Received: 15 July 2022 | Revised: 12 October 2022 | Accepted: 30 October 2022
DOI: 10.1002/oby.23641

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

ORIGINAL ARTICLE

Sleep and Metabolic Health

Validation of the Entrainment Signal Regularity Index and associations with children's changes in BMI

Jennette P. Moreno [1] | Kevin M. Hannay [2,3] | Amy R. Goetz [4] | Olivia Walch [3,5] | Philip Cheng [6]

[1]USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA

[2]Department of Mathematics, University of Michigan, Ann Arbor, Michigan, USA

[3]Arcascope, Chantilly, Virginia, USA

[4]Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Texas, USA

[5]Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA

[6]Sleep Disorders and Research Center, Henry Ford Health, Detroit, Michigan, USA

Correspondence
Jennette P. Moreno, USDA/ARS Children's Nutrition Research Center, 1100 Bates Ave., Houston, TX 77030, USA.
Email: palcic@bcm.edu

Funding information
Texas Children's Hospital Pediatric Pilot Research Fund; Eunice Kennedy Shriver National Institute of Child Health and Human Development, Grant/Award Number: R00HD091396; National Heart Lung and Blood Institute, Grant/Award Numbers: K23HL138166, R01HL159180, R41HL163783; U.S. National Science Foundation, Grant/Award Number: DMS-1853506; United States Department of Agriculture (USDA/ARS), Grant/Award Numbers: Cooperative Agreement 58-3092-5-001, 58-3092-5-001.

Abstract

Objective: This study examined the validity of a novel metric of circadian health, the Entrainment Signal Regularity Index (ESRI), and its relationship to changes in BMI during the school year and summer.

Methods: In a longitudinal observational data set, this study examined the relationship between ESRI score and children's ($n = 119$, 5- to 8-year-olds) sleep and physical activity levels during the school year and summer, differences in ESRI score during the school year and summer, and the association of ESRI score during the school year and summer with changes in BMI across those time periods.

Results: The ESRI score was higher during the school year (0.70 ± 0.10) compared with summer (0.63 ± 0.11); $t(111) = 5.484$, $p < 0.001$. Whereas the ESRI score at the beginning of the school year did not significantly predict BMI change during the school year ($\beta = 0.05 \pm 0.09$ SE, $p = 0.57$), having a higher ESRI score during summer predicted smaller increases in BMI during summer ($\beta = -0.22 \pm 0.10$ SE, $p = 0.03$).

Conclusions: Overall, children demonstrated higher entrainment regularity during the school year compared with the summer. During summer, having a higher entrainment signal was associated with smaller changes in summertime BMI. This effect was independent of the effects of children's sleep midpoint, sleep regularity, and physical activity on children's BMI.

INTRODUCTION

One contributing factor to the prevalence of overweight and obesity among elementary school students is significant weight gain during the summer [1, 2]. A recent study of 119 children aged between 5 years and 8 years found that children shifted their sleep timing later by 1.5 hours during summer compared with the school year, and later sleep timing during summer was associated with greater increases in

Jennette P. Moreno and Kevin M. Hannay contributed equally to this work.

summertime body mass index (BMI) [3]. Given that the sun sets later during summer, it is not entirely unexpected that children's sleep timing was shifted later, but it is curious that a potentially natural shift in sleep would be related to accelerated weight gain. The Circadian and Circannual Rhythm Model (CCRM) is a conceptual model that posits that children's accelerated summer weight gain may be explained by differences in children's circadian timing and the robustness of their circadian rhythms during the school year and summer [4, 5].

Human circadian rhythms are synchronized or entrained primarily through exposure to light via the light–dark cycle [6]. Whereas the length of children's circadian rhythm is unknown, adults have daily cycles of about 24.18 hours on average in the absence of this entraining signal [7]. Because this intrinsic period is slightly longer than 24 hours, consistent input from the light–dark cycle is needed to maintain a 24-hour day. Without consistent entraining input, circadian timing may shift or vary [8]. Circadian rhythms are regulated primarily by the central or master clock known as the suprachiasmatic nucleus (SCN) [9]. The SCN is entrained by inputs from the light–dark cycle through light signals received by the eyes [10]. The SCN uses the inputs from the light–dark cycle to determine the time of day and communicates timekeeping signals to the body's peripheral clocks located throughout the central nervous system and the body, such as the liver, pancreas, muscle, and adipose tissue (i.e., fat) [9, 11]. Sleep, physical activity (PA), and eating patterns are behavioral outputs of the circadian clock. The CCRM proposes that the social demands of the school year and summer environments result in differences in children's sleep and behavioral patterns during these periods of time, leading to differential exposure to the light–dark cycle [4, 5]. Changes in one's exposure to the light–dark cycle can result in circadian misalignment (e.g., jet lag, social jet lag, shift work disorder) or blunting of circadian rhythmicity, both of which have been linked with adverse health effects such as obesity [12–16].

