Molecular and Cellular Endocrinology 418 (2015) 101–107

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

The role of sleep in the regulation of body weight

Damien Leger*, Virginie Bayon, Alice de Sanctis

Université Paris Descartes, Sorbonne Paris Cité, APHP, Hôtel Dieu, Centre du Sommeil et de la Vigilance de l'Hôtel Dieu de Paris, Equipe d'accueil VIFASOM EA, Paris, France

ARTICLE INFO

Article history:
Received 12 March 2015
Received in revised form
2 June 2015
Accepted 5 June 2015
Available online 27 June 2015

Keywords:
Sleep
Weight
Biological clock
Obesity
Sleep debt
Epidemiology
Energy expenditure
Energy intake
Ghrelin
Leptin

ABSTRACT

Sleep participates in the regulation of body weight. The amount of sleep and synchronization of the biological clock are both necessary to achieve the energy balance and the secretion of hormones that contribute to weight regulation. In this review, we first reconsider what normal physiological sleep is and what the normative values of sleep are in the general population. Second, we explain how the biological clock regulates the hormones that may be involved in weight control. Third, we provide some recent data on how sleep may be disturbed by sleep disorders or reduced by sleep debt with consequences on weight. Finally, we explore the relationships between sleep debt and obesity.

1. Introduction

Having a regular good night of sleep is recommended as one of the major requirements for good health in children, but also in adults (WHO, 2005; NIH, 2015). Sleep has a crucial role in many somatic, cognitive, and psychological processes and sleeping well appears to be a health imperative, essential for survival (Siegel, 2009; Diekelmann and Born, 2010; Dolgin, 2013; Luister et al., 2012; Benedict et al., 2014). Although scientists are still studying the concepts of basal sleep needs, increasing evidence shows that sleeping too little may impact severely on metabolism with a higher risk of diabetes, overweight or obesity (Stranges et al., 2008; Buxton and Marcelli, 2010; Cappuccio et al., 2010a; Cohen-Mansfield and Perach, 2012; Knutson, 2010; Cappuccio et al., 2011; Chao et al., 2011; Theorell-Haglöw et al., 2012; Faraut et al., 2013; Guo et al., 2013; Kronholm et al., 2013; Nagai et al., 2013; Ramos et al., 2013a, 2013b) and even mortality risks (Kripke et al., 2002; Stranges et al., 2008; Gallichio et al., 2009; Cappuccio et al., 2010b; Grandner et al., 2010; Kronholm et al., 2013; Kurina et al., 2013; Maia et al., 2013) across populations. Sleep research has already shown that sleeping too little can affect memory and immunity, and can jeopardize safety (Buxton et al., 2010; Cappuccio et al., 2010a; Cohen-Mansfield and Perach, 2012; Knutson, 2010; Cappuccio et al., 2011; Chao et al., 2011; Theorell-Haglöw et al., 2012; Faraut et al., 2013; Guo et al., 2013; Kronholm et al., 2013; Nagai et al., 2013; Ramos et al., 2013a, 2013b) and even survival (Kripke et al., 2002; Stranges et al., 2008; Gallichio et al., 2009; Cappuccio et al., 2010b; Grandner et al., 2010; Kronholm et al., 2013; Kurina et al., 2013; Maia et al., 2013). In recent years, chronic short sleep duration (<6 h) has also been associated with an increased risk of overweight, obesity, diabetes, hypertension and cardiovascular diseases (Buxton et al., 2010; Cappuccio et al., 2010a; Cohen-Mansfield and Perach, 2012; Knutson, 2010; Cappuccio et al., 2011; Chao et al., 2011; Theorell-Haglöw et al., 2012; Faraut et al., 2013; Guo et al., 2013; Kronholm et al., 2013; Nagai et al., 2013; Ramos et al., 2013a).

However, it is not clearly understood whether extending the duration of sleep may have a protective metabolic impact in short duration sleepers, as has been suggested by some preliminary studies (Gumenyuk et al., 2013; Markwald et al., 2013).

* Corresponding author. Université Paris Descartes, APHP, VIFASOM, Centre du Sommeil et de la Vigilance de l'Hôtel Dieu de Paris, Hôtel Dieu. 1, Place du Parvis Notre-Dame, 75181 Paris Cedex 04, France.
E-mail address: damien.leger@htd.aphp.fr (D. Leger).

http://dx.doi.org/10.1016/j.mce.2015.06.030
0303-7207/

Several meta analyses and reviews have been recently devoted to the association between sleep loss and obesity or diabetes (Bayon et al., 2014; Capuccio et al., 2010; Galicchio et al., 2009; Knutson and Van Cauter, 2008; Kurina et al., 2013; Magee and Hale, 2012; Schmid et al., 2015). All underlined the significant association between sleep deficit and the regulation of weight. In this review, we want however to describe more precisely the basis of sleep physiology and the biological clock in order to help readers to understand how sleep is useful for weight regulation.

The goal of this review is to better understand the role of sleep in the regulation of body weight. It would be then first necessary to describe what normal physiological sleep is, and what the normative values of sleep are in the general population.

In the second part we would give details on how the biological clock regulates hormones that may contribute to weight control.

Thirdly we will try to better understand, on the basis of recent epidemiological data, how sleep may be disturbed by sleep disorders or reduced by sleep debt with consequences on weight.

Finally we will try to carefully explore the pathways explaining the relationships between sleep debt and obesity.

2. Part 1, normal physiological sleep

2.1. Sleep physiology

It is still mysterious to observe that most of the species on the planet are regulated by a permanent alternation of sleep and wakefulness around a 24-h period. Consciousness and activity appear every morning and our days are spent performing occupational and social activities (including meals and physical activity, which directly affect body weight). Then, every evening, we retire to lie down and sleep for several hours in an unconscious state, except for dreaming. This period, which has always been considered as non-active, and unproductive by some, is probably one of the most important times of the 24-h day for conservation of energy, modulation of brain activity and clarification and organization of mood and cognition. Sleep is frequently viewed as a part of the 24-h cycle and a response to the previous period of wakefulness. It is less often described in its own merit. Physiologists have, however, described sleep in humans, which is now recorded and analyzed according to international consensus rules (Littner et al., 2003).

