Plenary Lecture 1

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Impact of Sleep and Sleep Loss on Neuroendocrine and Metabolic Function

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Ghrelin · Leptin · Insulin resistance · Obesity · Diabetes

Abstract
Background: Sleep exerts important modulatory effects on neuroendocrine function and glucose regulation. During the past few decades, sleep curtailment has become a very common behavior in industrialized countries. This trend toward shorter sleep times has occurred over the same time period as the dramatic increases in the prevalence of obesity and diabetes. ***Aims:*** This article will review rapidly accumulating laboratory and epidemiologic evidence indicating that chronic partial sleep loss could play a role in the current epidemics of obesity and diabetes. ***Conclusions:*** Laboratory studies in healthy young volunteers have shown that experimental sleep restriction is associated with a dysregulation of the neuroendocrine control of appetite consistent with increased hunger and with alterations in parameters of glucose tolerance suggestive of an increased risk of diabetes. Epidemiologic findings in both children and adults are consistent with the laboratory data.

Hormones and Sleep: An Introduction

It has been known for several decades that sleep exerts profound modulatory effects on hormones and metabolism. The secretion of growth hormone (GH) and prolactin (PRL) is markedly increased during sleep, whereas the release of cortisol and thyrotropin (TSH) is inhibited. Conversely, awakenings interrupting sleep inhibit nocturnal GH and PRL secretions and are associated with increased cortisol and TSH concentrations. Modulatory effects of sleep on endocrine release are not limited to the hormones of the hypothalamic-pituitary axis. Indeed the hormonal control of carbohydrate metabolism and water and electrolyte balance is also different during total sleep deprivation as compared with normal sleep.

The release of GH is particularly dependent on the occurrence and quality of sleep. In the late 1960s it was recognized that the most reproducible GH pulse occurs shortly after sleep onset [1]. In men, the sleep-onset GH pulse is generally the largest, and often the only, secretory pulse observed over the 24-hour span. In women, daytime GH pulses are more frequent, and the sleep-associated pulse, although still present, does not account for the majority of the 24-hour secretory output. As illustrated in figure 1, stimulation of GH release during sleep is evident in children as well. Sleep onset elicits a pulse in

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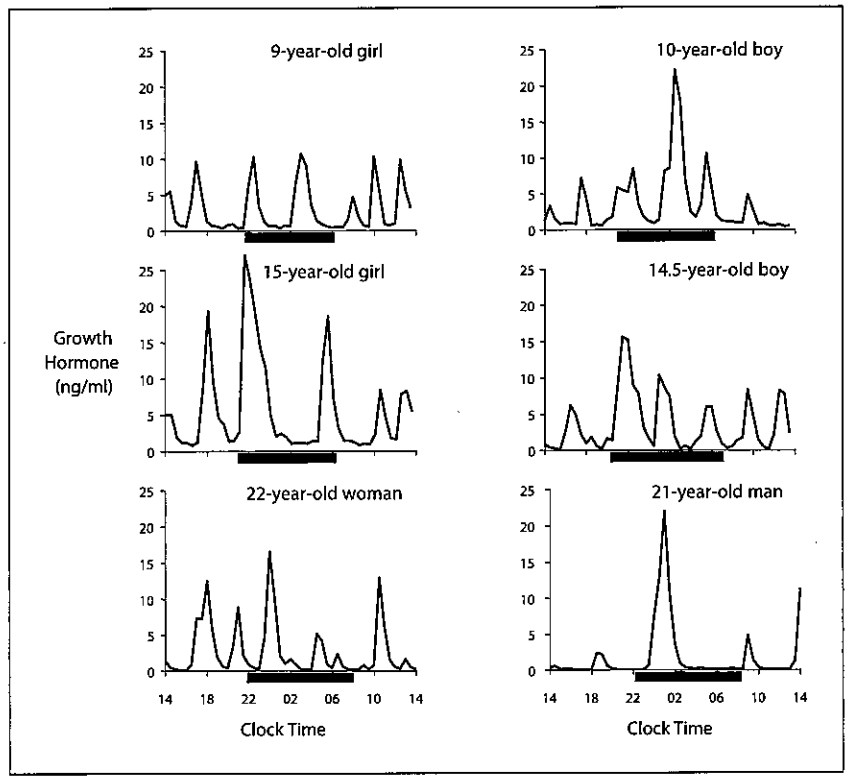

Fig. 1. 24-hour profiles of plasma GH in prepubertal children, pubertal children and adults. The black bar represents the sleep period. Note that a large pulse of GH release consistently follows sleep onset, irrespective of age or gender. Data in children were obtained courtesy of Professor Zvi Zadik (Kaplan Medical Center, Rehovot, Israel).

