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Sleep and Metabolic Syndrome

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Introduction

Health, according to the World Health Organization, is conceptualized as not only the absence of disease but full human physical, emotional, mental, and social function.[1] Obtaining an adequate quantity of restorative sleep each night is a basic requisite for human health; however, the function of sleep in maintaining metabolic homeostasis has not been fully elucidated. During the last 20 years, there has been an increased study of the role of inadequate sleep and sleep disorders on cardiometabolic factors such as the pathogenesis of obesity, hypertension, dyslipidemia, and hyperglycemia. This review examines studies on impaired sleep (i.e., insufficient, fragmented, or poor quality), sleep disorders (i.e., obstructive sleep apnea [OSA] and insomnia), and circadian misalignment of sleep (evening chronotype, social jetlag, shift work) and metabolic syndrome (MetS).

Many factors may be associated with the epidemic increase in prevalence of sleep disorders in the United States (U.S.) including the aging population and modern lifestyle factors that do not favor sleep and contribute to overweight and obesity. Sleep disordered breathing (SDB), nocturnal breathing disorders that include OSA, central sleep apnea (CSA), and nocturnal hypoventilation syndrome, are also prevalent. Depending upon age and disease severity, the estimated prevalence of mild SDB ranges from 24.0% to 83.8% in men and 9.0% to 76.6% in women. Moderate-to-severe SDB ranges from 7.2% to 67.2% in men compared to 4.0% to 50.9% in women, in whom the rate of SDB increases by up to 6% after menopause approaching the rate for men.[2] Likewise, 20% to 40% of U.S. adults report insomnia symptoms, i.e., having difficulty initiating sleep, maintaining sleep, early morning wakening, or non-refreshing sleep, and 9% to 15% have insomnia symptoms accompanied by daytime sleepiness or fatigue.[3,4]

Over the past 20 years, the prevalence of MetS in U.S. adults has increased in parallel with that of obesity. The prevalence of MetS increased from 25.3% to 36.9% between 1988 and 2016.[5,6] A comparative study of National Health and Nutrition Examination Survey (NHANES) data during that time period found that the prevalence of obesity (BMI ≥ 30 kg/m^2) in men increased from 27.5% to 43.0% and the rate of severe obesity (BMI ≥ 40 kg/m^2) more than doubled from 3.1% to 6.8%. Rates of obesity among adult women, increased from 33.4% to 41.9%, and 6.2% to 11.5% for severe obesity.[7]

The paper will describe 1) epidemiologic evidence on the prevalence and association of impaired sleep with MetS, 2) potential mechanisms where impaired sleep desynchronizes and worsens metabolic control, and 3) interventions to improve sleep and potentially improve MetS. While there are a vast number of studies that separately examine each different condition that contribute to MetS, we only discuss studies in adults that consider MetS as the whole cluster of conditions.

Metabolic Syndrome: Definition and Prevalence

Metabolic Syndrome (MetS) is a cluster of endogenous risk factors for development of cardiometabolic disease: increased triglycerides (TG), decreased high-density lipoprotein cholesterol (HDL), increased blood pressure (BP), increased central adiposity, and increased

fasting glucose.[10,11] While each cardiometabolic risk factor is known to independently increase the likelihood of developing diabetes and/or CVD, the co-occurrence of these interrelated risk factors is known to compound the risk.[12,13] Various organizations have supported slightly different definitions of MetS. The following three definitions are commonly used for clinical and research purposes: National Cholesterol Education Program Adult Treatment Panel III (ATP III), International Diabetes Federation (IDF), and the American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) (see Table 1).[10,11]

