REVIEW

Role of sleep quality in the metabolic syndrome

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Abstract: Emerging evidence has assigned an important role to sleep as a modulator of metabolic homeostasis. The impact of variations in sleep duration, sleep-disordered breathing, and chronotype to cardiometabolic function encompasses a wide array of perturbations spanning from obesity, insulin resistance, type 2 diabetes, the metabolic syndrome, and cardiovascular disease risk and mortality in both adults and children. Here, we critically and extensively review the published literature on such important issues and provide a comprehensive overview of the most salient pathophysiologic pathways underlying the links between sleep, sleep disorders, and cardiometabolic functioning.

Keywords: sleep apnea, circadian clock, insulin resistance, obesity, cardiovascular risk

Introduction

Obesity has reached epidemic proportions worldwide – in the US, 17% of children are now overweight or obese.[1–3] In parallel, there has been a rise in the prevalence of obesity-related comorbidities, such as insulin resistance (IR), type 2 diabetes mellitus (T2DM), and the metabolic syndrome (MetS), collectively referred to as cardiometabolic risk.[4,5] The MetS is a cluster of metabolic disorders encompassing central obesity, impaired fasting glucose, dyslipidemia (specifically, triglyceride elevation and/or low levels of high-density lipoprotein [HDL] cholesterol), and hypertension and is associated with an increased risk of T2DM and, in adulthood, cardiovascular disease (CVD) and overall mortality.[6,7] The underlying pathophysiology of MetS is thought to include IR and/or an inflammatory state, which accompanies obesity.[8,9] The specific criteria for the MetS in adults have been defined by the National Cholesterol Education Program or Adult Treatment Panel III and the World Health Organization. The MetS is now endemic in the US – 35% of all adults and 50% of those older than 60 years suffer from this condition.[10] The prevalence of the MetS phenotype in children has also increased, doubling between 1988 and 2006, from 4% to 8.6%.[11,12] The prevalence of the MetS in obese children and adolescents varies somewhat depending on ethnicity and on which specific pediatric diagnostic criteria are used (as there is no specific consensus on the definition of the MetS in children) but ranges between 30% and 50%, with higher prevalence in those with more severe obesity.[13–18] The underlying etiology of the rise in the frequency of these conditions is multifactorial, with well-recognized contributions from diet (large portion sizes, nutrient-dense foods, and others) and physical inactivity;[19] however, such factors alone do not explain the significant epidemic of obesity and the MetS.

There is increasing recognition that disturbances of sleep, including chronic sleep restriction and alterations in sleep architecture, such as obstructive sleep apnea, and other causes of sleep disruption and fragmentation, are also the risk factors for obesity and cardiometabolic risk in both adults and children. Most recently, a body of data has begun to emerge on the links between chronotype and circadian rhythm disorders and obesity and the MetS. In this review, we focus on the contributions of disturbances of sleep and circadian biology to the development of obesity, IR, and the MetS in adults, prepubertal children, and adolescents, with a special emphasis on the potential mechanisms underlying these links, as these serve as potential targets for preventing the MetS and its complications.

Sleep restriction and sleep architecture: impact on the MetS and cardiometabolic risk in adults and children

Chronic sleep restriction

Chronically insufficient sleep is endemic and has been declared as a public health problem by the Centers for Disease Control.[20] Recent data from the 2014 Behavioral Risk Factor Surveillance System poll found that 41.3% of the 44,306 adults polled reported ≤6 hours (11.8% ≤5 hours) of sleep, 29.5% reported 7 hours, 27.7% reported 8 hours, 4.4% reported 9 hours, and 3.6% reported ≥10 hours; taking into account the sleep durations of 7–9 hours recommended for age, only 65.2% reported obtaining the recommended healthy sleep duration.[21] In studies of children and adolescents, ~27% of school-aged children and 45% of adolescents report sleeping less than recommended for age,[22,23] with lower levels of parental education, lack of regular enforcement of rules about caffeine, and presence of electronics in the child's bedroom overnight being the most predictive of age-adjusted insufficient sleep duration.[24]

In adult and pediatric populations, chronic sleep restriction and poor sleep quality are associated with an increased risk of obesity, IR, and the MetS or components thereof.[25–33] Epidemiological adult studies have also found associations between insufficient sleep, and in some cases, long sleep duration and T2DM risk, T2DM severity, and CVD incidence and mortality.[34–39] Epidemiological reports cannot ascertain causality; however, numerous laboratory sleep restriction studies have now demonstrated the causal nature of the relationship between behavioral sleep restriction and obesity, IR, and changes in other metabolic functions that together lead to MetS. These data and recent updates are discussed in greater detail in the following sections.

Epidemiological data

Adults

A large body of evidence has emerged over the last 50 years implicating insufficient and/or excessive sleep duration in all-cause mortality and in CVD and cardiometabolic risk factors, including the MetS, a cluster of interrelated CVD risk factors (central obesity, elevated triglycerides, low HDL, hypertension, and elevated fasting glucose). Later, we examine the associations between sleep duration and elements comprising cardiometabolic risk, as well as all-cause mortality.

Sleep duration and all-cause mortality

The first study to report an association between insufficient sleep and mortality was a study of 1,064,004 adults aged <30 to >80 years published in 1964, which found that those reporting a sleep duration of 7 hours had the lowest mortality rate.[40] Similarly, in 1983, the Alameda County Study found that men sleeping for <6 hours or >9 hours exhibited a 1.7-fold greater total age-adjusted death rate vs men sleeping for 7–9 hours per night and that women with shorter vs normal sleep durations had a 1.6-fold greater relative mortality risk.[41] A number of prospective cohort studies conducted since these early landmark studies have also found an inverse relationship between sleep duration and all-cause mortality risk in a number of different populations, and a 2010 meta-analysis of all relevant prospective cohort studies of >3 years duration found that both short sleep durations (variably defined as <4 hours to <7 hours) and long sleep durations (variably defined as >8 hours to >12 hours) were associated with greater all-cause mortality risk (short sleep: relative risk [RR] 1.12, 95% confidence interval [CI] 1.06–1.18; long sleep: RR 1.30, CI 1.22–1.38).[42] A more recent meta-analysis found a J-shaped relationship between all-cause mortality and sleep duration, with greatest RR seen in long sleepers rather than short sleepers; subgroup analyses showed that short sleep duration (<7 h/night) increased the RR of all-cause mortality in women but not in men.[43]

Thus, a number of prospective cohort studies have now found that insufficient and/or long sleep is associated with an increased all-cause mortality over time, with a variable degree of risk. Alterations of sleep duration associate with a number of different conditions, which could increase the risk of all-cause mortality; while an entire enumeration is outside the scope of this review, many of these are examined later.

Sleep duration and obesity

The secular trends of chronic sleep restriction have paralleled those of obesity in recent years, suggesting epidemiological

links between the two. Indeed, hundreds of studies in adult and pediatric populations have now been published examining the associations between insufficient sleep and obesity risk. The plurality of such studies in adults and the majority of the studies in children have found that insufficient sleep is associated with an increased risk of obesity. A 2008 meta-analysis of epidemiological studies that encompassed 634,511 participants (30,002 children and 604,509 adults) aged from 2 years to 102 years found a pooled odds ratio (OR) for short sleep duration (usually defined as ≤5 hours in adults and ≤10 hours in children) and obesity of 1.55 (range 1.43–1.68) in adults and 1.89 (range 1.46–2.43) in children.[25] Since then, the majority of cross-sectional or longitudinal studies have reported significant associations between short sleep duration and overall obesity risk and/or central adiposity,[44–46] although it should be stressed that some of the studies did not find significant associations after adjusting for other variables.[47] Interestingly, the relationship between sleep duration and obesity is not necessarily linear; the Wisconsin Sleep Cohort Study found an U-shaped association between sleep duration and obesity, wherein both short and long sleep durations link to an increased risk for the presence of a higher body mass index (BMI); the lowest BMI was seen in individuals sleeping for an average of 7.7 h/night.[48] Similarly, a longitudinal follow-up cohort study with ~6 years average follow-up found that both short sleepers (≤6 hours) and long sleepers (>9 hours) are more likely to accumulate visceral adipose tissue (assessed by computerized tomography) than those sleeping 7–8 hours and that those who switched from sleeping ≤6 hours to sleeping 7–8 hours accumulated less visceral adipose tissue.[46] In contrast, analysis of data from 13,742 participants aged ≥20 years from the 2005–2010 National Health and Nutrition Examination Survey (NHANES) examining associations between sleep duration and obesity risk did not find such an U-shaped relationship. In this cohort, in which participants were categorized as short sleepers (≤6 h/night), average sleepers (7–9 h/night), or long sleepers (≥10 h/night), a negative linear association was found between sleep duration and both BMI and waist circumference among participants without depression or a diagnosed sleep disorder and without notable differences by race or sex, but with regression coefficients that were notably stronger among adults aged 20–39 years. In other words, short sleepers were more likely to be overall obese and to have abdominal adiposity, especially in the young-middle age adult groups.[49] While this study did not find that the sleep–obesity risk differed by race or ethnicity, other studies have found variations in the

relationship between short sleep and obesity in other ethnic groups,[50,51] including one large study that found that the risk of obesity with short sleep duration was significantly greater in African Americans than in Caucasians.[52] Variations in the associations between short sleep and obesity by ethnicity have also been noted in other studies.

Thus, the preponderance of the epidemiological evidence suggests that insufficient sleep increases the OR of being or becoming obese. As discussed in subsequent sections, the risk of obesity-related comorbidities is also increased by insufficient sleep.

