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Metabolic and Glycemic Sequelae of Sleep Disturbances in Children and Adults

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Abstract

The prevalence of obesity in adults and children has increased greatly in the past three decades, as have metabolic sequelae, such as insulin resistance and type 2 diabetes mellitus (T2DM). Sleep disturbances are increasingly recognized as contributors to this widespread epidemic in adults, and data are emerging in children as well. The categories of sleep disturbances that contribute to obesity and its glycemic co-morbidities include the following: (1) alterations of sleep duration, chronic sleep restriction and excessive sleep; (2) alterations in sleep architecture; (3) sleep fragmentation; (4) circadian rhythm disorders and disruption (i.e., shift work); and (5) obstructive sleep apnea. This article reviews current evidence supporting the contributions that these sleep disorders play in the development of obesity, insulin resistance, and T2DM as well as possibly influences on glycemic control in type 1 diabetes, with a special focus on data in pediatric populations.

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Compliance with Ethics Guidelines

Conflict of Interest Dorit Koren declares that she has no conflict of interest.
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Keywords

Obstructive sleep apnea; OSA; Sleep restriction; Sleep fragmentation; Insulin resistance; Type 2 diabetes; Children

Introduction

The prevalence of obesity in the USA is now considerable; 17 % of children ages 2–17 are obese [1]. The prevalence of obesity-related co-morbidities, such as the metabolic syndrome and type 2 diabetes mellitus (T2DM) has also risen [2, 3]. A growing number of epidemiological studies have linked sleep disturbances, including insufficient sleep, fragmented sleep, circadian dysregulation, and obstructive sleep apnea (OSA), with adverse metabolic sequelae, including obesity, insulin resistance (IR), and T2DM in adults. The causal role of these sleep disturbances in T2DM risk has been addressed by multiple laboratory studies that examined healthy adults before and after a sleep intervention. Emerging data over the past few years suggest that insufficient sleep and OSA may also contribute to obesity, IR, and dysglycemia in children. The purpose of this review is to provide an update on the effect of sleep disturbances on IR and the risk of T2DM as well as the effect of sleep on glycemic control in individuals with type 1 diabetes mellitus (T1DM), with a special focus on data in pediatric populations.

Insufficient Sleep/Poor Sleep Quality and Its Impact Upon Glycemia

Chronic sleep deprivation is endemic in both adults [4] and children [5]. The 2014 National Sleep Foundation Sleep in America poll found that average sleep for children ages 6–17 years fell 1–2 h short of the recommendations for age. Other secular changes have included increased prevalence of shift-work and longer working days. Multiple studies have found that chronic sleep restriction and poor sleep quality increase the risk of developing metabolic sequelae, such as obesity [6] and IR [7, 8]. The associations between sleep duration and both IR and T2DM risk have been extensively examined in epidemiological studies, and the causal nature of the relationship has been demonstrated via rigorous laboratory-based interventional sleep-restriction studies. These data and recent updates are discussed more extensively below and listed in Table 1.

Epidemiological Data: Sleep, Obesity, Glycemia, and T2DM Risk—Adults and Children—Numerous epidemiologic studies in adults have found that short sleep (usually defined as <5 [6] or <6 h/night [9]) increases risk of obesity [6], especially in combination with other sleep disturbances [10]. Multiple epidemiologic studies in adults have also indicated that short sleep is associated with increased risk of T2DM [11, 12] independently of obesity [13, 14]. While some studies only found associations between short sleep duration and T2DM risk [15], a number of other studies have found a U-shaped association, with both short and excessively long sleep (usually defined as >8–9 h/night in adults) associating with increased T2DM risk [11, 12, 16], with one meta-analysis finding greater risk of incident T2DM in long vs. short sleepers [17]. Nocturnal awakenings, self-perceived insufficient or poor quality sleep [18], and difficulty initiating or maintaining sleep [17] also increase the odds of developing T2DM, and subjective complaints such as daytime

sleepiness and insomnia associate with greater IR and post-challenge glycemic excursions [19]. Overall, these data indicate that short sleep and possibly excessive sleep, poor sleep quality, and daytime sleepiness are associated with increased risk of obesity, IR, and incident T2DM in adults. One potential limitation that should be borne in mind is that in the majority of these large-scale epidemiological studies, sleep duration was self-reported, which may overestimate sleep. Additionally, studies reporting risk of dysglycemia with increased sleep duration are limited by the inability to distinguish time in bed from total sleep time.