Due to the heterogeneity inherent in the diagnostic criteria employed by various expert panels, the true global and country specific prevalence of MetS remains uncertain, and current estimates vary based on the criterion used.[14] Despite these limitations, multiple studies have estimated the incidence and prevalence of MetS. It is estimated that about 25% of the world population has MetS.[14] In the U.S., estimates using the 2003-2006 NHANES suggest that the overall age-adjusted prevalence of MetS is about 34% based on the ATP III criteria.[15] In this study, non-Hispanic white men had a higher prevalence of MetS (37%) compared to non-Hispanic black men (25%), but there were no significant differences in prevalence among women based on race/ethnicity.[15] The prevalence of MetS (IDF criteria) in the U.S. has increased from 1988 to 2012 regardless of sociodemographic characteristics (such as ethnicity, gender, and age) and the prevalence of MetS was 34.2% during the period of 2007-2012.[6] In 2015-2016, the prevalence (ATP III criteria) increased to 36.9% among adults aged 20 years or older, and to 50.4% among those aged at least 60 years.[5]

The interplay of this cluster of metabolic aberrancies, spurred on by an accumulation of visceral fat and linked to insulin resistance increases the risk of diabetes, atherosclerosis, and allcause mortality.[8] Each component of MetS is an independent risk factor for cardiometabolic disease (CVD), and the combination of these factors elevates rates and severity of systemic inflammation and cardiovascular conditions. Having MetS is associated with a 5-fold increase in the risk of type 2 diabetes (T2DM) and a 2-fold risk of developing CVD over a period of 5 to 10 years.[9]

Sleep Duration and Metabolic Syndrome

Adequate sleep duration, the amount of time spent sleeping within a 24-hour period of time to maintain optimal health and well-being, ranges from 7 to 9 hours for adults and 7 to 8 hours for older adults.[16] A review of studies with population-level data found the prevalence of objectively measured short sleep duration, i.e., less than 6 hours, ranged from 22.1 to 53.3% of U.S. adults[17] while 9.2% of the population report having long sleep duration (≥ 9 hours).[18] Reasons for short sleep duration include long work hours, early morning awakening because of long commutes to work, house and childcare responsibilities in working parents, and increased use of technology in the evening with sleep delayed.[19] A study using NHANES 2007-2008 data examined the association of sleep duration ranging from “very short < 5 hrs/night” to “long ≥ 9 hrs/night” by social determinant factors with “normal sleep duration 7 to 8 hrs/night” as the reference.[20] Shorter sleep durations were significantly more likely in persons who were African-American, Hispanics/Latino, Asians,

low-income, low education level, and with public insurance, or with low food security ($p < .05$).[20]

Multiple studies report a U-shaped distribution between persons with normal sleep duration and those with short or long sleep duration and worse health outcomes (i.e., obesity, T2DM, and hypertension).[21,22] A meta-analysis evaluated prospective studies (N=15) that had baseline data on sleep duration and data from at least a 3-year follow up period. This study found a significantly increased risk for short duration for incidence and death from CVD and stroke; long sleep duration had significantly increased risk for incidence and death for cardiac heart disease, stroke, and total CVD.[21] Although long sleep duration is associated with increased morbidity, it is hypothesized that the association between long sleep and poor cardiovascular outcomes is an indicator of poor health rather than a risk factor or potential mechanism for negative health outcomes.[18,21]

A study with the 2013-2014 NHANES of a population-level sample examined the association between sleep duration and MetS severity (ATP III criteria).[22] In this study, individuals sleeping 7 to 7.5 hours per night showed the lowest risk for MetS. In a U-shaped association between sleep duration and MetS, those sleeping less than 7 hours or more than 7 hours were at higher risk than those sleeping 7 hours, and those sleeping 5 hours or 9 hours showed similar risk.