2.1.1. Three states of vigilance during the night (wakefulness, NREM and REM sleep)

To observe the physiological states of sleep, it is necessary to perform polysomnography (PSG): a simultaneous recording of electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG). Other recordings are also sometimes, but not always, performed: respiration, electrocardiogram (ECG) and internal temperature (Littner et al., 2003).

When we are awake, the EEG is characterized by alfa waves (8–12 Hz oscillations), EMG shows high muscle tone and the EOG shows fast saccadic movements. When we lie down and fall asleep, oscillations appear on the EEG, including alpha and theta waves (4.5–8 Hz), K-complexes (isolated sharp negative deflections) and spindles (12–15 Hz 0.5–2 s long periods), which are characteristics of stage 2. At the same time, muscle tone decreases on the EMG and the EOG shows slow rolling eye movements. After a sufficient period of sleep, slow-wave (0–4 Hz) large amplitude oscillations appear that progressively dominate the EEG, with no eye movements on the EOG. This period is called SWS or non-rapid eye movement (NREM) sleep (Iber et al., 2004; Silber et al., 2007).

Rapid eye movement (REM) sleep is a totally different state of consciousness that usually appears abruptly following a first period of 60–90 min of NREM. It is characterized by an association of low amplitude theta-like oscillations, muscle tone is drastically decreased on EMG and the EOG shows rapid and symmetric eye movements (Iber et al., 2004; Silber et al., 2007).

In normal good sleepers, NREM and REM sleep alternate throughout the night with a periodicity of 60–90 min called the sleep cycle. A sleep cycle begins by a transition from wake or from first stages of SWS (Stage 1 and 2) to deeper and continuous Stage 3 SWS and then followed by an episode of REM. A typical 7–8 h night of sleep includes four to five sleep cycles. The duration of each cycle is about the same throughout the night, but the durations of the NREM and REM components are not. At the beginning of the night, REM episodes are short and NREM long; at the end, REM periods are longer and NREM shorter (Iber et al., 2004; Silber et al., 2007).

Good quality sleep is defined by several criteria: the sleep onset latency (SOL), the total sleep time (TST), wake after sleep onset (WASO) and the percentages of NREM and REM sleep. SOL is defined as the time period between switching off the light and the first period of sleep. It usually takes less than 30 min to fall asleep for adults. Most good sleepers report an SOL of 10–15 min. WASO is defined as the time spent awake during sleep (less than 30 min a night for good sleepers). The TST is the time between the first period of sleep and the final awakening (with WASO deducted). The TST varies from childhood (10–12 h) to the elderly (6–7 h) and is usually around 7 h in the general population on weekdays (Ohayon et al., 2004).

2.2. Normative data on sleep

Exactly how many hours of sleep per day are needed in adults according to their age and environmental and socio-cultural issues is unknown. Some authors recommend 8 h of sleep, whereas others believe 7 h may be sufficient for adults, with a shorter duration being necessary in the elderly (Ohayon et al., 2004; Horne, 2011; Leger et al., 2011, 2012; National sleep foundation, 2013; Leger et al., 2014; Grandner et al., 2014).

Most experts agree that sleep has to compete with multiple tasks in today's 24-h society, which may have resulted in a marked reduction in sleep duration around the planet, especially for adolescents and young adults (Leger et al., 2012; Bin et al., 2013). However, a recent survey in an impressive sample of adults (328 018 subjects) from 10 countries, showed that sleep times had not reduced in several countries, except in the most active and young subjects (Bin et al., 2012, 2013).

3. Part 2: the biological clock and its circadian regulation of hormones contributing to body weight

3.1. The biological clock

The sleep–wake cycle in humans is driven by two inter-related processes: the homeostatic process (which describes the progressive impact of time spent awake on the need for sleep) and the circadian process, which is dependent on the biological clock (Borbély, 1998). This clock is situated in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, at the top of the optic chiasm and next to the third ventricle, and has been shown to synchronize many physiological and behavioral variables on a 24-h rest and activity pattern. Studies conducted in the 1970s on subjects isolated from all environmental factors provided evidence of an endogenous circadian rhythm of the SCN (Moore-Ede, 1983), which can be considered as a central circadian clock, but with other, peripheral clocks located in most of the peripheral tissues and organs, allowing independent expression of some local physiological cell groups (Pilorz et al., 2014; Summa and Tureck, 2014).

The biological clock is mainly influenced by light, the most potent synchronizer of the clock (Gronfier et al., 2004, 2007). Light is detected by specific retinal ganglion cells (containing melanopsin, a photo pigment), which transmit the light signal to the SCN via the retino-hypothalamic tract. The effect of light on the clock depends on the internal time of exposure: light is, for example, more powerful in the first part of the night and phase delays the circadian system. It is also dependent on the light intensity, duration and wavelength (e.g., blue light is considered the most powerful).

3.2. The circadian regulation of hormones that contribute to body weight regulation

Several hormones participating in metabolism have been shown to have a circadian secretion profile that depends on the biological clock. However, this circadian effect is sometimes modulated by the balance between REM and non-REM SWS. Most of the results collected have concerned the hormones of the hypothalamic–pituitary axis and those implicated in the regulation of glucose metabolism, appetite and water and salt balance (Leproult and Van Cauter, 2010).

Many studies have been devoted to observing the relationship between sleep and hormones, but most of them have been conducted in small numbers of young and healthy adults, under strictly controlled conditions. The interaction of hormones with sleep in older and non-healthy persons is certainly much more complex. Nevertheless, it is interesting to understand how sleep and hormones are normally linked (Leproult and Van Cauter, 2010).

