

Clinical Importance of Screening for Sleep Disorders for Chronic Disease

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ABSTRACT

Sleep is an important recovery function for human body, energy and the mind. Sleep disorders are associated with many adverse health outcomes. Modern lifestyle choices (24-hour operations, poor diet, physical inactivity, increased stress and tobacco/alcohol consumption) are known to affect sleep and at the same time insufficient sleep (and recovery) creates adverse effects on the autonomic nervous system, metabolism and immune system.

This review examines the evidence of sleep disorders on health—especially on two specific markers of chronic disease (chronic inflammation and metabolic syndrome) and documents the complex relationship between sleep disorders, chronic disease risk factors, pathophysiology, and development of chronic disease. The review develops a case for evaluating the presence of sleep disorders for physicians regardless of the presence of chronic disease. Finally, the review identifies and documents commonly used tools for screening for physicians to get insights for the treatment plan.

Keywords: Sleep Disorders, Screening for Insomnia, Metabolic Syndrome, Chronic Disease, Chronic Inflammation

INTRODUCTION

There are five stages of sleep. Scientists categorised the stages of sleep based on the characteristics of the brain and body during sleep. Stage 1, 2, 3, and 4 are categorised as "non-REM sleep", and the 5th stage, is REM sleep. Generally, brainwave frequencies and amplitudes from an electroencephalogram (EEG) are used to differentiate between the stages of sleep, along with other biological rhythms including eye movements (EOG or electrooculography) and muscle movements (EMG or electromyography). Each sleep stage serves a unique role in brain and body restoration. There are many studies that have

demonstrated that depriving subjects of specific sleep stages has an adverse effect on body and brain functions.²⁻⁸

Sleep disorders are marked by changes in the way that you sleep.² Some of the signs and symptoms of sleep disorders include excessive daytime sleepiness, irregular breathing or increased movement during sleep, and difficulty falling asleep. There are many different types of sleep disorders and are classified into categories based on its cause or the effect on the individual. Sleep disorders can also be grouped according to behaviours, problems with your natural sleep-wake cycles, breathing problems, difficulty

sleeping or how sleepy you feel during the day.

Some common types of sleep disorders include:³

- Insomnia, in which the subject has difficulty falling asleep or staying asleep throughout the night.
- Obstructive sleep apnoea (also known as OSA), in which the subject experiences abnormal patterns in breathing while being asleep. There are several types of sleep apnoea.
- Restless legs syndrome (RLS), (a type of sleep movement disorder, also called Willis-Ekbom disease) causes an uncomfortable sensation and an urge to move the legs while the subject tries to fall asleep.
- Narcolepsy, a condition characterised by extreme sleepiness during the day and falling asleep suddenly during the day.
- Sleep disturbance is comprehensively and independently associated with poor health-related quality of life in middle-aged and older adults.⁵

METHODOLOGY OF THE REVIEW

Given the number of articles on sleep, this nonsystematic review focused studying the research based on risk factors, pathophysiology, disease formation, energy/mind impact and screening. The search classified the articles mainly on (a) consequences of sleep disruption on pathophysiology impacting the three core systems, i.e., nervous system, endocrine system and the immune system

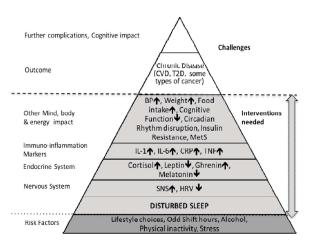


Figure 1: Pathophysiology of sleep disruption (Sources: References 4 to 7 and Table 1)

and (b) on the vicious cycle between sleep disruption and common chronic diseases.

CONSEQUENCES OF SLEEP DISRUPTION AND PATHOPHYSIOLOGY

Sleep disruption has major adverse effects on nervous system (specifically autonomic nervous system), endocrine system and immune/circulatory systems. A disturbed homeostasis in any of these core systems has far reaching implications on the body, energy and the mind. Table 1 captures important evidence (based on non-systematic review) demonstrating the relationship between sleep disruption, metabolic syndrome and immuno-inflammation markers.