Circadian misalignment and Metabolic Syndrome

Sleeping and eating outside of the normal light-dark cycle and out-of-phase with the central clock cause circadian misalignment.[23] Circadian misalignment is associated with impaired glucose control and increased inflammatory markers. Individuals with long-term circadian misalignment are at increased risk for an elevated body mass index, diabetes, CVD, and stroke.[24]

Chronotype, social demands, and work schedules are factors that impact the circadian system and contribute to circadian misalignment. Chronotype is the natural variation in circadian rhythms that manifests in preferred bedtime and peak performance.[25] There are three basic chronotypes: early (morning), intermediate, and late (evening). Numerous factors impact chronotype and it changes throughout the lifespan. There are genetic variants that help determine the length of the endogenous circadian cycle; a shorter length of the cycle may be associated with the early chronotype.[26] Prevalence of the late chronotype may be higher in males compared to females. The early chronotype is more prevalent in children, but with puberty this shifts to the late chronotype. Then in middle age, a shift back to the early type is observed.[26] The evening chronotype is associated with having excess weight and diabetes.[25]

Social jetlag is the misalignment between an individual's circadian system and their actual sleep and wake times due to social demands. This misalignment occurs due to the difference in sleep and wake demands imposed by schedules on workdays and the sleep and wake times based on preference during days off.[25] In a population-based cohort of the Dutch population, among individuals less than 61 years of age, social jetlag of ≥ 2 hours was

associated with increased risk of MetS (ATP III criteria) and diabetes/prediabetes (prevalence ratio = 2.13, 95% confidence interval [CI] 1.3-3.4 and 1.75 (95% CI 1.2-2.5, respectively) after adjustment for sex, employment status, and education level.[27] While MetS was not specifically examined, a study of 447 adults in the U.S. found social jetlag to be associated with greater insulin resistance and adiposity along with lower HDL, higher TG, and higher fasting plasma insulin levels (all p-values < .05).[25]

Lastly, shift work often involves sleeping during the day and eating during the night along with inadequate sleep duration which dramatically alters the circadian system. With 15% of U.S. workforce engaged in work outside of traditional work hours, shift work is prevalent.[28] When eating late in the evening or in the middle of night, food intake occurs when circulating leptin levels, which help signal satiety, are lower than when eating at normal times or when inphase with our biological clocks. This results in overeating of high-fat, calorie-dense foods which impairs glucose tolerance and insulin sensitivity.[24] Misaligned sleep may alter the makeup of the gut microbiome while misaligned eating disturbs its rhythmic expression which contributes to insulin resistance, inflammation, and adiposity.[24,29]

Insomnia and Metabolic Syndrome

Insomnia is one of the most common sleep disorders and is characterized by sleep-specific complaints of difficulty falling asleep, staying asleep, or poor sleep quality despite adequate opportunity for sleep and impairments in daytime functioning. Prevalence rates of insomnia in the general population range from 4% to 48% depending on the stringency of criteria used to define insomnia.[4] Insomnia can be chronic or acute depending on the duration of sleep difficulties and is often comorbid with medical and psychiatric disorders. Various risk factors for insomnia have been identified including female sex, older age, ethnic minorities, minimal education, unemployment, depression, anxiety, substance use and abuse, and medical comorbidities.[30] Insomnia is associated with adverse physical and emotional health outcomes including cardiometabolic disease, poor health-related quality of life, and psychiatric disorders, workplace accidents and lost work productivity, and increased risk for all-cause mortality.[30]

Multiple cross-sectional studies have shown a significant relationship between insomnia and MetS. Zou and colleagues assessed the relationship between insomnia and MetS (ATP III criteria) among 830 middle-aged (50-64 years old) adults from Sweden, in which 12.4% had insomnia defined by an Insomnia Severity Index score of ≥ 15.[31] Insomnia independently increased the risk of MetS (odds ratio [OR] 1.97, 95% CI 1.00-3.86) even controlling for sleep duration and physician diagnosed sleep apnea. Individuals with insomnia had lower HDL cholesterol and higher TG than those without insomnia. Similarly, insomnia symptoms significantly increased the odds of having each component of MetS including high waist circumference, low HDL, and high LDL, TG, and fasting plasma glucose (IDF criteria) after controlling for sleep duration in a large sample (N = 26,016) of Taiwanese adults aged 35 years and older.[32]