Sleep duration and hypertension

Hypertension, a component of the MetS, is a well-known cardiovascular risk factor; alterations in sleep duration have been associated with an increased risk of developing this condition. The Sleep Heart Health Study, a long-term longitudinal multicenter cohort study of sequelae of sleep and sleep-disordered breathing, examined 2,815 men and 2,097 women aged 30–100 years and found that hazard ratios (HRs) for hypertension increased with insufficient sleep duration (<6 hours, HR 1.66, CI 1.35–2.04; 6 hours to <7 hours, HR 1.19, CI 1.02–1.39) and with prolonged sleep duration (8 hours to <9 hours, HR 1.19, CI 1.04–1.37; >9 hours, HR 1.30, CI 1.04–1.62).[53] In the same year, data from the first NHANES survey of 4,810 men and women, aged 32–59 years at baseline who were followed for nearly four decades, showed that sleep duration of ≤5 h/night was associated with a significantly increased risk of incident hypertension (HR 2.10, CI 1.58–2.79), an association that held up after adjusting for confounders.[54] Other studies have also found associations between risk of hypertension and both short sleep duration and long sleep duration.[45,55] Age may modulate the relationship between sleep duration and hypertension; several studies suggested that the association between short sleep duration and/or long sleep duration is stronger in younger and middle-aged adults than in older adults; indeed, several studies have found no association between sleep duration and risk of hypertension in adults older than 58 years, 60 years, or 65 years, possibly because other risk factors for hypertension mask such association.[55–58] Other studies have found that the association between insufficient sleep and high blood pressure is greater in premenopausal women vs postmenopausal women.[59] Interestingly, the association between sleep duration and hypertension risk may differ in degree and in directionality between men and women: the Whitehall II study of 10,308 English men and women aged 35–55 years at baseline, who were followed for

an average of 15 years, found that the association between short sleep and hypertension risk was detectable in women but not in men.[60] Other studies in different populations have also found that the associations between insufficient sleep duration and hypertension are stronger in women than in men.[59] At the other end of the sleep duration spectrum, at least one study reported that the association between long sleep duration and hypertension risk is detectable in men but not in women.[61] These findings suggest that in adults, there may be age- and sex-specific sensitivity to the detrimental effects of chronic sleep deprivation.

Sleep duration, IR, and T2DM

In the past 25 years, there has been an explosion of studies linking insufficient sleep with the risk of IR, incident type 2 diabetes, and poorer glycemic control in adults with T2DM;[35,62–64] long sleep duration (≥9 hours) has also been associated with an increased risk of IR and incident T2DM.[62,65,66] The association between sleep duration and incident T2DM risk in multiethnic cohorts may be modulated by ethnicity, although the relationship is unclear: one study found that non-Hispanic whites and Hispanic adults sleeping for ≤7 hours vs 8 hours were predisposed to T2DM, while African American participants were not,[67] while another study that used data from a nationally representative sample of >130,000 Caucasian and African American NHANES participants found a U-shaped rather than a linear relationship between sleep duration and likelihood of T2DM (both sleeping for <7 hours and >8 hours associated with the risk of T2DM), which was stronger in the Caucasian participants, but found that the ethnic disparities were significantly attenuated after adjusting for socioeconomic status, suggesting that societal rather than biological factors might be partially responsible for ethnic disparities in these relationships.[68] Interestingly, a recently published study of a multiethnic cohort found that the associations between short sleep duration (<7 h/night) and obesity, T2DM risk, and cardiovascular risk factors varied between the different cohorts examined.[51] Thus, chronic sleep restriction and potentially excessive sleep duration appear to increase the risk of IR and T2DM, this relationship being modulated by age, race, and ethnicity, although the degree to which these differences have underlying biological rather than socioeconomic underpinnings remains uncertain.

Sleep duration, the MetS, and CVD

A number of studies in a wide variety of cohorts of different ethnic backgrounds and in both men and women have now shown that sleep duration is a risk factor for the MetS.[69–74] In a cohort of 1,214 adults participating in the Adult Health and Behavior Project registry, being a short or a long sleeper increased the OR of having the MetS by 45%.[33] While the association between insufficient sleep and risk of the MetS is detected in most studies, the association between longer sleep and MetS is less consistent.[72,75] Interestingly, one study found that after adjusting for confounders, long (≥9 hours) but not short (<6 hours) sleep duration was associated with an increased risk of the MetS.[76] A recent meta-analysis of 18 studies encompassing 75,657 participants and using adults sleeping for 7–8 hours as a reference group found a dose–response relationship between sleep duration and the MetS, with increasing risk of the MetS in sleep categories all the way up to a 1.5-fold OR (95% CI 1.1–2.08, P=0.01) among those sleeping for <5 h/night; however, they did not find a significant association between long sleep duration and the MetS – OR 1.13 (95% CI, 0.97–1.32; P=0.10).[71] The question of causality is difficult to assess in cross-sectional studies; however, a prospective cohort study of 2,579 adults aged 40–70 years without MetS at baseline, who were followed for an average of 2.6 years, found a significantly higher risk of incident MetS for those sleeping for <6 hours – adjusted OR (95% CI) 1.41 (1.06–1.88). Breaking the MetS down to its components, short sleepers had higher OR (95% CI) for elevated waist circumference (1.30 [0.98–1.69]), low HDL cholesterol (0.75 [0.56–0.97]), elevated triglycerides (0.82 [0.60–1.11]), high blood pressure (1.56 [1.19–2.03]), and high fasting glucose (1.31 [0.96–1.79]).[77]

Given the associations between insufficient or prolonged sleep duration and the many cardiovascular risk factors enumerated in the sections examining associations between sleep duration and all-cause mortality, hypertension, and T2DM above, it is, therefore, unsurprising that an association exists between sleep duration and CVD. Several large prospective cohort studies published in recent decades have indicated that insufficient sleep duration and long sleep duration are associated with an increased risk of coronary heart disease (CHD) and its predisposing risk factors. The Whitehall II study of 10,308 adult English men and women aged 35–55 years at baseline, who were followed for an average of 15 years, found that participants with short sleep duration (≤6 hours) and restless, disturbed sleep had the highest hazard ratios of CHD (RR: 1.55, 95% CI: 1.33–1.81).[78] Similarly, in the Nurses' Health Cohort of 71,617 US female health professionals, aged 45–65 years and after 10 years of follow-up, the adjusted RR values (95% CIs) of CHD for individuals reporting 5 or fewer, 6, and 7 hours of sleep per night on

average were 1.45 (1.10–1.92), 1.18 (0.98–1.42), and 1.09 (0.91–1.30), respectively. The RR for ≥9 hours of sleep was 1.38 (1.03–1.86).[79] A number of other studies have found similar results in a variety of different adult populations of varying ages and ethnic backgrounds: some have found associations only between insufficient sleep (with or without poor sleep quality) and CHD risk and/or mortality,[37] while others have found U-shaped associations, with both short sleep and excessive sleep being associated with an increased risk of CHD.[80,81] In particular, a 2011 meta-analysis found that short sleep duration was associated with a greater risk of incident CHD and CHD mortality (RR 1.48, 95% CI 1.22–1.80) and incident stroke (RR 1.15, 95% CI 1.00–1.31), while long sleep duration was associated with a greater risk of incident CHD (RR 1.38, 95% CI 1.15–1.66), stroke (RR 1.65, 95% CI 1.45–1.87), and total CVD (RR 1.41, 95% CI 1.19–1.68).[39] More recently, a prospective cohort study of 8,128 Dutch men and 9,579 Dutch women aged 20–65 years, free of CVD at baseline and followed for 10–14 years, found that in the context of eating a healthy diet, maintaining a moderate level of physical activity, nonsmoking status, and moderate alcohol consumption, sleeping sufficiently (defined as >7 years) lowered composite CVD risk by 65% (HR 0.35, 95% CI 0.23–0.52) and lowered the risk of fatal CVD by 83% (HR 0.17, 95% CI 0.07–0.43).[82] Additionally, several studies have found that the risk between sleep duration and CHD is modulated by sex, with some studies showing higher risk of incident myocardial infarction in women vs men who were short or long sleepers[83,84] and others showing no difference in risk by sex.[39] Age may also modify the association, as one study reported an U-shaped association between sleep duration and cardiovascular mortality risk, an association that was stronger in females than in males and stronger in older adults than in younger adults.

In summary, a large number of cross-sectional and prospective epidemiological studies have demonstrated that restricted sleep and, less consistently, longer sleep duration predispose to obesity, IR, T2DM, MetS, CVD, and all-cause mortality.

Children and adolescents
Normal sleep in childhood
Normal sleep duration varies across the lifespan. Recently, the National Sleep Foundation convened an 18-member multidisciplinary expert panel and issued an expert set of guidelines reflecting sufficient sleep duration across the lifespan: 14–17 hours for newborns, 12–15 hours for infants, 11–14 hours for toddlers, 10–13 hours for preschoolers, 9–11 hours for school-aged children (aged 6–13 years), and 8–10 hours for adolescents (aged 14–18 years), as compared to 7–9 hours in young adults and middle-aged adults.[85]

Epidemiology of insufficient sleep
Insufficient sleep is widespread. The 2014 Sleep in America Poll found that 30% of school-age children aged 6–11 years (as reported by their parents) sleep less than the recommended 9 hours.[86] However, the prevalence of behavioral sleep restriction increases substantially in adolescents: the 2006 National Sleep Foundation Sleep in America poll found that 45% of children aged 11–17 years and 75% of twelfth graders surveyed reported <8 h/night of sleep,[87] and in the 2009 United States Youth Risk Behavior Survey, only 31% of adolescents polled (28% of females and 33% of males, with some variability across ethnic groups) reported ≥8 h/night of sleep.[88] Sleep durations may vary in children of different ethnic and/or socioeconomic backgrounds: one study that objectively measured sleep using actigraphy in African American and Caucasian 14–18-year olds in the US found that sleep insufficiency was even more prevalent among African American than Caucasian adolescents,[89] and a recent study of 9–10-year-old children in the UK found that white European children slept longer than South Asian and Black African children.[90] The preponderance of epidemiological data, thus, clearly shows that chronic short sleep is a problem that has its roots in childhood and adolescence.