- For the hypothalamic-pituitary-somatotrophic system, many studies have shown a clear relationship between growth hormone (GH) release in humans and the occurrence of SWS (Van Cauter et al., 2004). GH levels are increased during sleep with the major pulse occurring soon after the beginning of sleep during the first phase of SWS. Van Cauter et al. (1992) first showed that a pulse of GH occurs approximately every 2 h, associated with the cyclic occurrence of SWS. The largest pulse of GH is suppressed when the subject is kept awake at the beginning of the night. Reciprocally, GH is increased when SWS is stimulated pharmacologically by gamma-hydroxybutyrate (GBH) (Van Cauter et al., 2004).
- In the hypothalamic-pituitary-adrenocortical system, the circadian power is more clearly shown (Guyon et al., 2014). The level of cortisol in humans reaches a nadir at sleep onset, shows a rapid increase in the middle of the night at the moment of the deepest sleep, and peaks in the morning, close to the habitual wake time. The secretion of cortisol is not affected by sleep restriction or restoration after sleep deprivation, confirming the influence of the circadian clock via the SCN pathway on its secretion (Weitzman et al., 1983). Blood infusion of cortisol in human increases SWS and decreases REM sleep but the physiological pathway explaining these effects is poorly understood (Friess et al., 2004).
- Thyroid-stimulating hormone (TSH) release also has a clear circadian profile, with its nadir during daytime, increasing before sleep onset and reaching its maximum in the middle of the night (Allan and Czeisler, 1994). One night of sleep deprivation increases the peak of TSH the subsequent night, but not two nights later (Gronfier and Brandenberger, 1998), explained by a possible interaction of associated T3 increase on the TSH level. No circadian rhythms have been shown for triiodothyronine (T3) or thyroxine (T4) concentrations (Allan and Czeisler, 1994).
- Ghrelin and leptin levels are both increased during sleep. These two peripheral hormones, leptin (a 16 kDa polypeptide cytokine) and ghrelin act on the hypothalamic nuclei to regulate energy balance and food intake (Spiegel et al., 2004). Leptin is produced mainly by adipocytes and inhibits appetite, whereas ghrelin is released by the stomach and stimulates appetite (Leproult and Van Cauter, 2010). A ghrelin peak occurs during the beginning of the night and is suppressed in case of sleep deprivation. However, there is no evidence linking ghrelin to any specific REM or SWS stages (Schuessler et al., 2005). Infusion of ghrelin increases SWS and decreases REM sleep probably via its effect on GH (Weikel et al., 2003).

The circadian rhythm of leptin has also been shown, with a steady increase at the onset of sleep and a peak at the end of sleep in the morning (Shea et al., 2005). Leptin has not always been shown to be altered by sleep restriction. In 14 healthy young men who underwent 24 h total sleep deprivation, Benedict et al. (2011) found no change in the leptin circadian rhythm. Similar findings were reported in a prospective study in 21 lean teenage boys (15–19 years) after 3 consecutive nights of 4 h sleep (Klingenberg et al., 2012). Finally, no change in leptin levels was observed in young men (20–40 years old) submitted to a single night of 4.5 h sleep compared to one night of 7 h sleep, despite increased ghrelin levels and hunger (Schmid et al., 2008).

In the Wisconsin Sleep Cohort, after controlling for confounding factors, a U-shaped curvilinear association was found between sleep duration and body mass index (BMI). Subjects sleeping less than 8 h had an increased BMI proportional to the decreased length of sleep. Short sleep duration was associated with low leptin and high ghrelin levels independently of BMI, age, sex, and other confounding factors (Leproult and Van Cauter, 2010). No significant correlation was found between sleep duration, insulin, glucose and lipid profiles.

- Plasma glucose concentrations remain stable during the night despite the absence of meals. This is largely due to modulation of endogenous glucose production by the liver and the kidney. This is despite changes in insulin sensitivity in the second part of the night and increased glucose consumption during REM sleep (Spiegel et al., 2000).

Some experimental studies of sleep restriction have shown a link between sleep debt and impaired glucose metabolism leading to a risk of type 2 diabetes. In 11 young men, Spiegel et al. (1999) compared glucose tolerance, cortisol levels and activity of the sympathetic nervous system after sleep restriction of 4 h in bed for 6 nights and 12 h sleep recovery for 7 nights. During the sleep restriction period, insulin sensitivity was not significantly different, and glucose tolerance was lower than in recovery conditions ($p < 0.02$). Glucose effectiveness (the ability of glucose to mediate its own disposal independent of insulin) was 30% lower during sleep restriction than during recovery, as was the acute insulin response ($p = 0.05$). Glucose tolerance returned to the normal range after sleep recovery.

4. Part 3: epidemiology of sleep disorders and of short sleep

The epidemiology of sleep disorders has been well documented as a result of international consensus on classifications with two recent updates of the International Classification of Sleep Disorders, third edition (American Academy of Sleep Medecine, 2014), and the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (American Psychiatric Association, 2013). Among the various classified sleep disorders, three may be considered as having a possible association with weight: obstructive sleep apnea (OSA), insufficient sleep syndrome and narcolepsy. No specific association has been

found between the most frequent sleep disorder, insomnia, and any weight problem. Insomnia concerns 20% of adults, women more than men (Léger et al., 2010 Ohayon, 2002). The incidence of insomnia increases with age until 65 years and then decreases consistently. Ten percent of adults have severe insomnia on a regular basis with 50% using hypnotic drugs on a daily basis.

- Sleep apnea syndrome is almost always associated with overweight or obesity. According to the ICSD-3 (American Academy of Sleep Medicine, 2014), OSA is defined as the association of non-restoring sleep, sleepiness during the day, snoring or awakening with breath holding, gasping or choking. The diagnosis is made on PSG, which shows 5 or more apneas or hypopneas per hour of sleep. Snoring is a very common complaint, reported by at least 10–50% of males and 4–17% of females (Punjabi, 2008). The reference prevalence study on OSA is the one conducted in the Wisconsin Cohort (Young et al., 1993), which reported that 2% of women and 4% of men had an apnea index greater than 5. Excess body weight is a major risk factor for OSA, with 70% of OSA patients being overweight or obese. Overweight acts mechanically by mass loading on the upper airway tract (Deegan and McNicholas, 1995). It is frequently reported that the neck circumference is a better predictor of OSA than the BMI.
- Narcolepsy is a rare disease with a prevalence of around 0.002–0.005%, which is characterized by chronic excessive sleepiness and specific cataplexies (possible episodes of muscle weakness promoted by positive emotions) (American Academy of Sleep Medicine, 2014). Narcolepsy is associated with a subtotal loss of wake-promoting hypocretin (orexin) neurons in the lateral hypothalamus. Orexin also has an orexigenic effect and the deficit of these neurons may be associated with overweight, especially when the disease first appears (Inocente et al., 2013).