A couple of cross-sectional studies have examined the relationship between specific insomnia symptoms (i.e., difficulty initiating sleep, difficulty maintaining sleep, early morning awakening) and MetS. In a population-based sample from Taiwan (N = 4,197), difficulty initiating sleep (OR 1.24, 95% CI 1.01-1.51) and difficulty maintaining sleep (OR 1.28, 95% CI 1.02-1.61) were associated with the MetS (IDF and AHA/NHLBI criteria) after controlling for sleep duration.[33] Among an elderly community-dwelling population aged 65 years or older in France (N = 6,354), difficulty maintaining sleep was independently associated with MetS (ATP III criteria) (OR 1.23, 95% CI 1.06-1.43) and central obesity (OR 1.20, 95% CI 1.06-1.36).[34]

Studies investigating sex and age differences in the relationship between insomnia and MetS have reported conflicting results. In a study of Chinese adults (N = 8,017),[35] a significant association between insomnia and MetS (IDF criteria) was found only for men (OR 1.36 95% CI 1.02-1.77) and middle-aged (40-59 years) adults (OR 1.40, 95% CI 1.09-1.79). However, there was no significant association between insomnia and MetS in women or in younger (< 40 years) or older (≥ 60 years) adults. In a study of French adults (aged 18-65 years) with major depressive episode (N = 624),[12] severe insomnia increased the prevalence of MetS (ATP III criteria) (OR 2.2, 95% CI 1.3-3.9) and IDF (OR 1.8, 95% CI 1.1-2.9) definitions in women, not men. Furthermore, women aged over 50 years had a greater risk of MetS than those under 50 years. However, in a study of postmenopausal Ecuadorian women (N =204; mean age 56 years),[36] insomnia was not significantly associated with the MetS (ATP III criteria) nor its components.

Studies using a longitudinal design have estimated the risk of incident MetS associated with insomnia. Among a sample of 242 Italian police officers (mean age 36 years), insomnia at baseline significantly increased the risk for incidence of MetS (IDF and ATP III criteria) at 5-year follow-up after controlling for sleep duration, excessive daytime sleepiness, and sleep satisfaction (OR 11.04, 95% CI 2.57-42.49).[37] More specifically, insomnia was associated with abdominal obesity (OR 5.83, 95% CI 1.34-25.45) and low HDL cholesterol (OR 6.97, 95% CI 1.06-45.99). In a study of Taiwanese older adults (aged 65 and older),[38] those with insomnia were over two times more likely to have the MetS (ATP III criteria) at one year follow-up (OR 2.15, 95% CI 1.09-4.22) after controlling for the components of MetS at baseline.

Obstructive Sleep Apnea and Metabolic Syndrome

Obstructive Sleep Apnea (OSA), the most common sleep-related breathing disorder, is characterized by repetitive occurrences of complete (apneas) or partial (hypopneas) upper airway obstruction during sleep that results in hypoxia and frequent arousals.[2] The apnea-hypopnea index (AHI) measures OSA severity and is calculated by dividing the total number of apneas and hypopneas by the total time of evaluated nasal airflow.[39] Commonly reported symptoms include breathing pauses during sleep, loud snoring, waking up choking or gasping for air, frequent awakenings, morning headaches, and excessive daytime sleepiness.[2]

Primary risk factors for OSA include central adiposity and the male sex. Women's rates of OSA increase during the menopause transition.[40] The risk for OSA increases with older age and greater weight gain and is generally more prevalent and severe among persons with morbid obesity.[41–42]

While the different metabolic disorders in MetS have specific pathogenic pathways, in common is the visceral adiposity obesity phenotype.[43] As a result, there has been considerable research searching for a common link between OSA and visceral adiposity and their combined roles in MetS. Clinically, people with OSA may be more likely to gain weight and have difficulty losing it.[44] With OSA, recurrent obstructed breathing events result in repeated cycles of hypoxia-reoxygenation with subsequent disruption of sleep throughout the night.[42] This may lead to stress-related neurohumoral activation and was shown in animals to be a potential mechanistic pathway for metabolic dysregulation in OSA.[42] The repeated cycles of hypoxia-reoxygenation affect different organs and adipose tissue with dysfunctional adipose tissue playing an important role in the disposition towards development of MetS in persons with OSA.[42]

