Principles and Practice of Geriatric Sleep Medicine

S. R. Pandi-Perumal, MSc
President and Chief Executive Officer, Somnogen Inc, New York, USA

Jaime M. Monti, MD
Department of Pharmacology and Therapeutics, University of the Republic School of Medicine, Montevideo

Andrew A. Monjan, PhD, MPH
Chief, Neurobiology of Aging Branch, Division of Neuroscience, National Institute on Aging, NIH/DHHS, Bethesda

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Eve Van Cauter and Rachel Leproult

Introduction: the epidemic of diabesity

The prevalence of obesity is increasing worldwide, particularly in the US [1]. Obesity is a major risk factor for type 2 diabetes mellitus (T2DM), and it is estimated that more than 20 million Americans are currently diabetic and that one third of them remains undiagnosed (Diabetes statistics from the American Diabetes Association available at: http://www.diabetes.org/diabetes-statistics.jsp, accessed April 28, 2006). A new term has been coined to describe the common clinical association of T2DM and obesity: "diabesity." As diabetes risk increases with age, the impact of the epidemic of obesity on the prevalence of diabetes is particularly important for adults in midlife and late life.

Nearly 25% of American adults between the age of 50 and 69 years were obese in 2001 as compared to approximately 15% in 1991. The epidemic of obesity has not spared the older segment of the population, as the proportion of obese individuals 70 years and older has increased from 11 % in 1991 to 17% in 2001. Food marketing practices (i.e. portion size, accessibility of inexpensive, calorie-dense fast food) and reduced physical activity are the most common lifestyle explanations for the epidemic of obesity but experts agree that they do not fully explain the magnitude and chronology of the secular changes in obesity prevalence.

One behavior that seems to have developed during the past few decades and has become highly prevalent, particularly amongst Americans, is sleep curtailment. In 1960, a survey study conducted by the American Cancer Society found modal sleep duration to be 8.0 to 8.9 hours [2] while in 2008, participants in the survey conducted by the National Sleep Foundation poll reported sleeping on average 6 hours and 40 minutes during weekdays [3]. Analyses of national data indicate that a greater percentage of adult Americans reported sleeping 6 hours or less in 2004 than in 1985 [4]. In 2004, more than 30% of adult men and women between the ages of 30 and 64 years reported sleeping less than 6 hours per night [4]. For adults 65 years and older, the proportion was 20% for men and more than 25% for women. In a recent study of early-middle-aged adults where sleep duration was measured objectively using wrist actigraphy [5], mean sleep duration was only 6.1 hours.

While factors other than voluntary bedtime curtailment undoubtedly contribute to shorter sleep in older adults, the fact that the proportion of short sleepers in the older age groups has increased substantially over the past two decades suggests that behavior plays a role. Interestingly, the decrease in average sleep duration in the USA has occurred over the same time period as the increase in the prevalence of obesity and diabetes.

Detailed reviews of the prevalence of sleep disorders in older adults have been presented in other chapters of this volume. The two most common sleep disorders in the elderly are sleep-disordered breathing (SDB) and insomnia. The prevalence of both types of sleep disorders has also increased with the epidemic of obesity as obesity is the major risk factor for SDB [6] and a substantial proportion of obese individuals suffer from insomnia [7]. Thus, the epidemic of obesity has been paralleled by an increased prevalence of *short sleep* and *poor sleep*.

The present chapter examines the existing evidence relating reduced sleep duration and quality – as occurs in a majority of older adults – and the epidemic of diabesity. In the first two sections, we describe how glucose regulation and the neuroendocrine regulation of appetite vary across the sleep–wake cycle in young and older adults. The following section discusses the impact of age-related alterations in sleep on hormonal function. The fourth and fifth sections summarize the laboratory and epidemiological studies that have provided evidence for an adverse impact of reduced sleep duration or quality on the risks of diabetes and obesity, respectively. We conclude with a

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brief discussion of the putative benefits of improving sleep duration and quality as a strategy for successful metabolic aging.

Glucose regulation and the sleep–wake cycle: impact of age

Blood levels of glucose are tightly regulated within a narrow range to avoid hypoglycemia and hyperglycemia as both conditions have serious adverse consequences. Glucose tolerance refers to the ability to metabolize exogenous glucose and return to baseline blood glucose concentrations. Glucose tolerance is dependent on the balance between glucose production by the liver and glucose utilization by insulin-dependent tissues, such as muscle and fat, and non-insulin dependent tissues, such as the brain. Glucose tolerance is critically dependent on the ability of pancreatic beta cells to release insulin (beta cell responsiveness) and on the ability of insulin to inhibit glucose production by the liver and promote glucose utilization by peripheral tissues (i.e. insulin sensitivity). Reduced insulin sensitivity, or insulin resistance, occurs when higher amounts of insulin are needed to dispose of the same amount of glucose. Glucose tolerance is also critically dependent on cerebral glucose uptake since the brain represents at least 40% of total glucose metabolism.

In normal individuals, glucose tolerance varies across the day such that plasma glucose responses to exogenous glucose are markedly higher in the evening than in the morning, and glucose tolerance is at its minimum in the middle of the night [8]. The reduced glucose tolerance in the evening is at least partly due to a reduction in insulin sensitivity concomitant with a reduction in the insulin secretory response to elevated glucose levels. The further decrease in glucose tolerance during the night is dependent on the occurrence of sleep. Indeed, a variety of mechanisms intervene to maintain stable glucose levels during the extended overnight fast associated with sleep [8]. Overall glucose utilization is greatest during wake and lowest during non-REM (stages 2, 3, and 4) sleep with intermediate levels during REM sleep [9]. In the first half of the night, glucose metabolism is slower, partly because of the predominance of slow wave sleep that is associated with a marked reduction in cerebral glucose uptake [10, 11], and may also be because of a reduction in peripheral glucose utilization. The release of growth hormone (GH) during early sleep contributes to prevent the decline of glucose levels. These effects are reversed during the second half of the night, when light non-REM sleep and REM sleep are dominant, GH is no longer released, and awakenings are more frequent.