A number of epidemiological studies and meta-analyses in children have reported that short sleep for age (generally defined as <10 h per day for school-age children [6] and <9 h/day for adolescents [20]) and increased variability in sleep duration [21] predispose to obesity in children and adolescents [6, 22]. One adolescent study found that each additional hour of sleep was associated with lower BMI [23]. The sleep-obesity association may be stronger in boys than in girls [22]. Poor sleep quality, other sleep disturbances and delayed sleep phase also predict increased adiposity independently of total sleep duration and other confounders [24]. These studies reveal a consistent, moderate-strength association between chronic insufficient sleep and obesity in children and adolescents, with smaller studies indicating a strong association between fragmented or poor-quality sleep and adiposity.

Epidemiological studies have examined the associations between sleep duration and IR/T2DM risk in children. Several studies have shown an inverse association between sleep duration and homeostasis model assessment of insulin resistance (HOMA-IR, a measure of insulin resistance calculated from fasting insulin and glucose levels) [20], which may be primarily due to weekday sleep [25]. The negative association between sleep duration and HOMA-IR is synergistic with other risk factors, such as sugared beverage consumption and screen time, leading to higher HOMA-IR [7]. A cross-sectional analysis of data from the Cleveland Children's Sleep and Health Cohort uncovered a U-shaped association between actigraphically measured sleep duration and HOMA-IR, with 20 % higher predicted HOMA-IR in adolescents sleeping <5 or >10.5 vs. 7.75 h [26]. Another community-based study that used both self-reported sleep and actigraphically measured sleep duration in adolescents confirmed the association between short sleep duration and HOMA-IR [25]. However, the association between HOMA-IR and long sleep duration was not apparent in this study [25]. Chinese pre-school-age children sleeping <8 vs. 9–10 h were more likely to have fasting glucose levels above 100 mg/dL [27]. Epidemiological data examining the link between sleep duration and incident T2DM in children and adolescents are quite scarce.

In summary, these studies found associations of different strengths between short sleep duration and IR as measured by HOMA-IR—with one study reporting a U-shaped rather than linear association that echoes the adult findings of U-shaped relationships between sleep duration and T2DM risk. However, no consistent association has been found between sleep duration and glucose homeostasis in children in community-based studies, although the data to date are very limited. Many of these studies are limited either due to small-to-moderate sample size, not having ruled out OSA via polysomnography or having sleep assessed by self-report; however, some of the moderate-sized studies above utilized

actigraphy, a validated measure of sleep duration [28], increasing the reliability of the findings.

Sleep Duration and Glycemia in Adults and Children—Laboratory and Experimental Data—A number of sleep restriction studies have been performed in healthy young adults, beginning with the landmark study published by Spiegel et al. in 1999, which found that in 11 healthy young men, restricting sleep from a baseline 9 to 4 h for six nights led to a significant decrease in glucose clearance and increased post-prandial glucose levels [29]. A number of subsequent experimental sleep restriction laboratory-based adult studies found that partial sleep restriction, typically to 4–5 h per night for 1–7 nights but as long as 3 weeks [30], leads to IR [8] without compensatory increases in insulin secretion [31], lower glucose effectiveness [32], and increased glucose levels [30]. While most sleep restriction studies have been laboratory-based, which allows enforcement of compliance and control of pertinent variables (e.g., diet) but which does not represent the home environment, one recent study found that 3 weeks of mild sleep restriction (1.5 h less than baseline) at home, as documented by actigraphy, led to increased IR initially, followed by a return of insulin sensitivity to baseline [33].

Pediatric studies have also shown associations between sleep duration and sleep architecture measures from laboratory-based polysomnography and insulin sensitivity and glucose levels [34–36]. Some studies showed only associations between short sleep and insulin resistance (HOMA-IR) [34] and 2-h post-prandial glucose levels [35], while another found U-shaped associations between sleep duration and glycemic measures, with increased glucose levels at both higher and lower sleep durations independent of obesity [36]. Finally, one interventional sleep restriction study was performed in lean adolescent males and found that, while sleep restriction increased IR, fasting and post-prandial glucose were unchanged between the two conditions [37•].

