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Mechanisms of Association of Sleep and Metabolic Syndrome

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ABSTRACT

There is a U-shaped association between sleep duration and risk of metabolic syndrome. The related mechanisms can be grouped into two categories: I. Too little slow-wave sleep; II. Too much REM sleep.

Too little slow-wave sleep. 1) Stage 3 is the most crucial sleep stage because growth hormone (GH) and GH releasing hormone (GHRH) are released during this stage. They induce fat burning, bone building, and general repair and regeneration. The greater the volume of GH and GHRH released, the more restorative the sleep. The longest part of stage 3 in sleep takes place before midnight. Delayed sleep onset until midnight or later, would suppress the largest GH pulse. 2) Sleep restriction induces high levels of ghrelin and low levels of leptin. Ghrelin stimulates appetite whereas leptin does the reverse. 3) Advanced glycation end products (AGEs) are significantly increased in chronic sleep insufficiency and are also associated with insulin resistance in males with chronic sleep insufficiency. 4) Sleep insufficiency increases sympathetic activity and pro-inflammatory cytokines, both of which increase insulin resistance. 5) Accumulations of extracellular β amyloid protein plaques and intracellular tau neurofibrillary tangles in brain tissues start immediately after one night of sleep insufficiency. These plaques and tangles are neurotoxins that potentiate each other's destructive effects on the structures and functions of brain cells and cause neuronal death. The consequence is a global decrease in cognition and decision making, manifested in increased consumption of fatty foods and unhealthy snacks in late sleepers. 6) High levels of β amyloid and proteins might lead to sleep fragmentation, worsening of sleep quality and daytime somnolence. Concentration will be more difficult, and performance will be reduced. 7) Astrocytes are special giant cells in brain interstitial fluids that play a major role in β amyloid and tau cleanup. Their activity is increased by growth hormone. As a result, slow-wave sleep insufficiency may lead to impaired peripheral clearance of β amyloid and tau proteins predisposing the brain to Alzheimer's disease.

Too much REM sleep. 1) The REM stage is the dreaming stage. The level of cortisol starts to rise in the middle of night based on circadian rhythm, and peaks in the morning. Cortisol is the fight or flight hormone, equipping the individual both to meet the demands of daily life and to handle stressful situations. It stimulates the release of epinephrine and norepinephrine. These hormones increase heart rate and blood pressure as they prepare the body to initiate activity quickly. These reactions occur on top of heart rate variability and a rise in blood pressure induced by REM sleep. If the individual wakes up early in the morning, he will use the cortisol properly to prepare for the new day. If instead he or she remains asleep, there will be no physical activity, and the cortisol levels that are normal for a person who is awake will be high levels for the one who is asleep. Then, the sleeper may experience higher blood sugar, heart rate, and blood pressure. 2) A simulation of fight or flight reactions may be reflected in dreams. The prevalence of bizarre dreams in the morning is double of that at the beginning of the night. Moreover, emotionally charged dreams are significantly more frequent in the morning than early in the night. Bad dreams bring negative physical effects such as accelerated heartbeat, blood vessel spasms, increased blood pressure, and so on. Acute exacerbations of many chronic disorders occur in early morning sleep. 3) Waking up during the REM stage can make an individual feel more sleepy or tired during the day than waking up during stages 1-2.

Keywords
Metabolic syndrome, Sleep stage, Hormones.

Normal Sleep Cycle

Figure 1 shows the normal sleep cycle. Each cycle lasts between 90 and 120 minutes and proceeds through 4 stages as stage 1, stage 2, stage 3 and REM (rapid eye movement). The stages are categorized based on brain waves and body reactions. Stages 1 to 3 are called non-REM stages; during them most parts of the brain are non-active.