Most studies examining the association between variability of behavior and BMI have focused on outputs of the clock such as the day-to-day timing of sleep, children's rest/activity patterns, or the likelihood of being awake or asleep at the same time each day [17]. Variability in these behavioral outputs is assumed to be associated with variability in exposure to the light–dark cycle, resulting in potential circadian misalignment or blunting of circadian rhythms. A recent test of the CCRM found that average variability in the midpoint between sleep onset and wake time across 7 days did not differ during the school year and summer, and it was not related to change in BMI during the school year or the summer [3]. This study added to a body of literature that has failed to find associations between day-to-day variability in children's sleep and weight status [18–20], whereas other studies have found day-to-day variability in sleep duration [21–25] and timing [26–30] to be associated with adiposity. However, by assessing variability using an output of the clock (sleep patterns), we may be overlooking important influences affecting circadian entrainment, for example, the strength of the entraining signal over the course of the day, as well as effects of the temporal distribution of different light/dark patterns that accumulate over successive days. As a result, our group sought to develop a novel measure of entrainment regularity based on the physiological interpretation and usage of inputs to the clock, such as light exposure and activity.

Study Importance

What is already known?

- During summer, children gain weight at an accelerated rate compared with the school year. Having a later sleep midpoint during summer has been shown to predict greater increases in body mass index (BMI) during summer.
- The Hannay Model of circadian entrainment has been shown to predict children's circadian phase within ±31 minutes of the gold standard assessment of circadian phase (dim-light melatonin onset).

What does this study add?

- The Entrainment Signal Regularity Index (ESRI) is a novel metric of circadian health. Entering wearable activity data into the Hannay Model, the ESRI quantifies the change in model amplitude over time. Stronger, more regular, and more appropriately timed activity patterns produce greater increases in amplitude, resulting in a higher ESRI score.
- After controlling for sleep midpoint, sleep regularity, and activity levels, having a lower ESRI score during summer predicted greater changes in BMI during summer.

How might these results change the direction of research or the focus of clinical practice?

- These findings suggest that the timing of physical activity relative to one's circadian phase might have a stronger impact on change in BMI than the total amount of physical activity that children engage in.
- Further research is needed to understand how the ESRI is related to changes in children's BMI.

The Hannay Model is one of several mathematical models of the human circadian system. Unlike other models that use a van der Pol oscillator, the oscillators in the Hannay Model are based on network-level physiology of the SCN and thus they may behave more like the human circadian system. As with other models, estimates of circadian phase are based on inputs to the clock such as light exposure or activity as measured by a wearable wrist-worn device [31]. Using children's activity patterns, the Hannay Model was shown to predict children's circadian phase as assessed by dim-light melatonin onset with a mean absolute error of 31 minutes among a sample of 29 children aged 5 to 8 years [32]. The Hannay Model also has been used to accurately

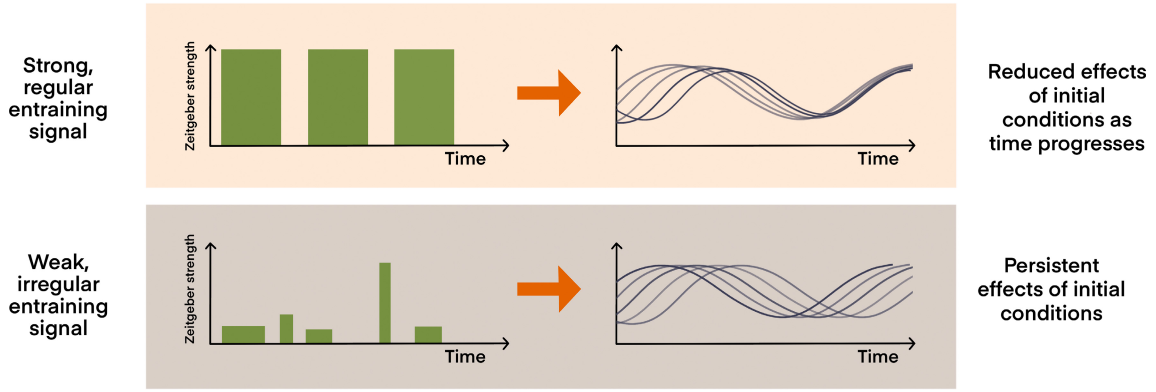

FIGURE 1 Conceptual illustration of the Entrainment Signal Regularity Index [Color figure can be viewed at wileyonlinelibrary.com]