The coexistence of MetS, previously referred to as "Syndrome X," with OSA, sometimes referred to as "Syndrome Z,"[45] has been supported in multiple studies. A study of 228 consecutive patients evaluated in a sleep clinic found that MetS (AHA/NHLBI criteria) coexisted in 60% of the 146 patients with OSA.[46] Another study in China (N=178) of persons with severe OSA (AHI ≥ 30) found a significantly higher prevalence of coexisting MetS (ATP III criteria) in patients with excessive daytime sleepiness compared to those who without sleepiness (78.2% vs. 28.6%, $p<.001$).[47] Patients with severe OSA and excessive daytime sleepiness met more of the diagnostic criteria for MetS compared to those with severe OSA but without excessive daytime sleepiness (3.22 ± 0.94 vs. 1.96 ± 1.06, respectively, $p<.001$).[47]

A meta-analysis examined the association between OSA and MetS parameters (ATP III criteria) in 10 studies (pooled total sample = 2053).[48] The analysis found that patients with OSA had significantly poorer values in MetS components (i.e., higher systolic BP, lower HDL, higher LDL), compared to those without OSA, all p-values <.001.

Recent evidence suggests that OSA and insomnia frequently coexist. Troxel and colleagues (2010) longitudinally examined the relationship between sleep symptoms including symptoms of insomnia and SDB and MetS (N = 812; U.S. adults aged 45-75 years; ATP III criteria).[49] Difficulty initiating sleep, unrefreshing sleep, and loud snoring were significantly associated with an increased risk of developing the MetS over a 3-year follow-up period after controlling for demographics, lifestyle factors, and depressive symptoms. However, after further adjustment for AHI, only loud snoring remained a significant predictor of the incidence of MetS (OR 3.01, 95% CI 1.39-6.55), whereas difficulty initiating sleep and unrefreshing sleep were reduced to non-significance. This may suggest that the MetS is more strongly associated with SDB than insomnia.

Assessment and Interventions to Improve Sleep

Since sleep is an essential part of maintaining health, it should be part of the health provider's routine assessment in persons with MetS. This assessment should cover both factors that are integral for sleep health and signs/symptoms of common sleep disorders.[50] There are five dimensions that characterize sleep health that are important to evaluate as part of an assessment, i.e., **s**atisfaction of sleep quality, **a**lertness, **t**iming of sleep, sleep **e**fficiency, and sleep **d**uration, or the acronym "SATED".[50] Because sleep disorders are prevalent in persons with MetS, it is especially important for health providers to ask focused questions to elicit information about symptoms of sleep disorders of insomnia, misalignment of circadian rhythms, and OSA. Responses that suggest a problem with sleep can be further screened with a validated instrument which may suggest further evaluation by a specialist in sleep medicine.

There are validated self-report instruments to screen for potential sleep problems. One of the most widely used instruments to evaluate subjective sleepiness is the Epworth Sleepiness Scale,[51] a 8-question instrument that asks the likelihood of falling asleep in various circumstances with responses that range from "no likelihood of dozing or sleeping" to "strong likelihood of dozing or sleeping." Two questionnaires that can be used to evaluate the risk of OSA are the Berlin Questionnaire[52] and the STOP BANG.[53] The presence and severity of OSA requires an overnight sleep study that may be done either in-laboratory or at-home. Insomnia severity can be evaluated by use of the Insomnia Severity Index, a 7-item questionnaire that queries whether there is difficulty in falling asleep, maintaining sleep, or waking too early and whether these symptoms affect nighttime sleep quality or daytime functional ability.

