diabetes who curtail their sleep. Obesity (Silver Spring) 20: 278–284
29. **Roehrs T, Turner L, Roth T** 2000 Effects of sleep loss on waking actigraphy. Sleep 23:793–797
30. **Schmid SM, Hallschmid M, Jauch-Chara K, Wilms B, Benedict C, Lehnert H, Born J, Schultes B** 2009 Short-term sleep loss decreases physical activity under free-living conditions but does not increase food intake under time-deprived laboratory conditions in healthy men. Am J Clin Nutr 90:1476–1482
31. **Brondel L, Romer MA, Nougues PM, Touyarou P, Davenne D** 2010 Acute partial sleep deprivation increases food intake in healthy men. Am J Clin Nutr 91:1550–1559
32. **Bosy-Westphal A, Hinrichs S, Jauch-Chara K, Hitze B, Later W, Wilms B, Settler U, Peters A, Kiosz D, Muller MJ** 2008 Influence of partial sleep deprivation on energy balance and insulin sensitivity in healthy women. Obes Facts 1:266–273
33. **McEwen BS, Wingfield JC** 2010 What is in a name? Integrating homeostasis, allostasis and stress. Horm Behav 57:105–111
34. **Leibel RL, Rosenbaum M, Hirsch J** 1995 Changes in energy expenditure resulting from altered body weight. N Engl J Med 332:621–628
35. **Bromley L, Booth JN, Alcantar L, Imperial J, Penev P** 2011 Experimental sleep restriction reduces physical activity in adults with parental history of type 2 diabetes. Endocr Rev 32:P2–535
36. **Saris WH, Blair SN, van Baak MA, Eaton SB, Davies PS, Di Pietro L, Fogelholm M, Rissanen A, Schoeller D, Swinburn B, Tremblay A, Westerterp KR, Wyatt H** 2003 How much physical activity is enough to prevent unhealthy weight gain? Outcome of the IASO 1st Stock Conference and consensus statement. Obes Rev 4:101–114
37. **Spiegel K, Tasali E, Penev P, Van Cauter E** 2004 Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med 141:846–850
38. **Spiegel K, Leproult R, L'hermite-Balériaux M, Copinschi G, Penev PD, Van Cauter E** 2004 Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. J Clin Endocrinol Metab 89: 5762–5771
39. **Taheri S, Lin L, Austin D, Young T, Mignot E** 2004 Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Medicine 1:e62
40. **Chaput JP, Després JP, Bouchard C, Tremblay A** 2007 Short sleep duration is associated with reduced leptin levels and increased adiposity: results from the Quebec family study. Obesity (Silver Spring) 15:253–261
41. **Hayes AL, Xu F, Babineau D, Patel SR** 2011 Sleep duration and circulating adipokine levels. Sleep 34:147–152
42. **Knutson KL, Galli G, Zhao X, Mattingly M, Cizza G** 2011 No association between leptin levels and sleep duration or quality in obese adults. Obesity (Silver Spring) 19:2433–2435
43. **Omisade A, Buxton OM, Rusak B** 2010 Impact of acute sleep restriction on cortisol and leptin levels in young women. Physiol Behav 99:651–656
44. **Pejovic S, Vgontzas AN, Basta M, Tsaoussoglou M, Zoumakis E, Vgontzas A, Bixler EO, Chrousos GP** 2010 Leptin and hunger levels in young healthy adults after one night of sleep loss. J Sleep Res 19:552–558
45. **Simpson NS, Banks S, Dinges DF** 2010 Sleep restriction is associated with increased morning plasma leptin concentrations, especially in women. Biol Res Nurs 12:47–53
46. **Schmid SM, Hallschmid M, Jauch-Chara K, Born J, Schultes B** 2008 A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. J Sleep Res 17:331–334
47. **Schmid SM, Hallschmid M, Jauch-Chara K, Wilms B, Lehnert H, Born J, Schultes B** 2011 Disturbed glucoregulatory response to food intake after moderate sleep restriction. Sleep 34:371–377
48. **Elder CR, Gullion CM, Funk KL, Debar LL, Lindberg NM, Stevens VJ** 2012 Impact of sleep, screen time, depression and stress on weight change in the intensive weight loss phase of the LIFE study. Int J Obes (Lond) 36:86–92