predict circadian phase in shift workers [33]. In circadian biology, an entrainment signal is called a zeitgeber, which is German for "time-giver." The strength of zeitgebers cannot be measured without knowing the phase of the oscillator they are entraining, because the impact of the signal is time dependent based on the oscillator state. The intuition behind the Entrainment Signal Regularity Index (ESRI) measure resides in the following thought experiment: For each subject, imagine we fix the light exposure pattern for a period of D days and then we run a series of experiments in which the subject begins the light exposure schedule from a sampling of circadian phases uniformly spread around the clock. Now measure the circadian phase at the end of those D days. For schedules with strong zeitgeber signals, the samples will be highly clustered together at the end of the experiment, and for weak, irregular, or poorly timed schedules, the samples will be spread out in phase (Figure 1). The spread-in phase of a collection in oscillators can be quantified as the collective amplitude. Greater spread will result in lower collective amplitude. We can leverage this idea by simulating the Hannay Model with a low initial amplitude and observing amplitude changes in response to a given zeitgeber history. In doing so, we gain a composite score (ESRI) of the zeitgeber's strength as measured by its effect on a model of the system that it is entraining.

The aims of this article were to establish preliminary support for the validity of the ESRI by (1) examining whether the ESRI was able to detect differences in children's entrainment stimuli that might occur when children are living under school year conditions, versus out-of-school summer vacation conditions; (2) examining its association with other characteristics of children's objectively measured sleep and activity patterns, such as sleep duration, sleep timing, the Sleep Regularity Index (SRI), and PA levels; and (3) testing the association of the ESRI with children's change in BMI during the school year and summer. It was hypothesized that in this cohort, the ESRI, derived from actigraphy data, would differ during the school year and summer because of differences in the social demands between these conditions that result in differences in children's exposure to the light/dark cycle and activity patterns. Finally, we hypothesized that the ESRI would be associated with changes in children's BMI during the school year and summer.

METHODS

As has been previously described in detail [3], a prospective, observational cohort study of 119 children in Houston, Texas, was conducted. Eligible children were between the ages of 5 and 8 years and in kindergarten through second grade (the first 3 years of primary or elementary school). The child had to be enrolled in a school with a 10- to 12-week summer holiday and had to have the ability to participate in physical education. Exclusion criteria were as follows: the child having a medical condition affecting diet, PA, sleep, or weight (e.g., celiac disease, diabetes, attention-deficit/hyperactivity disorder, sleep apnea, sleep disorders); being a homeschooled student; attending a year-round school; having been held back two or more grade levels; and planning to move from the Houston area. Participants were recruited through flyers distributed at elementary schools and from a volunteer database. The Institutional Review Board at Baylor College of Medicine approved the study protocol (H-39431).

Demographic information such as child age, sex, and race and ethnicity were obtained via a parent-report questionnaire at the initial school year assessment. BMI data were collected at the beginning of the school year (range: September 7, 2016–December 3, 2016; mean: October 19, 2016), at the end of the school year (range: April 1, 2017–June 7, 2017; mean: April 20, 2017), and at the beginning of the following school year (range: August 18, 2017–October 16, 2017; mean: September 11, 2017). Children's heights were measured without footwear using a Holtain stadiometer. Weights were assessed in light clothing without footwear using a Healthometer digital scale. Because BMI is the preferred proxy measure for change in fat mass over intervals of less than 1 year, BMI (weight in kilograms divided by height in meters squared) was computed [34].

Children wore activity monitors (ActiGraph GT3X-BT) on the wrist of their nondominant hand to assess their sleep and activity patterns for 7 days and 8 nights during the school year and again during the summer break from school. Dates of the school year actigraphy assessment ranged from September 16, 2016, through December 12, 2016, although nine children completed their accelerometer assessment in May 2017 (also during the school year). School holidays and Daylight Saving Time changes were avoided. The dates of the summer accelerometer assessment ranged from June 2, 2017, through August 16, 2017. Weeks when families reported being on vacation were avoided. A parent-report daily sleep diary was used to facilitate the accurate identification of sleep periods in the actigraphy data [35]. The Sadeh algorithm in ActiLife was used to code 60-second epochs as wake versus sleep [36]. The scoring criteria used to determine sleep duration and sleep midpoint in this data set have previously been described in detail [3]. Python code developed by Avery-Lunsford et al. [37] was used to calculate the SRI, which quantifies the probability of being awake or asleep at the same clock time on consecutive days with scores ranging from 0 to 100 [38]. Higher scores on this measure reflect greater day-to-day consistency in sleep–wake. Activity levels were quantified as total daily activity counts.