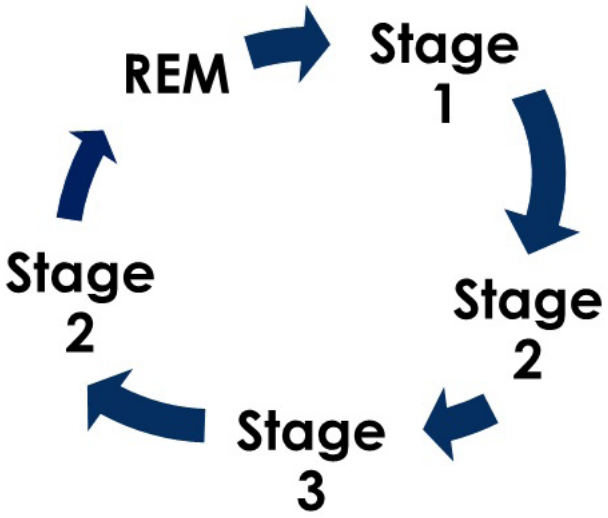

Figure 1: The normal sleep cycle. Usual duration is 90-120 minutes.

Stage 1, the first stage, begins immediately after sleep onset. In less than 10 minutes, brain and body experience stage 2 in which the sleep is established, and all five senses are blocked. Heart rate and respiratory rate are slowed down. Blood pressure is reduced, and body temperature decreases. The last non-REM stage of sleep is stage 3, which is the most important non-REM stage. After stage 3, brain and body first transition back into stage 2 and then into REM. At the end of REM, the first sleep cycle ends, and the body experiences a new sleep cycle (Figure 2).

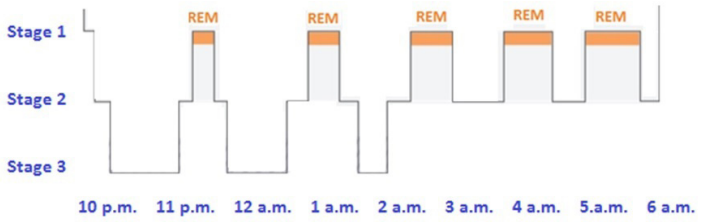

Figure 2: The normal nocturnal sleep cycles.

Two inter-related processes control the sleep-wake cycle

1) Circadian Rhythm. Circadian rhythm is controlled by biological clock, which is driven by light. The light effect is transferred to the brain through retinal cells. Light duration varies seasonally [1], a fact which may partly explain the effect modification of season on sleep duration and some components of metabolic syndrome in previous studies [2]. Furthermore, as one travels across the United States from the east to the west, sunrise and sunset times become later. Sunset is the trigger for the melatonin release that causes drowsiness. A new study showed that people living on the West Coast tend to go to bed about 19 minutes later than those on the East Coast, but they must wake up the next morning at the same time as residents in other time zones in order to go to work and school. These 19 minutes of missed sleep translate to a 115-hour sleep loss in one year and 1150 hours of lost sleep per decade. People living on the West Coast are also 5%, 11%, 21% and 19% more likely to have breast cancer, overweight, obesity and diabetes, respectively [3].

Homeostatic System. See the detailed description below.

Pathophysiology

Several studies have shown a U-shaped association between sleep duration and risk of metabolic syndrome, indicating short and long sleep duration, both increase the risk of metabolic syndrome [2,4] Several mechanisms may link sleep insufficiency to metabolic syndrome including hormonal imbalance, altered sympathetic-parasympathetic balance, decreased brain glucose utilization, brain dysfunction, increased pro-inflammatory cytokines and inflammation, all leading to insulin resistance and metabolic syndrome. Generally speaking, all the above-mentioned mechanisms of sleep-metabolic syndrome association can be grouped into two categories: I. Too little slow-wave sleep; II. Too much REM sleep.

Too Little Slow-wave Sleep

1) Stage 3, commonly called “deep sleep”, is referred to as delta wave sleep or slow-wave sleep. During this stage, the human body experiences the lowest possible heart rate, respiratory rate, body temperature, and blood pressure. This is the most crucial sleep stage because certain essential biochemical reactions happen at this time. For instance, growth hormone (GH) and GH releasing hormone (GHRH) are released by the hypophysis and hypothalamus, respectively. Their effects on sleep seem to be independent because hypophysectomy blocks the secretion of GH whereas it has no effect on sleep [5].

