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Associations Between Sleep and Metabolic Outcomes in Preadolescent Children

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Abstract

Context: Growing evidence suggests an important role for sleep for the metabolic health of children.

Objective: We aimed to determine how sleep is related to insulin sensitivity, insulin secretion, beta-cell function, and adiposity (BMI z-scores, body fat %, waist to height ratio) using objectively measured sleep and oral glucose tolerance test (OGTT)-derived measures.

Methods: Sixty-two children aged 7-11 years, born at Kaiser Permanente Southern California, wore wrist accelerometers for 7 days to objectively measure sleep, completed an OGTT, and had anthropometric measures (height [cm], weight [kg], waist [cm], body fat [%]) collected. Using linear regression, associations between Matsuda insulin sensitivity index (ISI), insulinogenic index (IGI), disposition index (DI), BMI z-score, waist to height ratio, and body fat % with sleep parameters [total sleep time (TST; min), sleep efficiency (SE; %), time in bed (TIB; min), wake after sleep onset (WASO; min), and sleep latency (SL; min)] were assessed. Body fat % was tested as a mediator of the relationship between TST and ISI.

Results: Longer TST was associated with better insulin sensitivity ($P = 0.02$), but not after adjusting for body fat %. Sleep parameters were not associated with IGI or DI. Longer TST was associated with lower % body fat ($P = 0.01$) and lower waist-to-height-ratios ($P = 0.05$). Body fat % explained 62% ($P = 0.01$) of the relationship between TST and ISI. Longer TIB was associated with lower adiposity measures ($P < 0.05$). There were no associations between SE, WASO, or SL and metabolic outcomes.

Conclusion: Objectively measured sleep duration was associated with lower adiposity, and the relationship between sleep duration and ISI appeared partly through adiposity levels in preadolescent children. Longer sleep duration may be important for metabolic health.

Key Words: preadolescence, actigraphy, sleep, insulin sensitivity, adiposity

Abbreviations: BMI, body mass index; DI, disposition index; HOMA-IR, homeostasis model assessment of insulin resistance; IGI, insulinogenic index; ISI, Matsuda insulin sensitivity index; KPSC, Kaiser Permanente Southern California; MVPA, moderate to vigorous physical activity; OGTT, oral glucose tolerance test; SE, sleep efficiency; SL, sleep latency; T2DM, type 2 diabetes mellitus; TIB, time in bed; TST, total sleep time; WASO, wake after sleep onset; WHtR, waist to height ratio.

There is mounting evidence demonstrating the important role of sleep during childhood for the maturation of biological pathways involved in metabolic health [1, 2]. Recent studies have suggested that short sleep duration and poor sleep quality are associated with increased adiposity and cardiovascular risk markers, such as elevated blood pressure and higher cholesterol levels, in youth [2-6]. Additionally, some studies have shown that short sleep duration is also associated with greater insulin resistance during childhood; however, findings are mixed, with other studies showing U-shaped or no

associations between sleep duration and/or sleep quality with insulin resistance [4, 7-16]. Differences in study design may explain some of these discrepant findings, such as the use of self-reported sleep data and/or only including fasting glucose and insulin measurements to estimate insulin resistance [4, 7-18]. The number of studies that have used accelerometers to objectively measure sleep duration combined with assessments of dynamic measures of glucose and insulin to estimate insulin sensitivity during childhood are limited. A few prior studies used the gold standard laboratory-based

polysomnography method to objectively measure sleep and showed that longer sleep duration and better sleep quality were associated with lower insulin resistance in youth [19-22]. However, lab-based settings may affect sleep duration and quality when compared with assessments of sleep in a naturalistic home environment. In addition, prior studies were limited to youth with obesity and included a wide age range of children spanning from preschool to adolescence [19-22]. The wide age range from preschool to adolescence may confound the relationship to sleep in a very complex way such that a simple adjustment of age is not sufficient. Therefore, assessing associations between sleep and insulin resistance among a narrower age range and including children with a range of body mass index (BMI), including those with a healthy weight, is necessary to further understand how sleep is related to insulin resistance during childhood. Lastly, few pediatric studies have examined how sleep duration and quality are associated with measures of insulin secretion and beta-cell function, which are important determinants of type 2 diabetes (T2DM) risk [23, 24].

With the prevalence of obesity, glucose intolerance, and T2DM among youth increasing at alarming rates [25, 26], it is essential to understand how modifiable lifestyle factors, such as sleep, affect adiposity, insulin sensitivity, and beta-cell function. Therefore, our study goal was to use objective measures of sleep combined with oral glucose tolerance test (OGTT)-derived estimates of insulin sensitivity, insulin secretion, and beta-cell function to illuminate the relationship between sleep parameters and adiposity and glucose metabolism in preadolescent children. We additionally sought to determine whether relationships between sleep parameters and glucose metabolism were independent or mediated by child adiposity.