TABLE 1 Sample characteristics ($N = 118$)

Variable	Mean ± SD or % (*n*)
Child age at baseline (y)	6.9 ± 0.85
Child sex, % female	48% (57)
Ethnicity, % Latino	31% (36)
Race	
Asian/Asian American	20% (23)
Black/African American	26% (31)
Caucasian/White	43% (51)
Multiracial	8% (10)
Other	3% (3)
Household income	
<$69,000	41% (49)
$70,000 or more	49% (57)
Decline	10% (12)
Parent education	
Some college or less	31% (37)
College degree	43% (50)
Graduate school	26% (31)
Weight classification	
Healthy weight	69% (81)
Overweight	16% (19)
Obesity	15% (18)

Computing the ESRI using the Hannay Model

The Hannay Model simulations were conducted using an explicit Runge–Kutta method of order 5 (4) numerical integration written in Python (https://github.com/khannay/Circadian-DLMO-Prediction). Because the Hannay Model was previously validated to predict dim-light melatonin onset among children using activity [32], activity data were used to compute the ESRI. Prior research has also indicated that, when using wrist-worn devices, activity data provide a more robust estimate of input to the circadian signal than light data [39, 40], likely because of various limitations of measuring light from the wrist (e.g., obstruction by apparel, a light sensor from the wrist may not correspond to retinal light input, accelerometer performance is typically more stable than light sensors).

Actigraph activity data were binned into 6-minute intervals. Activity counts were summed across the 6-minute bins, and total lux exposure was estimated using these activity levels. Linear interpolation was used to convert these counts to the light input in the Hannay Model. The Hannay Model was systematically derived from a model describing the phase of each circadian neuron in the SCN. It describes the collective phase (radians) and amplitude of the population of oscillators. The amplitude describes the phase coherence of the individual cellular oscillators and ranges between 0 (when oscillators are spread uniformly around the phase circle) and 1 (when all oscillators are in the identical phase). The amplitude initial condition was set to 0.10 to enforce an approximately uniform distribution at the start of the simulation. The exact value chosen for the initial amplitude does not significantly affect the conclusions as long as the value is set to a low initial value (0.0–0.20). The initial conditions for the mean phase were chosen to match a diurnal schedule with a bedtime of midnight and wake of 8 am. However, the analysis and conclusions are not sensitive to the initial phase conditions chosen, because the low amplitude initial condition implies high variance around this value. This insensitivity to the initial phase condition/assumption is a design feature of the ESRI algorithm. Additionally, the coupling between the individual oscillators was set to 0 along with the frequency heterogeneity. These changes are a matter of convenience to endow the system with the property that, in the absence of any light input, the amplitude will remain constant. If the coupling parameter is positive, this will have the effect of allowing the amplitude to increase steadily over time, even in the absence of zeitgeber inputs. For the heterogeneity parameter, nonzero values will cause the amplitude to decay. Zeroing these parameters allows the values to be compared against the null case of no zeitgeber input. The ESRI was calculated by quantifying the change in model amplitude after 4 days of entrainment under the lighting conditions estimated using activity data (Figure 1). The ESRI is a circular metric bounded by 0 and 1. An ESRI of 0 describes no organization of entrainment signals (e.g., zeitgebers occurring at random intervals and strengths leading to random disbursement of circadian phases; low collective amplitude), and an ESRI of 1 describes perfect synchrony and organization of entrainment signals that lead to stable entrainment of circadian phase (high collective amplitude).

Data analyses

A *t* test was used to examine school–summer differences in the ESRI. Bivariate correlations were used to test the relationship between the ESRI and other characteristics of children's objectively measured sleep and activity patterns. The association of the ESRI during the school year and summer with changes in BMI across those time periods was examined using mixed effects linear regression with change in BMI across the school year and summer as the outcome variable. The independent variables of interest included time (school year, summer) and