Several studies have also found associations between various sleep stages or other sleep architecture changes and insulin sensitivity and secretion—positive associations between percentage of sleep time (%TST) spent in slow wave sleep or stage 3 (N3) sleep and insulin secretory measures [36] and insulin sensitivity [36], and an inverse association between %TST in stage 1 (N1) sleep and insulin sensitivity [35, 36, 37•, 38] independent of total sleep duration. Insulin-resistant adolescents have also been shown to have lower slow wave activity (SWA) power (quantified by power spectral analysis of the electronencephalography) in the first nonrapid eye movement (NREM) period and had a significantly slower rate of SWA decay than insulin-sensitive adolescents [38].

Interventional studies in adults serve to confirm that the longitudinal epidemiological associations seen between chronic sleep restriction and incident T2DM are causally related —sleep restriction leads to increased IR, which without increased insulin secretion to compensate can cause hyperglycemia eventually culminating in T2DM. However, the finding in the 3-week sleep restriction study by Buxton et al. that the IR initially induced by mild sleep restriction resolves even as the sleep duration remains restricted [30] suggests that there may be other mechanisms underlying the association between chronic sleep restriction and T2DM risk. Therefore, more long-term sleep restriction studies are needed to

study this phenomenon. The data in children are more limited; short sleep duration may indeed predispose to IR and hyperglycemia and limited data suggest longer sleep duration may as well. Unlike the adult studies, the one pediatric experimental sleep restriction study did not reveal changes in glucose metabolism, suggesting that children may be more resilient to short-term sleep restriction [37•]. However, only limited conclusions can be drawn from one study that included lean adolescent boys; follow-up studies including females and obese adolescents should be performed.

Sleep and Glycemic Control in Diabetes Mellitus—Inadequate or disturbed sleep is a risk factor for incident T2DM and for poorer glycemic control and higher HbA1C in adults with previously diagnosed T2DM; some studies only found associations between short sleep and HbA1C [39], while others have shown U-shaped relationship between sleep duration and glycemic control, with shorter and longer sleep associated with higher HbA1C [40]. Poor sleep quality and low sleep efficiency have also been found to predict higher HbA1C [41].

The link between sleep duration and glycemic control in type 1 diabetes mellitus (T1DM) is less well-explored than in T2DM. In adults with T1DM, short sleepers (<6.5 h per night) had higher HbA1C than those sleeping >6.5 h/night [42]; experimental sleep restriction decreased insulin sensitivity [43]; and higher percentage of NREM slow wave sleep (N3) was inversely associated with HbA1C [44]. In adolescents, those with T1DM were found to sleep longer [45] and to have lower %TST in N3 and higher %TST in N2 than age-matched non-diabetic adolescents [46]. Questionnaire-assessed sleep duration did not associate with glycemic control in adolescents with T1DM [45], but %TST in N3 was inversely associated with HbA1C and %TST in N2 positively associated with hyperglycemia [46]. To our knowledge, no studies have examined sleep duration and its impact on glycemic control in pediatric T2DM.

Thus, existing data suggest that shorter sleep duration and possibly longer sleep duration in adults with T2DM predicts worse glycemic control and that shallower sleep (reduced levels of NREM slow wave sleep or N3) is more common in adults and adolescents with T1DM and associates with worsened glycemic control. While more studies need to be done, this suggests that adults and children with T1DM and T2DM should be counseled to avoid short sleep duration and perhaps to screen for potential disruptions to N3 sleep.

Pathophysiology of Link Between Short Sleep and T2DM Risk—A number of different underlying pathophysiological mechanisms may potentially connect acute sleep restriction to IR and T2DM pathogenesis in humans: hormonal and inflammatory changes, tissue-level responses, and epigenetic changes, as discussed further below.

Hormonal and inflammatory effects: Insufficient sleep is a pro-inflammatory condition; experimental sleep restriction increases levels of inflammatory cytokines [47] and inflammation is part of T2DM pathophysiology [48]. In addition, insufficient sleep increase levels of catecholamines [8], including the counter-regulatory epinephrine, which inhibit insulin secretion and promotes glycogen breakdown. Sleep restriction also alters levels of hormones that can influence insulin sensitivity and glucose metabolism—leptin, ghrelin, and

the counter-regulatory hormone, cortisol. A number of experimental sleep restriction studies with standardized meals found that sleep restriction leads to lower leptin and higher ghrelin levels [29], though studies in which subjects ate ad libitum showed either no change in leptin or ghrelin levels [49] or higher leptin and lower ghrelin levels post-sleep restriction [50]. Similarly, some [8], but not all [51], experimental sleep restriction studies have found 24-h cortisol secretion is higher following sleep restriction, contributing to a state of greater IR.