To study variations in glucose tolerance across a 24-hour cycle, a constant glucose challenge, such as identical meals or snacks, identical loads of oral glucose or an intravenous infusion of glucose at a constant rate, must be used. The latter procedure allows for the assessment of glucose tolerance during sleep as well as during wake. Further, the infusion of glucose inhibits hepatic glucose production and variations in blood glucose concentrations then directly reflect variations in glucose utilization. Figure 10.1 shows the mean 24-hour profiles of plasma glucose, insulin secretory rates (ISR), and plasma GH from groups of healthy, overweight, older men (mean ± SD of age: 65 ± 5 years; mean ± SD of BMI: 28.6 ± 1.9 kg/m^2) compared to those of similarly overweight young men (mean ± SD of age: 25 ± 4 years; mean ± SD of BMI: 28.3 ± 3.3 kg/m^2) and lean young men (mean ± SD of age: 25 ± 2 years; mean ± SD of BMI: 21.6 ± 1.5 kg/m^2). The comparison of the glucose and insulin profiles across age groups illustrates the deterioration of glucose tolerance and the increased insulin resistance that are typical of aging. Levels of slow wave sleep (SWS) and nocturnal GH release were drastically decreased in the older subjects. The sleep-associated increase in glucose levels was dampened in the older subjects, consistent with the absence of the hyperglycemic effects of GH but also with the fact that low amounts of SWS likely resulted in lesser decreases in brain glucose utilization. Remarkably, in the older subjects, insulin secretion largely failed to increase in response to the sleep-associated glucose rise, demonstrating the existence of a clear reduction in beta cell responsiveness in aging. Thus, decreased glucose tolerance in aging is not only associated with insulin resistance but also with a relative insensitivity of the beta cell to the modulation of glucose regulation by sleep.

The impact of age on the 24-hour profiles of glucose, insulin, and counter-regulatory hormones is further illustrated in Figure 10.2. The subjects were healthy older and young adults (ages 50–69 years versus 20–28 years, BMI: 22–28 kg/m^2 versus 21–25 kg/m^2) who received three identical high-carbohydrate meals. Total sleep time, sleep efficiency, and amount of slow wave sleep were lower in the older group than in the young volunteers. The 24-hour profiles of glucose and

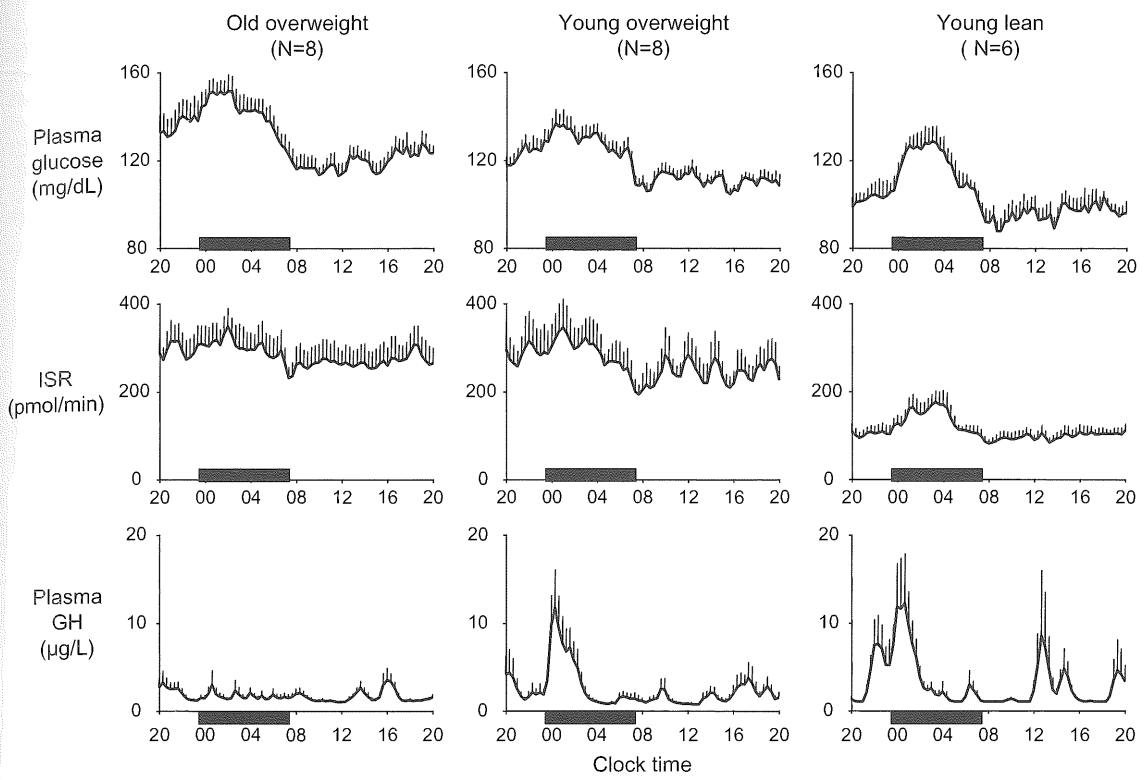

Figure 10.1. 24-hour profiles (mean + SEM) of plasma glucose (top panels), insulin secretory rates (middle panels), and plasma growth hormone (bottom panels) in overweight older adults (N=8, left panels), in overweight young adults (N=8, middle panels), and in lean young adults (N=6, right panels). Caloric intake consisted of a constant glucose infusion. The black bars represent the time allocated to sleep.

insulin (top panels) were similar in the two age groups with the older subjects showing a trend ($p = 0.056$) towards higher 24-hour mean glucose levels (105 ± 6 mg/dL) when compared with the young (98 ± 8 mg/dL). There was also a trend for higher insulin levels in older adults. When the profiles of Homeostatic Model Assessment (HOMA: insulin × glucose) values were calculated, this index of insulin resistance was elevated in older adults. Growth hormone levels were uniformly lower in the older subjects although a small sleep-related increase was still detectable. The amplitude of the 24-hour rhythm of plasma cortisol was dampened, mostly because of a failure to suppress hypothalamo-pituitary-adrenal (HPA) axis activity in the late evening and early part of sleep. A similar alteration of HPA regulation can be observed in young subjects submitted to partial or total sleep deprivation [12] and in insomniacs with reduced total sleep time [13]. Diurnal changes in epinephrine (E) and norepinephrine (NE) levels were present in both age groups with higher levels during the day and lowest levels during sleep. Consistent with the elevation of sympathetic nervous activity that is typical of aging, the older subjects had higher NE levels than the young throughout the 24-hour sleep–wake cycle, with the age difference being higher during sleep than during wake. The apparent higher E levels during sleep in older adults as compared to young volunteers failed to reach significance.