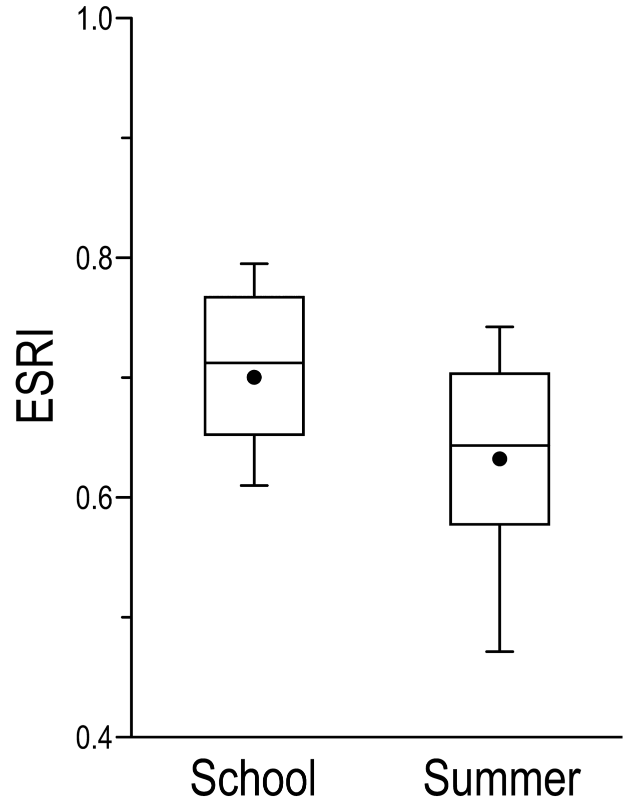

FIGURE 2 ESRI differences between school year and summer. ESRI, Entrainment Signal Regularity Index

ESRI at each time point. Participants were entered as random effects in the model to account for individual differences in BMI. During model building, sex, age, total sleep time, sleep midpoint, SRI score, and total activity counts during the school year and summer were used as covariates.

RESULTS

A total of 119 children between the ages of 5 and 8 were recruited to participate in the study. One participant was excluded from analyses due to missing actigraphy data during both the school year and summer. A total of 117 children provided accelerometry data at baseline, and 113 completed the summertime assessment. A total of 112 children provided data at both time points. Demographics of the sample with an ESRI score during either the school year or summer ($n = 118$) are displayed in Table 1.

ESRI scores ranged from 0.17 to 0.87 (0.70 ± 0.10) in the school year and from 0.36 to 0.83 (0.63 ± 0.11) in the summer. Whereas school year and summer ESRI scores were weakly correlated ($r = 0.19$, $p < 0.05$), ESRI scores were significantly lower in summer (0.63 ± 0.11) compared with the school year (0.70 ± 0.10), $t(111) = 5.484$, $p < 0.001$ (Figure 2).

During the school year, the ESRI was independent of sleep timing, duration, and sleep regularity. However, during summer, having a greater