Increasing evidence indeed suggests that not having enough sleep may be associated with adverse health effects, such as obesity, type 2 diabetes, hypertension and cardiovascular disease (Grandner et al., 2014; Guo et al., 2013; Altman et al., 2012). Reduced sleep duration and sleep quality are increasingly frequent in modern society and are likely linked to changes in the socioeconomic environment and lifestyle (Bixler, 2009). The percentage of adults who reported sleeping 6 h or less increased by 5–6% between 1985 and 2004 (National Sleep Foundation, 2005). Most studies in college students indicate that they are chronically sleep deprived with self-reported average sleep duration of around 7 h per night (Taylor and Bramoweth, 2010) versus the 9–10 h usually recommended for adolescents.

Numerous cross-sectional and longitudinal epidemiological studies have examined the association between sleep duration and weight gain in children, adolescents and adults and we will discuss the results of some recent meta-analyses on this issue.

- Cappuccio et al. provided quantitative estimates of the cross-sectional association between sleep duration and obesity in children and in adults (Cappuccio et al, 2008). Thirty-six studies were included in the meta-analysis, with a total of 30 002 children and 604 509 adults. In children, the pooled OR for short duration of sleep (<10 h) and obesity (BMI > 95th percentile) was 1.89 [1.43–1.68; $p < 0.0001$]. In adults, the pooled OR was 1.55 [1.43–1.68; $p < 0.0001$]. The authors also demonstrated that adults reporting five or less hours of sleep per night were at a higher risk of being obese, and that every additional hour of sleep was associated with a 0.35 kg/m^2 decrease in BMI.
- The same year, another meta-analysis of cohort and cross-sectional studies in the general pediatric population identified 17 studies (Chen et al., 2008). The pooled OR predicting obesity from short sleep duration was 1.58 [1.26–1.98]. This meta-analysis supported a sex difference in the association, with boys having a stronger inverse association than girls (OR = 2.50 [1.88–3.84] vs. OR = 1.24 [1.07–1.45]). The results also showed a significant linear dose–response relationship between decreased sleep duration and increased BMI in young children (<10 years old).
- A recent systematic review of 20 longitudinal studies reported similar results (Magee and Hale, 2012). Among the 13 studies performed in adults, 4 found an association between short sleep duration and weight gain, 4 found an association between short and long sleep duration and weight gain and 5 studies found no significant association. All the 7 longitudinal studies involving children reported an association between short sleep duration and increased weight.

These reviews suggest that children and adolescents may be more vulnerable to the effects of insufficient sleep. Sleep is important for brain development. Sleep loss at a young age may alter the hypothalamic mechanisms that regulate appetite and energy expenditure. Another possibility to explain the effect of age is that the impact of sleep duration on weight gain may alter over time such that short duration sleepers may not continue to gain weight linearly.

Interestingly one recent survey evaluated the association between sleep duration, body weight and adiposity (Bailey et al., 2014). Among 330 young women (aged around 20), inconsistent sleep patterns and poor sleep efficiency were related to adiposity. In this study, sleep was monitored by actigraphy and physical activity and body composition were also objectively measured. Interestingly, other sleep variables, such as sleep quality and sleep efficiency (SE), calculated as a ratio between total sleep time/total sleep periods, had a stronger association with BMI than did sleep duration. These findings support the importance of considering consistent sleep, which can be defined as sleep with no interruption, and wake schedules in future studies.

However, our review lets us understand that the results of the studies described were based on many different protocols. Thus, there is a lack of consensus on how to assess sleep duration in epidemiological studies. Some reported self-assessments; others used more validated sleep logs or questionnaires. It is also an issue to find how chronic diseases may reciprocally affect sleep quality and quantity; and furthermore, if disturbed sleep may be partly implicated in the process of these chronic diseases. I.e. chronic pain is associated with insomnia, which in turn increases pain sensitivity. Observational studies suggest that the effects of sleep loss on obesity appear to be stronger in children than in adults. To clarify the effects of sleep duration on the risk of weight gain, randomized prospective interventional trials are needed. Although depriving subjects of sleep for extended periods of time may be unethical, extending sleep in individuals with short sleep duration and obesity could help to clarify the relationships.

5. Part 4: the link between sleep debt and weight gain: hypothesis

In addition to epidemiological data, it may be of interest to show the various hormonal and behavioral pathways that have been studied in order to better understand the association between short sleep duration, overweight and obesity.

5.1. Hormonal pathways

As we previously noted, sleep deprivation has been found to be

associated with decreased leptin levels in some studies, but not in all, and increased ghrelin levels in numerous works. The imbalance between these hormones, which are part of the orexin system that integrates control of feeding, wakefulness and energy expenditure, may explain the change in hunger after sleep deprivation, with increased appetite for snacks, fat and carbohydrates, ultimately leading to weight gain (Knutson and Van Cauter, 2008). Sleep debt also decreases brain glucose utilization, which may be one of the mechanisms underlying the decrease in glucose tolerance (Spiegel et al., 2005). Altered sympathetic-vagal balance with an increase in sympathetic activity as shown by RR variability and increased catecholamine levels may be a pathway by which sleep loss exerts systemic effects, explaining the decreased insulin response to intravenous glucose perfusion (Spiegel et al., 2000, 2005). This altered balance may also be involved in the reduction in leptin levels during sleep debt conditions. Experimental studies have also demonstrated an increase in cortisol levels in the evening, which may impact on insulin sensitivity the following morning and promote a delayed night-time of GH secretion (when sleep time is delayed and sleep restricted). This effect may adversely influence glucose regulation, leading to transient insulin resistance in muscle cells, decreased glucose uptake, elevated blood glucose levels and increased insulin resistance in other tissues. GH secretion is indeed known to facilitate a regular glucose level during the night, despite fasting conditions (Spiegel et al., 2000, 2005). Increased sympathetic nervous activity can also decrease insulin secretion from pancreatic β-cells. Moreover, we know that sleep restriction is associated with increased levels of pro-inflammatory cytokines, predisposing to insulin resistance and diabetes (Spiegel et al., 2005).