Moreover, GH release is increased if stage 3 is stimulated by gamma-hydroxybutyrate [6]. GH and GHRH are responsible for many important homeostatic and metabolic reactions, including fat burning, bone building, and general repair and regeneration. They are the main hormones for body recovery. An imbalance of these hormones may lead to difficulty in fat burning and muscle repair, which predisposes the body to weight gain and obesity. In addition, insufficient release of GH and GHRH during the night leads to fatigue in the morning and throughout the day [1].

The longest part of deep sleep stage (stage 3) takes place before midnight if the individual goes to bed early enough to allow the brain to produce adequate stage 3 sleep based on circadian rhythm (Figure 2). Correspondingly, the largest portion of GH and GHRH secretions occurs before midnight. As morning approaches, stage 3 becomes shorter and shorter. Thus, if sleep onset is delayed until midnight or later, the largest GH pulse is suppressed [6]. The greater the volume of GH and GHRH released, the more restorative the

sleep. This is the principal reason that Dr. Matt Walker, the head of the Sleep and Neuroimaging Lab at the University of California, Berkeley, says that "every hour of sleep before midnight, is worth two after midnight" [7]. That's why 6 hours sleeping started at 10 p.m. is more restorative than 8 hours sleeping started at midnight. When we go to bed at 10 p.m. the volume of released GH and GHRH is much more than that when our sleep starts at midnight.

2) The roles of other hormones that contribute to the relationship of sleep and the development of metabolic syndrome have been demonstrated. Ghrelin, which is released by the stomach stimulates appetite whereas leptin, released from adipocytes, does the reverse. Both are increased during sleep. Ghrelin peaks at the beginning of the night and will be suppressed if you stay awake. Ghrelin stimulates GH and GHRH secretion and slow-wave sleep [8,9] and peaks when nocturnal GH is recorded [10]. Ghrelin interacts with GH, leptin and orexin to regulate feeding. Several studies have demonstrated low levels of leptin and high levels of ghrelin following sleep restriction. This could be the normal hunger response to the longer period of wakefulness to increase energy intake in order to meet the higher energy demands [8-11]. Furthermore, the interaction of ghrelin, leptin and GH follows a seasonal pattern. In winter, they work in synergy to enhance lipolysis to keep the body warm in response to cold temperatures. Most likely, levels of these hormones are modulated by melatonin, which is regulated by seasonal rhythms [11]. This may also partly explain the seasonal effect modifications observed in the relationship of sleep duration and metabolic syndrome components in previous studies [2].

3) Advanced glycation end products (AGEs) are lipoproteins that are glycated because of exposure to sugars seen in degenerative diseases such as atherosclerosis and diabetes mellitus [12]. They are significantly increased in chronic sleep insufficiency [13] and are also associated with insulin resistance in males with chronic sleep insufficiency [14]. AGEs can induce endothelial damage through apoptosis of endothelial cells. Two different in-vitro studies have demonstrated the protective effects of ghrelin on this process [15,16]. But animal studies on ghrelin administration and sleep-wakefulness have shown variable responses in terms of central vs. systemic administration, and the time and the dose of administration [8-11]. Differential responses to ghrelin and AGEs in males vs. females after sleep insufficiency have been shown [14] which may justify part of the effect modification by sex recorded in previous studies [2].

Moreover, sleep insufficiency increases sympathetic activity and pro-inflammatory cytokines, both of which increase insulin resistance [1]. Overall, human studies revealed the cumulative effects of chronic sleep insufficiency were linked to an imbalance of GH, GHRH, ghrelin, leptin, adrenalin, cortisol and glucose metabolism and the resultant increase in appetite, adiposity, weight gain, inflammation and endothelial damage [17,18].