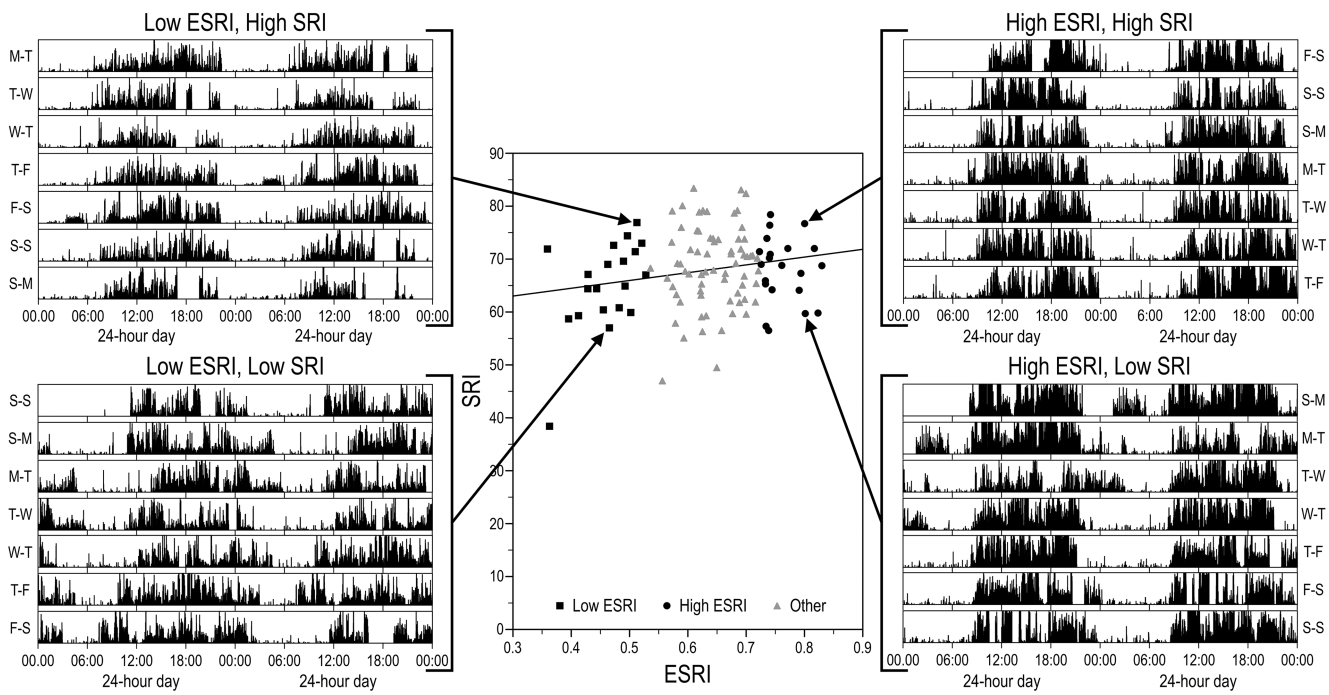

FIGURE 3 Association between the ESRI and SRI during summer. A total of 22 children were classified as being in the lower quintile based on summer ESRI score (low ESRI) with ESRI score ranging from 0.36 to 0.53, and 22 were classified as being in the upper quintile (high ESRI) with a summertime ESRI score ranging from 0.72 to 0.83. Going counterclockwise, starting at the upper right, the actograms reflect activity data from children classified as having a high ESRI and high SRI score, a high ESRI and low SRI score, a low ESRI and low SRI score, and a low ESRI and high SRI score. ESRI, Entrainment Signal Regularity Index; SRI, Sleep Regularity Index

TABLE 2 Correlations between the ESRI and sleep–wake behaviors during the school year

Variable	1	2	3	4	5	6	7	8	9	10
1. ESRI	1									
2. SRI	0.03	1								
3. Sleep midpoint	−0.14	−0.07	1							
4. Sleep onset	−0.15	0.00	0.94**	1						
5. Sleep offset	−0.10	−0.16	0.91**	0.72**	1					
6. Total sleep time	−0.04	0.27**	−0.11	−0.35**	0.20*	1				
7. Sedentary behavior	−0.28**	0.25**	0.03	0.15	−0.12	−0.14	1			
8. Light PA	0.51**	−0.06	0.00	0.01	−0.01	−0.15	−0.67**	1		
9. Moderate to vigorous PA	0.41**	0.03	0.02	0.01	0.03	−0.09	−0.46**	0.40**	1	
10. Outdoor light exposure	0.31**	0.12	−0.31**	−0.31**	−0.26**	0.06	−0.24*	0.28**	0.32**	1

Abbreviation: ESRI, Entrainment Signal Regularity Index; PA, physical activity; SRI, Sleep Regularity Index.
**p* < 0.05.
***p* < 0.01.

TABLE 3 Correlations between the ESRI and sleep–wake behaviors during the summer

Variable	11	12	13	14	15	16	17	18	19	20
1. ESRI	1									
2. SRI	0.20*	1								
3. Sleep midpoint	−0.01	−0.47**	1							
4. Sleep onset	−0.06	−0.48**	0.95**	1						
5. Sleep offset	0.07	−0.44**	0.94**	0.86**	1					
6. Total sleep time	0.25**	0.37**	−0.11	−0.31**	0.13	1				
7. Sedentary behavior	−0.32**	0.02	0.13	0.13	0.05	−0.04	1			
8. Light PA	0.37**	0.05	0.04	0.12	0.02	−0.18	−0.57**	1		
9. Moderate to vigorous PA	0.39**	0.18	−0.05	0.01	−0.07	−0.15	−0.48**	0.44**	1	
10. Outdoor light exposure	0.27**	0.05	−0.13	−0.07	−0.16	−0.11	−0.17	0.19	0.26**	1

Abbreviation: ESRI, Entrainment Signal Regularity Index; PA, physical activity; SRI, Sleep Regularity Index.
**p* < 0.05.
***p* < 0.01.

ESRI score was associated with having a longer sleep duration ($r = 0.25$, $p < 0.01$) and a higher SRI score ($r = 0.20$, $p < 0.01$; Figure 3).

The school year and summer ESRI scores were positively associated with total activity counts during the school year ($r = 0.35$, $p < 0.01$) and summer ($r = 0.30$, $p < 0.01$), time spent in light PA during both the school year ($r = 0.51$, $p < 0.01$) and summer ($r = 0.37$, $p < 0.01$), and time spent in moderate to vigorous activity during both the school year ($r = 0.41$, $p < 0.01$) and summer ($r = 0.39$, $p < 0.01$). The school year and summer ESRI score was negatively associated with time spent in sedentary activity during the school year ($r = -0.28$, $p < 0.01$) and summer ($r = -0.32$, $p < 0.01$), respectively. Time spent exposed to outdoor ambient light during the school year and summer was positively associated with the ESRI score in the school year ($r = 0.31$, $p < 0.01$) and summer ($r = 0.27$, $p < 0.01$; Tables 2 and 3).