GH secretion whether sleep is advanced, delayed or interrupted and reinitiated. Current evidence is consistent for a combined and probably synergic role of GH-releasing hormone stimulation and decreased somatostatinergic tone in the control of GH secretion during sleep. Nocturnal levels of ghrelin, a powerful GH secretagogue, are also higher during sleep than during wake, but it is unclear whether the nighttime elevation of ghrelin levels plays a role in the control of sleep-related GH release.

Hormonal events during sleep are dependent upon sleep quality. Sleep involves two states of distinct neuronal activity that are each actively generated in specific brain regions, and in the course of a normal night of sleep, brain activity oscillates between non-rapid eye movement (NREM) stages and REM stages. The periodicity of this oscillation is approximately 90 min and is normally repeated four to six times per night. During REM sleep, a cortical electroencephalogram (EEG) resembles that of active waking, with mixed high-frequency, low-amplitude waveforms; muscle tone is inhibited and bursts of REMs are present. NREM sleep is subdivided into stages I, II, III and IV, with the higher stages corresponding to deeper sleep that requires stronger stimuli for arousal. During deep NREM sleep (stages III and IV), the EEG becomes synchronized with low frequency (in the 0.5–4 Hz range), high-amplitude waveforms, referred to as slow waves or delta waves. Stages III and IV are therefore referred to as 'slow-wave sleep' (SWS). During a normal night in healthy young subjects, approximately 20% of the night is spent in SWS, 25% in REM, 50% in stages I and II NREM and only 5% awake. In adults over 60 years of age, SWS is generally reduced to only 5–10% and REM sleep to 10–15% while the proportion of time awake may occupy as much as 30% of the night.

The quantification of EEG recordings by spectral analysis provides useful information regarding sleep depth or sleep intensity that is not captured by stage scoring because, in contrast to stage scoring, spectral analysis is more sensitive to the amplitude of the waveform. The EEG signal is digitalized and, after appropriate filtering, spectral power is estimated in standard frequency bands. The low-frequency waves that are apparent during SWS are reflected in an increase in spectral power in the delta range (typically 0.5–4 Hz), often referred to as slow-wave activity (SWA). Higher SWA reflects more intense, deeper NREM sleep.

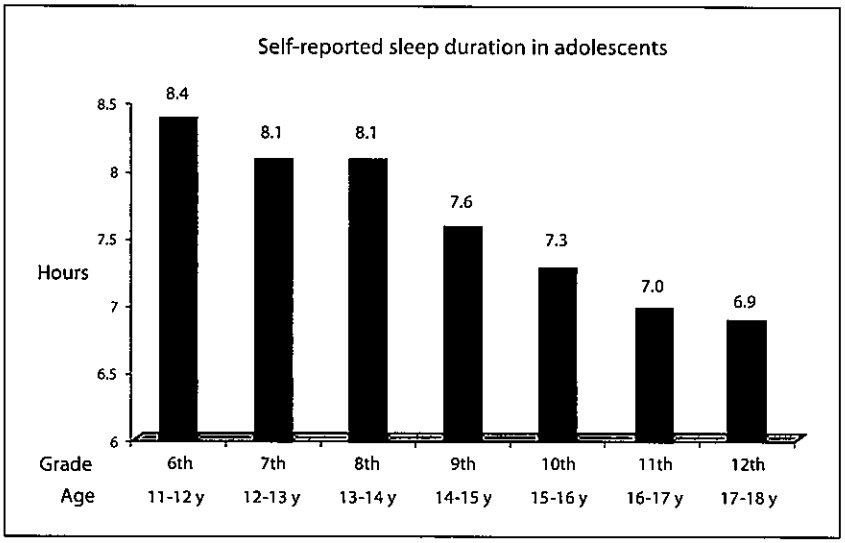

Fig. 2. Self-reported sleep duration during weekdays in American adolescents from 6th grade (11–12 years old) to 12th grade (17–18 years old). Data from the National Sleep Foundation '2006 Sleep in America Poll'.