5.2. Behavioral pathways

Acute or short-term sleep restriction is consistently reported in association with an increase in food intake, calorie consumption and poor dietary quality, and also alcohol consumption. After partial sleep deprivation, the increased meal and calorie intake was attributed to snacks with a higher carbohydrate or fat content. For example, 14 normal weight men received a standard breakfast and were told to purchase as much as they could (for a given fixed budget, from 20 high-caloric and 20 low-caloric foods) after a normal night of sleep or after total sleep deprivation (Chapman et al., 2013). After sleep deprivation, ghrelin concentrations were higher and men purchased significantly more calories and grams of food than after one night of sleep. Altered food purchasing and increased food intake may represent two behavioral mechanisms that explain weight gain in sleep-deprived men. A significant increase in calorie intake, especially fat, without change in energy expenditure was also found after 6 nights of 4 h in bed in non-overweight adults (St-Onge, 2013).

In addition to hormonal pathways, Chaput (2014) suggested that food intake can be overridden by hedonic rather than homeostatic factors. This suggestion was based on the recent observation that overeating and weight gain occurred after sleep restriction (5 days) in healthy adults despite increases in leptin and peptide YY (PYY) and decreases in ghrelin, which signaled food intake was in excess (Markwald et al., 2013). These hypotheses were confirmed by fMRI studies showing, in normal-weight adults, that inadequate sleep enhances hedonic stimulus processing in the brain underlying the drive to consume foods, and is consistent with the notion that reduced sleep may lead to a greater propensity to overeat (St-Onge et al., 2012). For example, it has been shown that sleep restriction (4 h/night for 6 nights) enhanced regional brain activity during food stimuli in regions involved in reward (St-Onge et al., 2012) and also enhanced the neuronal circuitry related to unhealthy food types (St-Onge, 2013). Hogenkamp et al. (2013) also showed that young men had increased feelings of hunger in the morning after total sleep deprivation, which were accompanied by overeating with a preference for snacks, specifically after breakfast and not in the fasted state. For these authors, the observed food behavior was driven by both homeostatic and hedonic factors.

Chaput, therefore, postulated that in an environment where energy-dense foods are highly palatable and readily available, caloric intake may be directly proportional to the time spent awake, especially if most of the time awake is spent participating in screen-based sedentary activities where snacking is common (Chaput, 2014). Increased television viewing and computer and internet use during adolescence have been shown to be associated with higher odds of consumption of sweetened beverages especially at the upper tail of the BMI distribution between ages 14–18 years (Mitchell et al., 2013).

Another possible behavioral link between sleep deficit and obesity is the time at which people go to sleep. Recent studies have shown that sleep timing can predict weight-loss effectiveness in humans (Garaulet et al., 2013). For these authors, eating late compared with early (e.g., lunch time after versus before 3:00 pm) impaired the success of a 20-week weight loss therapy in overweight/obese patients. Because energy intake, dietary composition, estimated energy expenditure, appetite hormones and sleep duration were similar in early- and late-eaters, the authors suggested that changes in the chronotype, genetic background, and/or the circadian system function may be implicated.

6. Discussion: limitations and perspectives

The link between sleep and weight now seems evident based on epidemiological data and on results from clinical and basic research in humans. However, we discussed previously how this strong association was based on a complex interaction between behavioral and hormonal pathways. Despite a huge amount of research on this issue this last decade, there are still some limitations in research which may reduce the impact of prevention: we would here therefore propose several tracks for future research:

- Sleep debt is associated with weight gain and obesity, but it is not actually known how sleep extension may improve weight regulation. One crucial issue is in children and adolescents. It would be important to observe prospectively sleep deprived and overweight children, encouraged to sleep more during a sufficient period of time. It may also be interesting to propose regular naps to adult short sleepers and to study how it may limit or reduce overweight.
- We presented results on how sleep deprived subjects had a tendency of eating high caloric food. However there is a lack of knowledge on which kind of nutrients and what type of meals may improve the quality and the quantity of sleep. On both epidemiology and basic research, it would be important to know better how nutriments are specifically implicated in weight gain in sleep deprived subjects.
- Another important research track is to try to adopt consistent tools in epidemiology and research in order to better define normative sleep amounts for each age group. Total sleep time is often assessed by a single question in big prospective surveys and/or on simple and unvalidated questionnaires. Polysomnography (PSG) is not an easy tool to use in big surveys. However it may be used more extensively in basic research conjointly with wrist actigraphy.

PSG has also to be used to better understand the link between sleep quality and weight control. There is a need of research on the

respective roles of NREM and REM sleep in the hormonal and behavioral pathways between sleep and weight.

- Finally education programs on nutrition, physical activity and sleep have also to be tested in children and adults to assess how they are powerful and possibly applicable at school or at the workplace.

Conflicts of interest

Professor Leger has received funding or has been main investigator in studies sponsored by SANOFI-AVENTIS, MERCK, VANDA, ACTELION, BIOPROJET, PHILIPS, RESMED, VITALAIRE in the last 5 years. He declares no conflict of interest for this manuscript.

Other authors declare no conflict of interest.

References

Allan, J.S., Czeisler, C.A., 1994. Persistence of the circadian thyrotropin rhythm under constant conditions and after light-induced shifts of circadian phase. J. Clin. Endocrinol. Metab. 79, 508–512.

Altman, N.G., Schopfer, E., Jackson, N., Izci-Balzerak, B., Rattanaumpawan, P., Gehrman, P.R., et al., 2012. Sleep duration versus sleep insufficiency as predictors of the cardiometabolic health outcomes. Sleep. Med. 13, 1261–1270.

American Academy of Sleep Medicine, 2014. International classification of sleep disorders. In: Darien, I.L. (Ed.), Diagnostic and Coding Manual, third ed. American Academy of Sleep Medicine.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Publishing, Washington DC USA and London England (DSM-V).

Bailey, B.W., Allen, M.D., LeCheminant, J.D., Tucker, L.A., Errico, W.K., Christensen, W.F., et al., 2014. Objectively measured sleep patterns in young adult women and the relationship to adiposity. Am. J. Health Promot. 29, 46–54.

Bayon, V., Leger, D., Gomez-Merino, D., Vecchierini, M.F., Chennaoui, M., 2014. Sleep debt and obesity. Ann. Med. 46, 264–272.

Benedict, C., Hallschmid, M., Lassen, A., Mahnke, C., Schultes, B., Schiöth, H.B., Born, J., Lange, T., 2011. Acute sleep deprivation reduces energy expenditure in healthy men. Am. J. Clin. Nutr. 93, 1229–1236.