5) Accumulations of extracellular β amyloid protein plaques and intracellular tau neurofibrillary tangles in brain tissues start immediately after one night of sleep insufficiency [19-23]. These plaques and tangles are neurotoxins that potentiate each other's destructive effects on the structures and functions of brain cells. They work together to disrupt mitochondrial functions, destroy synapses and cause neuronal death [19,24]. Extended periods of sleep deprivation, especially slow-wave sleep deprivation, lead to both impairment of normal tau metabolism and higher levels of β amyloid protein in brain tissues [25-37]. The consequence is a global decrease in brain functions which may be reflected in cognition, reward and decision making [18,38]. These, in turn, are manifested in increased consumption of fatty foods and unhealthy snacks. Studies have shown that late sleepers ate later (lunch after 3 p.m. and dinner after 8 p.m.), consumed more calories and fast foods and fewer fruits and vegetables [39]. In other words, sleep behavior can predict dietary behavior [40].

6) On the other hand, higher levels of β amyloid protein might lead to sleep fragmentation, a worsening of sleep quality and daytime somnolence. Concentration will be more difficult, and performance will be reduced [24,36,41-44]. Similarly, higher levels of abnormal tau proteins may interfere with the sleep-wake cycle [45,23].

7) The glymphatic system, the brain network of perivascular pathways, is responsible for removing β amyloid protein and abnormal tau from brain tissues [37,45,46]. It operates mainly when the brain is sleeping [47]. Astrocytes are special giant cells in brain interstitial fluids that play a major role in β amyloid and tau cleanup. Their activity is increased by growth hormone and insulin-like growth factor [48]. In adults, slow-wave sleep is the principal stage of sleep in which growth hormone secretion takes place. Thus, astrocytes are more active and more effective in clearing β amyloid and tau proteins during slow-wave sleep [49,50]. As a result, slow-wave sleep insufficiency may lead to impaired peripheral clearance of β amyloid and tau proteins [50,51]. Early night sleep is dominated by slow-wave sleep [52-56]. Therefore, an insufficiency of early night sleep leads to fewer periods of slow-wave sleep (stage 3), and consequently, lower levels of GH and GHRH secretion. This leads to reduced activation of astrocytes and therefore, suboptimal clearing of β amyloid and tau proteins. The result is brain dysfunction that may be invisible or negligible at the beginning. However, when the process becomes chronic, detectable brain dysfunctions will be observed; these can lead to neurotransmitter and hormonal dysregulation and homeostasis imbalance. Twenty years ago, it was estimated that most Americans have a sleep deficit of 1.5 hours per night [57]. Now, the deficit is worse. Over the years, the cumulative effects of chronic sleep insufficiency on brain activity are significant.

Too Much REM Sleep

The REM stage is the dreaming stage, in which the brain activity is increased (Figure 1). During this stage, the respiratory rate increases, the heart rate quickens and slows irregularly, body temperature is variable, and blood pressure rises irregularly [58].

As shown in Figure 3, the level of cortisol in the blood is minimal during the first half of sleep. It starts to rise in the middle of night

based on circadian rhythm, and peaks in the morning. Cortisol release is not affected by sleep insufficiency, indicating the direct influence of the circadian clock on cortisol release [1]. Cortisol is the fight or flight hormone, equipping the individual both to meet the demands of daily life and to handle stressful situations.

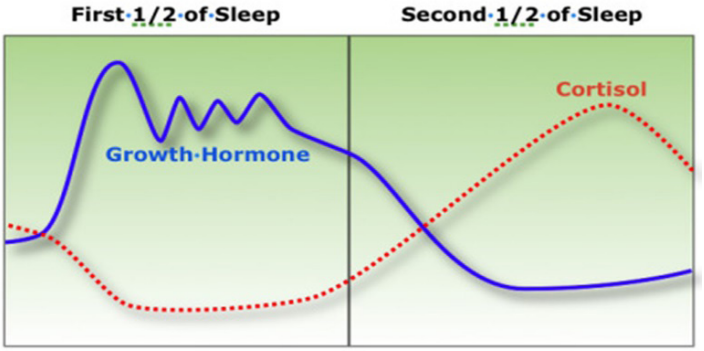

Figure 3: Normal patterns of cortisol and GH secretion during sleep [59].