Several of the more robust peripheral effects of sleep occur during SWS and are dependent on the intensity of SWS, as quantified by SWA. In particular, the stimulation of GH release occurs during SWS and is proportional to SWA [1]. Pharmacological stimulation of SWA results in a dose-dependent stimulation of nocturnal GH secretion. But sleep, and particularly SWS, is associated with multiple peripheral and central effects besides stimulation of GH release, including stimulation of PRL release, inhibition of corticotropic and thyrotropic activity, decreased heart rate, decreased blood pressure, decreased sympathetic nerve activity, increased vagal tone and decreased cerebral glucose utilization. While sleep deprivation has been clearly demonstrated to be associated with profound reductions in neurobehavioral performance, the multiple peripheral effects of sleep suggest that sleep loss might be associated with deleterious health effects. Until recently, nearly all studies of the peripheral impact of sleep loss examined the effects of acute total sleep deprivation, a condition that is necessarily of short duration in humans and invariably followed by sleep recovery. Alterations evidenced during acute total sleep deprivation are readily corrected following sleep recovery and therefore the possibility that sleep loss may result in long-term adverse effects appeared unlikely. Most individuals experience a full night of sleep loss only occasionally, if ever at all. As indicated below, a much more common condition that appears to have become increasingly prevalent in both adults and children is chronic partial sleep curtailment, i.e., having too little sleep night after night.

Chronic Partial Sleep Loss: An Endemic Condition of Modern Society

Sleep curtailment is a behavior that seems to have developed during the past few decades and has become highly prevalent, particularly among Americans. In 1960, the American Cancer Society conducted a survey study in adults that found modal sleep duration to be 8.0 to 8.9 h [2]. In 1995, a survey conducted by the National Sleep Foundation concluded that the mean had dropped to 7 h [3]. In 2004, more than 30% of adult men and women between the ages of 30 and 64 years reported sleeping less than 6 h/night [4].

Sleep need varies between individuals and is likely to be influenced by age. Several authors have distinguished between 'sleep need' and 'sleep capacity or ability', particularly in older populations [5–7]. Sleep 'capacity' may be estimated as the stable total sleep time achieved after several consecutive nights of extended bedtimes. A month-long experimental extension of the bedtime period to 14 h/day has provided evidence that a 'normal' 8-hour night does not meet the sleep capacity of healthy young adults who may carry a substantial sleep debt even in the absence of obvious efforts at sleep curtailment [8]. This study estimated 'sleep capacity' in young adults to be 8 h, 14 min with an SD of 51 min, suggestive of large interindividual differences. Several independent studies have consistently indicated that the average sleep capacity of young adults is between 8 and 9 h/night [9, 10]. Using a similar approach, Carskadon and Acebo [11] showed that sleep 'need', operationally defined as the amount of

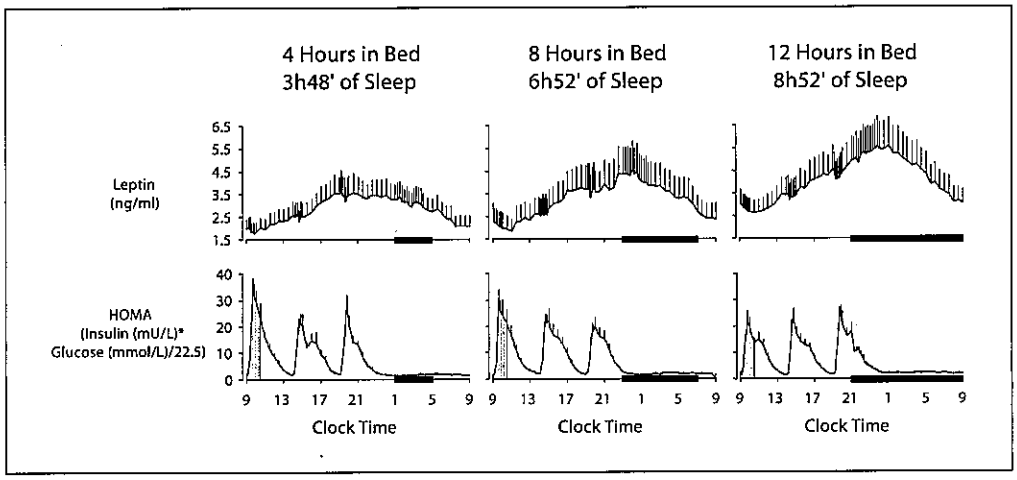

Fig. 3. 24-hour profiles of plasma leptin (upper panels) and homeostatic model assessment (HOMA; lower panels) in 11 healthy lean young men under three bedtime conditions. The black bars represent the bedtime period. The shaded areas in the lower profiles represent the area under the curve for the first 90 min after the morning meal. The vertical line at each time point represents the SEM. Note the progressive increase in leptin levels and decrease in breakfast response with increasing bedtime duration.

sleep obtained in a 10-hour sleep opportunity, does not change across the adolescent span (aged 10 to 17 years) and is about 9 h.