Benedict, C., Byberg, L., Cedernaes, J., Hogenkamp, P.S., Giedratis, V., Kilander, L., et al., 2014. Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. Alzheimers Dement. pii: S1552–S5260.

Bin, Y.S., Marshall, N.S., Glozier, N., 2012. Secular trends in adult sleep duration: a systematic review. Sleep. Med. Rev. 16, 223–230.

Bin, Y.S., Marshall, N.S., Glozier, N., 2013. Sleeping at the limits: the changing prevalence of short and long sleep durations in 10 countries. Am. J. Epidemiol. 177, 826–833.

Bixler, E., 2009. Sleep and society: an epidemiological perspective. Sleep. Med. 10, S3–S9.

Borbély, A.A., 1998. Processes underlying sleep regulation. Horm. Res. 49, 114–117. Review.

Buxton, O.M., Marcelli, E., 2010. Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States. Soc. Sci. Med. 71, 1027–1036.

Cappuccio, F.P., Taggart, F.M., Kandala, N.B., Currie, A., Peile, E., Stranges, S., Miller, M.A., 2008. Meta-analysis of short sleep duration and obesity in children and adults. Sleep 31, 619–626.

Cappuccio, F.P., D'Elia, L., Strazzullo, P., Miller, M.A., 2010a. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 33, 414–420.

Cappuccio, F.P., D'Elia, L., Strazzullo, P., Miller, M.A., 2010b. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. Sleep 33, 585–592.

Capuccio, F.P., Cooper, D., D'Elia, L., Strazzullo, P., Miller, M.A., 2011. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur. Heart J. 32, 1484–1492.

Chao, C.Y., Wu, J.S., Yang, Y.C., Shih, C.C., Wang, R.H., Lu, F.H., et al., 2011. Sleep duration is a potential risk factor for newly diagnosed type 2 diabetes mellitus. Metab. Clin. Exp. 60, 799–804.

Chapman, C.D., Nilsson, E.K., Nilsson, V.C., Cedernaes, J., Rångtell, F.H., Vogel, H., et al., 2013 Dec. Acute sleep deprivation increases food purchasing in men. Obes. (Silver Spring) 21 (12), E555–E560.

Chaput, J.P., 2014. Sleep patterns, diet quality and energy balance. Physiol. Behav. 134, 86–91.

Chen, X., Beydoun, M.A., Wang, Y., 2008. Is sleep duration associated with childhood obesity? A systematic review and meta-analysis. Obesity 16, 265–274.

Cohen-Mansfield, J., Perach, R., 2012. Sleep duration, nap habits, and mortality in older persons. Sleep 35, 1003–1009.

Deegan, P.C., McNicholas, W.T., 1995. Pathophysiology of obstructive sleep apnoea. Eur. Respir. J. 8, 1161–1178. Review.

Diekelmann, S., Born, J., 2010. The memory functions of sleep. Nat. Rev. Neurosci. 11, 114–126.

Dolgin, E., 2013. Deprivation: a wake-up call. Nature 497, S6–S7.

Faraut, B., Touchette, E., Gamble, H., Royant-Parola, S., Safar, M.E., Varsat, B., et al., 2013. Short sleep duration and increased risk of hypertension: a primary care medicine investigation. J. Hypertens. 30, 1354–1363.

Friess, E., Tagaya, H., Grethe, C., Trachsel, L., Holsboer, F., 2004. Acute cortisol administration promotes sleep intensity in man. Neuropsychopharmacology 29, 598–604.

Galicchio, L., Kalesan, B., 2009. Sleep duration and mortality: a systematic review and metaanalysis. J. Sleep. Res. 18, 148–158.

Garaulet, M., Gómez-Abellán, P., Alburquerque-Béjar, J.J., Lee, Y.C., Ordovás, J.M., Scheer, F.A., 2013. Timing of food intake predicts weight loss effectiveness. Int. J. Obes. 37, 604–611.

Grandner, M.A., Hale, L., Moore, M., Patel, N.P., 2010. Mortality associated with short sleep duration. The evidence, the possible mechanisms, and the future. Sleep. Med. Rev. 14, 191–203.

Grandner, M.A., Chakravorty, S., Perlis, M.L., Oliver, L., Gurubhagavatula, I., 2014. Habitual sleep duration associated with self-report and objectively determined cardiometabolic risk factors. Sleep. Med. 15, 42–50.

Gronfier, C., Brandenberger, G., 1998. Ultradian rhythms in pituitary and adrenal hormones: their relations to sleep. Sleep. Med. Rev. 2, 17–29.

Gronfier, C., Wright Jr., K.P., Kronauer, R.E., Jewett, M.E., Czeisler, C.A., 2004. Efficacy of a single sequence of intermittent bright light pulses for delaying circadian phase in humans. Am. J. Physiol. Endocrinol. Metab. 287, E174–E181.

Gronfier, C., Wright Jr., K.P., Kronauer, R.E., Czeisler, C.A., 2007 May 22. Entrainment of the human circadian pacemaker to longer-than-24-h days. Proc. Natl. Acad. Sci. U. S. A. 104 (21), 9081–9086.

Guo, X., Zheng, L., Wang, J., Zhang, X., Zhang, X., Li, J., Sun, Y., 2013. Epidemiological evidence for the link between sleep duration and high blood pressure: a systematic review and meta-analysis. Sleep. Med. 14, 324–332.

Guyon, A., Balbo, M., Morselli, L.L., Tasali, E., Leproult, R., L'Hermite-Balériaux, M., Van Cauter, E., Spiegel, K., 2014. Adverse effects of two nights of sleep restriction on the hypothalamic-pituitary-adrenal axis in healthy men. J. Clin. Endocrinol. Metab. 99, 2861–2868.

Gumenyuk, V., Korzyukov, O., Roth, T., Bowyer, S.M., Drake, C.L., 2013. Sleep extension normalizes ERP of waking auditory sensory gating in healthy habitually short sleeping individuals. PLoS One 8, e59007.

Hogenkamp, P.S., Nilsson, E., Nilsson, V.C., Chapman, C.D., Vogel, H., Lundberg, L.S., Zarei, S., Cedernaes, J., Rångtell, F.H., Broman, J.E., Dickson, S.L., Brunstrom, J.M., Benedict, C., Schiöth, H.B., 2013. Acute sleep deprivation increases portion size and affects food choice in young men. Psychoneuroendocrinology 38, 1668–1674.