Two recent pediatric experimental sleep restriction studies have examined the metabolic impact of sleep duration: in one, sleep restriction led to higher fasting leptin (as in adult studies) but unaltered ghrelin levels vs. the sleep-extended condition [52], and in the other, first-morning cortisol and 24-h norepinephrine levels did not differ between long and short sleep and 24-h epinephrine levels were *lower* in the sleep restriction state [37•].

Tissue effects: Sleep restriction reduced insulin sensitivity in adipocytes (measured as ability to phosphorylate Akt) collected via fat biopsy from seven healthy adults at baseline and post-sleep restriction [53•].

Epigenetic effects: Transcription of cellular stress markers and unfolded protein response is reduced in mice during sleep [54], and sleep restriction alters the mouse brain transcriptome by changing DNA methylation and hydroxymethylation and affecting biological processes relating to the stress response, circadian rhythms, and gene expression [55•]. The epigenetic impact of sleep restriction in humans has not yet been studied, but mouse data suggest that the underlying impact of sleep restriction upon target tissues may lie in the epigenome.

Sleep Architecture and Sleep Fragmentation

Sleep fragmentation results from disruption of sleep continuity, such as seen in depression, restless leg syndrome, sleep-disordered breathing, insomnia, and other environmental factors. Experimental sleep fragmentation for 3 nights in healthy young adults with selective disruption of NREM slow wave sleep (N3) led to IR and reduced glucose tolerance [56]. Similarly, non-stage specific disruption of sleep throughout the night decreased insulin sensitivity and glucose-mediated glucose disposal [57]. The mechanism linking sleep fragmentation and IR may be that decreased parasympathetic and increased sympathetic nervous system (SNS) activity associated with arousals [57], which in turn inhibit beta cell insulin secretion, stimulate hepatic gluconeogenesis and lipolysis [58] and decrease insulin-mediated glucose uptake [59].

In pediatric T1DM, sleep fragmentation with more frequent and longer overnight awakenings occurs frequently given the need for overnight glucose monitoring [60] and the presence of nocturnal hypoglycemia. Nocturnal awakenings in T1DM have been associated with rapid drops in glucose levels [61]. In addition to increased sleep fragmentation, some (but not all [61]) studies suggest that patients with both T1DM and T2DM spend more time in N1, N2, and REM and less time in N3 [62, 63]. This is relevant because, as previously discussed, %TST in N2 is positively associated with hyperglycemia and %TST in N3 associated is inversely associated with HbA1C [46]. These studies are summarized in Table 1.

Circadian Rhythm and Glucose Metabolism

The timing of food intake and sleep throughout the day is aligned in an endogenous 24-h circadian rhythm, synchronized by a clock mechanism in the suprachiasmatic nucleus of the hypothalamus. Sleep architecture and the circadian rhythm change throughout the course of development, with decreased sleep duration, decreased proportion of REM and N3 sleep, and altered sleep timing with age—adolescents have delayed sleep and wake onset compared with younger children or adults [64]. Various metabolic processes, including glucose tolerance, also change over the day and night—glucose tolerance is higher in the morning vs. the evening [65]—and in different sleep stages. During N3 sleep, cerebral glucose utilization is lowered, SNS activity decreases and vagal tone increases, and the pituitary is hyporesponsive to corticotropin-releasing hormone (CRH) [56].

Circadian rhythm disruption has been shown to alter neuroendocrine physiology, contributing to adverse metabolic consequences such as obesity and diabetes. Night-shift workers, who keep a schedule misaligned from the human circadian rhythm by being active and eating at night and sleeping during the day, have a higher risk of IR and T2DM [66]. Induced circadian misalignment in the laboratory setting without altering total sleep duration increases IR and levels of inflammatory markers [31] and interacts synergistically with sleep restriction in healthy young adults to lead to greater increase in IR [31] and post-prandial glucose [30] than those induced by experimental sleep restriction alone. Thus, circadian misalignment may increase T2DM risk independently from, and in addition to, sleep loss or fragmentation. Some individuals have an innate mild circadian misalignment, with an early or late chronotype (morningness vs. eveningness) vs. the general population. Adults with late chronotype tend to have a higher BMI [67], greater risk of developing T2DM independent of sleep duration [68], and in adults with T2DM, higher HbA1c levels vs. adults with normal chronotype [69].