Many medications that treat components of MetS can negatively affect sleep because of worsened insomnia symptoms or because of increased weight gain and new or more severe OSA.[54] Therefore, healthcare providers are encouraged to carefully review whether all medications prescribed to patients with MetS do not have unintended effects on sleep (see Table 2).

Sleep hygiene refers to routines and behaviors that are associated with good sleep. See Clinical Care Points to improve sleep. Components of good sleep hygiene include avoiding certain substances (i.e., caffeine, nicotine, and alcohol) before bedtime and reducing stress.[55] Other sleep hygiene recommendations include minimizing noise, maintaining a regular schedule for bedtime and wake-up, allowing adequate time in bed to obtain 7 to 9 hours of sleep, and avoiding long naps (>30 minutes) or evening naps, especially if disruptive to being able to sleep at night. Although there is universal agreement on the importance of sleep hygiene, unfortunately, sleep hygiene recommendations have not, to our knowledge, been evaluated on whether, or not, they directly improve MetS.

There have been interventions to improve total sleep time (TST) for short sleepers. Intervention feasibility and randomized control trial studies have looked at improvement of short sleep duration, but the findings are limited to sleep measures.[56] Results of a feasibility study that examined the effect of a personalized sleep extension protocol on nutrition found

a reduction in consumption of free sugar but the study did not measure MetS component outcomes.[57] A number of other studies focused on weight loss management programs (i.e., non-sleep interventions) and have shown mixed results for improvement of TST and metabolic outcomes.[58,59]

Numerous non-pharmacological countermeasures to mitigate circadian misalignment and its metabolic consequences exist. Bright light exposure at the appropriate time and the avoidance of light at the wrong time are effective strategies to accelerate circadian rhythm entrainment. Individuals with a late chronotype or who are experiencing social jetlag, might include bright light in the morning and blue-blocking glasses or use applications on electronic devices to block short-wavelength emissions.[60,61] For shift workers, this would include a total 3 to 6 hours of bright light exposure during the night shift along with the avoidance of bright light during the commute home.[60]

Time-restricted eating, which limits eating to a 10- to 12-hour window, thus allowing for daily fasting of 12 hours or more, is an emerging countermeasure.[62] Since energy intake is a zeitgeber that impacts the circadian system, the proposed mechanism for time-restricted eating is to resynchronize the circadian-system with the external environment in situations where circadian misalignment may occur.[62] This resynchronization is hypothesized to help prevent or reverse MetS through pathways that influence glucose metabolism and inflammation.[63]

Behavioral sleep interventions should be done before considering the use of hypnotic medications in persons with complaints of insomnia.[3] Modifiable factors associated with insomnia need to be evaluated such as medications, nocturia, and psychosocial factors. Persons with insomnia need to reduce their time in bed when not sleeping and to sleep when tired and ready to fall asleep. Things to be avoided are trying to fall asleep, daytime naps, clock watching, stimulants (e.g., caffeine, tobacco or prescribed medications that are intended for daytime), or alcohol as a sleep aid before bedtime.

Cognitive behavioral therapy for insomnia (CBT-I) is a behavioral treatment for chronic insomnia.[3,30] CBT-I focuses on addressing maladaptive behaviors and dysfunctional thoughts that perpetuate or exacerbate poor sleep quality and quantity and associate daytime impairments. The common therapeutic techniques of CBT-I include sleep restriction, stimulus control therapy, relaxation, cognitive therapies, mindfulness-based stress reduction, sleep hygiene education and the combination of these techniques. However, the effect of CBT-I has not been examined in persons with MetS. Given the close relationship between insomnia and MetS, the effect of CBT-I on MetS should be further investigated.