Figure 1 is an articulation of this process starting with the risk factors (at the bottom) to the chronic disease (at the top). The impact on key systems and also on the mind, body and energy is also articulated in the diagram. It is important to realise that the relationship is complex and works both ways. For example, one of the causes for obesity is physical inactivity. Physical inactivity also causes sleep disruption. At the same time, obesity (or physical inactivity) disturbs the homeostasis in some or all the three core systems. The disturbance in homeostasis increases inflammation and negatively impacts immune system, which further disturbs sleep. Obesity (or many of the lifestyle choices such as chronic stress or alcohol) also increases cortisol, reduces HRV (heart rate variability, the beat-tobeat variations between successive heartbeats, an important marker of disease and progression) and increases sympathetic nervous system dominance. All of these factors affect sleep and disturbed sleep further affects all the three systems and immuneinflammation markers.

Recent studies have also concluded that sleep disruption increases energy conservation and increases food intake (thereby increasing obesity, which further affects the sleep and various markers of the three core systems).⁸ It is important to note the role of OSA (a type of sleep disruption) in metabolic syndrome and chronic disease based on the studies captured in Table 1.⁴⁻¹⁸

To summarise, sleep disruption leads to metabolic disorder, increased inflammation and reduced immune system functionality. There is also a strong correlation between sleep disruption and many components of metabolic syndrome; more specifically glucose levels/type 2 diabetes, hypertension and obesity. ¹⁰ These changes lead to the pathophysiology that is precursor to any chronic disease. Next section captures the correlation between pathophysiology of sleep disruption and chronic diseases.

CHRONIC DISEASE AND SLEEP DISORDERS—THE VICIOUS CYCLE

Sleep is a complex dynamic activity. Initially thought of as a passive dormant process, now it is realised that there are significant changes occurring in the body and brain while at sleep. During sleep the consciousness is altered, sensory system, and the voluntary muscles of the body are relatively inhibited. It is different from coma wherein a person cannot be aroused from the state of unconsciousness.¹⁹

Chronic diseases are increasingly responsible for

significant morbidity and mortality. The prevalence of sleep disorders ranges from 10% to 48% and has been associated with chronic illnesses like hypertension, type 2 diabetes, obesity, cardiovascular disease, dyslipidaemia, bone disorders, and depression.²⁰

- Hypertension: There is a strong association observed. Possibly, intermittent hypoxia associated with sleep disordered breathing may lead to activation of the sympathetic system causing constriction of blood vessels, leading to hypertension.²¹
- *Diabetes*: Intermittent hypoxia and fragmented sleep are also responsible for causing physiological stress eventually causing insulin resistance which is the pathophysiology behind development of type 2 diabetes.^{22,23}
- Cardiovascular diseases: Studies have shown increased prevalence of arrhythmias, stroke, coronary artery diseases, and atherosclerosis in people suffering from sleep disorders as compared to their peers that do not suffer from sleep disorders.²⁴

References	Focus areas	Subjects	Outcome
4	Short-term and long- term consequences of sleep disruption	Non-systematic review from 97 references	Sleep disruption creates a short- and long-term impact even of healthy individuals. In the short-term, sleep disruption results in pain, depression, anxiety and cognition, impacts memory and performance and heightens the stress response. Long-term sleep disruption in healthy individuals results in hypertension, dyslipidaemia, CVD, weight gain, metabolic syndrome, and type 2 diabetes
5	Sleep disturbance and quality of life	397 adults (175 men and 222 women) aged 40 years and older	The study demonstrated that sleep disruption comprehensivel and independently impacts poor health-related quality of life i middle-aged and older adults
6	Inflammation, sleep apnoea and visceral fat (obesity)	392 adults	This study identified a strong relationship between abdomina obesity and OSA through increased level of <i>CRP</i> , <i>IL-6</i> , an <i>leptin</i> . The unique findings can be generalised to public healt given the nature of the study. Study also identified the role of inflammation in driving the obesity which further impacts slee and vice versa
7	Sleep, stress and metabolism	Review	The study observed the evidence in the modern society to demonstrate the role of sleep deprivation, over-nutrition, an chronic stress in increased incidence of <i>metabolic disorder</i> (obesity and type 2 diabetes)