Few studies have assessed the metabolic impact of circadian misalignment in children (Table 2). In one study, insulin secretion and glucose tolerance were lower in lean adolescents with circadian rhythm disorders [70], and in another, adolescents with late chronotype gained more weight in college [71]. To our knowledge, no pediatric studies have assessed the effect of circadian misalignment or chronotype on glucose metabolism. As irregular sleep-wake cycles and delayed chronotype are common in adolescents, this may increase risk of IR early in life and could cause poorer glycemic control in children with T2DM in synergy with short sleep duration.

Obstructive Sleep Apnea and Sleep

Obstructive sleep apnea (OSA) is a sleep disorder characterized by intermittent partial or complete upper airway obstruction during sleep that disrupts normal ventilation and sleep patterns and can result in intermittent hypoxemia, hypercapnia, and/or multiple arousals. The gold standard diagnostic test is overnight polysomnography (PSG), which quantifies the number of apneas and hypopneas per hour [the apnea-hypopnea index (AHI)] and other OSA severity measures. In adults, OSA is a strong risk factor for IR and T2DM [72]. The literature regarding OSA-related risk of IR in children is more limited. The risk appears to depend on several factors, including age and presence of obesity (Table 2). OSA adversely

impacts glucose metabolism via two mechanisms: sleep fragmentation and intermittent hypoxemia (IH). IH predisposes animals [73] and humans [74] to developing IR. Potential underlying mechanisms include SNS activation [75], possibly via elevations of catecholamines, C-reactive protein (CRP) [76], pro-inflammatory cytokines (e.g., TNF-alpha, IL-6 [77]), increase in corticosteroids, and alterations in adipokines, including leptin [78].

In adults, OSA is a consistent risk factor for IR and T2DM, independent of obesity [72]. In lean, healthy adults, OSA associates with IR but with compensatory increased insulin secretion, maintaining euglycemia [79]; if the compensatory mechanism fails, T2DM may develop. In children, the relationship between OSA and IR is less clear; several studies showed no association between OSA and IR [80–82], while others found associations between presence or severity of OSA and IR and between OSA components (respiratory disturbance index, mean oxyhemoglobin saturation, duration of hypoxemia) and insulin sensitivity or glycemia independent of BMI [83–87].

The converse relationship between OSA and T2DM is also true—the prevalence of OSA (defined in adults by AHI ≥5 events per hour) among adults with known T2DM ranges between 58 and 86 % [88], which is substantially higher than recent estimates in the community-based study of the Wisconsin Sleep Cohort with 17 % in women and 34 % in men [89]. The difference in pediatric OSA (defined as AHI ≥1.5 events per hour [76]) prevalence in children and adolescents with and without T2DM has been examined in only one pediatric (pilot) study, which found no difference in OSA frequency among 11 obese children and adolescents with T2DM (45.5 %) vs. 30 BMI-standard deviation score (SDS)-matched controls (18.2 %) [90•]. This study's conclusions were limited by the small sample size; further studies with larger cohorts are needed to determine whether the presence of T2DM confers a risk for OSA in children as it does in adults. Finally, although this review primarily focuses upon the link between sleep disturbances and T2DM, one noteworthy study found more frequent and longer apneas during sleep in children with T1DM than non-diabetic children, that the presence of apneic events correlated with duration of diabetes, and that more apneas were seen in poorly controlled vs. well-controlled T1DM [91]. This study suggests that even in the absence of endogenous beta-cell function, OSA impacts glycemic control, emphasizing the importance of screening children with T1DM and T2DM for OSA symptoms.