Sleep duration and obesity
The epidemic of short sleep imposes health sequelae in childhood. While not every study has found an association between sleep duration and obesity,[91] the majority of cross-sectional and longitudinal studies have shown that insufficient sleep duration in children associates with concurrent or long-term risk of obesity – in infancy,[92] early childhood,[93–95] school-age years,[94,96–98] and adolescence.[97,99,100] A meta-analysis of 13 pediatric studies that included >30,000 children found a pooled OR of 1.89 for obesity in children who were short sleepers.[25] However, short sleep duration may not be the only factor in play: obese children were found to be less likely than their nonobese peers to experience catch-up sleep on the weekends.[101] Interestingly, the same pattern may not hold true in adolescents, where high variability in sleep duration may predispose to higher energy intake and more snack consumption.[102] Shorter sleep duration in childhood may also promote adult obesity independently of childhood BMI, parental BMI, and adult sleep duration.[103] Some studies have shown associations in males but not in females,[98,104]

while other studies have shown similar associations in both sexes.[105] Several studies have reported that short sleep in childhood and adolescence is associated with a higher waist circumference, a surrogate measure of visceral adiposity and one of the features of the MetS.[96,106–108] In a UK study, sleep duration associated negatively not only with the ponderal index (a measure of adiposity) but also with fat mass – that is, school children who slept less had greater adipose tissue mass than children who slept more.[90] Again, sleep deprivation may have adverse metabolic effects later in life: a recent prospective cohort study of 3,964 Brazilian children assessed at the age of 11 years and 18 years found that in girls those with insufficient self-reported sleep duration at age 11 years but sufficient sleep duration at age 18 years, were more likely to have higher BMI and fat mass than their peers with adequate sleep at both time points.[109] Thus, sleep restriction and lack of catch-up sleep on weekends in children and adolescents appear to associate with an increased risk of increased weight gain, central obesity, and increased fat mass that can possibly persist or become apparent several years later.

Sleep duration associations with the MetS and its components

A number of studies have now found associations of chronic short sleep duration in children and adolescents with elements of the MetS.

High blood pressure

Chronic sleep restriction has been found to associate with an increased blood pressure in children and adolescents.[108,110–112] Poor sleep quality is also associated with higher blood pressure in obese adolescents.[113] This association may be primarily driven by the blunting of the usual nocturnal dip in blood pressure: insufficient actigraphically measured sleep duration was associated with elevated nocturnal blood pressures in African American and Caucasian adolescents independently of BMI.[114] Interestingly, variability in sleep patterns and sleep duration may also have adverse effects: the Penn State Child Cohort study recently found that an increased sleep variability associated with a decreased heart rate variability,[115] a marker of cardiovascular risk. Studies of younger children have been more equivocal than studies in adolescents regarding the association between sleep duration and blood pressure. One study found that this association was primarily mediated by BMI rather than sleep duration per se,[116] and another study found that while short sleep duration was associated with lower sympathetic nervous system activation and higher cardiac activation under stress (both risk factors for high blood pressure), there was no

association with blood pressure itself.[117] Thus, while the association between insufficient sleep and hypertension risk in adolescents is similar to that data in adults, the impact in younger children is less obvious.

IR and T2DM risk

Although there are considerably less available data in children examining these associations than in adults, several studies have shown that insufficient sleep is associated with IR in obese children (but not in normal-weight children) and normal-weight and obese adolescents independently of obesity.[118–121] Lower sleep efficiency (the percentage of time in bed that is spent asleep) also predisposes to IR in overweight and obese adolescents.[121] In one study, more variability in sleep duration was associated with higher insulin levels.[101] In at least one study of adolescents, long sleep duration (>10 hours overnight) was also associated with greater IR,[119] but these findings have not yet been replicated.

The majority of studies in children examining the association between sleep duration and insulin sensitivity have utilized either fasting insulin measures or the homeostasis model assessment of IR calculated from fasting insulin and glucose levels, but one recent study notably examined associations between self-reported habitual sleep duration and insulin sensitivity as measured by the gold standard hyperinsulinemic–euglycemic clamp in 615 obese adolescents and found that adolescents sleeping for <8 hours had lower insulin sensitivity even after controlling for age and sex.[122]

Few pediatric studies have examined associations between sleep duration and glycemic levels. A study of Chinese preschool-age children (aged 3–6 years) found that short sleep duration of <8 hours was associated with higher fasting glucose in obese but not in nonobese children.[123] Duration of slow wave (nonrapid eye movement stage 3 slow wave sleep) sleep has also been found to associate positively with insulin sensitivity and insulin secretion, both of which are protective against the development of T2DM.[124,125] Shorter sleep duration has also been found to associate with higher fasting and postglucose challenge (during oral glucose tolerance test) glucose levels in normal-weight and obese children.[124,126] One study in obese adolescents found U-shaped associations between sleep duration in the sleep lab and fasting glucose, postchallenge glucose levels, and hemoglobin A1C (HbA1C), with both short sleep (especially <6 hours) and long sleep durations being associated with greater levels.[125] While these studies do suggest that insufficient (and perhaps long) sleep duration would increase the risk of developing T2DM in children older than 10 years (the age at which the risk

of developing diabetes rises to appreciable levels)[127] and adolescents, we are not aware of any pediatric data examining the associations between sleep duration and incident T2DM, or the impact of sleep on glycemic control in those children with existing T2DM.

Dyslipidemia

The data on associations between sleep duration and dyslipidemia in children and adolescents are conflicting. One study found that sleep duration in children is directly associated with HDL cholesterol levels (ie, longer sleepers had higher HDL levels),[119] and another study found that sleep duration in children and adolescents is inversely associated with high total cholesterol/high low-density lipoprotein (LDL) levels (ie, longer sleepers had lower LDL and total cholesterol levels).[98] In the National Longitudinal Study of Adolescent Health study, in which adolescents were followed up for an average of 7 years, a significant longitudinal association between insufficient sleep duration in adolescence and risk of being diagnosed with hypercholesterolemia emerged in females but not in males.[128] Not all studies show linear associations between sleep duration and dyslipidemia; long sleep duration may be a risk factor for dyslipidemia as well, as one study of Korean adolescents found that long sleep duration but not short sleep duration was associated with hypertriglyceridemia,[129] and a study of Iranian children and adolescents found that long sleep duration (>8 hours) was associated with higher LDL levels in females and higher total cholesterol levels in males.[130] Additionally, several other studies found no significant associations between sleep duration and lipid levels in children and adolescents,[131–133] and the 2007–2009 Canadian Health Measures Survey found that there were no significant associations between sleep duration and lipid levels after adjusting for body weight.[97] Thus, sleep duration (short and/or long) may associate with dyslipidemia in children and adolescents, but the association may be mediated by obesity.

MetS risk

Data in children regarding associations between sleep duration and MetS risk are sparse and mostly negative: one study of 723 8–11-year-old Danish children reported that insufficient sleep (among other risk factors) was associated with a number of elements comprising the MetS (a "MetS score").[134] Similarly, a recent study of 1,361 Malaysian adolescents aged 13 years found an U-shaped association between self-reported sleep duration and MetS risk, with the lowest risk seen in those sleeping for 7–9 hours.[135] However, several other clinic and population-based studies in children

and adolescents have failed to find an association between sleep duration and the MetS.[129,131,133,136]

In summary, insufficient sleep and, less consistently, long sleep in children and adolescents is associated with obesity and with several components of the MetS, including higher blood pressures (more consistently in adolescents and inconsistently in younger children), and with higher glucose levels in a few adolescents studies, the association of sleep duration and dyslipidemia is highly inconsistent; evidence regarding an association between sleep duration and the MetS in children and adolescents is lacking. The obvious divergence from the findings in adults may be in part because there are several different competing definitions of the MetS in children or because the more chronic sequelae of sleep restriction may require time to develop and become manifest. IR is thought to be a central component of the pathophysiology of the MetS; it is interesting that the associations between sleep duration and IR are more consistently reported in adolescents, while in prepubertal children, these associations have been primarily reported in those who are obese and thus already predisposed to IR. Thus, future studies should focus on adolescents.

Experimental evidence and pathophysiology
Adults

Experimental sleep restriction, even in healthy and lean young adults, can lead to adverse metabolic consequences. Although no human studies have shown that experimental changes in sleep restriction induce the entirety of the MetS, experimental sleep restriction studies have examined the impact of sleep deprivation on weight gain and on individual components making up the MetS.

Alterations in sleep duration and obesity

As discussed above in the sleep duration and obesity section, epidemiological studies show that insufficient sleep is independently associated with an increased risk of obesity; in fact, even a few days of experimental sleep restriction to 4h/night can lead to a mean 1 kg weight gain in just 4 days,[137] despite increases seen in 24-hour energy expenditure in some studies (though not in others).[137–141] These a priori paradoxical findings are at least partially explained by the increase in subjective hunger and in energy intake (at mealtimes and/ or as snacks, often late at night) in sleep-restricted adults allowed free access to food during experimental sleep restriction (although the increase in sleep deprivation-related caloric intake may be greater in men than in women[139,142]), exceeding the sleep restriction-induced increase in energy expenditure.[137,139,141–144] In addition, a change in macronutrient

distribution of food intake favoring (variably) either more carbohydrates or more high-fat foods further accounts for the positive energy intake balance.[141,142] Experimental sleep restriction has also been found to reduce physical activity in adults with T2DM.[145] Conversely, a pilot study to extend sleep in ten overweight adults found that caloric intake decreased and that the participants expressed a decreased desire for sweet and salty foods.[146] Alterations in the anorexigenic adipocyte-derived hormone leptin and the orexigenic gut hormone ghrelin may play a role: lower leptin and higher ghrelin in most though not all experimental sleep restriction studies in adults were reported.[48,147,148] However, some studies find higher rather than lower leptin levels, suggesting leptin resistance,[149] and other studies find no change in leptin or ghrelin;[141,147] one study, intriguingly, found higher levels of ghrelin after sleep restriction in men but not in women,[150] paralleling some of the data on differences in weight gain in response to experimental sleep restriction. Elevated ghrelin levels may predict an increased food intake during experimental sleep restriction.[151] Other changes induced by sleep restriction include blunting of the usual nocturnal decline in cortisol levels[149,152,153] and increases in levels of peptide YY (which acts to inhibit food intake).[154] Conversely, experimental sleep extension has been carried out, albeit by fewer investigators, and found to reduce leptin and peptide YY levels.[155] These neuroendocrine alterations may underlie the observed changes in caloric intake which, along with decreased physical activity, appear to promote weight gain in sleep restriction (possibly more in men than in women) despite unchanged or even increased energy expenditure.