1) When an individual is under pressure, but release of cortisol is insufficient, he or she will be unable to respond appropriately or make correct decisions. This condition is seen in adrenocortical insufficiency [60]. The opposite condition is seen in Cushing syndrome, when extra cortisol is present and the body cannot use it properly, which leads to obesity and diabetes mellitus. The excess cortisol induces fight or flight reactions in a body that does not need it or is unprepared to respond appropriately [61]. One of the main neuropsychological findings in these patients is disturbed sleep patterns [62]. A similar condition of much lower magnitude appears to occur during early morning when people are sleeping, and the levels of blood cortisol are high. Cortisol increases blood sugar in order to fuel the body's movements. It stimulates the release of epinephrine and norepinephrine through the sympathetic nervous system. These hormones increase heart rate and blood pressure as they prepare the body to initiate activity quickly [61]. These reactions occur on top of heart rate variability and a rise in blood pressure induced by REM sleep. High cortisol levels around 5 or 6 a.m. function to prepare the body for a new day. It is required for daily physical activities in an awake person. In order to start the day, the body requires extra blood sugar and an active sympathetic nervous system. If the individual wakes up early in the morning, he will use the cortisol properly to prepare for the new day. If instead he or she remains asleep, there will be no physical activity, and the cortisol levels that are normal for a person who is awake will be high levels for the one who is asleep. Then, the sleeper may experience blood sugar, heart rate, and blood pressure higher than is proper for the sleeping state. Thus, over time the cumulative harmful effects of habitual late morning sleeping could be substantial. Basically, the message of high cortisol levels during early morning is like "Hey, get up buddy; it is time to wake up and start your day".

2) In addition, this is a simulation of fight or flight reactions that may be reflected in dreams. The sleeper may have bad dreams such as fighting, arguing, falling, drowning, failing an exam, suffering a sickness/injury, being chased, or having a broken car/laptop/cell phone. The content of dreams varies during the night, from early night to late morning. The prevalence of bizarre dreams in the morning is double of that at the beginning of the night. Moreover, emotionally charged dreams are significantly more frequent in the morning than early in the night [63]. This explains why evening-type people and evening chronotype individuals ("night owls") more frequently experience nightmares [64]. They typically wake up later than the morning chronotype people ("larks"). Evening chronotype people have poorer sleep quality and lower professional performance [65], higher mortality and reduced longevity [66].

Do the contents of our dreams really matter? In order to answer this question, imagine a cup of lemon juice. Now imagine you are drinking the juice. Your salivary glands immediately begin to secrete saliva, and in a few seconds, your mouth is full. Did you see, touch, or drink real lemon juice? Of course not. But you experienced the physical effects of drinking lemon juice in your imagination. This is a clear example of thought-induced physical effects. The mind-body interaction has been studied extensively through placebo effects, imageries, and somatoform and functional disorders [67-71]. While we have only a limited awareness or understanding of the physical effects of psychological processes, bizarre dreams enhance the recall of dream contents [72]. Therefore, in the long term, the content of our dreams really does matter. Bad dreams bring negative physical effects such as accelerated heartbeat, blood vessel spasms, increased blood pressure, and so on. The cumulative effects of these incidents could be enormous. Depressed patients with higher suicidal scores and more severe symptoms had a higher mean REM percentage than non-suicidal patients [73,74]. Acute exacerbations of many chronic disorders occur in early morning sleep. For instance, the highest incidence of ischemic heart diseases and myocardial infarctions in sleep occurs during early morning sleep [75,76]. The same is true for many chronic diseases that have a tendency towards circadian flare-ups during sleep such as hypertension [77], inflammatory bowel disease, irritable bowel syndrome, gastrointestinal cancers and cirrhosis [78-80], epilepsy and sudden death in epilepsy [81]. It is likely that many of these acute exacerbations of chronic disorders could have been prevented if the patients had been early risers in the long term. For example, early morning administration of light significantly improved depression in an intervention group vs. the control one [82]. Patients with irritable bowel syndrome, hypertension, inflammatory bowel disease, epilepsy, anxiety, depression, and diabetes may experience fewer exacerbations of their conditions if they wake up in the early morning every day.