Next, we examined the association of the ESRI score during the school year and summer with changes in BMI across those time periods, controlling for age, sex, sleep midpoint, SRI scores, and total activity counts (Table 4). Whereas the ESRI score at the beginning of the school year did not significantly predict BMI change during the school year ($\beta = 0.05 \pm 0.09$ SE, $p = 0.57$), the ESRI score during summer was significantly predictive of BMI change across summer. Specifically, each SD increase in ESRI score during summer predicted a 0.22 SD decrease in BMI during summer ($\beta = -0.22 \pm 0.10$ SE, $p = 0.03$; Figure 4).

DISCUSSION

The ESRI represents a novel metric of circadian health derived from the Hannay Model of human circadian entrainment. The Hannay Model models the entrainment of the SCN by light down to the cellular level and it can also model the seasonal encoding of day length

TABLE 4 Factors associated with change in BMI during the school year and summer

Variable	School year		Summer	
	Standardized β	SE	Standardized β	SE
Intercept	−0.37	0.27	−0.50	0.30
Sex	0.28	0.18	0.33	0.19
ESRI	0.05	0.09	−0.22*	0.10
Sleep midpoint	0.14	0.10	0.25*	0.11
Activity counts (vector magnitude)	0.01	0.09	−0.07	0.10
SRI	−0.06	0.10	0.15	0.11

Abbreviation: ESRI, Entrainment Signal Regularity Index; SRI, Sleep Regularity Index.
*$p < 0.05$.

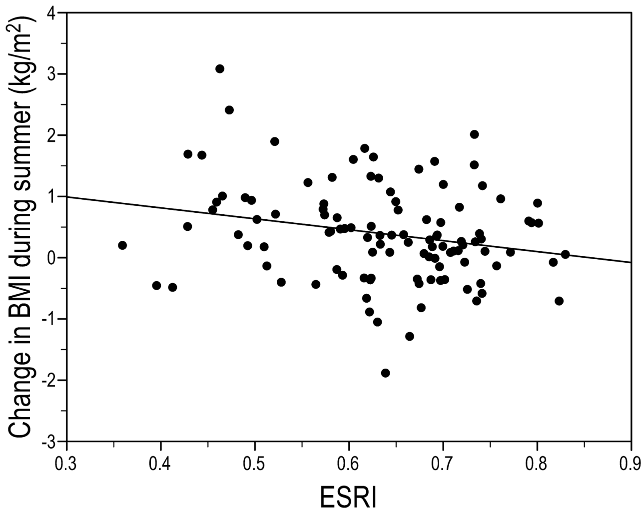

FIGURE 4 Association between change in BMI during summer and ESRI. ESRI, Entrainment Signal Regularity Index

[33, 41]. Previous studies have shown that activity data can be used instead of light data and can even offer more accurate predictions of circadian phase [39, 40]. Using wrist-worn activity data, the Hannay Model has demonstrated accuracy to predict children's dim-light melatonin onset with a mean absolute error of 31 minutes, which is smaller than errors obtained in similar studies with adults [38–40, 42]. Using activity data collected from wrist-worn devices across multiple days, the ESRI quantifies the strength and regularity of the circadian signal received by the SCN by computing the change in the model's amplitude in its prediction of circadian phase over time. The more robust and regular activity patterns result in increased model amplitude, resulting in a higher ESRI score, whereas weaker, more irregular signals result in smaller increases in model amplitude.

As expected, children demonstrated higher entrainment signal regularity during the school year compared with the summer, because the school year has higher social demands that support greater regularity in behavioral rhythms (e.g., school start times). We previously demonstrated in this sample that there were no significant differences in night-to-night variability of children's sleep midpoint during the school year and summer [3], underscoring the novel contribution of the ESRI to understanding circadian regularity. Additionally, our findings indicate that during the school year, the ESRI score was not associated with other sleep outcomes such as sleep duration, sleep midpoint, and the SRI score; however, during the summer, we observed that a higher ESRI score was weakly associated with having a longer sleep duration and greater sleep regularity. An examination of individuals in the upper and lower quintiles of the ESRI and SRI during summer (Figure 3) suggests that, although there was conceptual overlap in these metrics, there was also conceptual divergence. For example, it is possible to score high on the SRI and low on the ESRI and vice versa, suggesting that these metrics assess distinct aspects of regularity. Further differentiating these constructs, the ESRI was positively associated with PA and exposure to outdoor ambient light during the school year and summer, whereas the SRI was unrelated to PA and outdoor light exposure. Moreover, the ESRI was negatively associated with sedentary behavior during the school year and summer, whereas there was a positive correlation between the SRI and sedentary behavior during the school year but not summer. As such, the ESRI differs from the SRI in that the SRI assesses the regularity of sleep–wake patterns by quantifying the probability of being awake or asleep at the same time each day, whereas the ESRI considers the strength and regularity of light exposure and PA patterns as they relate to circadian entrainment.