8	Energy homeostasis and metabolism due to sleep loss	Review	There is metabolic cost (impact) of sleep lost (through neuroendocrine, metabolic and behavioural adaptation in the body that increases the food intake and conserves the energy). Metabolic adaptation-based on sleep loss often could undermine the behavioural interventions (e.g., reduced calorie diet, increased physical activity in obesity prone individuals). The conclusion indicated that any weight reduction intervention must not only focus on reduced calorie diet and physical activity. The intervention must include sufficient sleep also
9	Sleep and metabolism	812 (baseline without metabolic syndrome, 3 years after baseline)	The frequent loud snoring more than doubled the risk of developing the metabolic syndrome, and the prevalence of difficulty falling asleep increased the risk of metabolic syndrome by 80%, even after adjusting for demographic, psychosocial, and lifestyle characteristics
10	Review	Review (epidemiology, experimental data and pathophysiology)	This extensive review integrates insights from several studies. Some of the findings include (a) restricted sleep, and to some extent, longer sleep duration predispose to obesity, insulin resistance, type 2 diabetes, metabolic syndrome, cardiovascular disease and all-cause mortality. In terms of metabolic syndrome components, high blood pressure and higher glucose levels are more prevalent in adults
11	Sleep	15,753 individuals spanning 4 years	The study demonstrated that a decrease of 2 hours sleep (compared to 7 hours regular sleep in the reference group) significantly increased the risk of metabolic syndrome (in the group with HR = 1.23, 95% CI adjusted for age, sex, sleep duration at baseline, marital status, income/family member, education level, smoking status, drinking status, physical activity, body mass index, snoring status, and resting heart rate). After 3.4 years of follow-up, the overall incidence of metabolic syndrome in this study was 40%, which was significantly higher than a previously published report about midlife adults comprising a sub-cohort of ARIRANG and Quebec Family Study patients
12	Sleep, metabolic syndrome, and OSA	Review	It also appears that the <i>relationship between sleep and the metabolic syndrome goes beyond OSA</i> and probably also extends to other forms of sleep disturbance, especially sleep deprivation and shift work
13	Sleep and metabolic syndrome	1,214 individuals	The observed metabolic syndrome rate (22%) was similar to that of published health statistics for American adults. After covariate adjustment, the odds for having the metabolic syndrome increased by more than 45% in both short and long sleepers, compared with those sleeping 7–8 hours per night
14	Sleep and inflammation review	72 studies (n > 50,000)	Sleep disturbance and long sleep duration, but not short sleep duration, are associated with increases in markers of systemic inflammation
15	Sleep and cardiometabolic disease	Review	There is a strong and consistent association between short duration of sleep and cardio-metabolic risk factors and outcomes. The associations may reflect causality as the effects are strong (large relative risks); they are consistent (confirmed in different populations for several end-points), they show a temporal sequence (short sleep preceding end-points), there is a consistent threshold of effects, there are several potential plausible biological mechanisms involved (genetic, molecular, cellular, physiological), and the reversibility of the effect is confirmed when tested in controlled trial conditions (at least in the short-term)