Methods

Study Design

Sixty-two children from the larger BrainChild cohort [27, 28] were given wrist accelerometers to wear for 7 days following their initial study visit. The BrainChild Study examines intrauterine programming of metabolic disease in healthy, typically developing children [28]. Children aged 7 to 11 years without preexisting medical or psychiatric conditions who were born at Kaiser Permanente Southern California (KPSC) are recruited to participate in the BrainChild Study. The sociodemographic characteristics of KPSC members are representative of Southern California residents [29]. Consent to participate was obtained from participants' parents and assent was obtained from study participants. This study was approved by both the University of Southern California (USC) (# HS-14-00034) and KPSC (# 10282) institutional review boards. This study was in accordance with the Declaration of Helsinki principles.

Study Visit Overview

Participants came in for 2 study visits. During the first study visit at the Clinical Research Unit of USC's Diabetes and Obesity Research Institute, participants completed anthropometric and body fat measurements and an OGTT after a 12-hour overnight fast. Trained staff members took each participants' height (cm) using a stadiometer to the nearest 0.1 cm. The Tanita Body Composition Analyzer SC 331S (Tanita Corporation of America, Arlington Heights, IL) was used to measure weight (kg) and body fat %. Waist circumference (cm) was measured using a measuring tape positioned in a horizontal plane at the midpoint between the iliac crest and the lower costal margin in the midaxillary line. Tanner stage of puberty was assessed either by a physical exam or by a previously validated questionnaire [30]. At the end of the study visit, an ActiGraph GT3× triaxial accelerometer (ActiGraph, Pensacola, FL) was placed on each participant's dominant wrist and worn for 7 consecutive days. Participants were instructed to wear the accelerometer for 24 hours a day. Concurrently, participants were given a sleep log to record the time they went to sleep and the time they woke up each day.

Actigraphy-derived sleep measures

Each accelerometer was programmed to begin data collection at 6:00 PM the evening participants received the devices and end at 12:00 AM on the eighth day. Exclusion criteria or early device removal were considered if the participant was going to be engaging in contact sports or water-based sports (eg, football, martial arts, or swimming). This was to prevent damage to the device and injury to the participant. Non–wear time was determined using algorithms created by Choi et al [31, 32] with the vector magnitude option, which is recommended for wrist accelerometers. Similar to prior studies in children, valid days were defined as non–wear time less than 10 hours, and participants with fewer than 4 valid days were excluded from final analyses [33-35]. Raw accelerometer data were collected in 5-second epochs at 80 Hz, extracted with Actilife Software version 6.13.4 e (ActiGraph LLC), converted to 60-second epochs for processing in Actilife, and saved in raw data form as GT3X files. These data were then converted to AgileGraph Data (AGD) format for data analysis. The Cole-Kripke algorithm was used assess sleep measures [36, 37]. The following sleep measures were used: total sleep time (TST; min), sleep efficiency (SE; %), time in bed (TIB; min), wake after sleep onset (WASO; min), and sleep latency (SL; min) [38-40]. TST is the total number of minutes participants are sleeping. SE is the percentage of time participants spend sleeping out of the total time they spend in bed. TIB is the total number of minutes participants spend in bed. WASO is the number of minutes a participant spends awake after initial sleep onset. SL is the length of time it takes for a participant to fall asleep once they get into bed. Use of wrist-worn accelerometers to assess these sleep measures has previously been validated with polysomnography studies in children [41, 42]. Accelerometers were also used to capture child moderate to vigorous physical activity (MVPA) levels. MVPA can influence metabolic outcomes; thus, child MVPA levels were included as a covariate [43]. MVPA was the average time spent in MVPA per a day across the 7 days and was also calculated in Actilife using the following cutoffs, modified from Chandler et al [44] to reflect 60-second epochs: moderate (≥9805 to ≤2361623 616 counts) and vigorous (≥2361723 616 counts) [44].

Oral glucose tolerance tests

Participants received an oral glucose load (Glucola, Azer Scientific, Morgantown, PA) corresponding to 1.75 g/kg of body weight (up to 75 g). Assays were analyzed from blood samples collected at −10, 30, 60, 90, and 120 minutes relative to the glucose ingestion for determination of glucose and insulin concentrations. Assays were performed at the Diabetes and

Obesity Research Institute Metabolic Core lab at the University of Southern California.

Laboratory methods

Plasma glucose was measured using the enzymatic electrode YSI analyzer, YSI 2300 STAT PLUS (YSI incorporated, Yellow Springs, OH). Insulin was measured using an ELISA fluorescent colorimetric method (Millipore Cat# EZHI-14K, RRID:AB_2800327) with a reported intra-assay precision of 1.6% to 7% and inter-assay precision of 5% to 11%.