In summary, reduced sleep duration and quality in healthy older adults appear to be associated with – and perhaps partly responsible for – changes in GH, cortisol, E, and NE that could all adversely impact glucose tolerance and/or insulin sensitivity. Reduced sleep duration and quality are also likely to contribute to age-related declines in cerebral glucose utilization, particularly in the prefrontal cortex [14, 15].

Neuroendocrine regulation of appetite and the sleep–wake cycle: impact of age

Appetite is regulated by the interaction between metabolic and hormonal signals and neural mechanisms.

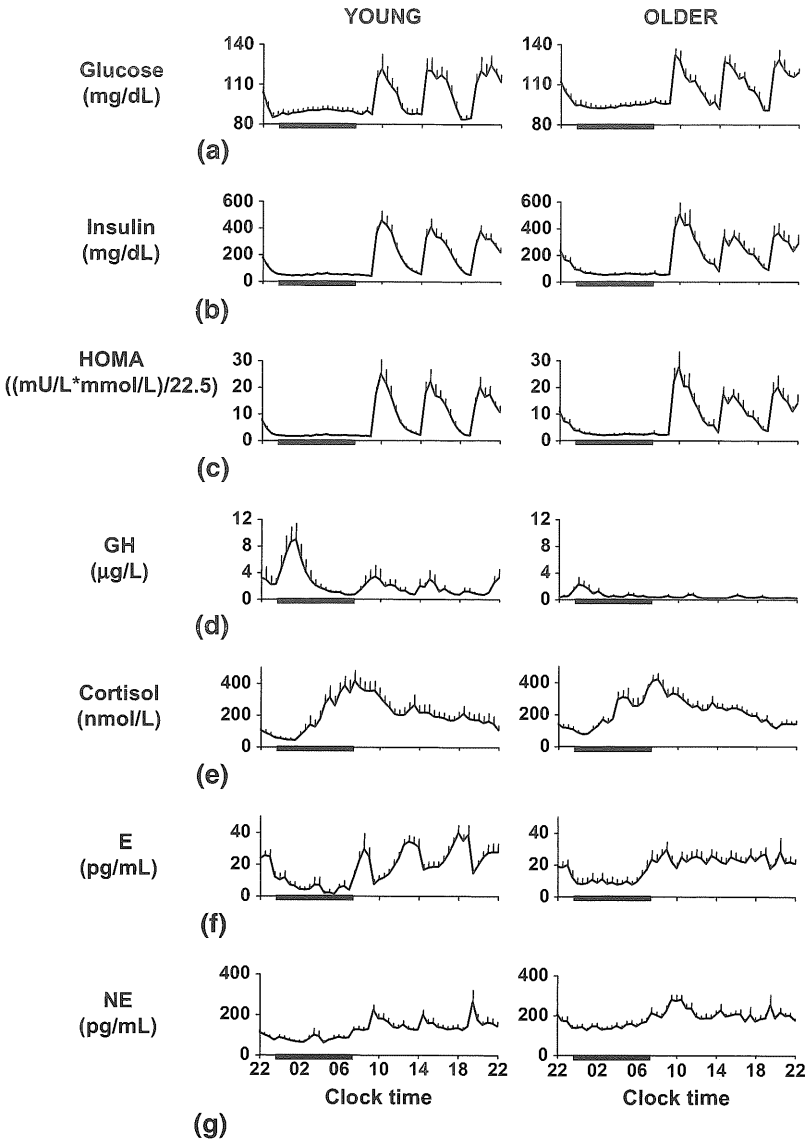

Figure 10.2. 24-hour profiles (mean + SEM) of (a) glucose, (b) insulin, (c) the Homeostatic Model Assessment (HOMA, product of glucose by insulin), (d) growth hormone, (e) cortisol, (f) epinephrine, and (g) norepinephrine in healthy young adults (left panels) and in healthy older adults (right panels). The subjects received three identical carbohydrate-rich meals. The black bars represent the time allocated to sleep.

The peripheral signals that affect appetite-regulating centers in the arcuate nucleus of the hypothalamus include leptin, an appetite-inhibiting hormone, and ghrelin, an appetite-stimulating hormone. The peripheral levels of leptin and ghrelin undergo large and consistent variations across the sleep–wake cycle, which is schematically illustrated in Figure 10.3. Leptin is primarily secreted by adipose tissue and promotes satiety [16]. Ghrelin is a peptide released primarily from the stomach and increases appetite and food intake [17]. In humans, plasma ghrelin levels are rapidly suppressed by food intake (particularly carbohydrate-rich foods) and then rebound after 1.5–2 hours, paralleling the resurgence in hunger. Thus, leptin and ghrelin exert opposing effects on appetite. As illustrated in Figure 10.3, under normal conditions, the 24-hour profile of human plasma leptin levels shows a marked nocturnal rise, which is dependent on meal intake [18]. However, a study using continuous enteral nutrition showed the persistence of a sleep-related leptin elevation during both nocturnal and daytime sleep [19]. The 24-hour profile of ghrelin levels also shows a nocturnal rise, which partly reflects the post-dinner rebound. Ghrelin levels spontaneously decrease in the second half of the sleep period, despite the maintenance of the fasting condition [20], suggesting that sleep may

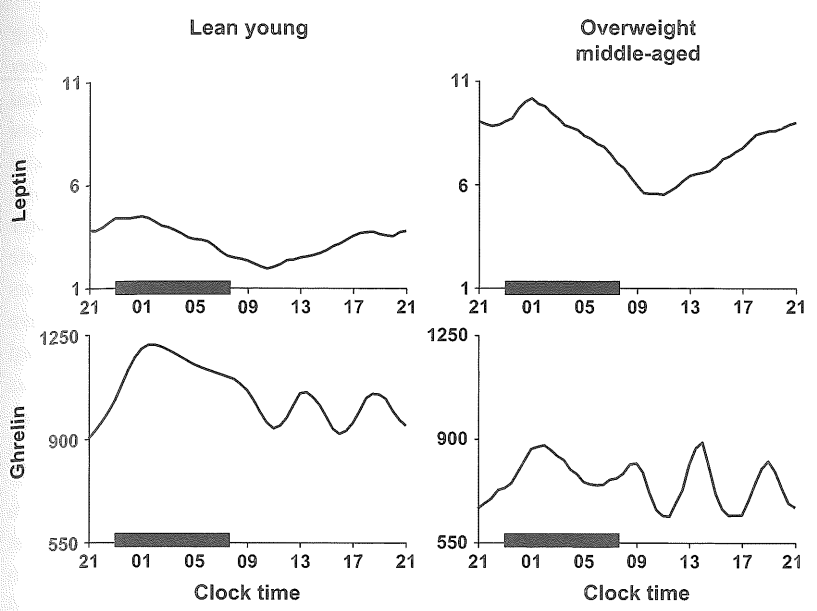

Figure 10.3. Schematic representation of 24-hour profiles of leptin (top panels) and ghrelin (bottom panels) levels under normal conditions including three identical meals in young lean (left panels) and overweight middle-aged (right panels). The black bars represent the sleep periods.