The gold standard for OSA treatment is continuous positive airway pressure (CPAP), a mask worn when sleeping in which a constant level of air pressure is continuously applied to the upper airway, but it is sometimes difficult to tolerate. Persons prescribed CPAP need to be encouraged to wear their devices every night for the entire night. If there is difficulty, communication with their health care provider may help problem-solve to improve adherence. For persons unable to tolerate CPAP, alternative treatments have arisen such as Hypoglossal Nerve Stimulation (small device is surgically implanted in the chest stimulates

a nerve that keeps the upper airway open), oral appliances that prevent the tongue from obstructive the upper airway, and behavioral modifications such as weight loss.[42]

Various studies have not been able to establish that treatment of OSA is consistently associated with improvements in the metabolic components of obesity, insulin-glucose dysmetabolism, dyslipidemia, or systemic inflammation.[64,65] Studies have been conflicting regarding weight loss and CPAP treatment. A recent meta-analysis suggest CPAP treatment may lead to increased weight unless patients are counseled to be proactive in not gaining weight.[66]

Summary

This paper reviewed evidence on relationships between sleep disorders and the development and severity of MetS and discussed effective interventions for sleep and MetS. Multiple studies report a U-shaped association between persons with normal sleep duration and about 7 hours sleep per night showed the lowest risk for MetS. Insomnia independently increases the risk of MetS in various populations; however, some studies have shown inconsistent findings across age and gender. While there is limited research on circadian misalignment with individuals with MetS, circadian misalignment is associated with impaired glucose control and increased inflammatory markers resulting in increased risk for cardiometabolic conditions. OSA and MetS are strongly associated. Multiple studies corroborate that visceral obesity as a component of Mets may contribute to increased risk for OSA. Excessive daytime sleepiness in the presence of OSA may contribute to worse MetS outcomes. Effective interventions to improve sleep included good sleep hygiene, weight loss programs, restricted eating time and sugar consumption, CBT-I, and CPAP for individuals with OSA. Based on significant relationships between sleep disorders and MetS, interventions to significantly improve sleep would have a potential to positively affect MetS.

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Clinical Care Points

- Evaluation of obesity needs to consider weight distribution because central adiposity is a hallmark of both MetS and OSA.
- Persons with MetS and any sleep problem should be encouraged to improve their basic sleep hygiene behaviors.
- Exercise should be encouraged to promote good sleep during the day.
- Avoidance of stimulating substances (i.e., caffeine, nicotine, prescribed medications that worsen sleep) close to bedtime.
- Sleep duration for adults and older adults is recommended to be between 7 to 9 hours a night.
- Persons with MetS need to be evaluated during their routine visits by their health care provider whether they snore or hold their breath while sleeping.
- Adherence to treatment with CPAP, if appropriate, is encouraged. Conventional medical approaches to OSA treatment including positional treatment, avoidance of alcohol and weight loss can also be incorporated.
- Persons with unintended “microsleeps” (i.e., falling asleep even briefly) should be evaluated for sleep disorders. This is especially true if sleep attacks occur during situations that require vigilance, i.e., driving a car.
- Maintaining a regular sleep routine promotes sleep health. Bedtime should be before midnight on most nights and wake time should stay constant even if it is difficult to fall asleep.
- Women with obesity, or at the menopausal transition, or who complain of insomnia, fatigue or depression should be evaluated for SDB.

Key Points

Metabolic syndrome and impaired sleep share many of the same phenotypical characteristics and risk factors including increased prevalence in middle aged and older adults, obesity with central adiposity, hypertension, dyslipidemia, and hyperglycemia.

There is a U-shaped association between sleep duration and health outcomes: individuals with short (≤5 hrs/day) or long (≥9 hours/day) sleep duration showed higher risk for metabolic syndrome than those with normal sleep duration (7-8hrs/day).

Misaligned sleep and nighttime eating negatively effects on cardiometabolic factors such as adiposity, glucose, and cholesterol.

Insomnia is found to be a risk factor for the development of metabolic syndrome. Specific insomnia symptoms, primarily difficulties in initiating and maintaining sleep, are associated with the metabolic syndrome and its components.

OSA frequently coexist with insomnia and individuals with OSA has shown significantly poorer values in metabolic syndrome components.