Impact on insulin and glucose homeostasis

Experimental sleep restriction has also been shown in a large number of studies in adults to induce IR (fasting and/or postprandial), with variable impact on insulin secretion.[30,153,156,157] Endogenous glucose production is increased and impairment of glucose tolerance occurs even in healthy lean adults, especially when combined with circadian disruption.[24,153,158] The metabolic changes accompanying experimental alterations in sleep duration are thought to be partially mediated by the same neuroendocrine perturbations discussed above in the alterations in sleep duration and obesity section, including higher evening cortisol levels (in some though not all studies) and increased sympathetic nervous system activity and catecholamine production in the sleep debt-condition.[152,153,157,159] Sleep restriction can also increase free fatty acid (FFA) levels, another contributor to IR, and induce a proinflammatory state by elevating the levels of cytokines, such as interleukin

(IL)-1β, IL-6, IL-17, and C-reactive protein (CRP), which can in turn promote IR.[158–160] The proinflammatory effect of sleep deprivation may be persistent; data from the Whitehall II study showed that each hour decrease in sleep duration per night was associated with higher levels of CRP (8.1%) and IL-6 (4.5%) averaged across measures both at baseline and after an average of 5 years of follow-up.[161] Decreased levels of glucagon-like peptide-1, which augments glucose-induced insulin secretion in response to ingestion of nutrients, were seen in experimentally sleep-restricted women[150] and could be one of the mechanisms by which sleep restriction increases IR. Interestingly, the metabolic alterations of sleep deprivation are not just seen at the systemic level – compared to normal sleep conditions, partial sleep deprivation leads to impairment of phosphorylation in adipocytes of the serine/threonine kinase Akt (part of the insulin signaling pathway), indicating insulin resistance at the cellular level.[162] Recent findings suggest that experimental sleep restriction can lead to tissue-specific epigenetic changes in the expression of circadian clock genes and the transcriptome affecting a wide variety of biological processes, including chromatin modification, gene expression regulation, macromolecular metabolism, and inflammatory, immune, and stress responses, providing yet another link between sleep deprivation and tissue responses.[163,164]

If sleep restriction exerts a causal impact on insulin and glucose homeostasis, then sleep extension should exert the opposite impact. Fewer experimental sleep extension studies have been conducted, but the results of those few studies that have been carried out are encouraging. Experiment sleep extension has been found to improve insulin sensitivity and reduce cortisol levels.[155,165,166] The experimental sleep restriction and extension data point to the causal impact exerted by acute changes in sleep duration on IR and glycemia and may help explain the associations between insufficient sleep duration and T2DM risk in epidemiological studies.

Hypertension

Experimental sleep restriction in adults raises blood pressure, especially nocturnal blood pressure, likely related to blunting of the nocturnal blood pressure dipping that normally occurs during sleep.[167–170] Possible mechanisms include elevations in cortisol and increased catecholamine production (as discussed above in the sections on alterations in sleep duration and obesity, insulin resistance and glucose homeostasis) leading to an increased sympathetic nervous system activity systemically, in combination with a decreased

parasympathetic activity, an increased muscle sympathetic nerve activity and resetting of the arterial baroreflex (with decreased sensitivity), an induced endothelial dysfunction, and impaired vasodilatation.[167,168,171–173] Acute sleep restriction also reduces heart rate variability.[174] More recently, acute sleep restriction has been found to promote arterial stiffness as measured by pulse wave velocity (PWV) (a marker of CVD risk) and to lead to subclinical left ventricular diastolic functional changes, with increases seen in myocardial performance index, isovolumetric relaxation time, and deceleration time values.[175,176]

Dyslipidemia

The impact of acute sleep restriction on serum lipids has been somewhat inconsistent across studies, with one study showing no impact of experimental sleep restriction on lipids in healthy normal-weight adults aged 30–45 years (in the setting of controlled caloric intake),[177] one study showing improvement in triglyceride levels in normal-weight young adult men following sleep restriction,[178] and another study showing increase in total cholesterol and LDL levels (as well as neutrophil levels) in healthy postmenopausal women receiving hormone replacement therapy following sleep restriction,[179] while yet another study of normal-weight young men (aged 22–29 years) showed a postsleep restriction rise in the levels of myeloperoxidase-modified LDL,[180] a substance that accumulates in macrophages to form foam cells and is thought to be atherogenic.[181] Very recently, an experimental partial sleep restriction study of 14 subjects vs seven controls found that sleep restriction decreased the expression of genes encoding cholesterol transporters and increased expression in pathways involved in inflammatory responses, although circulating LDL decreased rather than increased in the sleep-restricted subjects.[182] Metabolomic analyses in 2,739 adults also found that those reporting chronically insufficient sleep had lower circulating large LDL.[182] These findings suggest that while the impact on lipids is not necessarily apparent in acute sleep restriction, prolonged or chronic sleep deprivation can modify inflammatory and cholesterol pathways at the level of gene expression and serum lipoproteins, inducing changes that increase cardiometabolic risk.

Notwithstanding the limitations inherent to short-term rather than prolonged manipulation of sleep, the experimental sleep restriction and the few experimental sleep extension studies discussed above in the experimental evidence/pathophysiology sections examining sleep duration impact on obesity, insulin resistance and T2DM risk confirm the causal role of sleep restriction (though not the risk of long sleep) in the adverse metabolic changes, which predispose to the MetS and CVD.

Children and adolescents

Compared with the relatively more abundant body of adult data, very few experimental sleep restriction studies examining metabolic sequelae have been performed in school-age children, preadolescents, or even adolescents. The few published studies are discussed in the sections below are discussed in the sections below.

Prepubertal children

A recent study of mild experimental sleep restriction in 25 typically developing 8–12-year-old children found that attention-deficit hyperactivity symptoms increased, but there was no difference in overall activity levels, though the variability in activity increased.[183] A crossover sleep restriction/sleep extension study by 1.5 h/night ×1 week each in a cohort of 37 8–11-year-old children found that leptin levels were lower and children consumed ~134 kcal/d less and weighed 0.22 kg less in the sleep-extended condition than in the sleep-restricted condition.[184]

Adolescents

Adolescents with shorter actigraphically measured sleep duration (<8 hours) consume more calories than their longer-sleeping peers, and a higher percentage of calories derives from fat and a lower percentage from carbohydrates.[185] Beebe et al[186] restricted 41 typically developing adolescents, aged 14–16 years, to sleeping 6.5 h/night for five nights vs sleeping 10 h/night and found that their diets had a higher glycemic index and glycemic load and a trend toward more calories and carbohydrates, with no differences in fat or protein consumption. Another crossover sleep restriction/sleep extension study in 31 adolescents similarly found that after mild (6.5 h/night) experimental sleep restriction, the participants found sweet foods and desserts were more appealing, although their subjective hunger ratings did not change.[187] A pilot study of nine obese adolescents found that 1 hour of sleep restriction per night for 1 week mildly raised insulin and glucose levels and, unlike the adult data, led to a higher rather than lower leptin levels; participants also gained a mean of 0.8 kg.[188] In a more intensive sleep restriction study, 21 lean adolescent boys were restricted to sleeping 4 hours for three nights, leading to a significant increase in fasting and nonfasting insulin levels, but without any changes in fasting or postchallenge glucose levels, awakening cortisol response, daytime or 24-hour sympathovagal balance, and glucagon or norepinephrine levels; 24-hour epinephrine levels were lower in the sleep-restricted stage vs sleep recovery stage.[189] These limited studies compellingly reinforce the need for more experimental data in children prior to drawing any conclusions.

Obstructive sleep apnea and cardiometabolic risk

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a very common condition among obese adults and children.[190,191] OSA consists of repetitive upper airway collapse during sleep,[192] leading to recurrent oxyhemoglobin desaturation, sleep fragmentation, and hypercapnia.[193] A wide body of literature in adults now exists showing that OSA contributes to cardiometabolic risk independently of or additively to obesity–IR,[194,195] the MetS (presence or components thereof),[196,197] incident T2DM risk,[198,199] poor glycemic control in T2DM,[200–202] incident CVD,[203] stroke,[204] and cardiovascular[205] and all-cause[206] mortality. However, the differences between pediatric and adult OSA showcase the fact that these conditions are related but not identical disorders, with possible differences in attendant metabolic risk. Pediatric data about the association between OSA and metabolic risk is more contradictory. In addition to epidemiological data, numerous interventional studies, with the gold standard continuous positive airway pressure (CPAP) in adults and adenotonsillectomy (T&A) in children, have now been performed to examine causality. These data are discussed in the following paragraphs, following some background information about OSA.

OSA frequency across the lifespan, sex differences, and the impact of androgens

The diagnostic criteria for OSA differ between adults and children. In adults, OSA is frequently defined as having an apnea hypopnea index (AHI; number of events of decreased and/or complete cessation of airflow) or a respiratory disturbance index (RDI) >5 events/h total sleep time (TST),[207] while in children, the AHI cutoff for OSA has been variably defined >1 events/h, >1.5 events/h, or >2 events/h TST, but OSA is considered mild if AHI is <5 events/h TST.[208] This difference further reinforces the motto that "children are not small adults".

The prevalence of OSA across the lifespan differs among the sexes. In prepubertal children, OSA prevalence is nearly equal among the sexes,[209] while in adolescence, a male-predominant pattern becomes manifest.[210] In adults, OSA is considerably more common in men than in premenopausal women, and OSA in women is more likely to be milder.[203] However, the prevalence and severity of OSA in women rises strikingly after menopause.[211] These sex differences, which emerge in puberty and which are partially though not fully negated after menopause,[212] may be in part mediated by the higher androgen levels in men and consequent effects on both airway structure and airway rigidity – testosterone increases upper airway collapsibility.[213]

For all of these reasons, it is important to examine the metabolic effects of OSA separately in prepubertal children vs adolescents and separately in adult men vs premenopausal women.