in fact inhibit ghrelin release. Elevated leptin levels in association with decreasing ghrelin levels during sleep may serve to suppress hunger during the overnight fast. Age and increased adiposity elevate leptin levels and suppress ghrelin levels but the diurnal variation is generally preserved (right panels of Figure 10.3).

The identification in 1998 of a small population of neurons that express two excitatory neuropeptides (orexin A and orexin B) that have potent wake promoting effects and stimulate food intake, particularly at a time when normal food intake is low, has provided a molecular link between sleep–wake regulation and the neuroendocrine control of appetite [21, 22]. Orexin neurons are mainly concentrated in the lateral hypothalamus and have excitatory projections to all the components of the ascending arousal system, and also project diffusely to the entire cerebral cortex [23]. The orexin system also activates the appetite-promoting neuropeptide Y neurons in the arcuate nucleus of the hypothalamus. Furthermore, orexin neurons have dense projections to the dopaminergic ventro-tegmental area (VTA) and nucleus accumbens (NA), which are important in the hedonic control of food intake [24, 25]. Thus, overactivation of the orexin system is likely to increase both hedonic and homeostatic feeding. Orexinergic activity is in turn influenced by both central and peripheral signals, with glucose and leptin exerting inhibitory effects while ghrelin promotes further activation [22].

Deficiencies in the orexin system are associated with sleep disorders involving chronic excessive daytime sleepiness, including narcolepsy and obstructive sleep apnea [26, 27]. In contrast, when sleep deprivation is enforced behaviorally rather than the result of a chronic pathological condition, the orexin system is overactive, as demonstrated by sleep deprivation studies in rats, dogs, and squirrel monkeys [28, 29, 30]. This overactivity of the orexin system during sleep deprivation may serve to maintain wakefulness against the increased sleep pressure but is also likely to be involved in increasing hunger and food intake.

Studies in senescent laboratory animals have indicated that aging may be associated with a decreased impact of orexin on food intake which could be responsible for reductions in appetite and food intake that are common in late life. A reduction in hypocretinergic innervation of basal forebrain nuclei of old hamsters and a lower concentration of orexin A in the cerebrospinal fluid of older rats has also been demonstrated. Taken together, these findings suggest that late life may be associated with an overall decrease in orexin system activity, which could contribute to weakening the waking drive and explain the increased daytime sleepiness and napping behavior of the elderly.

Age-related alterations in sleep: hormonal implications

There is increasing evidence that age-related alterations in sleep quality may result in disturbances of endocrine function, raising the hypothesis that some of the hormonal and

metabolic hallmarks of aging partly reflect the deterioration of sleep quality. In particular, hormones that affect determinants of glucose regulation and adiposity are profoundly affected by sleep duration and quality.

There is good evidence for a role of decreased SWS in the age-related decline of GH, a hormone that plays an important role in the control of body composition, with lower amounts of GH linked to higher adiposity and lower lean mass and vice versa. Sleep loss and poor sleep quality have been associated with increases in evening cortisol levels, an alteration that promotes insulin resistance.

Several studies have shown that decreases in amount of SWS occur rapidly in adulthood (30–40 years of age) and precede the appearance of significant sleep fragmentation or declines in REM sleep. Figure 10.4 illustrates the chronology of aging of SWS and REM sleep (upper panels) as compared to age-related changes in nocturnal GH release and evening cortisol concentrations (lower panels) from a retrospective analysis of sleep and concomitant profiles of plasma GH and cortisol in 149 normal, healthy, non-obese men, aged 16–83 years. It may be seen that the impact of aging on GH release occurred with a chronology similar to that of the decline in SWS, characterized by major decrements from early adulthood to midlife [31]. The statistical analysis further indicated that reduced amounts of SWS, and not age *per se*, are associated with reduced GH secretion in midlife and late life. The observation that, in older adults, levels of insulin-like growth factor (IGF-1), the hormone secreted by the liver in response to stimulation by GH, are correlated with the amounts of SWS [32], is consistent with this finding. The relative GH deficiency of the elderly is associated with increased fat tissue and abdominal obesity, reduced muscle mass and strength, and reduced exercise capacity. The persistence of a consistent relationship between SWS and GH secretion in older men suggests that drugs that reliably stimulate SWS in older adults may represent a novel strategy for GH replacement therapy. In contrast to the rapid decline of SWS and GH secretion from young adulthood to midlife, the impact of age on REM sleep does not become apparent until later in life and the age-related elevation of evening cortisol levels follows the same chronology (right panels of Figure 10.4) [31]. Analysis of variance indicates that low amounts of