Sleep disorders are prevalent in persons with metabolic syndrome; therefore, a sleep assessment should be part of the health provider’s routine assessment in persons with metabolic syndrome.

Synopsis

Metabolic syndrome (MetS) refers to the clustering of risk factors for cardiovascular disease and diabetes including central adiposity, hypertension, dyslipidemia, and hyperglycemia. During the last twenty years there has been a parallel and epidemic increase in MetS and impaired sleep. This paper describes evidence on the association between MetS and short sleep duration, circadian misalignment, insomnia, and sleep apnea. Potential mechanisms where impaired sleep desynchronizes and worsens metabolic control and interventions to improve sleep and potentially improve MetS are presented.

Table 1:

Definitions of metabolic syndrome

	National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), 2001	**International Diabetes Federation (IDF), 2006**	**The American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI), 2005**
Mandatory Risk Factor	None	Central obesity (waist circumference with ethnicity specific value: ≥94 cm for men; ≥80 cm for women in Caucasians and ≥ 90cm for men, ≥ 80cm for female in Asians) OR BMI > 30kg/m^2	None
Additional Risk Factors	At least **three** of the following risk factors:	Any **two** of the following risk factors:	At least **three** of the following risk factors:
	Central adiposity (waist circumference >40 inches for men; >35 inches for women)		Central adiposity (waist circumference >40 inches for men; >35 inches for women)
	Elevated fasting triglycerides (≥150 mg/dl)	Elevated triglycerides (≥150 mg/dL) OR drug treatment,	Elevated triglycerides (≥150 mg/dL) OR drug treatment
	Low fasting HDL cholesterol <40 mg/dL for men or <50 mg/dL for women)	Low HDL cholesterol (<40 mg/dL for men or <50 mg/dL for women) OR drug treatment	Low HDL cholesterol (<40 mg/dL for men or <50 mg/dL for women) OR drug treatment,
	High blood pressure (≥130/85 mmHg)	High blood pressure (≥130/85 mmHg) OR drug treatment	High blood pressure (≥130/85 mmHg) OR drug treatment
	Elevated fasting blood glucose levels (>110 mg/dL)	Elevated fasting blood glucose levels (≥100 mg/dL) OR Previously diagnosed T2DM	Elevated fasting blood glucose levels (≥100 mg/dL) OR drug treatment

Table 2:

Medications prescribed for metabolic syndrome conditions that affect sleep[54]

Indication	Classification	Example	Effect on sleep
Hypertension	Beta blockers	Metoprolol (Lopressor), atenolol (Tenormin), Propranolol (Inderal)	Insomnia, nighttime awakenings, nightmares
	Alpha-agonist	Clonidine (Catapress)	Daytime drowsiness and fatigue, disrupted REM sleep, restlessness, early morning awakenings, nightmares
	Alpha-blockers	Tamulosin (Flomax) Prazosin (Minipress)	Daytime drowsiness and fatigue, decreased REM
	Thiazide diuretics	Hydrochlorothiazide, chlorthalidone	Increased nighttime urination, nocturnal leg cramps
	ACE Inhibitors	Losartan (Cozaar) Valsartan (Diovan)	Disruptive cough and leg cramps
	Angiotension Receptor blockers (ARB's)	Losartan (Cozaar) Valsartan (Diovan)	Disruptive leg cramps, muscle aches
Cholesterol	Statins	Simvastatin (Zocor); Atorvastatin (Lipitor)	Insomnia, disrupted sleep due to muscle pain
Hyperglycemic medications	Insulin, sulfonylureas	Humalog, glargine, glipizide, glyburide	Weight gain (OSA risk)
Obesity	Weight loss medications	Phentermine (Adipex P); phentermine/ topiramate ER (Quizmia); Phendimetrazine (Bontril); Bupropion/naltrexone (Contrave)	Insomnia symptoms, difficulty falling asleep or staying asleep