Epidemiological data

Adults

OSA and obesity

OSA prevalence is estimated to be ~26% in all US adults aged 30–70 years and as high as 45% in obese adults.[214,215] Conversely, >70% of adults with OSA are obese.[216] Thus, obesity, in particular central obesity, clearly predisposes to the development of OSA.[203,217] Numerous studies have shown the development or worsening of OSA with increasing weight and, conversely, substantial improvement in OSA with weight reduction. Supporting the causal role of obesity in OSA, weight loss (especially in the context of bariatric surgery) ameliorates OSA, though such surgical interventions do not necessarily lead to full OSA resolution.[218] However, the relationship between OSA and obesity is not unidirectional – OSA itself may cause further weight gain and predispose to visceral adiposity.[215,219,220] A randomized controlled trial testing the impact of CPAP vs sham CPAP on weight in 1,105 adults with OSA found that those treated with CPAP gained an average of 0.35±5.01 kg, with the degree of weight gain proportional to the degree of CPAP adherence, while those treated with sham CPAP lost a mean of 0.70±4.03 kg.[221] The weight increase may be due to a treatment-related decrease in sleep-related energy expenditure, which is typically elevated in OSA.[222]

OSA associations with the MetS

Having OSA increases risk of having the MetS and its various components;[196,197] with increasing OSA severity, the number of MetS features increases independently of BMI.[223]

OSA and insulin sensitivity, beta cell function, and T2DM

An extensive body of literature has now demonstrated that OSA is associated with an increased IR in adults independently of obesity.[194–196,223,224] OSA has also been found to associate with impairment of beta cell function (having a lower disposition index on intravenous glucose tolerance test).[225] Similarly, the Sleep Heart Health Study, a multicenter cohort study examining the cardiovascular and other consequences of sleep-disordered breathing, also found that increasing OSA

severity associated with incrementally greater OR of glucose intolerance.[196] These data suggest that OSA may increase the risk of T2DM incidence; indeed, several cross-sectional studies have reported that OSA associates with increased OR of having T2DM independently of obesity.[226,227] The Wisconsin Sleep Cohort Study (a longitudinal study of 1,387 adult participants followed for more than two decades) found a significant association between moderate–severe OSA presence and OR of T2DM even adjusting for obesity (OR 2.3).[228] Several additional longitudinal studies have also shown that having OSA at baseline increases the likelihood of incident T2DM over time independently of other risk factors,[224,228–230] an effect found to be more notable in women than in men in at least one study.[231] The Sleep Heart Health Study also found that the association between OSA severity and likelihood of having T2DM was more prominent in younger adults rather than in older adults,[203] possibly because other T2DM risk factors may play a larger role in diabetes prevalence in the latter. A recent population-based study examining the OSA–T2DM association in 8,678 adults with OSA followed for a mean of 67 months found a cumulative T2DM 5-year incidence rate of 9.1% (95% CI 8.4%–9.8%) over 5 years in the cohort (n=1,017), with a 30% higher risk in those with severe OSA (AHI >30 events/h TST) vs those without OSA (AHI <5 events/h TST).[232] Additionally, those with T2DM and OSA usually had poorer glycemic control than those without OSA.[200–202]

The converse relationship between OSA and T2DM has also been observed – ie, the prevalence of OSA among adults with known T2DM ranges between 58 and 86%,[233] substantially higher than recent estimates from a community-based cohort without T2DM of 17% in women and 34% in men.[214] As these two conditions are so frequently comorbid, the International Diabetes Federation recommends that a patient who presents with one condition should be screened for the other.[234]

Despite the epidemiological data described earlier in the Epidemiology of OSA segment of this review, the metabolic, the metabolic impact of OSA treatment is somewhat variable. CPAP therapy in adults has been shown to improve insulin sensitivity in many studies,[235,236] although some studies show no impact on insulin sensitivity,[237] and one recent study even found an increase in IR following initiation of CPAP treatment (which appeared to be primarily due to CPAP-associated weight gain).[238] Recently, a randomized, parallel-group 6-month trial of CPAP, weight loss, or both CPAP and weight loss in obese adults with OSA found that IR decreased only in response to weight loss; there was no independent impact of CPAP therapy on insulin sensitivity.[237]

Data regarding the impact of CPAP therapy on lowering blood glucose levels and HbA1C have also been somewhat unpredictable,[239,240] though a recent study found lowering of HbA1C in adults with T2DM and OSA who received CPAP therapy when compared to those who did not receive CPAP therapy.[241]

In summary, although epidemiological data associating OSA with IR and T2DM risk in adults are substantially and relatively consistent, the impact of OSA treatment on insulin sensitivity and glycemia in adults is more contradictory, and it appears that the CPAP-associated weight gain may confound the impact of treatment on insulin and glucose metabolism.

Hypertension

A number of cross-sectional and longitudinal studies have found that OSA associates with an increased risk of hypertension (both systolic and diastolic) independently of BMI.[242–245] The Wisconsin Sleep Cohort Study found a linear relationship between 24-hour blood pressure and AHI, independent of potential confounders, including the degree of obesity.[246] However, at least one study found no association between OSA and hypertension independent of other risk factors.[247] One of the ways in which OSA may affect blood pressure may relate to a blunting of the normal nocturnal blood pressure dipping, which can be seen in adults with OSA who are otherwise normotensive as well as in those with OSA and frank hypertension.[248–250] The lack of blood pressure dipping does not seem to be solely mediated by poor sleep quality[250] but appears to preferentially relate to the RDI, a measure of respiratory disturbance in sleep, or more specifically to the intermittent hypoxia (IH) that results from the respiratory disturbances.[248]

As might be expected given the abovementioned data, there is a high prevalence of OSA in adults with drug-resistant hypertension, with prevalence being reported as high as 83%.[251] Indeed, OSA has been deemed the most common cause of secondary hypertension in adults with drug-resistant hypertension.[252]

A number of studies have examined the impact of CPAP therapy on blood pressure (BP); several meta-analyses concluded that CPAP had significant but modest effects on blood pressure, with more significant improvements seen in those with more severe OSA.[253–255] CPAP therapy for 12 weeks in adults with drug-resistant hypertension and OSA led to a significant decline in 24-hour mean BP and diastolic BP and to improved nocturnal BP pattern.[256] Interestingly recent meta-analysis found that intraoral appliance devices (which are generally better tolerated than CPAP) may be as effective in improving BP in adults with OSA.[257]

These data suggest that adults with OSA should be regularly screened for hypertension and, conversely, that adults with drug-resistant hypertension should be screened for OSA.

Dyslipidemia

OSA is associated with an increased risk of atherogenic dyslipidemia in adults. A number of cross-sectional studies in different populations have found higher total cholesterol and LDL cholesterol levels, higher triglycerides levels, lower HDL levels, or all of the above in adults with vs without OSA.[258–262] The Sleep Heart Health Study found an inverse association between the RDI and HDL levels in all participants and a positive association between the RDI and triglycerides in younger men and women only.[203] There is some evidence that both sleep fragmentation and IH contribute to dyslipidemia: a recent cross-sectional study in the People's Republic of China found that the associations between OSA and high LDL levels were driven by sleep fragmentation,[259] while two other studies have recently found that the AHI associates with dyslipidemia.[260,263]

MetS

Multiple cross-sectional studies have reported an epidemiological association between OSA and the MetS[261,264] and that greater OSA severity increases the OR of having the MetS.[265] These associations have since been found in a number of other cohorts.[266] The frequency of MetS in adults with OSA is quite high, with estimates ranging from 43% in those with mild–moderate OSA to 81% in those patients with severe OSA.[267] Conversely, OSA is quite frequent in those patients with MetS: in a cohort of 228 obese adults, the frequency of OSA in the MetS was 60%.[197]

Atherosclerosis, arterial stiffness, CVD, stroke, and cardiovascular and all-cause mortality

OSA has been associated with an increased risk of atherosclerosis, independently of the degree of obesity. Several adult studies have now identified increased carotid intima media thickness (cIMT; a surrogate measure of atherosclerosis) in adults with OSA, and duration of hypoxemia has been strongly associated with cIMT.[268] Even in the context of existing dyslipidemia, having OSA was associated with an increased risk of the presence of atherosclerosis.[263]

OSA is also associated with an increased arterial stiffness, a consequence of decreased vascular compliance which occurs as a result of a combination of structural changes in arterial walls and endothelial dysfunction.[269–271]

Given the associations between OSA and a multitude of risk factors, it should come as no surprise that OSA also increases the risk of cardiovascular and cerebrovascular diseases. The Sleep Heart Health study found that OSA is a significant, independent risk factor for CHD and heart failure in men aged 40–70 years but not in older men and women,[272] that significant increases in all-cause mortality and CHD-related mortality are attributable to OSA (especially in men aged 40–70 years),[273] and that OSA (specifically, obstructive AHI) associated significantly with incident ischemic stroke; the increased stroke risk in men was seen even in those with very mild OSA (AHI 5 events/h sleep and wake-up), while in women, an increased risk of incident stroke was seen only in those with fairly severe OSA (AHI >25 events/h TST).[274] The hypoxemia associated with OSA also increases the risk of sudden cardiac death.[275]

In summary, epidemiological evidence in adults shows that OSA increases the risk of cardiometabolic morbidities in the context of obesity, but that it also contributes independently toward the risk of hypertension, IR, and T2DM, variably to dyslipidemia, overt MetS, arterial stiffness, atherosclerosis, incident CVD, stroke risk, and CVD-related mortality and all-cause mortality.

Children and adolescents

Pediatric OSA appears to have two different phenotypic variants, which we have previously termed as OSA Type I and OSA Type II.[276] OSA Type I, which predominates in younger children and affects males and females near-equally, relates predominantly to the presence of lymphadenoidal hypertrophy leading to airway obstruction rather than to obesity. In contrast, OSA Type II predominates in obese prepubertal children, adolescents, and adults, is seen much more commonly in males than in females, primarily develops in the context of obesity, and bears a greater resemblance to the OSA clinical phenotype seen in adults, even though lymphadenoidal hypertrophy is still an important part of the pathophysiology of OSA.[277] A recent publication from the Cleveland Children's Sleep and Health Study found that a majority of cases of childhood OSA remit and that most cases of OSA in adolescents represent incident cases, supporting the hypothesis of phenotypically different childhood OSA variants.[278] It is possible that OSA type may confer a different underlying predisposition to metabolic sequelae.