Impact of Untreated and Treated OSA on Glucose Metabolism—Several studies have found that untreated OSA is associated with worsened glycemic control in adults with T2DM [92–94]. In one study, severity of OSA assessed by AHI was associated with glycemic control after adjusting for important confounders [92]. OSA severity in REM sleep seems to be a stronger predictor of glycemic control than OSA severity in NREM sleep in adult T2DM [94]. The hypoxemic burdens of OSA (e.g., total sleep time below 90 % oxygen saturation or oxygen saturation nadir) have also been reported to be associated with glycemic control in T2DM [93]. In contrast, the Sleep AHEAD study found no association between glycemic control and AHI [95]. Finally, adults with T2DM and severe OSA are at greater risk of developing diabetes complications vs. those without OSA [96, 97]. Taken together, these studies demonstrate the importance of screening adults with T2DM for OSA

and encouraging compliance with OSA treatment, which may improve glycemic control and reduce the risk of comorbidities. In light of the data in adult T2DM and pediatric T1DM, it seems advisable to do the same in children with T2DM. However, as the increased incidence of pediatric T2DM is relatively recent, studies examining the glycemic impact of OSA in youth have not yet been published.

In adults, the first-line treatment of OSA is continuous positive airway pressure (CPAP) therapy. In non-diabetic adults with OSA, two meta-analyses have reported that CPAP therapy modestly decreases HOMA-IR [98, 99]. A few studies of T2DM patients with OSA reported a beneficial effect of CPAP treatment on glycemic control [100, 101]. However, in the only randomized controlled trial of CPAP in patients with T2DM, the average CPAP compliance was 3.6 h per night [102]. In this study, CPAP use did not lead to any improvement in glycemic control compared to sham CPAP. As most of REM sleep occurs in the early morning hours before habitual awakening, one possibility is that with suboptimal adherence to CPAP therapy, obstructive apneas and hypopneas during REM sleep were disproportionately untreated vs. events in NREM sleep [94]. The conflicting results from studies that examined the response to CPAP treatment may be partly attributed to differences in sample sizes and populations, variable durations of therapy, and poor CPAP compliance. In children, the first-line treatment of OSA is adenotonsillectomy [76]. In non-diabetic lean children without OSA, adenotonsillectomy does not alter fasting insulin or glucose. However, in obese children with OSA, there was improvement in fasting insulin and glucose levels following adenotonsillectomy even in the absence of any BMI changes [82]. In children with OSA treated with CPAP, there appears to be a significant decrease in leptin levels [103], which may be an indirect mediator of IR [104].

Conclusion

Sleep disturbances such as chronic sleep restriction, obstructive sleep apnea, and circadian misalignment are quite prevalent in the adult population; chronic sleep restriction is also common in children and adolescents, as is circadian misalignment in adolescents. OSA is becoming more common as the prevalence of obesity increases in children and adolescents. These sleep disorders, along with sleep fragmentation and alterations in sleep architecture, are associated with increased risk of obesity, IR, and T2DM and with worsening glycemic control in known T2DM in adults. In children, there is accumulating evidence that these sleep disorders are associated with obesity, IR, and various degrees of dysglycemia and may play a role in worsening glycemic control in type 1 diabetes. Thus, interventions on an individual and societal level to minimize sleep restriction and circadian misalignment (e.g., by delaying high school start times given the wide prevalence of delayed sleep phase in adolescence) and treating other sleep disorders such as OSA, in addition to other lifestyle interventions, may reduce the risk of developing T2DM in children and adults and may improve glycemic control and reduce the risk of complications in those with existing diabetes mellitus.

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Table 1

Notable pediatric studies examining sleep duration or sleep architecture and glucose metabolism relationship, 2011-2014