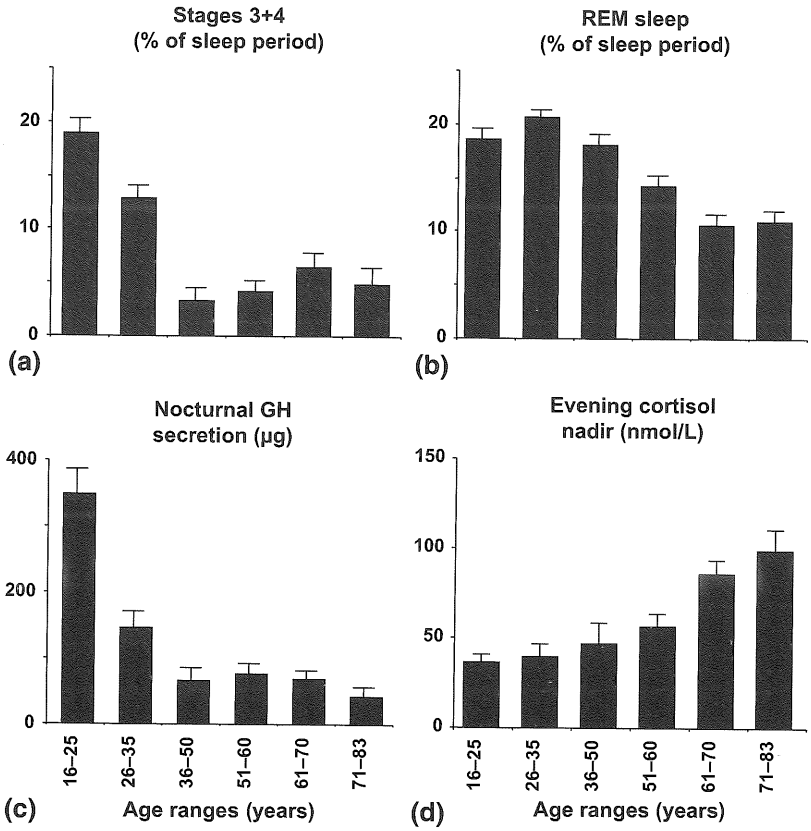

Figure 10.4. Chronology of aging (mean + SEM in each age range) of (a) percentage of slow wave sleep (stages 3+4), (b) percentage of REM sleep, (c) amount of growth hormone secreted during the night-time, and (d) evening cortisol nadir.

REM sleep were a significant predictor of the elevated cortisol nadir, after controlling for age and BMI. Both animal and human studies have indicated that deleterious effects of HPA hyperactivity are more pronounced at the time of the trough of the rhythm than at the time of the peak. Therefore, modest elevations in evening cortisol levels could facilitate the development of insulin resistance [33], and further promote sleep fragmentation. Indeed, several studies have demonstrated that elevated corticosteroid levels result in increased propensity for awakenings [34, 35].

Impact of reduced sleep duration and quality on diabetes risk

We briefly review below the laboratory and epidemiological evidence supporting the hypothesis that reduced sleep duration and quality may be novel risk factors for type 2 diabetes. While published laboratory studies have involved only young adults, the findings are nonetheless highly relevant to the well-documented age-related decreases in total sleep time and amount of SWS.

Laboratory studies

Our group published the first laboratory study designed to address the metabolic and hormonal consequences of recurrent partial sleep restriction [36]. Eleven young, healthy men were studied after 6 days of sleep restriction with 4-hour bedtimes followed by 7 days of sleep recovery with 12-hour bedtimes [36, 37, 38]. Examination of glucose metabolism included a frequently sampled intravenous glucose tolerance test (ivGTT) administered in the morning of the fifth day of each bedtime condition. This test allows for the simultaneous evaluation of beta cell responsiveness (acute insulin response to glucose; AIRg), insulin sensitivity (SI), and glucose effectiveness (Sg; a measure of non-insulin-dependent glucose utilization). A mathematical model referred to as "the minimal model" is fitted to the simultaneous glucose and insulin values to extract AIRg, SI, and Sg. In individuals with normal glucose tolerance, the product AIRg × SI, termed disposition index (DI), remains constant because their beta cell function is able to compensate for insulin resistance with increased insulin release. Type 2 diabetes occurs when beta cell function is unable to be sufficiently upregulated to compensate for insulin resistance, resulting in hyperglycemia. Thus low DI values represent a higher risk of type 2 diabetes. The results of the ivGTT are summarized in the upper part of Table 10.1. AIRg was reduced by more than 30% in the state of sleep debt even though SI tended to decrease. Sg was also significantly decreased. As a result, the DI was decreased by an average of 40% in the state of sleep debt as compared to the fully rested state. This large decrease in DI was of clinical significance since 3 of the 11 subjects had a DI<1000 at the end of the sleep debt period, indicative of a very high risk of diabetes. We subsequently confirmed the deleterious impact of sleep restriction on glucose metabolism in a follow-up study using a randomized cross-over design [38]. Recently, our findings were confirmed by an independent group that used the hyperinsulinemic euglycemic clamp to assess insulin sensitivity in healthy men after 1 week of sleep restriction to 5 hours per night and demonstrated a significant reduction in SI [39].

Table 10.1. ivGTT findings in a protocol of reduced sleep duration (upper part) and in a protocol of reduced sleep quality (lower part)

	Fully rested	After sleep intervention	*p* level
After 5 nights of 4 hours in bed *n* = 11 (all men)			
Sg (% per minute)	2.6 ± 0.2	1.7 ± 0.2	<0.0005
AIRg (mU/L. min)	566 ± 144	403 ± 125	0.04
SI (mU/L. min)	7.10 ± 1.04	5.19 ± 0.51	0.15
Disposition index (DI)	3123 ± 537	1724 ± 343	0.003
After 3 nights of SWS suppression *n* = 9 (4 women)			
Sg (% per min)	2.4 ± 0.3	1.9 ± 0.2	0.18
AIRg (mU/L. min)	314 ± 41	323 ± 36	0.73
SI (mU/L. min)	8.4 ± 1.1	5.9 ± 0.7	0.009
Disposition index (DI)	2347 ± 299	1745 ± 144	0.02