Horne, J., 2011. Obesity and short sleep: unlikely bedfellows? Obes. Rev. 12, e84–e94.

Iber, C., Redline, S., Kaplan Gilpin, A.M., Quan, S.F., Zhang, L., Gottlieb, D.J., Rapoport, D., Resnick, H.E., Sanders, M., Smith, P., 2004. Polysomnography performed in the unattended home versus the attended laboratory setting—-Sleep Heart Health Study methodology. Sleep 27, 536–540.

Inocente, C.O., Lavault, S., Lecendreux, M., Dauvilliers, Y., Reimao, R., Gustin, M.P., Castets, S., Spiegel, K., Lin, J.S., Arnulf, I., Franco, P., 2013 Jul. Impact of obesity in children with narcolepsy. CNS Neurosci. Ther. 19 (7), 521–528.

Klingenberg, L., Chaput, J.T., Holmback, U., Jennum, P., Astrup, A., Sjodin, A., 2012. Sleep restriction is not associated with a positive energy balance in adolescents boys. Am. J. Clin. Nutr. 96, 240–248.

Knutson, K.L., 2010. Sleep duration and cardio metabolic risk: a review of the epidemiologic evidence. Best. Pract. Res. Clin. Endocrinol. Metab. 24, 731–743.

Knutson, K.L., Van Cauter, E., 2008. Associations between sleep loss and increased risk of obesity and diabetes. Ann. N. Y. Acad. Sci. 1129, 287–304.

Kripke, D.F., Garfinkel, L., Wingard, D.L., Klauber, M.R., Marler, M.R., 2002. Mortality associated with sleep duration and insomnia. Arch. Gen. Psychiatry 59, 131–136.

Kronholm, E., Laatikainen, T., Peltonen, M., Sippola, R., Partonen, T., 2013. Self-reported sleep duration, all-cause mortality, cardiovascular mortality and morbidity in Finland. Sleep. Med. 12, 215–221.

Kurina, L.M., McClintock, M.K., Chen, J.H., Waite, L.J., Thisted, R.A., Lauderdale, D.S., 2013. Sleep duration and all-cause mortality: a critical review of measurement and associations. Ann. Epidemiol. 23, 361–370.

Léger, D., Partinen, M., Hirshkowitz, M., Chokroverty, S., Hedner, J., 2010. EQUINOX (Evaluation of daytime QUality Impairment by Nocturnal awakenings in Outpatient's eXperience) Survey Investigators. Characteristics of insomnia in a primary care setting: EQUINOX survey of 5293 insomniacs from 10 countries. Sleep. Med. 11, 987–998.

Leger, D., du Roscoat, E., Bayon, V., Guignard, R., Paquereau, J., Beck, F., 2011. Short sleep in young adults : prevalence and clinical description of short sleep in a representative sample of 1004 young adults from France. Sleep. Med. 12, 454–462.

Leger, D., Beck, F., Richard, J.B., Godeau, E., 2012. Total sleep time severely drops during adolescence. PLoS One 7 (10), e45204. http://dx.doi.org/10.1371/journal.pone.0045204.

Léger, D., Beck, F., Richard, J.B., Sauvet, F., Faraut, B., 2014 Sep 16. The risks of sleeping “too much”. Survey of a National Representative Sample of 24671 adults (INPES health barometer). PLoS One 9 (9), e106950.