Estimates of insulin sensitivity, insulin secretion, and β-cell function derived from OGTT

Insulin sensitivity was estimated from plasma glucose and insulin concentrations using the Matsuda whole body insulin sensitivity index (ISI), which was calculated using the following formula, $[(10\,000)/(\text{fasting insulin } (\mu\text{mol/mL}) \times \text{fasting glucose } (\text{mg/dL}) \times \text{mean insulin } (30, 60, 90, 120 \text{ minutes}, (\mu\text{mol/mL})) \times \text{mean glucose } (30, 60, 90, 120 \text{ minutes}, (\text{mg/dL}))]$ [45]. The homeostatic model assessment of insulin resistance (HOMA-IR) was used to estimate insulin resistance and calculated from fasting glucose and insulin levels using the following formula, $[(\text{fasting insulin} \times \text{fasting glucose})/(22.5)]$ [46]. Insulin secretion was estimated using the insulinogenic index (IGI) defined as Δ insulin (0-30, μmol/mL)/Δ glucose (0-30, ml/dl) [47]. The oral disposition index (DI) is a surrogate measure of β-cell function and was calculated as the product of ISI and IGI during the OGTT [48].

Anthropometric measures and body composition

Using the Center for Disease Control (CDC) standards, each child's BMI z-score (BMIZ) and BMI percentile were calculated from their height and weight [49]. Children with BMI percentiles 5th to < 85th were classified as healthy weight; BMI percentiles 85th to <95th percentile classified as overweight, and BMI percentiles ≥95th classified as obesity. Waist to height ratio (WHtR) was calculated as waist circumference divided by height. Body fat % was measured using bioelectrical impedance analysis (BIA) with the Tanita scale using the frequency current, 50 kHz, 90 μA.

Statistical Analysis

Demographic and cohort characteristics were summarized using descriptive statistics. Linear regression was then used to analyze the relationship between sleep measures and metabolic outcomes. The primary sleep variables of interest were TST and SE. TIB, SL, and WASO were secondary variables of interest. TST and SE were chosen as the primary sleep parameters because TST is a common measure of sleep duration and sleep efficiency is a common measure of sleep quality, while only a handful of studies have looked at SL and WASO in association with metabolic outcomes [4, 11, 16, 17, 50-52]. Our primary metabolic measures of interest were the OGTT-derived ISI, IGI, and DI. We were interested in exploring associations with IGI and DI based on adult literature showing that the disposition index is reduced and insulin secretion is increased following sleep deprivation [53, 54]. We additionally included the fasting sample derived HOMA-IR as a secondary outcome because most prior studies used this measure to estimate insulin resistance [5, 9, 11, 16, 17, 21, 55-58.] We also assessed associations between sleep parameters and adiposity outcomes including BMI z-score, body fat %, and WHtR. To account for potential confounding variables, age in years, sex, socioeconomic status (income estimated based on census tract of residence and expressed as a continuous variable, and maternal education extracted from birth certificates in the EMR as a categorical variable [completed high school, completed some college, and completed college and above]), MVPA (minutes), and Tanner stage of development were all used as a priori covariates. For the OGTT-derived measures and HOMA-IR, we further included child's body fat % in the regression models to assess whether associations between sleep and glucose homeostasis measures were independent or mediated by child adiposity. The OGTT-derived measures and HOMA-IR were not normally distributed. Thus, ISI was cubic root transformed to normalize its distribution, and HOMA-IR, IGI, and DI were log transformed. SL and MVPA were also not normally distributed and were cubic root transformed. Standardized regression coefficients were reported such that unit-free direct comparisons can be made across different sleep parameters with different measurement units. Each standardized regression coefficient represents 1 SD change in sleep parameters with 1 SD change in OGTT-derived measures or HOMA-IR. The mediation analysis was done using proc causalmed without bootstrapping options. *P* values less than 0.05 were interpreted as statistically significant. SAS OnDemand for Academics (SAS Institute, Cary, NC) was used for all the statistical analyses.

Results

Participants' Demographics

Sixty-two children from the larger BrainChild cohort [27, 28] completed this substudy with accelerometer-derived measures of sleep. Table 1 shows a summary of participant demographics. The mean (± SD). age of participants was 8.9 (1.2), 52% were girls, 84% were Tanner Stage 1. The mean BMI z-score was 0.9 (SD), and 55% of children were of a healthy weight, while 13% were overweight and 32% had obesity. Participants' adiposity measures, OGTT-derived measures, actigraphy-derived sleep measures, and MVPA are also presented in Table 1. On average, participants slept 9 hours and 20 minutes a night and had 86.2% sleep efficiency. The ISI was highly correlated to BMI z-score (Spearman $R_s = -0.54$, $P < 0.001$), body fat % ($R_s = -0.53$, $P < 0.001$), and WHtR ($R_s = -0.57$, $P < 0.001$). The IGI was also highly correlated with adiposity measures ($P < 0.001$) (see Supplemental Information, Table S1 for correlations between OGTT-derived measures or HOMA-IR with adiposity measures [59]). MVPA was not correlated with any sleep parameters (Table S2 [59]). TST was correlated with TIB ($R_s = 0.84$, $P < 0.001$) and SE ($R_s = 0.35$, $P = 0.01$). SE was also correlated with SL ($R_s = -0.40$, $P = 0.001$), and WASO ($R_s = 0.94$, $P < 0.001$) (see Table S2 for correlations between actigraphy measures [59]).