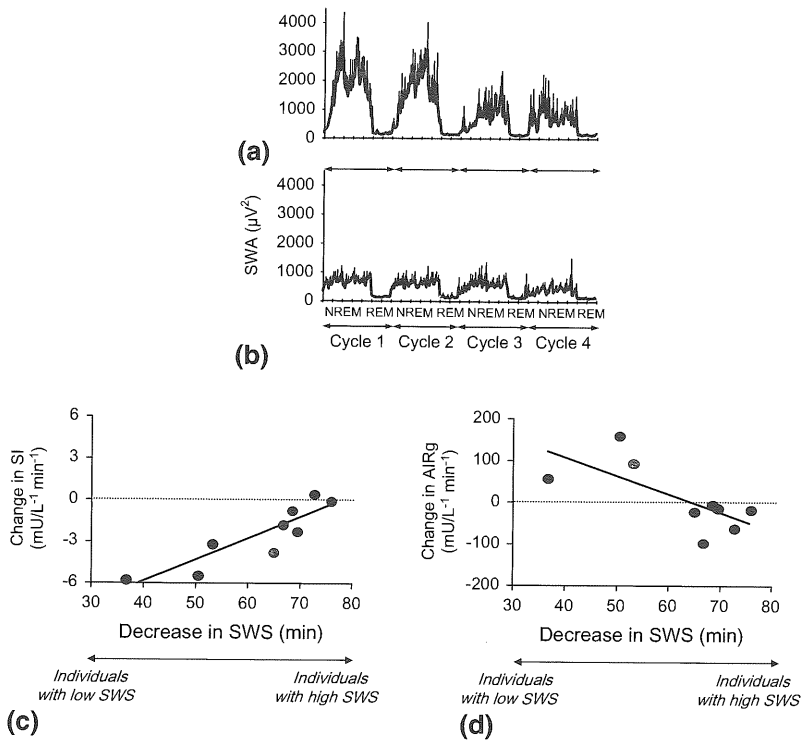

Figure 10.5. Results from the slow wave sleep (SWS) suppression study [40]. (a,b) The profiles (mean + SEM) of slow wave activity (SWA) for the first four normalized NREM/REM cycles during an undisturbed night (a) and during the third night of SWS suppression (b). SWA was calculated as the EEG spectral power in the 0.5–4 Hz frequency range. (c,d) The relationship between the changes in SWS, and the changes in insulin sensitivity and in acute insulin response to glucose, respectively, after 3 nights of SWS suppression. The individual with low SWS during baseline, before SWS suppression, ended up with extremely low amount of SWS after the intervention. Those subjects had also the biggest decrease in insulin sensitivity (c) without sufficient compensation in acute insulin secretion (d).

Normal aging is associated with a marked reduction in SWS and with an increased risk of diabetes. A recent study tested the hypothesis that a decrease in SWS could have an adverse impact on diabetes risk, in the absence of any other age-related condition [40]. The study achieved a selective suppression of SWS without change in sleep duration by delivering acoustic stimuli of varying frequencies and intensities to amplifiers located on each side of the bed. The sounds were calibrated in order to suppress delta activity while avoiding a full arousal. Nine healthy young volunteers were each tested under two conditions, in randomized order (1) after two consecutive nights of undisturbed "baseline" sleep, and (2) after three nights of suppression of SWS were achieved. Glucose regulation was assessed by ivGTT at the end of each condition. The amount of SWS was decreased by nearly 90% without any change in total sleep time, or in the duration of REM sleep. This decrease in SWS is similar to that which occurs over the course of four decades of normal aging. The upper part of Figure 10.5 illustrates the impact of the experimental intervention on levels of SWA. SWA was markedly reduced while spectral EEG power in other frequency bands including theta, alpha and sigma was unaffected. The findings from the ivGTT are summarized in the lower part of Table 10.1.

After three nights of suppression of SWS, insulin sensitivity (SI) was decreased by ~25%. The magnitude of the change in SI was comparable to that associated with a difference in weight of 8–13 kg. The decrease in SI associated with the reduction of SWS was not compensated for by an increase in insulin release, as AIRg remained virtually unchanged. Consequently, the DI was ~20% lower after SWS suppression.

Importantly, as shown in the lower part of Figure 10.5, the magnitude of changes in SI and AIRg was correlated with the magnitude of the reduction in SWS. The individuals who had low levels of SWS at baseline had the largest decrements in insulin sensitivity without adequate compensatory increases in AIRg. This indicates that older adults are likely to be at a greater risk of diabetes when sleep quality further deteriorates. There were no correlations between the measures of sleep fragmentation and the decrease in SI, suggesting that the alterations observed after SWS suppression are unlikely to be related to a decrease in sleep continuity.

Epidemiological studies

At least seven studies have examined the cross-sectional analyses of the association between sleep duration and quality and the prevalence of diabetes (reviewed in

[41]). In this chapter, we will focus on prospective studies because they provide some evidence regarding the direction of causality. Tables 10.2 and 10.3 summarize the prospective studies that have related, respectively, sleep duration and sleep quality to diabetes risk. This literature review was completed in October 2008. For sleep duration, four of the six studies found an association between being a short sleeper and having an increased risk of developing diabetes. For sleep quality, five out of six studies had positive findings. All the studies relied on self-reported sleep and it may be argued that poor sleep quality may lead to a misperception of time spent asleep. In sum, the bulk of the epidemiological evidence from prospective studies is consistent with the laboratory work in supporting a causal link between reduced sleep duration and/or quality and increased risk of T2DM.

Impact of reduced sleep duration and quality on obesity risk

Assessment of leptin and ghrelin levels

To date, four published laboratory studies have examined the impact of recurrent partial sleep restriction (2–14 days) on the neuroendocrine regulation of appetite. In a preliminary study published in 2003, Guilleminault *et al.* assessed leptin levels at six time points of the 24-hour cycle in volunteers studied after 7 days of sleep restriction to 4 hours per night and reported a significant decrease in peak leptin levels [51]. Two studies published in 2004 confirmed and extended these findings. One study compared the 24-hour profiles of plasma leptin levels obtained after sleep restriction (6 days of 4 hours in bed), after sleep extension (6 days of 12 hours in bed) and after regular bedtimes (2 days of 8 hours in bed) in the same volunteers. A remarkable "dose–response" relationship between sleep length and characteristics of the leptin profile was observed [37]. Indeed, the overall mean leptin concentration, the level of the nocturnal acrophase and the amplitude of the diurnal variation gradually increased from the 4-hour to the 12-hour bedtime condition.Importantly, these differences in 24-hour regulation of leptin levels between the three bedtime conditions occurred despite identical amounts of caloric intake and similar low levels of physical activity, as well as stable BMI. Of note, the reduction in mean peak leptin (26%) between the 4 hours and the 12 hours in bed condition was similar to

Table 10.2. Prospective studies linking short sleep duration and risk of type 2 diabetes