Pediatric OSA and obesity

As in adults, obese children are at increased risk of OSA,[279] with higher risk in obese African American vs Caucasian children;[280,281] a recent community-based study of OSA

prevalence in obese Spanish children aged 3–14 years found a prevalence of 21.5%,[282] considerably higher than the estimate in all children of 7.5%. However, the obesity-related increased risk of OSA may differ in prepubertal children vs adolescents.[283] Also, several studies have found that obesity increases OSA risk significantly more in adolescents compared to younger children,[284,285] that having OSA may be associated with visceral adiposity in adolescents,[283] and that bariatric surgery in extremely obese adolescents leads to significant improvement in sleep-disordered breathing.[286]

IR and glucose metabolism

In opposition to the adult data, the relationship between OSA and IR in children is more inconsistent. Several pediatric studies have shown no association between OSA and IR or MetS risk,[287–294] while others found associations between the presence or severity of OSA and IR and between OSA components (RDI, mean oxyhemoglobin saturation, and duration of hypoxemia) and insulin sensitivity or glycemia independent of BMI.[291,293–296] Another study did not find an association between OSA and IR overall but did report that in children with OSA, there was an association between hypoxemia and IR.[297] Yet another study noted an association between OSA and IR only in obese pubertal children (ie, adolescents) and not in nonobese or prepubertal children.[295] In the largest study published to date (n=459) examining these associations in children and preadolescents, we found that sleep fragmentation was significantly associated with IR and that in the context of obesity, OSA was associated with an increased IR.[126] Treatment of OSA via adenotonsillectomy has been found to improve IR in some but not all studies; however, the majority of treatment studies have focused on prepubertal children, in whom IR is seldom manifesting at baseline.[289,298,299]

OSA has been associated with higher fasting glucose levels in adolescents.[300] The data on OSA and T2DM in children are quite scarce, with only one study having examined this particular question to date: Shalitin et al compared the rate of OSA among adolescents and young adults with obesity, impaired glucose tolerance, and T2DM and found frequencies of OSA (defined as AHI >5 events/h TST) of 18%, 25%, and 46% respectively, although the differences did not achieve statistical significance due to the small sample size.[301] Further studies are needed to assess the association between OSA and risk of T2DM in the pediatric population.

Hypertension

Many (though not all[302]) studies have shown that OSA associates with elevated daytime and nocturnal BP in children independently of obesity,[303,304] and the community-based Tucson Children's Assessment of Sleep Apnea found that in preadolescents, systolic BP and diastolic BP (DBP) were associated with poor sleep quality and the RDI and, for DBP only, obesity.[305] Even in the absence of OSA, poor sleep quality in adolescents associates with higher blood pressure and prehypertension.[112] OSA has also been shown to be an independent predictor of nocturnal hypertension in children,[306] which relates to oxyhemoglobin desaturation.[304] Diastolic BP may be more impacted than systolic BP.[307] Oxyhemoglobin desaturation has also been shown to correlate with a decreased nocturnal BP dipping.[303]

Treatment of OSA with T&A has been shown to improve BP in children in some but not all studies;[308,309] the multicenter randomized study on adenotonsillectomy for OSA in children aged 5–9 years (Childhood Adenotonsillectomy Trial) did not find any improvements in BP after T&A,[310] although it should be stressed that these were prepubertal children with relatively mild OSA. Thus, the data on OSA and hypertension in children are somewhat mixed, and further studies are needed.

Dyslipidemia

Children with OSA are more likely to have abnormal lipids than children without OSA in some studies,[311,312] though other studies have found that obesity rather than OSA was the primary mediator of dyslipidemia.[288] The impact of T&A on lipids in children has been variable – some studies have shown increased HDL,[298] lower both LDL and apolipoprotein B,[289] and/or total cholesterol,[299] while others have shown no impact of T&A on lipid levels.[313]

MetS

OSA has been associated with the MetS in children and even more strongly in adolescents:[314] in adolescents, the MetS was seen in 16% of those without OSA and in 59% of those with OSA, a 6.5-fold increased risk after adjusting for confounders, and similarly, that 25% of those with OSA had the MetS.[293] This study also found that the frequency of respiratory events, the degree of oxyhemoglobin saturation, and sleep efficiency were all associated with an increased MetS risk. A more recent case–control study of obese children found that OSA was more common in those with vs without the MetS.[315] A study of 104 obese children and adolescents, of whom 58% were prepubertal, found an association between oxyhemoglobin desaturation measures and MetS risk.[314] A recent meta-analysis found that OSA associated with a 2.3-fold increased RR of the MetS.[316] However, not all studies

are consistent: at least one study in obese prepubertal as well as pubertal children found no association between obesity and the MetS.[317] Finally, no studies to our knowledge have examined the impact of treating OSA on MetS frequency or risk in children. Most likely because of the long nature of follow-up that would be required. However, the cross-sectional data suggest an interaction between pediatric MetS and OSA, particularly in adolescents, in which one increases the risk for the other, and suggest that in adolescents diagnosed with either the MetS or OSA, screening for the other may be warranted.

Endothelial dysfunction, atherosclerosis, and arterial stiffness

While adult CVD likely has its roots in childhood,[318] overt cardiovascular or cerebrovascular disease is extremely rare during early life. However, antecedents of CVD, such as endothelial dysfunction, subclinical atherosclerosis, and arterial stiffness, have been reported in childhood.[319–323] Similar to adults, OSA is associated with all such predisposing risk factors, but in children, the relationships are not as overtly established. Our group has published extensively on the obesity-independent association between OSA in childhood and endothelial dysfunction, a risk factor for atherogenesis: blunting of postocclusive hyperemia has been reported in both nonobese and obese school-age children with OSA.[324–326] Pediatric data regarding endothelial dysfunction have been gathered in prepubertal school-age children; no study of which we are aware has examined endothelial dysfunction in association with OSA in adolescents. Early arterial alterations with impaired flow-mediated dilation have also been reported in children with OSA and severe obesity.[327]

The data about OSA and reversible endothelial dysfunction would seem to support a role for pediatric OSA as a contributor to the pediatric roots of adult CVD; however, the more overt measures of CVD (atherosclerosis and arterial stiffness), which are associated with OSA in adults, do not necessarily exhibit the same associations in children. Very few pediatric studies have examined the associations between OSA and these more overt cardiovascular risk factors, with somewhat contradictory results. Two pediatric studies (including a mixed child–adolescent cohort and an adolescent-only cohort) found no association between OSA and cIMT as a surrogate measure of atherosclerosis independently of obesity,[328,329] but a more recent study of 40 children with adenotonsillar hypertrophy aged 5–10 years and 36 age- and BMI-matched controls found a higher cIMT in the adenotonsillar hypertrophy group.[330] One study of 30 children and adolescents with primary snoring vs

BMI-, age-, and sex-matched controls found a greater degree of peripheral arterial stiffness as measured by brachial–ankle PWV in those with primary snoring,[329] but two subsequent studies found no association between OSA and central arterial stiffness and carotid–femoral PWV.[330,331] Finally, one study of preschool-aged and school-aged children with OSA found a reduced left ventricular ejection fraction (although no clinical signs of heart failure) and that in some of the subjects, treatment of OSA improved left ventricular ejection fraction.[332]

These data illustrate that while OSA in children may be associated with early measures of CVD risk, such as obesity, IR, hypertension, dyslipidemia, the MetS, and endothelial dysfunction, which are variably reversible upon treatment of OSA (generally less reversible in the obese), there is not necessarily a consistent progression to an association between OSA and vascular changes prior to adulthood. Future longitudinal and interventional studies are needed to examine these associations in larger pediatric cohorts, separating out children and adolescents.

Experimental data and pathophysiology
Adults

OSA has been associated with sympathetic/adrenomedullary activation as well as (more variably) with activation of the hypothalamic–pituitary–adrenal (HPA) axis.[333,334] OSA is also a well-recognized proinflammatory state, accompanied by increased levels of CRP and other inflammatory cytokines.[335–338] In addition, activation of macrophages is seen in OSA; these activated macrophages in turn reduce the activity of peroxisome proliferator-activated receptor-gamma (a negative regulator of inflammation and regulator of lipid and glucose metabolism) in alveolar macrophages even in the absence of overt lung disease, to a greater degree than seen in obesity alone.[339] There is also an improvement seen in a number of inflammatory factors upon OSA treatment with CPAP.[340,341]

As described earlier in the OSA epidemiology section of this review, OSA is also associated with a number of cardiometabolic sequelae independently of obesity in adults, to which the sympathetic activation, HPA axis activation, and inflammation variably contribute.

Obesity

It is well-recognized that obesity predisposes to OSA development, and in fact, specific fat depots (upper airway, tongue, and abdominal adipose deposition) appear to predispose to OSA.[342–344] However, OSA may also predispose to obesity due to daytime somnolence, decreased activity,

and decreased sleep duration, as well as due to neurohumoral changes seen in OSA, including elevation in the orexigenic hormones ghrelin and orexin and suppression of the anorexigenic hormone leptin (seen in many though not all studies of adults with OSA).[343,345–347] As discussed in the OSA epidemiology section above, although there is a strong association between OSA and obesity, treatment of OSA in adults may result in weight gain, possibly due to a decrease in resting energy expenditure (which has been found to be proportional to the decrease in AHI and in urinary catecholamine production and also to CPAP adherence),[348] suggesting that decreased sympathetic activation promoted the weight gain with CPAP therapy. However, CPAP-induced weight gain in adults with OSA may not be due to fat mass gain: lean body mass has been found to increase in both sexes with CPAP treatment, which in the male participants may have been mediated by increased growth hormone levels, as levels of insulin-like growth factor-1 (produced in response to growth hormone) increased in the men treated with OSA.[349] Regardless of effect on total body weight, OSA treatment with CPAP may lead to a reduction in visceral fat even in the absence of significant weight loss.[220] Treatment of OSA may also induce neurohumoral changes, which can predispose to changes in weight, such as lower leptin and/or ghrelin levels.[220,238] However, whether these findings translate to behavioral differences is uncertain; a recent study found no change in diet (or in physical activity patterns) in adults with OSA treated with CPAP.[350]
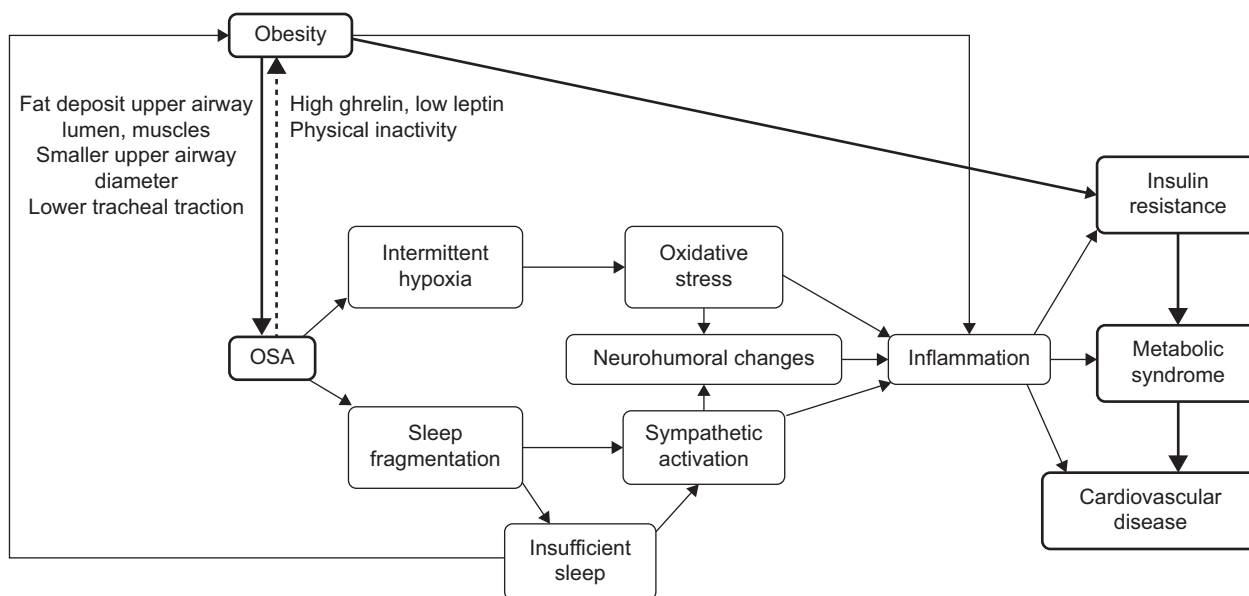
OSA and the MetS