Leproult, R., Van Cauter, E., 2010. Role of sleep and sleep loss in hormonal release and metabolism. Endocr. Dev. 17, 11–21.
Littner, M., Hirshkowitz, M., Kramer, M., Kapen, S., Anderson, W.M., Bailey, D., Berry, R.B., Davila, D., Johnson, S., Kushida, C., Loube, D.I., Wise, M., Woodson, B.T., 2003. American academy of sleep medicine; standards of practice committee. Practice parameters for using polysomnography to evaluate insomnia: an update. Sleep 26, 754–760.
Luister, F.S., Stollo Jr., J., Zee, P.C., Walsh, J.K., 2012. Sleep: a health imperative. Sleep 35, 727–734.
Magee, L., Hale, L., 2012. Longitudinal associations between sleep duration and subsequent weight gain: a systematic review. Sleep. Med. Rev. 16, 231–241.
Maia, Q., Grandner, M.A., Findley, J., Gurubhagavatula, I., 2013. Short and long sleep duration and risk of drowsy driving and the role of subjective sleep insufficiency. Accid. Anal. Prev. 59, 618–622.
Markwald, R.R., Melanson, E.L., Smith, M.R., Higgins, J., Perreault, L., Eckel, R.H., Wright Jr., K.P., 2013. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. Proc. Natl. Acad. Sci. 110, 5695–5700.
Mitchell, J.A., Rodriguez, D., Schmitz, K.H., Audrain-McGovern, J., 2013. Greater screen time is associated with adolescent obesity: a longitudinal study of the BMI distribution from ages 14 to 18. Obesity 21, 572–575.
Moore-Ede, M.C., 1983. The circadian timing system in mammals: two pacemakers preside over many secondary oscillators. Fed. Proc. 42, 2802–2808.
Nagai, M., Tomata, Y., Watanabe, T., Kakizaki, M., Tsuji, I., 2013. Association between sleep duration, weight gain, and obesity for long period. Sleep. Med. 14, 206–210.
National Institute of Health. US Department of Health and Human Services. Your Guide to Healthy Sleep. NIH Publication No. 11–5271. [Updated 2015; cited 2015, February 24]. Available from: http://www.nhlbi.nih.gov/health/public/sleep/healthy_sleep.pdf?bcsi_scan_43167910db6ab4d9=0&bcsi_scan_filename=healthy_sleep.pdf.
National Sleep Foundation, 2005. American Poll. Washinghton DC [Updated 2015; cited 2015, February 24] Available from: http://sleepfoundation.org/sleep-polls-data/sleep-in-america-poll/2004-children-and-sleep.
National Sleep Foundation. How Much Sleep Do We Really Need? [Updated 2015; cited 2015, February 24]. Available from: http://www.sleepfoundation.org/article/how-sleep-works.
Ohayon, M.M., 2002. Epidemiology of insomnia: what we know and what we still need to learn. Sleep. Med. Rev. 6, 97–111.
Ohayon, M.M.1, Carskadon, M.A., Guilleminault, C., Vitiello, M.V., 2004. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 27, 1255–1273.
Pilorz, V., Cunningham, P.S., Jackson, A., West, A.C., Wager, T.T., Loudon, A.S., Bechtold, D.A., 2014. A novel mechanism controlling resetting speed of the circadian clock to environmental stimuli. Curr. Biol. 24, 766–773.
Punjabi, N.M., 2008. The epidemiology of adult obstructive sleep apnea. Proc. Am. Thorac. Soc. 5, 136–143.
Ramos, A.R., Jin, Z., Rundek, T., Russo, C., Homma, S., Elkind, M.S., et al., 2013a. Relation between long sleep and left ventricular mass (from a multiethnic elderly cohort). Am. J. Cardiol. 112, 599–603.
Ramos, A.R., Dong, C., Elkind, M.S., Boden-Albala, B., Sacco, R.L., Rundek, T., et al., 2013b. Association between sleep duration and the mini-mental score: the Northern Manhattan study. J. Clin. Sleep. Med. 9, 669–673.
Schmid, S.M., 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.
Schmid, S.M., Hallschmid, M., Schultes, B., 2015. The metabolic burden of sleep loss. Lancet Diabetes Endocrinol. 3, 52–62.
Schuessler, P., Uhr, M., Ising, M., Schmid, D., Weikel, J., Steiger, A., 2005. Nocturnal ghrelin levels—relationship to sleep EEG, the levels of growth hormone, ACTH and cortisol—and gender differences. J. Sleep. Res. 14, 329–336.
Shea, S.A., Hilton, M.F., Orlova, C., Ayers, R.T., Mantzoros, C.S., 2005. Independent circadian and sleep/wake regulation of adipokines and glucose in humans. J. Clin. Endocrinol. Metab. 90, 2537–2544.
Siegel, J.M., 2009. Sleep viewed as a state of adaptive inactivity. Nat. Rev. Neurosci. 10, 747–753.
Silber, M.H., Ancoli-Israel, S., Bonnet, M.H., Chokroverty, S., Grigg-Damberger, M.M., Hirshkowitz, M., et al., 2007 Mar 15. The visual scoring of sleep in adults. J. Clin. Sleep. Med. 3 (2), 121–131.
Spiegel, K., Leproult, R., Van Cauter, E., 1999. Impact of sleep debt on metabolic and endocrine function. Lancet 354, 1435–1439.
Spiegel, K., Leproult, R., Colecchia, E.F., L'hermite-Balériaux, M., Nie, Z., Copinschi, G., Van Cauter, E., 2000. Adaptation of the 24-h growth hormone profile to a state of sleep debt. Am. J. Physiol. Regul. Integr. Comp. Physiol. 279, R874–R883.
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 grehlin levels, and increased hunger and appetite. Ann. Intern Med. 141, 846–850.
Spiegel, K., Knutson, K., Leproult, R., Tasali, E., Van Cauter, E., 2005. Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. J. Appl. Physiol. 99, 2008–2019.
St-Onge, M.P., 2013. The role of sleep duration in the regulation of energy balance: effects on energy intakes and expenditure. J. Clin. Sleep. Med. 9, 73–80.
St-Onge, M.P., McReynolds, A., Trivedi, Z.B., Roberts, A.L., Sy, M., Hirsch, J., 2012. Sleep restriction leads to increased activation of brain regions sensitive to food stimuli. Am. J. Clin. Nutr. 95, 818–824.
Stranges, S., Dorn, J.M., Shipley, M.J., Kandala, N.B., Trevisan, M., Miller, M.A., et al., 2008. Correlates of short and long sleep duration: a cross-cultural comparison between the United Kingdom and the United States. The Whitehall II study and the Western New York Health Study. Am. J. Epidemiol. 168, 1353–1364.
Summa, K.C., Turek, F.W., 2014. Chronobiology and obesity: interactions between circadian rhythms and energy regulation. Adv. Nutr. 14, 312S–319S.
Taylor, D.J., Bramoweth, A.D., 2010. Patterns and consequences of inadequate sleep in college students: substance use and motor vehicle accidents. J. Adolesc. Health 46, 610–612.
Theorell-Haglöw, J., Berglund, L., Janson, C., Lindberg, E., 2012. Sleep duration and central obesity in women. Differences between short sleepers and long sleepers. Sleep. Med. 13, 1079–1085.
Van Cauter, E., Kerkhofs, M., Caufriez, A., Van Onderbergen, A., Thorner, M.O., Copinschi, G., 1992. A quantitative estimation of growth hormone secretion in normal man: reproducibility and relation to sleep and time of day. J. Clin. Endocrinol. Metab. 74, 1441–1450.
Van Cauter, E., Latta, F., Nedeltcheva, A., Spiegel, K., Leproult, R., Vandenbril, C., Weiss, R., Mockel, J., Legros, J.J., Copinschi, G., 2004. Reciprocal interactions between the GH axis and sleep. Growth Horm. IGF Res. 14 (Suppl. A), S10–S17. Review.
Weikel, J.C., Wichniak, A., Ising, M., Brunner, H., Friess, E., Held, K., Mathias, S., Schmid, D.A., Uhr, M., Steiger, A., 2003. Ghrelin promotes slow-wave sleep in humans. Am. J. Physiol. Endocrinol. Metab. 284, E407–E415.
Weitzman, E.D., Zimmerman, J.C., Czeisler, C.A., Ronda, J., 1983. Cortisol secretion is inhibited during sleep in normal man. J. Clin. Endocrinol. Metab. 56, 352–358.
World Health Organisation World Regional Office for Europe. European Centre for Environment and Health. WHO technical meeting on sleep and health. [Updated 2015; cited 2015, February 24]. Available from: http://www.euro.who.int/__data/assets/pdf_file/0008/114101/E84683.pdf.
Young, T., Palta, M., Dempsey, J., Skatrud, J., Weber, S., Badr, S., 1993. The occurrence of sleep-disordered breathing among middle-aged adults. N. Engl. J. Med. 328, 1230–1235.