3) Waking up during the REM stage can make an individual feel more sleepy or tired during the day than waking up during stages 1-2 [83]. As the night progresses towards morning, REM becomes longer and longer (Figure 2); it is usually the shortest at the beginning of sleep. In other words, if an individual wake up during this period, the probability of waking up during the REM and consequently feeling tired is at its lowest. On the other hand, since REM usually becomes longer towards morning [1], an individual who wakes up late in the morning (after 5 a.m.) has a much higher probability of waking up during REM and thus

feeling tired throughout the day [84]. In the morning, the REM stage forms the main part of each sleep cycle, so any adult who wakes up in late morning most likely feels tired during the day, regardless of when he or she went to bed the night before. We have probably all experienced nights when we woke up and it was dark outside, but we felt very refreshed and so thought it was early morning, like 4 or 5 a.m. Then, when we checked the time and found out that it was actually only 1 or 2 a.m., we decided to sleep for a few more hours. When we woke up at 7 or 8 a.m., we felt less refreshed than we had a few hours earlier. That's because at 1 or 2 a.m., we are usually waking up at the end of the sleep cycle or during stages 1-2 because REM is short, whereas at 7 or 8 a.m., we more frequently wake up during the REM stage because REM is prolonged. As previously mentioned, REM is the dreaming stage and the brain is active. Waking up during REM is more likely to make you feel tired throughout the day.

To sum up, potentially having too much REM and its consequent biochemical and psychological reactions, explained above, can explain some of the consequences of being late to bed and late to rise. An excess of REM sleep may also provide a reasonable explanation for the harmful effects of long sleep duration, in addition to the obvious reason of extended inactivity induced by prolonged sleep.

Contributing Epidemiologic Factors

Alarmingly, according to the Institute of Medicine, 70 million Americans suffer from a chronic sleep disorder [85]. The National Sleep Foundation reported that only 44 percent of Americans experience a good night's sleep every night [86] whereas >30% sleep less than 6 hours per night. Modal sleep duration in 1960, 1995 and 2004 was 8, 7 and ≤6 hours, respectively [87-89]. This decreasing trend paralleled the increasing trend of obesity in the US. In fact, what we observe now in terms of high incidence and prevalence of metabolic syndrome/overweight/obesity/diabetes mellitus [90] is the consequence of a web of causations including genetic interactions, socioeconomic status, stress, unsatisfactory diet patterns, smoking, alcohol, opioid epidemics, sedentary lifestyles, and insufficient sleep patterns over the past 30-40 years [85,91-110]. According to a National Health Interview Survey, the age-adjusted mean sleep duration in the US in 1985 was 7.4 (SE, 0.01) hours, which significantly decreased to 7.18 (SE, 0.01) hours in 2012 [90]. The age-adjusted percentage of adults sleeping 6 hours or less was 22.3 percent (SE, 0.3) in 1985, which significantly increased to 29.2 percent in 2012 [111]. More than 70 million adults in the US reported sleeping 6 hours or less in 2012 [112]. The median bedtime of adults reported in the NHANES study of 11,951 individuals was 2:45 a.m. on weeknights and still later, on Fridays, Saturdays and Sundays [86]. The pattern was even worse in teenagers and young adults. Given what we know about the current American sleep patterns and if the current imbalance between slow-wave sleep and REM sleep continues, we may expect a skyrocketing incidence of diabetes mellitus and adverse cardiovascular outcomes 20-30 years from now.