Citation	Follow-up	Population/setting	N	Key findings
Studies that support an association				
Ayas *et al.* 2003 [42]	10 years	Female nurses ages 30–55 years	70026	15–30% increased risk of incident diabetes associated with sleep duration ≤6 hours relative to 7–8 hours but no longer significant after adjusting for BMI. Symptomatic diabetes remains significant after adjusting for BMI
Mallon *et al.* 2005 [43]	12 years	Random sample of the middle-aged Swedish population	2663	Difficulties in maintaining sleep or sleep duration ≤5 hours are associated with an increased incidence of diabetes in men but not women
Yaggi *et al.* 2006 [44]	15–17 years	Massachusetts Male Aging Study	855	Compared with those reporting sleep duration of 7 hours/night, men reporting short sleep duration (≤6 hours/night) were twice as likely to develop diabetes (RR: 1.95; 95% CI: 0.95–4.01)
Gangwisch *et al.* 2007 [45]	10 years	Participants in the NHANES I study	8992	Participants reporting short sleep duration (<5 hours per night) were significantly more likely to have incident diabetes during the 10-year follow-up
Studies that did not support an association				
Bjorkelund *et al.* 2005 [46]	32 years	Swedish women ages 38–60 years	661	No association between hours of sleep and incident diabetes
Hayashino *et al.* 2007 [47]	4.2 years	High-risk and Population Strategy for Occupational Health Promotion Study (HIPOP-OHP)	6509	Sleep duration did not predict incidence of diabetes

Table 10.3. Prospective studies linking poor sleep quality and risk of type 2 diabetes

Citation	Follow-up	Population/setting	N	Key findings
Studies that support an association				
Kawakami *et al.* 2004 [48]	8 years	Japanese men	2649	High frequency of difficulty initiating or maintaining sleep is associated with an increased age-adjusted risk of developing type 2 diabetes
Nilsson *et al.* 2004 [49]	7–22 years	Swedish men aged 35–51	6599	Increased risk of incident diabetes among those who reported difficulty falling asleep or use of sleeping pills at baseline
Mallon *et al.* 2005 [43]	12 years	Random sample of the middle-aged Swedish population	2663	Difficulties in maintaining sleep or short sleep duration are associated with an increased incidence of diabetes in men but not women
Meisinger *et al.* 2005 [50]	11 years	MONICA surveys, Germany	8269	Difficulty maintaining sleep significantly associated with higher risk of T2DM post adjustment. Difficulty initiating sleep was not associated with T2DM in adjusted models
Hayashino *et al.* 2007 [47]	4.2 years	High-risk and Population Strategy for Occupational Health Promotion Study (HIPOP-OHP)	6509	Medium and high frequency of sleep initiation disturbance was associated with an increased risk of developing diabetes
Studies that did not support an association				
Bjorkelund *et al.* 2005 [46]	32 years	Swedish Women – population-based sample	661	Sleep problems at baseline (1968; duration & quality) did not increase risk of developing diabetes over 32- year follow-up

what has been reported in healthy volunteers fed only 70% of their energy requirement during 3 consecutive days, i.e. a caloric restriction by nearly 1000 calories per day. In a randomized cross-over design study of normal young adults after 2 nights of 4 hours in bed versus 2 nights of 10 hours in bed, the daytime leptin and ghrelin profiles were assessed simultaneously and the subjects completed validated scales for hunger and appetite for various food categories at hourly intervals. Caloric intake was strictly controlled in the form of an intravenous glucose infusion at a constant rate calculated to match normal caloric requirements. In the short sleep condition as compared to the long sleep condition, overall leptin levels were decreased by an average of 18%, while ghrelin levels increased by 24%, and the ghrelin:leptin ratio increased by more than 70%. Hunger showed a 23% increase and appetite for calorie-dense foods with high carbohydrate content was increased by more than 30% [52]. Importantly, the increase in ghrelin:leptin ratio accounted for nearly 70% of individual variability in increased hunger [52]. If the observed increase in hunger ratings during sleep restriction were to translate into an increase in food intake, significant weight gain would occur over time. A recent study of overweight, middle-aged adults studied in the laboratory during 2 weeks of sleep extension (+1.5 hours per night) as compared to 2 weeks of sleep restriction (−1.5 hours per night) in a randomized cross-over design has indeed shown an increased food intake from snacks during the short sleep condition [53]. The participants remained in the sedentary environment of the laboratory and were exposed to unlimited amounts of palatable food during both sleep conditions. Weight gain occurred under both sleep conditions and profiles of leptin and ghrelin assessed at the end of each 14-day study did not differ according to time in bed.

Figure 10.6 summarizes the findings of all the studies (laboratory based and epidemiological) that have so far examined the impact of sleep loss on leptin and ghrelin levels. Two large epidemiological studies have shown an elevation of leptin level in a single morning blood sample, after controlling for BMI or adiposity, in habitual short sleepers [54, 55]. In the larger study [54], the level of ghrelin was also measured and was found to be positively associated with short sleep [54]. A recent study examined the effects of one night of sleep restriction (4.5 hours vs. 7 hours) and showed an increase in ghrelin but no change in leptin [56]. A subsequent smaller study involving only post-menopausal women did not confirm the link between sleep duration, BMI, and leptin and ghrelin