49. **Gluck ME, Venti CA, Salbe AD, Votruba SB, Krakoff J** 2011 Higher 24-h respiratory quotient and higher spontaneous physical activity in nighttime eaters. Obesity (Silver Spring) 19:319–323
50. **Knutson KL, Van Cauter E, Zee P, Liu K, Lauderdale DS** 2011 Cross-sectional associations between measures of sleep and markers of glucose metabolism among subjects with and without diabetes. The Coronary Artery Risk Development in Young Adults Sleep Study. Diabetes Care 34:1171–1176
51. **Chaput JP, Després JP, Bouchard C, Astrup A, Tremblay A** 2009 Sleep duration as a risk factor for the development of type 2 diabetes or impaired glucose tolerance: analyses of the Quebec Family Study. Sleep Med 10:919–924
52. **Boulé NG, Chaput JP, Doucet E, Richard D, Després JP, Bouchard C, Tremblay A** 2008 Glucose homeostasis predicts weight gain: prospective and clinical evidence. Diabetes Metab Res Rev 24:123–129
53. **Nishiura C, Noguchi J, Hashimoto H** 2010 Dietary patterns only partially explain the effect of short sleep duration on the incidence of obesity. Sleep 33:753–757
54. **Weiss A, Xu F, Storfer-Isser A, Thomas A, Ievers-Landis CE, Redline S** 2010 The association of sleep duration with adolescents' fat and carbohydrate consumption. Sleep 33:1201–1209
55. **Grandner MA, Kripke DF, Naidoo N, Langer RD** 2010 Relationships among dietary nutrients and subjective sleep, objective sleep, and napping in women. Sleep Med 11:180–184
56. **Karnani MM, Apergis-Schoute J, Adamantidis A, Jensen LT, de Lecea L, Fugger L, Burdakov D** 2011 Activation of central orexin/hypocretin neurons by dietary amino acids. Neuron 72:616–629
57. **Cota D, Proulx K, Smith KA, Kozma SC, Thomas G, Woods SC, Seeley RJ** 2006 Hypothalamic mTOR signaling regulates food intake. Science 312:927–930
58. **Furihata R, Uchiyama M, Takahashi S, Konno C, Suzuki M, Osaki K, Kaneita Y, Ohida T** 2011 Self-help behaviors for sleep and de-

pression: a Japanese nationwide general population survey. J Affect Disord 130:75–82
59. **Vgontzas AN, Lin HM, Papaliaga M, Calhoun S, Vela-Bueno A, Chrousos GP, Bixler EO** 2008 Short sleep duration and obesity: the role of emotional stress and sleep disturbances. Int J Obes (Lond) 32:801–809
60. **Meisinger C, Heier M, Löwel H, Schneider A, Döring A** 2007 Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA Augsburg cohort study. Sleep 30:1121–1127
61. **Chaput JP, Després JP, Bouchard C, Tremblay A** 2011 The association between short sleep duration and weight gain is dependent on disinhibited eating behavior in adults. Sleep 34:1291–1297
62. **Kilkus JM, Booth JN, Bromley LE, Darukhanavala AP, Imperial JG, Penev PD** 2012 Sleep and eating behavior in adults at risk for type 2 diabetes. Obesity (Silver Spring) 20:112–117
63. **Bonnet MH, Arand DL** 2010 Hyperarousal and insomnia: state of the science. Sleep Med Rev 14:9–15
64. **Kezirian EJ, Kirisoglu CE, Riley RW, Chang E, Guilleminault C, Powell NB** 2008 Resting energy expenditure in adults with sleep disordered breathing. Arch Otolaryngol Head Neck Surg 134:1270–1275
65. **Grandner MA, Patel NP, Gehrman PR, Perlis ML, Pack AI** 2010 Problems associated with short sleep: bridging the gap between laboratory and epidemiological studies. Sleep Med Rev 14:239–247
66. **Horne J** 2011 Obesity and short sleep: unlikely bedfellows? Obes Rev 12:e84–94
67. **Greaves CJ, Sheppard KE, Abraham C, Hardeman W, Roden M, Evans PH, Schwarz P** 2011 Systematic review of reviews of intervention components associated with increased effectiveness in dietary and physical activity interventions. BMC Public Health 11:119
68. **Chaput JP, Després JP, Bouchard C, Tremblay A** 7 June 2011 Longer sleep duration associates with lower adiposity gain in adult short sleepers. Int J Obes (Lond) doi: 10.1038/ijo.2011.110