When examining the pathophysiology of the association of OSA with the MetS, this process essentially entails examining the impact of OSA on MetS components: IR, dysglycemia, hypertension, and dyslipidemia.

OSA, IR, and T2DM

Classically, OSA is thought to adversely impact glucose metabolism via a combination of IH and sleep fragmentation.[225,351,352] Potential underlying mechanisms for the OSA–IR association include onset and propagation of oxidative stress and inflammation with the elevation of inflammatory mediators, such as CRP and proinflammatory cytokines, increased corticosteroid levels, sympathetic activation, catecholamine elevations, and/or alterations in adipokines.[353–356] Some of the putative relationships between OSA and IR (as well as its sequelae) are illustrated in Figure 1.

Evidence for causality is supported by an experimental study in which hypoxia was induced in healthy adult volunteers by decreasing oxygen saturation to 75% (vs 96% in control subjects) for 30 minutes while undergoing a euglycemic clamp; the acute hypoxia induced an increase in plasma epinephrine concentration, heart rate, and symptoms of anxiety – signs of sympathetic activation – and also a decreased rate of dextrose infusion, suggesting acute IR.[357] Also supporting the causality of the link between OSA and IR, several studies have shown that CPAP therapy improves IR,[358] including IR as measured by the gold standard hyper-

Figure 1 Putative relationships between OSA and obesity, insulin resistance, the metabolic syndrome, and cardiovascular disease.
Abbreviation: OSA, obstructive sleep apnea.

insulinemic–euglycemic clamp,[235] although the improvement in IR may take several months to manifest.[235] The improvement in insulin sensitivity and glycemia may be mediated by changes in plasma leptin,[200] adiponectin (an insulin-sensitizing adipokine),[359] or by improvements in sympathetic activation and/or HPA activation as as described earlier in the OSA epidemiology section.

As discussed in the OSA epidemiology section above, results of studies examining the impact of CPAP therapy on glycemia and T2DM in adults are somewhat contradictory: while many studies show improvement in HbA1C and in postchallenge glucose levels in adults with OSA after CPAP therapy, some show no effect.[199,200,240,360–362] The impact of OSA treatment on glycemia may relate to the degree of underlying metabolic derangement, as a recent study found no improvement in HbA1C following CPAP therapy in 298 adults with relatively well-controlled T2DM (HbA1C <8.5%).[363] Some of the differences in study results may also be related to the adherence to CPAP therapy: suboptimal adherence (<4 h/night) may not be sufficient to improve glycemia, as it would not sufficiently impact the AHI in rapid eye movement sleep, which is an independent predictor of HbA1C in adults with T2DM.[201]

Hypertension

The connection between OSA and hypertension has a number of potential mediators. OSA is well-known to lead to chronic IH, which can be severe, and to sympathetic nervous system activation, with elevations in catecholamines and increased sympathetic nerve activity as measured by microneurography.[222,364,365] Sleep fragmentation with recurring overnight arousals is also associated with pulsatile and increased cortisol release.[333] Nocturnal IH can also be associated with a disruption of the autonomic and hemodynamic changes seen during normal sleep,[366] including increased sympathetic activity in peripheral blood vessels leading to vasoconstriction and acute increases in blood pressure.[367] The OSA–hypertension link may also be mediated in part by the renin–angiotensin–aldosterone axis; primary hyperaldosteronism may be more common in adults with OSA and hypertension.[368] The causality of the association between hypoxia and blood pressure is supported by experimental studies in human volunteers, which showed that chronic hypoxia induced by altitude changes increases sympathetic activation and norepinephrine levels[369] and that even an acute 6-hour exposure to IH elevates high blood pressures in normotensive adults, an elevation which was blocked by the type I angiotensin receptor antagonist losartan.[370]

Treatment of OSA with CPAP has been shown to improve BP,[255,363,371] restore normal nocturnal BP patterns, and prevent nocturnal blood pressure surges in many but not all studies.[254,372,373] A placebo-controlled CPAP vs sham-CPAP trial found that CPAP was especially effective at improving nocturnal BP in those using CPAP for >3.5 h/night and those with more frequent oxyhemoglobin desaturations,[374] supporting the causal role of hypoxemia in addition to sympathetic activation and the renin–angiotensin–aldosterone axis in causing OSA-related hypertension.

Hyperlipidemia

OSA-related dyslipidemia is thought to be mediated by chronic IH; evidence from murine models shows that experimental IH leads to hyperlipidemia, upregulation of the expression of genes promoting hepatic lipid synthesis, and in the presence of diet-induced dyslipidemia, chronic IH leads to the development of atherosclerosis.[375–378]

The increased cardiovascular risk of OSA has been attributed, at least in part, to the lipid abnormalities induced by IH.[378] The mechanism for the impact of IH on lipids may be due to the IH-mediated increases in gene expression of the hypoxia inducible factor family, generation of reactive oxygen species, stearoyl-coenzyme A desaturase-1, altered lipid peroxidation, and sympathetic system dysfunction.[379,380] Catecholamines, whose levels are elevated in OSA, modulate the activity of adipocyte hormone-sensitive lipase via their counter-regulatory effects of antagonizing insulin, leading to the lipolysis and consequent breakdown of triglycerides into free fatty acids (FFA) and glycerol, which then will be resynthesized in the liver to form very low density lipoprotein (VLDL).[381] Supporting this putative mechanism, adults with OSA have elevated levels of FFA;[382] these nocturnal surges in hepatic FFA production in adults with OSA may accelerate CVD progression and concomitant cardiac dysfunction.[383] Additionally, LDL clearance may be impacted on OSA, so that LDL-B (a LDL form that is more resistant to being cleared from the circulation) can stay in the circulation for an extended period of time, increasing the risk that LDL could be oxidized and subsequently lead to vascular damage.[383] Finally, acute hypoxia decreases the transcription of lipoprotein lipase and peroxisome proliferator-activated receptor-gamma leading to increased triglyceride levels in mice.[384] However, the pathophysiology of dyslipidemia is multifactorial, and the connections with OSA do not necessarily translate to treatment effects: several studies have found no impact of CPAP therapy on lipids independent of weight loss.[237,385] Thus, the ramifications of OSA interactions with lipids in the context of obesity remain to be fully elucidated.

MetS

A randomized crossover trial of OSA with CPAP vs sham CPAP was conducted in 86 adults, 87% of whom had the MetS; CPAP treatment was associated with significant decreases in systolic and diastolic BP, total cholesterol, LDL, triglycerides, and HbA1C, and the MetS resolved in 13% of patients undergoing CPAP therapy vs 1% of those undergoing sham therapy.[386] Other studies have shown that CPAP therapy improves the MetS,[386] likely via the mechanisms discussed earlier for individual MetS components.

OSA and CVD risk

There may be a number of different routes by which OSA contributes to CVD risk, in addition to the associations with obesity, IR, T2DM, hypertension, dyslipidemia, and the MetS. One such connection may reside in the presence of endothelial dysfunction, a state of impairment of endothelial vasodilatation, which promotes atherogenesis. Several studies have shown that OSA is associated with endothelial dysfunction independently of obesity[387,388] and that OSA treatment with CPAP improves endothelial function;[389,390] the beneficial effects of CPAP therapy on endothelial function are quickly reversed if CPAP therapy is withdrawn.[391] Similarly, as previously discussed, OSA can increase the risk of atherosclerosis as well as lymphocyte activation,[392] increase circulating endothelial microparticles, and reduce endothelial progenitor cells among other mechanisms.[393] Long-term CPAP therapy can reverse atherosclerosis.[394] OSA also increases the risk of arterial stiffness, mediated by hypertension, respiratory events, and desaturation,[395] suggesting a role for IH in its pathophysiology. CPAP therapy can improve cIMT and PWV, correlating with reductions in urinary catecholamines and in CRP, respectively; these results suggest that sympathetic activation is a significant contributor to the association of OSA with atherosclerosis, while inflammation plays more of a role in arterial stiffness.[396] Other studies have since shown improvements in arterial stiffness with CPAP therapy independently of age, BMI, and other risk factors,[397–399] with one study identifying an association with changes in sympathovagal balance (reduced sympathetic activity) but not with CRP.[400]

Thus, OSA increases the risk of incident CVD,[401] increases the risk of secondary CV events,[402] and decreases the OR of survival of cardiovascular and cerebrovascular events;[403] however, effective CPAP therapy can significantly reduce the OR of incident and secondary CVD and reduce cardiovascular mortality.[401,402]

The preponderance of evidence in adults suggests that OSA is a significant and independent cardiometabolic risk factor operating through a variety of mechanisms related to sympathetic activation, hypoxemia, inflammation, neuroendocrine changes, and endothelial and vascular dysfunction. Although CPAP therapy may be associated with weight gain rather than weight loss, effective OSA treatment with CPAP (only with adequate adherence and if used for least 4 h/night) may reverse some of these adverse cardiometabolic changes caused by OSA.