Associations Between Sleep Parameters and Metabolic Outcomes

Total sleep time and metabolic outcomes

Longer TST was positively associated with ISI before ($P = 0.03$) and after adjusting for child age, sex, Tanner stage, MVPA, and SES ($P = 0.02$) (Fig. 1A; Table 2). However, after further adjusting for body fat %, TST and ISI were no longer significantly associated ($P = 0.32$), although the relationship remained in the same direction (Fig. 1B; Table 2). Longer

Table 1. Participant demographic characteristics (n = 62)

Variable	Mean (SD) or N (%) or Median (IQR)
Age (years)	8.9 (1.2)
Sex	Male: 52%
	Female: 48%
Tanner stage of development	1: 52 (84%)
	2: 6 (10%)
	3: 4 (6%)
BMI z-score	0.9 (1.2)
BMI percentile	70.7 (28.6)
Child BMI category	Healthy weight: 34 (55%)
	Overweight: 8 (13%)
	Obesity: 20 (32%)
Total body fat (%)	26.4 (9.7)
Waist to height ratio	0.5 (0.1)
Fasting glucose (mg/dl)	79.6 (76.7, 84.2)
Fasting insulin (mg/dL)	3.9 (1.5, 8.3)
2-hr glucose (mg/dL)	110.7 (99.8, 122.9)
HOMA-IR	0.8 (0.3, 1.6)
Matsuda insulin sensitivity index	8.8 (3.8, 14.1)
Insulinogenic index (IGI) (mmol/l)	1.3 (0.8, 2.0)
Beta-cell function, oral disposition index (DI)	9.5 (5.9, 16.0)
Total sleep time (min)	474.8 (43.9)
Sleep efficiency (%)	86.2 (4.4)
Total time in bed (min)	551.9 (46.3)
Sleep latency (min)	9.0 (5.7, 15)
Wake after sleep onset (min)	66.6 (23.8)
MVPA (min)	75.8 (54.1, 90.7)
Estimated household income by residence at birth ($)	55663.3 (25574.6)
Maternal education	College and postgraduate: 32 (52%)
	High school or less: 15 (24%)
	Some college: 15 (24%)

Data presented as N (%) or mean (SD) or median (25th quartile, 75th quartile).
Abbreviations: BMI, body mass index; DI, disposition index; HOMA-IR, homeostatic model assessment for insulin resistance; IGI, insulinogenic index; IQR, interquartile range; MVPA, moderate to vigorous physical activity.

TST was also associated with lower HOMA-IR, adjusting for child age, sex, Tanner stage, MVPA, and SES ($P = 0.04$), but further adjusting for child body fat % also attenuated this relationship ($P = 0.32$) (Table 3 [59]). TST was not associated with IGI, DI, fasting plasma glucose, fasting plasma insulin, or plasma glucose levels at 120 minutes after glucose ingestion (Table 2 and Table S3 [59]).

In both unadjusted and adjusted models, longer TST was associated with lower body fat % (Unadjusted $P = 0.003$; Adjusted $P = 0.01$) and lower WHtR (Unadjusted $P = 0.009$; Adjusted $P = 0.05$). Longer TST was also associated with lower BMI z-scores ($P = 0.02$), but this association was slightly weakened in the adjusted model ($P = 0.06$) (Fig. 2; Table 3).

The mediation analysis showed that before adjusting for covariates, body fat % was a significant mediator of the association between TST and ISI (77% mediated; $P = 0.02$). Body fat % remained a significant mediator even after adjusting for child age, sex, Tanner stage, MVPA, and SES (62% mediated; $P = 0.01$) (Fig. 3). Waist circumference was also a significant mediator of the association between TST and ISI (Fig. S1 [59]), before (73% mediated; $P = 0.02$) and after adjusting for the same covariates (46% mediated; $P = 0.02$).

Sleep efficiency and metabolic outcomes

In both unadjusted and adjusted models, SE was not significantly associated with ISI, IGI, DO, HOMA-IR, fasting glucose, fasting insulin or glucose levels at 120 minutes post glucose load (Fig. 1; Table 2, Table S3 [59]), or adiposity measures (Fig. 2; Table 3), although all betas were in the expected directions.

Secondary sleep parameters and metabolic outcomes

More TIB was associated with better ISI ($P = 0.02$) but adjusting for body fat % weakened this association such that it was no longer significant ($P = 0.41$) (Table S4 [59]). In the unadjusted model, longer TIB was associated with lower insulin secretion ($P = 0.02$), but this relationship was eliminated in adjusted models ($P > 0.14$). TIB was not associated with DI, fasting glucose, fasting insulin, or glucose levels at 120 minutes. (Table S4 [59]). In both unadjusted and adjusted models, more TIB was significantly associated with lower BMI z-scores (Unadjusted $P = 0.02$; Adjusted $P = 0.05$), lower body fat % (Unadjusted $P = 0.002$; Adjusted $P = 0.01$), and lower WHtR (Unadjusted $P = 0.01$; Adjusted $P = 0.03$) (Table S5 [59]). SL and WASO were not significantly associated with any OGTT-derived measures (Table S4 [59]) or adiposity measures (Table S5 [59]).