In 2005 the National Sleep Foundation conducted a poll regarding sleep duration among US children and adolescents. This 25-min telephone survey of 1,602 individuals aged 11–17 years assessed sleep habits based on responses to questions addressed to the children as well as to the parent or caregiver. The sample was representative of the distribution of home telephones in the U.S. and included similar proportions of boys and girls. The margin of error was estimated at ±2.5%. As shown in figure 2, modern-day US adolescents do not satisfy their sleep need, as mean self-reported sleep duration is under 9 h at all ages and decreases markedly from 11 to 18 years of age. Adolescents 16 to 18 years of age appeared to have an average sleep deficit of roughly 2 h during the week. The poll further revealed that the adolescents were well aware that they had insufficient sleep. An astounding 28% of high school students admitted falling asleep at school at least once a week. Those reporting that they had sufficient sleep (≥9 h) were more likely to have better grades than those with insufficient sleep.

Neuroendocrine and Metabolic Implications of Short Sleep: Clinical Studies

While the concept that 'sleep is for the brain, not for the rest of the body' has long prevailed, recent studies of subjects submitted to repeated curtailment of the bedtime period in the laboratory have demonstrated that chronic partial sleep loss is associated with deleterious hormonal and metabolic alterations that are consistent with an increased risk of obesity and diabetes.

The first detailed laboratory study that examined the neuroendocrine and metabolic effects of recurrent partial sleep deprivation on glucose metabolism involved healthy young men who were subjected to 6 nights of 4 h in bed ('sleep debt') followed by 7 nights of 12 h in bed ('sleep recovery') [12]. The subjects ate identical carbohydrate-rich meals and were on continuous bed rest on the last 2 days of each condition. They underwent an intravenous glucose tolerance test (ivGTT) followed by a 24-hour period of frequent blood sampling to assess hormonal levels [12]. A control condition with 8-hour bedtimes was performed on a separate occasion and involved similar experimental procedures.

Figure 3 illustrates the highlights of the findings. The levels of leptin, a secretory product of the adipocytes that signals energy balance to the brain and promotes satiety, were clearly and markedly dependent on sleep duration (upper panels). When the subjects had only 4 h in bed for 6 nights, mean leptin levels were 19% lower, the nocturnal acrophase was 26% lower and the amplitude of the diurnal variation was 20% lower than when sleep had been extended to 12 h in bed for 7 nights [13]. These changes occurred despite similar levels of caloric intake

and physical activity with no change in body mass index (BMI) [13]. Maximal leptin levels between the state of sleep debt and the fully rested state differed on average by 1.7 ng/ml, which is somewhat larger than the decrease reported in young adults after 3 days of dietary restriction by approximately 900 kcal/d [13]. The leptin profiles observed during the 8-hour bedtime condition were intermediate. The lower panels of figure 3 illustrate the profiles of homeostatic model assessment (HOMA) levels, an index of insulin resistance directly proportional to the product of insulin × glucose. It can be seen that the area under the HOMA curve for the breakfast meal decreased with increasing sleep duration and was more than 50% higher after 6 days of sleep restriction than when the subjects were fully rested [13, 14].

Although the HOMA has only been validated as a measure of insulin resistance under fasting conditions, these results suggest that insulin resistance may develop progressively with increasing exposure to partial sleep loss. The results of the ivGTT, analyzed using the minimal model [15], revealed a nonsignificant trend for reduced insulin sensitivity (SI) during the sleep debt condition. When the short sleep condition was compared with the fully rested condition, the rate of glucose clearance during the initial phase of the test was 40% lower; glucose effectiveness, a measure of the ability of glucose to mediate its own disposal, was 30% lower; and the acute insulin response to glucose (AIR_G) was also 30% lower. The disposition index (DI) is the product of $AIR_G \times SI$, and it is a marker of diabetes risk. Low DI values represent a higher risk of type 2 diabetes. DI values of 2,000 and above are typical of subjects with normal glucose tolerance while DI values under 1,000 have been reported in populations at high risk for type 2 diabetes, such as Hispanic women with prior gestational diabetes [16]. In the short sleep condition, the DI was 40% lower than after sleep recovery ($p < 0.001$), and three of the 11 subjects had DI values under 1,000. In summary, the findings of this first 'sleep debt study' revealed that recurrent partial sleep loss results in a clear-cut dysregulation of a key component of appetite regulation as well as in important alterations of carbohydrate metabolism.