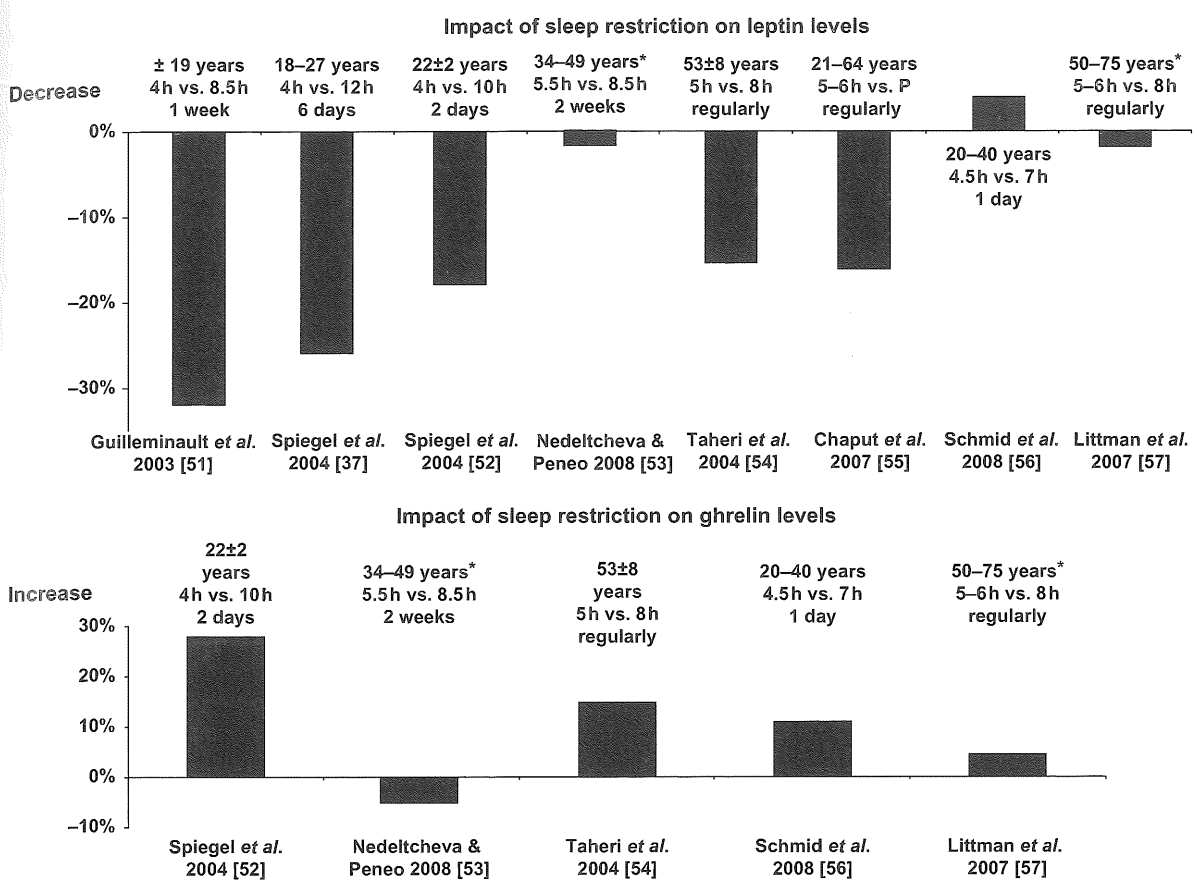

Figure 10.6. Percentages of changes due to sleep restriction in leptin (top panel) and in ghrelin (bottom panel) levels – laboratory and epidemiological studies.

*indicates that the subjects studied were overweight.

levels [57]. Difference in age of the sample may play a role in the divergent findings as orexigenic signals are generally thought to be weaker in older adults.

Epidemiological studies

An ever-growing number of cross-sectional epidemiological studies (numbering 52 as of September 2008) have provided evidence of an independent link between short and/or poor sleep and the risk for obesity. A recent meta-analysis including more than 600 000 adults and 30 000 children worldwide attempted to quantify the link between short sleep and obesity risk. The pooled odds ratio (OR) linking short sleep to obesity was 1.89 (95% CI: 1.46–2.43; $p < 0.0001$) in children and 1.55 (95% CI: 1.43 to 1.68; $p < 0.0001$) in adults [58]. An independent recent review similarly concluded that short sleep duration appears independently associated with weight gain, particularly in younger age groups [59].

Out of the six prospective studies that investigated the impact of short sleep on obesity risk in adults, three reported that shorter sleep durations are associated with an increased risk for overweight and obesity over the follow-up period [60]. Two of the three negative studies had very short follow-up periods, i.e. 2 years [61] and 5 years [62].

In summary, the body of epidemiological evidence has supported the hypothesis that sleep curtailment may be one of the more plausible "non-traditional" lifestyle factors contributing to the epidemic of obesity [63]. Increasing sleep duration for short sleepers has been suggested as a means to improve the health of the population as a whole [64]. Critics have argued that the effect size of short sleep (≤5 hours) in longitudinal studies involving a 10-year follow-up is small (with short sleepers gaining an excess weight ranging from 1 to 7 kg) [65]. Yet, the difference in weight gain between short and normal sleepers is well within the range of

weight loss that can be achieved with pharmacological interventions.

A limitation of nearly all epidemiological studies examining the relationship between sleep duration and BMI is that they were based on self-report sleep and did not simultaneously assess sleep quality. Thus, it remains to be determined whether short sleep in obese individuals is the result of bedtime curtailment or is due to the presence of a sleep disorder. Two recent reports have contributed to clarify this issue. First, a large-scale study [7] where participants reported sleep duration as well as subjective sleep disturbances (insomnia, excessive daytime sleepiness, sleep difficulty) and a measure of chronic emotional stress concluded that self-reported short sleep in obese adults may be a surrogate marker of subjective sleep disturbance and psychosocial stress [66]. This hypothesis is consistent with the existence of a "vicious circle" where short sleep may initially promote weight gain and the resulting excess adiposity would then induce sleep disturbances and psychological stress, with a net further decrease in total sleep time. Second, the cross-sectional association between sleep duration and obesity in a large number of older adults (3055 men: 67–96 years; 3052 women: 70–99 years) has been examined using wrist actigraphy for an average of 5.2 nights in all participants. Remarkably strong associations between objectively assessed short sleep and BMI emerged after controlling for multiple risk factors and medical conditions. For older adults who sleep less than 5 hours compared to those who sleep 7–8 hours, the odds of obesity (BMI >30 kg/m^2) was 3.7-fold greater in men and 2.3-fold greater in women. These associations persisted after adjusting for sleep apnea, insomnia, and daytime sleepiness.

Taken together, the epidemiological evidence suggests that reduced sleep duration and reduced sleep quality may both be novel risk factors for weight gain and obesity.

Conclusions

There is increasing evidence to indicate that the decreases in sleep duration and quality and the increased incidence of sleep disorders that occur in the course of aging are likely to play a role in the senescence of the endocrine system and in the development and severity of age-related metabolic disorders, including type 2 diabetes. Conversely, metabolic disorders may contribute to impair sleep quality, resulting in a "vicious cycle" linking sleep–wake regulation and metabolism in aging. Strategies to improve sleep quality may have beneficial metabolic and endocrine effects in older adults by delaying the development or reducing the severity of age-related metabolic disorders.

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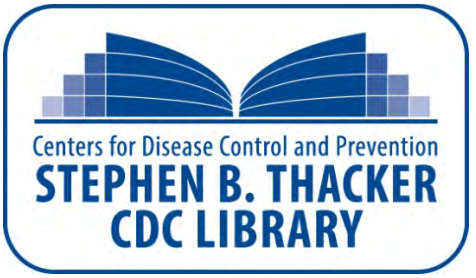

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