Discussion

To our knowledge, this is the first study to combine actigraphy-based measures of sleep with measures of adiposity and OGTT-derived estimates of insulin sensitivity, insulin secretion, and beta-cell function to examine associations between sleep and metabolic outcomes in childhood. We found that longer sleep duration was associated with lower adiposity, and that the relationship between sleep duration and insulin sensitivity was partly mediated through child adiposity in preadolescent children. These findings provide evidence to support the important benefits of sleep duration on metabolic health in childhood. Considering that the average age of youth-onset T2DM is 14 years, and adolescence is a known time period for significant increases in insulin resistance [60, 61], preadolescence may serve as a critical developmental window for promoting healthy behaviors to mitigate the risk for the development of obesity and T2DM.

We found that longer sleep duration was associated with better insulin sensitivity and that this relationship was partly mediated through child adiposity levels. These findings are in line with a recent study in adolescents, which reported that waist circumference mediated the association between sleep and insulin resistance [57]. Similarly, recent intervention studies in adults show promising effects of increasing sleep duration on measures of glucose homeostasis [62-64.] Collectively, these findings suggest that by ameliorating adiposity, longer sleep duration may indirectly lower insulin resistance. However, future studies are needed to determine causal pathways through which sleep duration benefits glucose homeostasis, particularly during childhood.
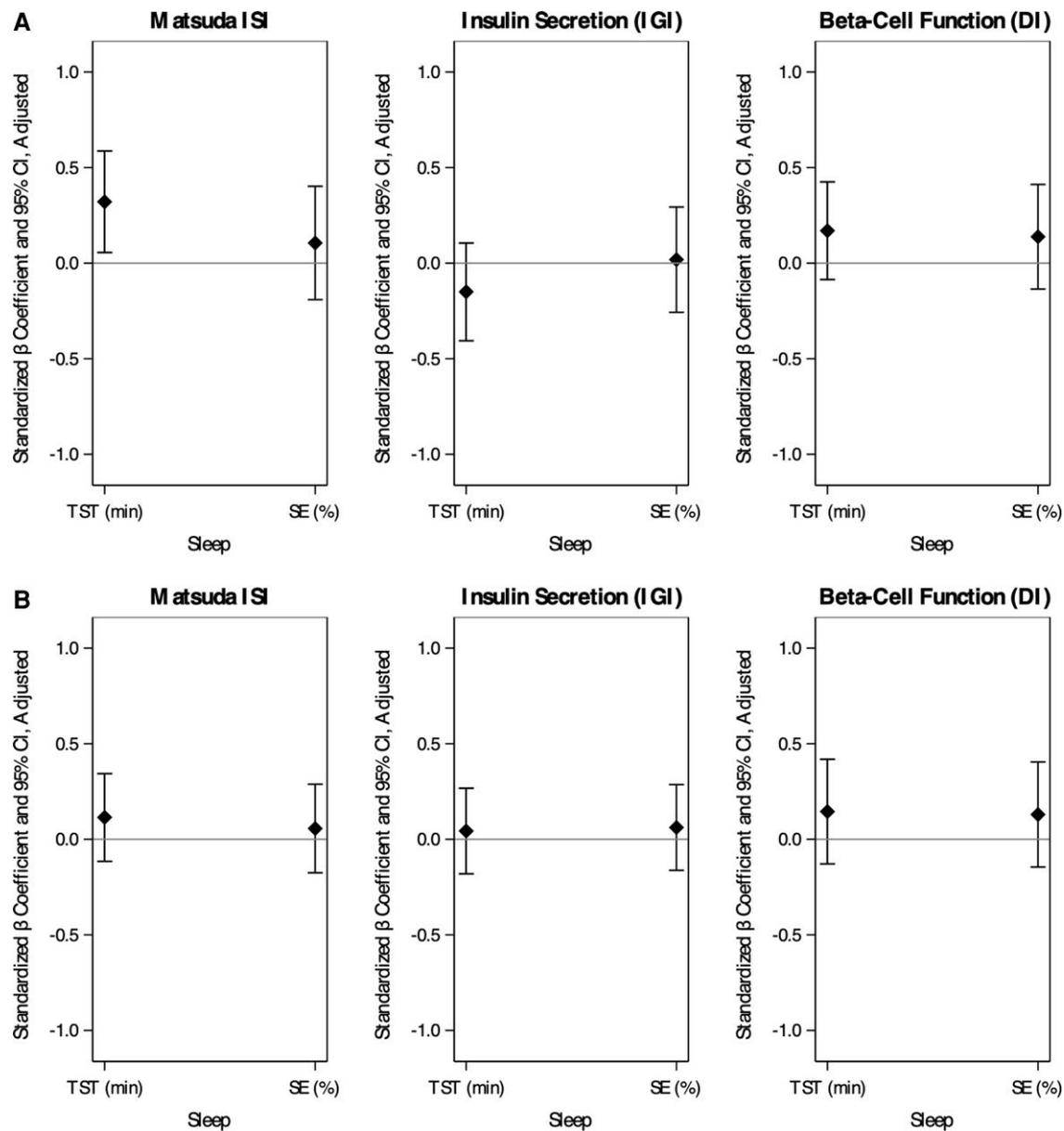
Figure 1. Sleep Parameters with OGTT-derived measures before (panel A) and after (panel B) adjusting for BMI Z-score associations between total sleep time (TST) and sleep efficiency (SE) with OGTT-derived measures before (Panel A) and after (panel B) adjusting for body fat %. A, Standardized β coefficient (represents 1 SD increase/decrease in sleep parameters with 1 SD change in OGTT-derived measures) with 95% CI, adjusted for child age, sex, Tanner stage of development, moderate to vigorous physical activity, and socioeconomic status. B, Further adjusted for child body fat %. Abbreviations: DI, disposition index; IGI, insulinogenic index (IGI); ISI, Matsuda insulin sensitivity index. *Indicates significant *P* value, $P < 0.05$.