Several factors contribute in drawing the current picture of sleep insufficiency. Internet addiction, obesity, physical inactivity, stress, alcohol, the opioid epidemic, night work, incorrect lifestyle habits such as eating late, exercising late, and/or an irregular/imbalanced lifestyle as well as living on the western edge of a time zone, all can disrupt sleep homeostasis [3,79,93,113-117]. In most instances, the relationship is bidirectional [32,85,93,114,115,118-124]. One of the main obstacles to early bedtimes are electronic devices and social media [116,125]. People who went to bed late, experienced less slow-wave sleep and more REM sleep than those who went to bed earlier [86,126]. Early night sleep is the time for the body to repair itself, and early morning (before 5 a.m.) is the time for beginning a new day with the high energy level produced by body homeostasis. If people stay awake until midnight, they lose the critical part of slow-wave sleep. Also, they can't wake up early or refreshed. So, they gain unnecessary extra REM sleep in the morning which disrupts the balance between slow-wave and REM stages. This habit is like to trade slow-wave sleep for REM sleep. This means, trading the deep sleep stage with the lowest possible heart rate, respiratory rate, body temperature, and blood pressure for the REM sleep stage with a high heart rate, respiratory rate, body temperature, and blood pressure. Although REM sleep is necessary, more than enough can have negative consequences. The time that people stay awake until midnight and beyond, will be consumed to build inflammation, plaques and tangles in brain, increased appetite, fat accumulation and no recovery rather than removing the plaques, tangles and inflammation and inducing the recovery. The makeup sleep in the morning cannot reverse these harmful effects. It will be spent to build more stress and disrupt body metabolism. The magnitude risk of this sleep imbalance-inducing insulin resistance is similar to or more than the risk of no physical activity [127]. Observational studies on healthy female nurses who had 3 sequential night shift works revealed significantly worse blood vessel dysfunctions than those in the control group although the night shift nurses had significantly higher physical activity levels. In other words, adverse effects of sleep deprivation superseded the benefits of physical activity [128]. Also, one-night sleep deprivation was associated with higher decrease in insulin resistance than six-month high-fat diet, which means poor sleep superseded the harmful diet [129].

Conclusion

Sleep insufficiency is a chronic stressor, and sleep is a modifiable risk factor and a tractable target to tackle metabolic syndrome pathogenesis in its early stages. The earlier the time to bed, the longer the stage 3 sleep, and the earlier the time to bed, the earlier to rise. Having balanced sleep of slow-wave and REM and regular early time to bed are keys to reduce health risk. Forza Supplements monitored the body clocks of 1000 people, and revealed that the best time to go to bed for adults in order to get the longest stage 3 before midnight was 10:10 p.m. This allows 20 minutes to fall sleep and to experience one 90-minute cycle before midnight [130]. By this habit, it would be possible to experience 4 sleep cycles in summer, translated as 6-hour sleep, and waking up at 4:30 a.m. Seasonal effect modification has been observed in the relationship of sleep and metabolic syndrome [2]. Given the sleep started at 10:30 p.m., this 6-hour sleep is enough for shorter

nights of summer season. Melatonin release starts earlier in the long nights of winter season. Going to bed at 9 p.m. in winter, will let you experience two sleep cycles before midnight. Waking up at 4:30 a.m. will let you experience 5 sleep-cycle and avoid unnecessary REM and its side effects. Also, it is important to limit the daytime napping to 30 minutes, to have enough exposure to natural sunshine and avoid stimulants such as coffee or intense physical activity before going to bed [111,131,132].

Altogether, evidence-based medicine strongly suggests that Benjamin Franklin's aphorism, "early to bed, early to rise, makes a man healthy, wealthy and wise" is correct. Given the high negative impact of poor sleep on productivity and the associated costs [133,134] and the huge positive impact of good sleep on performance [133,135], happiness [136] and health [1,2,22,92, 102-105,109,127,128,137], it is clear early to bed, early to rise, makes a man not only healthy, wealthy and wise but promotes a natural happiness that will be deeply rooted in long-term.

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