16	OSA and metabolic syndrome	Review (2,456 patients with OSA and 1,705 subjects without OSA)	OSA is shown to be associated with metabolic syndrome, although causality between these two factors has not been demonstrated yet. Future cohort and randomised controlled studies are needed
17	OSA exacerbates the risk due to obesity and metabolic syndrome	Review	Results support the concept that OSA exacerbates the cardio-metabolic risk attributed to obesity and the metabolic syndrome. Recognition and treatment of OSA may decrease the cardiovascular risk in obese patients. There is consistent evidence from animal models and clinical studies suggesting that OSA augments metabolic, inflammatory, autonomic, vascular, and cardiac dysfunction of obesity and exacerbates the metabolic syndrome
18	Review	Sleep and metabolism	Several common sleep problems including insufficient sleep schedules, insomnia, sleep apnoea, narcolepsy, shift work, and shift work disorder are known to cause sleep deficiencies that likely contribute to metabolic diseases. Importantly, bi-directional relationships exist between metabolic dysfunction and some of these sleep problems, most notably for OSA and obesity and type 2 diabetes. Evidence for the treatment of sleep and circadian problems to improve metabolic health is emerging, with treatment of sleep apnoea showing the most evidence thus far.

- Obesity: Sleep deprivation is associated with increase in ghrelin and decrease in leptin hormone. This leads to increased hunger and appetite. However, obesity per se is also responsible further for causing sleep disorders. Thus, this forms a vicious cycle.^{25,26}
- Bone disorders: Increased inflammatory cytokines in response to sleep disorders promote bone metabolism dysfunction leading to bone resorption and subsequent osteoporosis.^{27,28}
- Depression: The association between sleep disorders and depression is complex. Depressive symptoms have been observed amongst patients suffering from sleep disorders. Thus, it is necessary to screen for sleep disorders in a depression patient and vice versa. Improvement in sleep has shown to improve depressive symptoms as well.²⁹
- Cognitive function: Sleep disruption of any kind is associated with impact on memory and cognitive function. Cognitive impairment is also associated with long-term management and side effects of chronic diseases. Thus, the evidence indicates a complex relationship between sleep disruption (including OSA) and cognitive impairment.³⁰⁻³²

Evidence demonstrates the role of sleep disruption impacting pathophysiology and also in major chronic diseases as captured above. The complex nature of the relationship between various types of sleep disruption, the pathophysiology (including chronic inflammation, metabolic syndrome, and immune system impact) and chronic diseases makes it imperative to screen and manage the challenges posed by sleep disruption since it plays a very important role in management of any chronic diseases.

THE CASE FOR SCREENING FOR SLEEP DISORDERS

To summarise, the evidence demonstrates that sleep disruption (of any kind) is a major risk factor for many chronic diseases and causative factor resulting in disturbed homeostasis leading to chronic inflammation, metabolic syndrome and immune system impairment. Given the evidence, it is critical to not just identify a sleep disorder but also put in place an integrated approach to management of sleep in any high risk or chronic disease subjects. Managing sleep also positively impacts quality of life.³³

The findings indicate a need to formally measure sleep and incorporate the data in the clinical treatment plan for chronic disease management since the symptoms suggestive of sleep disorders are common but are not routinely screened for in the primary care setting. Validated questionnaires can efficiently identify patients at risk for common sleep disorders and the studies show that this is not commonly done even in urban healthcare setting.³⁴ Table 2 captures common assessment tools available for the physician starting with simple questionnaire leading to polysomnography tests in the laboratory environment. The physician can choose the tool based on the risk factor, the ease of use for the tool and the quality of data since the outcome of the result (indicating the extent of sleep disorder) could play an important role not only in clinical management but also in the subject's lifestyle intervention to maximise the quality of treatment and the quality of life. 35,36 A simple process for screening is available in.³⁷⁻⁴¹