A second study that examined the impact of sleep restriction (4 h/night for 2 nights) as compared with sleep extension (10 h/night for 2 nights) used a randomized crossover design and confirmed the findings of the 'sleep debt' study in a similar subject population. In both bedtime conditions, daytime levels of plasma leptin, ghrelin, glucose and insulin were measured at frequent intervals following the second night of sleep restriction or extension [17]. Caloric intake was replaced by iv glucose infusion at a constant rate. Hunger and appetite were assessed hourly using standardized scales. Table 1 summarizes the major findings [17]. Morning glucose levels were higher, and insulin levels tended to be lower, after 2 nights with 4 h in bed as compared to 2 nights with 10 h in bed [14]. Daytime levels of leptin were decreased in the short sleep condition while ghrelin levels were higher. Ghrelin is a peptide released primarily from the stomach that increases appetite and food intake [18]. Thus, leptin and ghrelin exert opposing effects on hunger and appetite. Importantly, the change in the ghrelin-to-leptin ratio between the two conditions was strongly correlated with the change in hunger ratings, suggesting that the changes observed in these appetite hormones were partially responsible for the increase in appetite and hunger. These observed changes suggest that these subjects, if allowed food ad libitum, would have increased their food intake.

Very similar findings regarding associations between leptin, ghrelin and sleep duration were obtained in a population study that involved more than 1,000 men and women [19]. This study collected sleep diaries from which average nightly sleep duration was calculated, and each subject underwent one night of sleep recording in the laboratory. In the morning following the sleep study, a single blood sample was obtained for the measurement of leptin and ghrelin. After controlling for BMI, having a usual sleep time of 5 h as compared with 8 h was associated with leptin levels 18% lower and ghrelin levels 15% higher [19].

In ongoing studies from our laboratories that involve longer periods of bedtime restriction (8 days of bedtime restriction to 5 h/night or 15 days of bedtime restriction by 1.5 h/night) than the initial sleep debt study, a consistent finding that emerges from preliminary data is a marked reduction in insulin sensitivity. Thus, more prolonged exposure to chronic partial sleep restriction appears associated with increased insulin resistance.

Epidemiologic Studies of Sleep Loss and Risk of Obesity and Diabetes

Between 2000 and 2006, ten publications have reported an association between short sleep and high BMI in adults based on epidemiologic data [19–28]. The various studies originated from Spain, France, Germany, Switzerland and the U.S. and involved different BMI ranges. Only two studies involved a longitudinal design [27, 28]; all others were cross-sectional. Sleep duration was obtained by self-report in all of these studies. Despite these

Table 1. Levels of morning (9:00 to 10:00) glucose and insulin, daytime (9:00 to 21:00) leptin and appetite and afternoon and early evening (12:00-21:00) ghrelin in 12 healthy lean young men after 2 days of 4- or 10-hour bedtimes

Mean (±SEM) levels	After 2 days of 4-hour bedtimes	After 2 days of 10-hour bedtimes	Change (%)	P value
Glucose, mg/dl	123±3	116±3	+6%	<0.05
Insulin, pM	133±22	154±23	–4%	<0.12
Leptin, ng/ml	2.1±0.4	2.6±0.5	–18%	0.04
Ghrelin, ng/ml	3.3±0.2	2.6±0.2	+28%	<0.04
Ghrelin:leptin ratio	2.3±0.4	1.6±0.3	+71%	<0.07
Hunger, 0–10 cm	7.2±0.4	6.0±0.5	+24%	<0.01
Global appetite, 0–70 cm	47.7±3.4	39.7±3.0	+23%	0.01
Appetite for high-carbohydrate food, 0–30 cm*	20.6±1.4	16.3±1.3	+32%	<0.02
Appetite for other food types (0–40 cm)*	27.1±2.2	23.4±1.8	+18%	<0.2

*Hunger and appetite were measured on visual analogue scales.