Similar to several prior studies, we found that longer sleep duration was associated with measures of both central and total adiposity, in both unadjusted and fully adjusted models [2]. Notably, prior longitudinal studies also showed that longer sleep duration was predictive of decreases in fat mass and lower obesity risk at follow-up visits [65-67.] Altogether, these findings suggest that sleep duration may be an important target for obesity prevention during childhood. Similarly, sleep intervention studies among children have shown that increasing sleep duration can lead to decreases in BMI, further lending support to the important role of sleep in obesity prevention [68, 69]. However, experimental studies are needed to elucidate the mechanisms behind this association. To this end, one relevant study examined potential pathophysiological underpinning of associations between sleep duration and

obesity in children, and their findings suggest that longer sleep duration may reduce obesity risk at least in part through reductions in caloric intake as well as through changes in appetite-regulating hormones, such that changes in leptin levels were related to larger decreases in body weight [70]. Moreover, studies in adults demonstrated that acute sleep deprivation leads to increased food intake, decreases in the satiety hormone leptin, and increases in the hunger hormone ghrelin, providing additional support for the important role of sleep in modulating hormones that help regulate food intake and body weight [71, 72]. Additional studies in children are needed to determine the potential role of appetite-regulating hormones as a physiological mediator of the association between sleep duration and child adiposity. Studies in animal models have suggested additional pathophysiological pathways that may underlie the

Table 2. Sleep parameters with HOMA-IR and OGTT-derived measures

Outcome	Model 0, β (95% CI), *P* value	Model 1, β (95% CI), *P* value	Model 2, β (95% CI), *P* value
Total sleep time			
Matsuda ISI	0.28 (0.04, 0.53), **0.03** *	0.32 (0.06, 0.59), **0.02** *	0.11 (-0.11, 0.34), 0.32
Beta-cell function (DI)	0.09 (−0.16, 0.35), 0.47	0.17 (−0.09, 0.42), 0.19	0.145 (−0.13, 0.42), 0.29
Insulin secretion (IGI)	−0.19 (−0.44, 0.06), 0.13	−0.15 (−0.41, 0.11), 0.24	0.04 (−0.18, 0.27), 0.70
Sleep efficiency			
HOMA-IR	−0.08 (-0.34, 0.17), 0.51	−0.19 (−0.49, 0.10), 0.20	−0.15 (−0.41, 0.11), 0.24
Matsuda ISI	0.01 (−0.24, 0.27), 0.92	0.11 (−0.19, 0.40), 0.48	0.06 (−0.18, 0.29), 0.63
Beta-cell function (DI)	0.17 (−0.08, 0.42), 0.20	0.14 (−0.14, 0.41), 0.31	0.13 (−0.15, 0.40), 0.35
Insulin secretion (IGI)	0.14 (−0.11, 0.39), 0.27	0.02 (−0.26, 0.29), 0.89	0.06 (−0.16, 0.29), 0.58

Standardized β coefficient (represents 1 SD increase/decrease in sleep parameters with 1 SD change in OGTT-derived measures/HOMA-IR). Model 0: Unadjusted; Model 1: Adjusted for child age, sex, Tanner stage of development, moderate to vigorous physical activity, and socioeconomic status; Model 2: Further adjusted for child body fat %.
Abbreviations: DI, disposition index; HOMA-IR, homeostatic model assessment for insulin resistance; IGI, insulinogenic index; ISI, Matsuda insulin sensitivity index.
*Indicates significant *P* value, *P* < 0.05.