Children and adolescents

Studies examining the impact of OSA treatment upon metabolic derangements in children have been somewhat contradictory, with some showing improvements and others showing no effects. One possible explanation for the contradictory findings in the pediatric literature is that the associations between OSA and metabolism change during puberty: the majority of pediatric studies have either focused on prepubertal children or studied a mixture of prepubertal children and adolescents, thereby not allowing for the differential phenotypes to manifest more clearly. As experimental studies inducing hypoxia cannot ethically be performed in children, the majority of pathophysiological data derive from cross-sectional studies and pre–post interventional studies.

Pediatric OSA and obesity

As noted earlier in the OSA epidemiology section, obesity is strongly associated with the risk of OSA[404] (especially in older children and adolescents), due to anatomical changes. However, OSA also predisposes to the worsening of obesity due to daytime sleepiness, decreased physical activity, and neuroendocrine changes, such as resistance to the anorexigenic hormone leptin;[405–407] data regarding associations between OSA and levels of the orexigenic hormone ghrelin in children are inconsistent.[406,407] Treatment of OSA (primarily T&A, but CPAP in one study) may improve leptin and possibly ghrelin levels, although again, data are somewhat contradictory.[407] However, despite these favorable changes, treatment of OSA in children does not necessarily lead to weight loss; as in adults, a number of studies have reported post-T&A weight gain in children and adolescents,[408,409] likely due to a reduction in energy expenditure during sleep as well as other hormonal changes. However, despite the weight gain, treatment of OSA may have favorable metabolic implications.

Pediatric OSA and the MetS

IR in pediatric OSA associates with systemic inflammation,[410] oxidative stress,[411] and (in adolescents but not in prepubertal children) with lower levels of the insulin-sensitizing hormone

adiponectin.[295] As in adults, OSA in children leads to sympathetic nervous system activation, increased heart rate variability, and increased catecholamine production,[295,355,405,412–414] which likely underlie many of the associations between OSA and blood pressure in children.[415] Oxidative stress in children with OSA relating to IH has been found to increase lipid peroxidation, which can accelerate atherosclerosis. We and others have found that in younger children, the gold standard therapy for OSA, T&A, has been associated with the modest improvements in lipid profiles,[299,416] BP (more in nonobese children than in obese children),[417] and improved fasting insulin levels and inflammatory biomarkers (including CRP) even in the absence of obesity, suggesting a causal role for OSA.[289,298,418–420] However, another study found no improvements in blood pressure following T&A,[308] and a study of Greek children found no metabolic improvements following T&A.[309] There are very limited data on the metabolic effects of OSA treatment with CPAP in children; one study of 34 children and adolescents found an improvement in leptin levels but not in insulin levels.[313]

Pediatric OSA and CVD antecedents

In addition to the pathophysiological associations discussed earlier in the OSA epidemiology section and in the pathophysiology of OSA connections with T2DM, hypertension and the metabolic syndrome, OSA is associated with endothelial dysfunction in children, possibly mediated by reduced circulating endothelial progenitor cells,[421] alterations in plasma-derived exosomes leading to disruption of the endothelial barrier,[422] and alterations in exosomal microRNA.[422] Endothelial dysfunction can deteriorate overnight,[423] supporting the causal role of sleep-disordered breathing in the genesis of endothelial dysfunction. Treatment data also support a causal role for OSA in endothelial dysfunction in children: the blunting of postocclusive hyperemia in prepubertal children can be reversed 4–6 months after adenotonsillectomy.[325]

In summary, many studies have focused on prepubertal children but have not separated out pubertal from prepubertal states; future studies should be undertaken to focus more specifically on adolescents, who are more metabolically vulnerable to the MetS and related outcomes.

Circadian rhythm and the MetS
Circadian rhythm

Most mammalian metabolic and behavioral processes are regulated by the circadian system, centrally controlled by the suprachiasmatic nucleus (SCN) of the hypothalamus

as well as circadian oscillators in peripheral tissues; this system entrains to the 24-hour light/dark cycle but may also adjust its timing to external stimuli, such as light and food.[424] Circadian rhythms are regulated by core clock genes, such as *Clock* (circadian locomotor output cycles kaput), *Bmal1* (brain and muscle arnt-like protein-1), *Cryptochrome* (*Cry1* and *Cry2*), and *Period* (*Per1*, *Per2*, and *Per3*),[425] which function in transcriptional feedback loops. Circadian misalignment refers to the mismatch between circadian rhythms and lifestyle behaviors[426] and may be caused by factors such as changes in sleep/wake cycles seen in shift workers or lack of light exposure interfering with light/dark cycle entrainment.[427] The continuum of circadian misalignment includes blindness, shift work, social jet lag, chronotype (a behavioral preference in the timing of sleep or food intake or physiological manifestation of timing of body temperature nadir or hormonal release), and such sleep disorders as Advanced Sleep Phase Syndrome. Circadian misalignment has strong links to obesity, IR, and the MetS, which is briefly discussed here.

Epidemiological data
Adults

Epidemiological studies of circadian disruption have been conducted primarily in shift workers and indicate worsening of cardiometabolic function. One study found higher levels of triglycerides and obesity as measured by BMI and lower HDL cholesterol levels among Swedish shift workers when compared to daytime workers; of these, female shift workers more frequently had impaired glucose tolerance.[428] Higher levels of postprandial glucose, insulin, and triglycerides were noted among British night shift workers when examining food intake schedules that were changed to accommodate work schedules.[429] A study of Japanese male shift workers showed an increased age-adjusted incidence of T2DM, defined by HbA1c ≥6.1%, in shift workers compared to daytime workers.[430] Additionally, the Nurses' Health Study II found a positive association between incidence of T2DM and night shift workers; however, this effect was mediated by body weight.[431] Increased CHD incidence rates in shift workers have also been linked to circadian misalignment.[432] Furthermore, nonshift work studies specifically focused on chronotype show a positive association between evening chronotype and diagnosis of arterial hypertension, higher weight, and greater waist circumference.[433] Evening chronotype is also associated with higher HbA1c levels and worsening glycemic control in adults with T2DM.[434]

Children and adolescents

Adolescent population studies assessing for the disruption of glucose metabolism have shown that evening chronotype is associated with a higher BMI, increased meal portion sizes, reduced dietary restraint, and less healthy dietary habits,[435–437] but studies focused on risk of the MetS have not been done in children and adolescents.

In summary, the abovementioned findings from epidemiological studies suggest that circadian misalignment is associated with increased risks of MetS, T2DM, and CVD in adults. More importantly, the evidence is very scarce and will require much greater attention in the future considering the 24-hour lifestyles that permeate our modern societies.

Experimental data
Animal models

Animal and human experimental models have been used to assess the impact of circadian misalignment on metabolic variables. Specifically, rodent studies demonstrate increases in body mass when subjected to work,[438] feeding,[439] and light exposure during the biological day (normal rest phase).[440] Additionally, studies in *Clock* mutant mice demonstrate the development of hyperglycemia, relative hypoinsulinemia, hyperlipidemia, and obesity due to changes in their diurnal feeding patterns subsequent to circadian disruption.[441]

Adults

In human adults, a study demonstrated increased glucose and insulin levels in response to a mixed meal given at the same clock time following a 9-hour circadian phase advance when the test meal was preceded by a high-fat but not low-fat meal.[442] Furthermore, triglyceride levels were found to be elevated after the mixed meal following a 9-hour phase advance when a nonfat meal preceded the test meal in an extended study,[443] indicating the macronutrient meal content before or during the phase advance may impact the subsequent metabolic changes and confound the contribution of circadian disruption alone. When healthy adults were subjected to a 28-hour "day" with four scheduled isocaloric meals, they were found to have elevated postprandial glucose into the prediabetic range, decreased insulin sensitivity, elevated leptin levels, and elevated wake time BP independent of sleep efficiency,[444] demonstrating the direct effect of circadian misalignment on metabolic outcomes.

Children and adolescents

Almost no studies have been carried out manipulating chronotype in a pediatric population. However, Beebe et al recently carried out a study of experimental sleep extension in adolescents and found that those with early chronotypes reduced their evening caloric intake during healthy sleep, while those with evening chronotype did not.[445]

Pathophysiology
Circadian misalignment/chronotype and MetS

The underlying mechanisms of the adverse effects of circadian disruption on metabolic and hormonal factors remain undefined. These effects of circadian misalignment do not appear to be mediated by sleep efficiency or sleep quantity.[425,444] One potential mechanism is the dysregulation of hormones such as insulin and leptin, known to be under circadian control. A study protocol of 8-hour nocturnal sleep, 28-hour extended wakefulness, and 8-hour nocturnal sleep in adults resulted in an increased glucose and insulin secretion during the biological night,[446] demonstrating circadian rhythmicity of these metabolic factors. Other studies have shown leptin elevation during nocturnal sleep.[447,448] Furthermore, lesions to the SCN in mice demonstrate circadian disruption in the secretion of insulin, glucose, and leptin.[424] Circadian rhythmicity has also been reported in BP.[427] Thus, elevations in these endocrine and metabolic factors subsequent to circadian misalignment result in hyperglycemia, IR, obesity, and hypertension, well-known risk factors for the MetS.[449] Another described possible mechanism underlying the effects of circadian disruption is the internal desynchrony due to shifted feeding patterns that may uncouple peripheral oscillators present in tissues such as the liver, pancreas, and heart from the SCN.[427] The relationships between such internal desynchrony and its effects on metabolism have not been studied. Lastly, molecular clock genes contribute to the function of metabolic processes, as previously described in rodent studies. In addition to the aforementioned findings in *Clock* mutant mice, *Cry* mutant mice have elevated fasting glucose levels,[450] and pancreas-specific *Bmal1* mutant mice have impaired glucose tolerance and reduced insulin sensitivity.[451] Thus, mutations in core clock genes responsible for circadian rhythmicity may induce the glucose/insulin dysregulation found in MetS.

Conclusion

We have presented a comprehensive overview of the causative and associative links between sleep, sleep-disordered breathing, and MetS or its constitutive elements. The overwhelming majority of the data suggests that such sleep–metabolic interactions not only exist but also are operational in specific settings. Considering the adverse consequences associated with MetS, there is a great need for more accurate identification

of mechanisms and personalized markers of risk. No time to sleep on these issues!

Disclosure

The authors report no conflicts of interest in this work.

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