Table 2. Summary of findings from studies examining the association between sleep and obesity in children

Authors	Country	Study design	Subjects	Age, years	Results
Locard et al., 1992 [33]	France	Case-control	1,031	5	Odds ratio (OR) for obesity was 4.9 (95% CI 1.9–12.7) for <10 h/night; 2.8 (95% CI 1.2–6.3) for 10–11 h/night vs. >12 h/night.
Gupta et al., 2002 [34]	US	Cross-sectional	383	11–16	Total sleep time-adjusted OR was 0.20 (95% CI 0.11–0.34) predicting obesity.
von Kries et al., 2002 [35]	Germany	Cross-sectional	6,862	5–6	Adjusted OR for being overweight was 0.77 (95% CI 0.59–0.99) for sleep times 10.5–11 h/night; 0.54 (95% CI 0.40–0.73) for ≥11.5 h/night relative to ≤10 h/night. Adjusted OR for being obese was 0.53 (95% CI 0.35–0.80) for 10.5–11 h/night and 0.45 (95% CI 0.28–0.75) for ≥11.5 h/night.
Sekine et al., 2002 [36]	Japan	Cross-sectional	8,274	6–7	OR for obesity relative to ≥10 h sleep/night was 3.06 (95% CI 1.72–5.36) for <8 h; 2.01 (95% CI 1.43–2.91) for 8–9 h.
Agras et al., 2004 [37]	US	Prospective	150	Sleep at 3–5; weight at 9.5	The difference in mean sleep at ages 3–5 years between those who became overweight and those who did not was 30 min, most of which was daytime sleep.
Reilly et al., 2005 [38]	UK	Prospective	8,234	Sleep at 3.2; weight at 7	OR for obesity was 1.45 (95% CI 1.10–1.89) for <10.5 h and 1.32 (95% CI 1.02–1.79) for 10.5–11.4 h relative to ≥12 h per night.
Chaput et al., 2006 [39]	Canada	Cross-sectional	422	5–10	OR for overweight/obesity was 3.45 (95% CI 2.61–4.67) for 8–10 h and 1.42 (95% CI 1.09–1.98) for 10.5–11.5 h relative to 12–13 h per night.
Knutson, 2005 [40]	US	Cross-sectional	4,486	Mean 16	OR for overweight among males was 0.90 (95% CI 0.82–1.00). Not significant among females.

limitations, the consistency of the findings is remarkable.

A limited number of prospective studies have examined the association between sleep duration and the development of diabetes. Results from the US Nurses Health Study, which included only women, found an increased risk of incident symptomatic diabetes over 10 years among those reporting sleep durations of 5 h or less instead of 7–8 h, even after controlling for many covariates such as BMI, shiftwork, hypertension, exercise and depression [29]. A study conducted in Sweden followed 1,187 men and women free of diabetes at baseline for 12 years [30]. Men who reported difficulty maintaining sleep or who reported sleep duration of 5 h or less had a significantly greater risk of developing diabetes, but no significant associations between sleep and diabetes risk was observed in women [30]. Another study from Sweden suggested that the impact of sleep loss on diabetes risk may be gender-dependent as the incidence of diabetes in more than 600 women followed for 32 years beginning in 1968 was not found to be associated with sleep duration at baseline [31]. Finally, the Massachusetts Male Aging Study observed that among men without diabetes at baseline, a sleep duration of 6 h or less per night was associated with twice the risk of developing diabetes after adjustment for a large number of covariates [32]. Thus, there is some epidemiologic evidence to indicate that short sleep may increase the risk of developing type 2 diabetes, particularly in men.

Table 2 lists the eight epidemiologic studies to date linking sleep duration and risk of overweight and obesity in children [33–40]. Again, the studies originated from a variety of industrialized countries. The age range of the participants varies widely from one study to another, but the findings are quite consistent. Of particular interest are the two prospective studies showing a relationship between short sleep at baseline and the development of overweight/obesity [37, 38].

Conclusions

A rapidly growing body of evidence suggests that chronic partial sleep loss, a behavior that is specific to the human species and appears to have become more and more prevalent during the past few decades, may increase the risk of obesity and type 2 diabetes. The major neuroendocrine and metabolic alterations associated with short sleep are an upregulation of appetite, with lower leptin and higher ghrelin levels, and a peculiar disturbance of glucose regulation that involves both reduced β-cell responsiveness and lower insulin sensitivity. Mechanisms underlying these adverse effects of sleep loss remain to be identified and are likely to be multifactorial.

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