Table 3. Sleep parameters and adiposity measures

Outcome	Model 0, β (95% CI), *P* value	Model 1, β (95% CI), *P* value
Total sleep time		
BMI z-score	−0.30 (−0.54, −0.05), 0.02[a]	−0.27 (−0.54, 0.01), 0.06
Body fat %	−0.38 (−0.61, −0.14), 0.003[a]	−0.33 (−0.58, −0.08), 0.01*
Waist to height ratio	−0.33 (−0.57, −0.09), 0.009[a]	−0.27 (−0.54, −0.01), 0.05*
Sleep efficiency		
BMI z-score	−0.05 (−0.30, 0.20), 0.69	−0.04 (−0.34, 0.26), 0.80
Body fat %	−0.04 (−0.30, 0.21), 0.74	−0.07 (−0.36, 0.21), 0.60
Waist to height ratio	−0.04 (−0.30, 0.21), 0.74	−0.01 (−0.31, 0.28), 0.94

Standardized β coefficient (represents 1 SD increase/decrease in sleep parameters with 1 SD change in OGTT-derived measures/HOMA-IR). Model 0: Unadjusted, Model 1: Adjusted for child age, sex, Tanner stage of development, moderate to vigorous physical activity, and socioeconomic status.
[a]Indicates significant *P* value, *P* < 0.05.

relationship between low sleep duration and obesity risk. For example, rodent studies have found that sleep deprivation decreases energy expenditure through neurobiological mechanisms such as changes in hypothalamic neuropeptide signaling [73, 74], which in turn could lead to weight gain. Future studies are needed to confirm the pathway through which sleep deprivation leads to obesity risk.

In contrast to prior studies in adolescents, we did not observe associations between SE and insulin resistance [22, 75]. One possible reason for the null findings in our study is that SE was calculated as the ratio of TST to TIB, which were highly correlated in our study, indicating that SE values may not have had sufficient variability to detect associations between SE and insulin resistance. Moreover, prior studies that examined associations between SE and adiposity outcomes in youth have been mixed [76-79.] Some studies showed that better SE was associated with lower adiposity [76, 78] and other studies reported no associations [76, 77]. Similarly, we did not observe associations between SE and adiposity outcomes. In addition to potentially not having sufficient variability in SE values, differences in accelerometer placement could also potentially explain these conflicting results. For example, both Xiu et al [79] and Michels et al [77] also used wrist accelerometers and observed no associations with SE and adiposity outcomes while

Wyszyńska et al [78] and Mcneil and et [76] used either hip- or waist-placed accelerometers. Recent studies suggest that wrist accelerometers, which were used in our study, are more reliable in assessing sleep than accelerometers placed on the hip [41, 80]. Collectively, differences in study methodologies may help explain why we did not observe associations between SE and metabolic outcomes.