First author, year	Study sample	Metabolic measure	Main findings
Androutsos et al., 2014 [7]	Healthy Growth Study, 2026 children (9-13 years), Greece	FPG/FPI	Combined self-reported short sleep, greater screen time and sugared beverage intake positively associated with HOMA-IR
Berentzen et al., 2014 [105]	1481 children (11-12 years), Netherlands	HbAlc	Self-reported TST not associated with HbAlc
Zhu et al., 2014 [35]	118 children and adolescents, China	2-h OGTT	TST (PSG) positively associated with lower 2-h glucose levels and insulin secretion
			Insulin sensitivity (Matsuda index) positively associated with %TST in N3 and negatively associated with %TST in Nl
Armitage et al., 2013 [38]	18 adolescents—9 IR, 9 insulin sensitive, (13-18 years), Ann Arbor, MI	2-h OGTT	IR vs. insulin-sensitive subjects had significantly more Nl and less N2, N3 sleep despite same TST
Klingenberg et al., 2013 [37•]	21 lean male adolescents (15-19 years), Denmark	Fasting and post-prandial glucose, insulin, C-peptide, glucagon	Experimental laboratory sleep restriction (4 h/night for 3 nights) raised HOMA-IR, post-prandial insulin sensitivity (Matsuda index) vs. long sleep duration (9 h)
			No difference between in fasting and post-prandial glucose or glucagon levels with sleep restriction
Pedrosa et al., 2013 [106]	140 overweight or obese children (5-18 years), Brazil	FPG/FPI, HbAlc	Self-reported short TST associated with higher HOMA-IR
Pateletal., 2012 [107]	332 adolescent children (13-20 years), India	FPG	No difference in FPG between self-reported insufficient (<7 h/night) vs. sufficient (>7 h/night) sleepers
Matthews et al., 2012 [25]	245 adolescents, Pittsburgh, PA	FPG/FPI	HOMA-IR higher in short vs. longer sleepers (actigraphy/diary), primarily due to weekday sleep; greater association in males
			SF associated with higher fasting glucose but not HOMA-IR
Koren et al., 2011 [36]	62 obese adolescents (8-17 years), Philadelphia, PA	3-h OGTT, FSIGT, HbAlc	U-shaped association of PSG TST and FPG, 2-h glucose, HbAlc %TST in N3 associated with insulin secretion (AIRg, IGI)
Javaheri et al., 2011 [26]	Cleveland Children's Sleep and Health Cohort, 387 adolescents, Cleveland, OH	FPI/FPG	TST (actigraphy) has U-shaped association with HOMA-IR—lowest in those sleeping ~7.75 h, highest in short (5 h) and long (10.5 h) sleepers

Matsuda index (OGTT-derived)=10,000/✓(fasting insulin×fasting glucose×mean insulin×mean glucose)

HOMA-IR homeostasis model assessment of insulin resistance [(fasting insulin × fasting glucose)/22.5 if SI units], *HbA1C* hemoglobin A1C, *OGTT* oral glucose tolerance test, *SF* sleep fragmentation, *FPI* fasting plasma insulin, *FPG* fasting plasma glucose, *TST* total sleep time, *N3* non-rapid eye movement (NREM) stage 3 slow wave sleep, *IR* insulin resistant, *PSG* polysomnography, *FSIGT* frequently sampled intravenous glucose tolerance test, *AIRg* acute insulin response to glucose (FSIGT), *IGI* insulinogenic index

Table 2

Notable pediatric studies examining chronotype and obstructive sleep apnea vs. glucose homeostasis, 2007-2014

	Study/year	Study sample	Measures of glucose metabolism	Main findings
Chronotype	Tomoda et al., 2009 [70]	18 adolescents (12-17 years) with circadian rhythm sleep disorders, Japan	3-h OGTT	Glucose levels higher at 30 and 120 min, insulin levels higher at 120 and 150 min, sigma glucose level higher, IGI lower in affected individuals vs. controls
Obstructive sleep apnea	Bhushan et al., 2014 [86]	76 obese children (2-12 years), Chicago, IL	FPI/FPG	Higher FPI, FPG, HOMA-IR in children with vs. without OSA FPI, HOMA-IR correlate with OSA severity independent of BMI
	Lesser et al., 2012 [84]	22 obese adolescent males, Los Angeles, CA	FSIGT	Log frequency of overnight desaturations negatively associated with insulin sensitivity independent of BMI
	Hannon et al., 2011 [87]	20 obese adolescents, Pittsburgh, PA	2-h OGTT	OSA severity positively associated with FPI, HOMA-IR, negatively associated with insulin sensitivity independent of BMI
	Gozal et al., 2008 [82]	62 obese and lean children with OSA, Louisville, KY	FPI/FPG	Adenotonsillectomy not associated with changes in FPI/FPG
	Redline et al., 2007 [85]	Cleveland Children's Sleep and Health Study, 270 adolescents Cleveland, OH	FPI/FPG	Higher FPI, HOMA-IR in children with vs. without OSA independent of BMI

OSA obstructive sleep apnea, *HOMA-IR* homeostasis model assessment of insulin resistance [(fasting insulin×fasting glucose)/22.5 if SI units], *OGTT* oral glucose tolerance test, *FPI* fasting plasma insulin, *FPG* fasting plasma glucose