CONCLUSION

The evidence demonstrates very strong impact of sleep disruption (of various types) on pathophysiology, energy and the mind. Evidence also confirms that any chronic disease is likely to have significant impact on sleep quality. This *vicious cycle between*

the sleep disruption, pathophysiology (e.g., chronic inflammation, metabolic syndrome) and chronic disease needs to be considered in clinical management and prevention of any disease. Moreover, the evidence indicates a strong need to screen for sleep disruption, specifically, for individuals with high blood pressure, insulin resistance (or type 2 diabetes and its complications) and central obesity. Studies also indicate that sleep disruption screening is not done commonly in urban care setting.³⁶ In addition to the mounting evidence of the sleep disruption and chronic disease connection, the modern lifestyle choices (tobacco/alcohol, physical inactivity, poor stress management and 24×7 connectivity) exacerbates the problem indicating a need for a multipronged approach that focuses on multiple factors in addition to the clinical management of the disease (e.g., diabetes) that must begin with screening for sleep disruption (regardless of the presence of chronic disease or risk factors).

The multi-pronged approach must include: (a) *screening for sleep disruption*, specifically for individuals with higher risk for chronic disease (i.e., one or more metabolic syndrome component present) and also for individual with any chronic disease, (b) *lifestyle interventions*—specifically physical activity driven weight management and regular

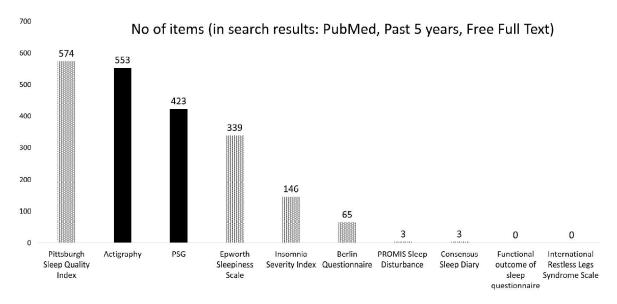


Figure 2: Number of items after PubMed search (Dec 3, 2018) on the keywords from Table 2 (Past 5 years, Free Full Text).

Objective assessment tools (Actigraphy, PSG) are highlighted in "black".

	Type of assessment ³⁸	Tools	Comments (Figure 2 for details)
Α	Subjective_assessment measures for sleep quality, daytime sleepiness, and functional outcomes	Pittsburgh Sleep Quality Index or PSQI (19 items) PROMIS sleep disturbance (27 items) Epworth Sleepiness Scale or ESS (8 items) Functional outcome of sleep questionnaire (30 items)	PSQI and ESS are common (based on PubMed keyword search) and are simple to use
В	Subjective assessment of insomnia	Consensus sleep diary Insomnia Severity Index or ISI (7 items) ³⁹	ISI is more popular (based on PubMed keyword search)
С	Subjective assessment of OSA and RLS	Berlin Questionnaire (10 items) or OSA50 (for OSA, 4 items) International Restless Legs Syndrome Scale (10 items)	BQ is more popular (based on PubMed keyword search)
D	Objective sleep measures	Actigraphy PSG or polysomnography (laboratory or home)	Many emerging technologies appear promising and are likely to provide cheaper alternative (compared to actigraphy) in the near future ^{40,41}

activities which would reduce the sympathetic activation, and (c) regular review of the progress during clinical management of the disease. For sleep screening tools, the selection of the tool can be on the basis of risk associated with the individual, ease of use and the quality of data needed. For lifestyle interventions, the emphasis (even based on just the phenotype) must include weight and diet management interventions and inclusion of activities needing parasympathetic nervous system activation (to reduce sympathetic activation). On a positive note, with advances in technology, the measurement of sleep disruption is going to be more accessible to the subjects—making it easier for physician to gather the insights.

FUTURE POSSIBILITIES

Over past decades, technology advances have created many alternatives for the subject to measure the quality of sleep. These measures often provide more meaningful insights as compared to subjective self-assessment by the subject and are usually cheaper compared to actigraphy or PSG.⁴⁰ At the same time, the physician must be aware that simple consumer grade wearable devices are not yet comparable with good quality actigraphy devices, though over time, with advances and availability of technology,

it is likely that these devices would provide a meaningful and affordable bridge between subjective assessments from surveys and extremely objective assessments from PSG. 42,43

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