Our study is the first that we know of that has examined relationships between objectively measured sleep and OGTT-derived measures of insulin secretion and beta-cell function in healthy, preadolescent children. Zhu and colleagues observed a positive association between sleep duration and beta-cell function (assessed using insulin secretion sensitivity index) in their adolescent cohort [22]; whereas, in our preadolescent cohort, we did not observe significant relationships between sleep duration or sleep efficiency with the insulinogenic index, an estimate of insulin secretion, or with the oral disposition index, an estimate of beta-cell compensation for insulin resistance. The timing of our measures during the preadolescent period may help to explain the discrepancy in our data with the prior report by Zhu et al, which was performed in adolescents [22]. It is possible that the benefits of sleep duration on adiposity and insulin sensitivity that we observed may play an important role in lowering secretory demands on the pancreatic beta cells as children transition to adolescence,
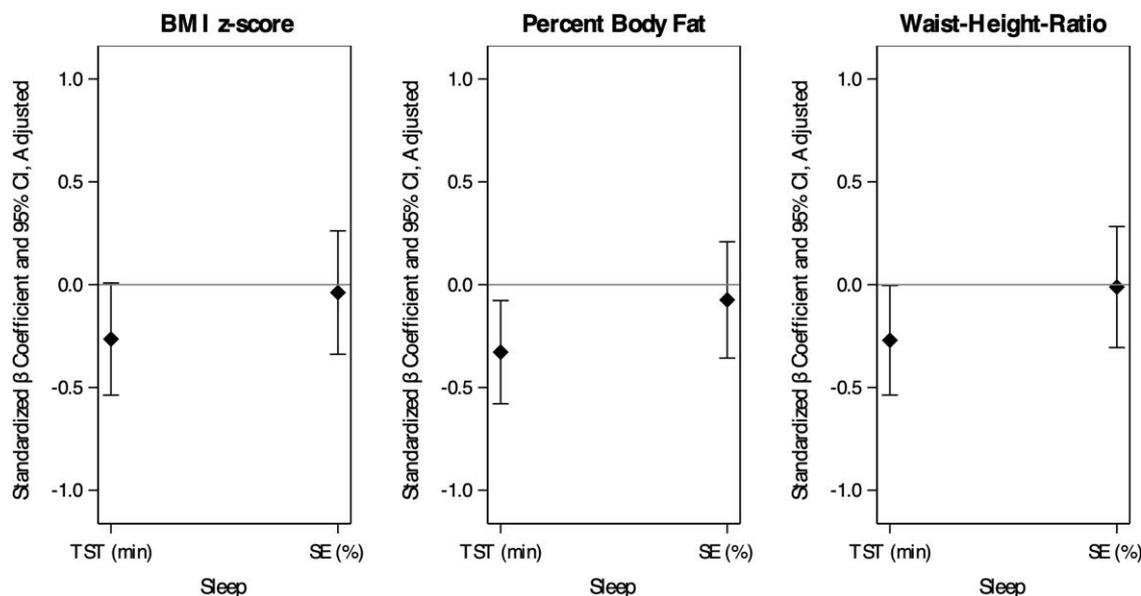
Figure 2. Sleep parameters and adiposity measures. Associations between total sleep time (TST) and sleep efficiency (SE) with adiposity measures. Standardized β coefficient (represents 1 SD increase/decrease in sleep parameters with 1 SD change in adiposity measures) with 95% CI adjusted for child age, sex, Tanner stage of development, moderate to vigorous physical activity, and socioeconomic status.
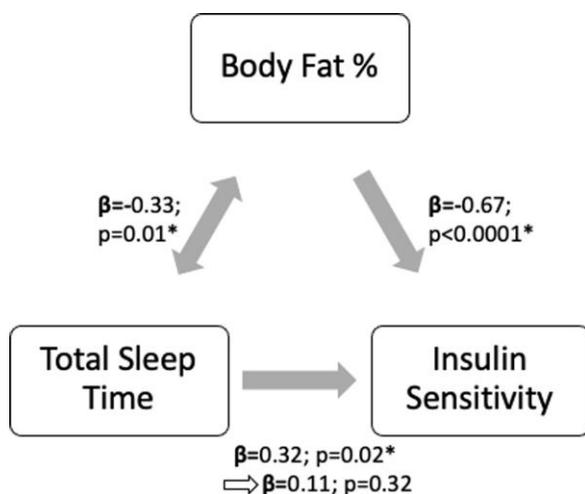

Figure 3. Body fat as a mediator between TST and ISI. Body fat % was a significant mediator of the association between total sleep time (TST) with ISI (Matsuda insulin sensitivity index) $P = 0.01$. Before adjusting for body fat %, TST was significantly associated with ISI ($P = 0.02$). After accounting for body fat %, the association between TST and ISI was attenuated ($P = 0.32$). Standardized β coefficient for direct comparisons. Analyses adjusted for child age, sex, Tanner stage of development, moderate to vigorous physical activity, and socioeconomic status.

when large changes in body composition and increases in insulin resistance typically occur [61]. Future longitudinal studies that extend from childhood through adolescence are necessary to examine that prediction.

There were many strengths to consider in our study. We assessed insulin sensitivity using glucose and insulin levels derived from the OGTT, and this method provides information on the dynamic role of insulin in response to a glucose load. To compare our findings to others in the literature, we also measured HOMA-IR, which is derived using fasting glucose and insulin levels. We used an objective and validated method to assess sleep duration (ie, TST, TIB) and measures of sleep quality

(SE, WASO, and SL). While lab-based measures such as polysomnography are considered the gold standard when assessing sleep, polysomnography does not capture a free-living environment [81]. Sleeping in a lab-based setting may affect sleep duration and quality when compared with sleeping in a home environment. Moreover, an accelerometer can be worn for up to 7 days, while most polysomnography studies are based on one night of sleep [19-22, 82]. Therefore, wrist accelerometers provide a distinct opportunity to assess sleep in a naturalistic setting. Additionally, the means of our sleep parameters lie within the 95% CI of a recent meta-analysis of 79 studies in children where accelerometers were used [83] suggesting that the sleep data in our cohort are generalizable to children of similar age ranges globally. Further, our cohort includes participants with a range of adiposity levels that are reflective children in the U.S. population; whereas most studies that have used objective measures of sleep were completed exclusively in youth with obesity [6, 16, 19, 20, 52]. Our study also has limitations, including the relatively small size, which limits the generalizability of our findings. A larger sample size is needed to test whether adiposity serves as a moderator or a mediator of the associations between sleep and insulin sensitivity. The cross-sectional design of our study negates causal inferences between sleep parameters and metabolic outcomes. Longitudinal studies that monitor how changes in sleep parameters are related to changes in metabolic markers would provide important temporal insights into associations between sleep and metabolic risk during childhood. Our study design also did not include measures of liver function. Furthermore, additional experimental studies that incorporate interventions aimed at improving sleep duration are also necessary to determine the utility of sleep as a potential strategy to improve metabolic health in children.

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Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author (K.A.P.) on reasonable request.

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