In a previous study, we demonstrated that greater increases in BMI during summer were associated with having a later sleep midpoint, whereas more traditional energy-balance–related behaviors (such as time spent in sedentary behavior and light PA and moderate to vigorous PA) appeared to be unrelated to change in BMI [3]. The lack of association between PA and change in BMI during summer has been observed by others as well [43]. In the current study, after controlling for the significant effects of sleep midpoint on change in BMI, we observed that having a lower ESRI during summer predicted larger increases in BMI during summer, suggesting that weaker, less regular circadian signals during summer were associated with greater increases in BMI. The SRI and PA were not associated with changes in children's BMI during summer. These results are intriguing because visual inspection of the actograms depicting high and low ESRI scores suggests that activity was highly correlated with the ESRI. The association of the ESRI with change in BMI during summer, when we have previously found that activity levels were unrelated to change in BMI, suggests that it may not be the total time spent in various levels of PA or sedentary behavior that is important for explaining weight gain but rather the timing of the activity relative to an individual's circadian phase.

A previous study examined the relationship between parametric and nonparametric models of circadian rhythm (interdaily stability, intradaily variability, etc.) [44] and BMI and inflammatory markers in children aged 8 to 12 years in Spain [12]. Whereas parametric methods such as the cosinor method assume rest–activity patterns can be fit to a cosine curve, nonparametric models do not require this assumption and therefore have been proposed as more adequate measures of biological rhythms [44]. This study by Qian and colleagues found that after adjusting for sleep duration and activity level, relative amplitude (i.e., the ratio of amplitude and mesor as calculated after fitting the rest-activity data to a cosine curve) was associated with having a higher standardized BMI and increased levels of C-reactive protein [12]. However, interdaily stability and intradaily variability were not associated with BMI but were negatively associated with MCP1 [12]. In the current study, we computed the SRI as a measure of day-to-day regularity in children's rest-activity patterns. Similar to the previous study, which found no cross-sectional association between nonparametric measures of children's circadian rhythms (interdaily stability and intradaily variability) [12], we found that day-to-day regularity (i.e., SRI) was not related to change in BMI during the school year or summer. The ESRI adds additional value to parametric and nonparametric models of circadian rhythms by quantifying the effects of inputs to the clock on the circadian pacemaker, taking into account that light and activity have different effects on the circadian system depending on the body's circadian timing and previous zeitgeber exposure.

Strengths of the study include the prospective nature of the study design and the multiple assessments of BMI and actigraphy data during the school year and summer allowing us to examine how behavior under various environmental conditions relates to change in BMI during these time periods. Although our data demonstrate associations between sleep midpoint and the ESRI during summer and change in BMI, we are not able to determine causation. Additional limitations include this being a secondary analysis of existing data and our limited sample size. Although we avoided the transitions to standard time and daylight savings time in our data collection, future studies should consider how the ESRI responds to these transitions and whether the seasonal differences in ESRI scores observed in this study are reflective of the robust evidence that the human circadian clock is disrupted by daylight savings time. However, it will be important to also control for the significant differences in children's social demands during the school year and summer that may also affect ESRI score [45]. Finally, data collection was limited to Houston, Texas, so the generalizability of these findings to other climates and communities is unclear.

CONCLUSION

The ESRI represents a novel metric of circadian health that quantifies the strength, compactness, and regularity of the circadian entrainment signal using either light input or activity as a proxy for light as measured by wrist-worn wearable devices while also accounting for the differential impact of light and activity on the circadian pacemaker, depending on its current phase and previous zeitgeber history. Additional translational work is needed to determine factors underlying or mediating the association between ESRI score and children's change in BMI during summer and how behavioral changes can impact ESRI score. Such work is necessary to identify modifiable behaviors that can be targeted to support stronger entrainment regularity. Acquiring this knowledge may lead to novel behavioral interventions for the prevention of child obesity.O

AUTHOR CONTRIBUTIONS

KMH conceived of the Entrainment Signal Regularity Index (ESRI). JPM, KMH, PC, and OW helped to refine the ESRI and developed the idea for this article. KMH and ARG contributed to the extraction of features from the actigraphy data. Data analyses were conducted by JPM and PC. JPM drafted the original version of the manuscript. All authors edited and had final approval of the submitted and published documents.

ACKNOWLEDGMENTS

The authors thank the participants and their families for their participation in this study; members of Dr. Moreno's research team (Hafza Dadabhoy, Jessica Christian, Ga On Jung, and Layton Reesor-Oyer) for their assistance with data collection; members of the interdisciplinary Consortium on Advanced Motion Performance (iCamp) research team (Mona Amirmazaheri, Javad Razjouyan, and Bijan Najafi) for their assistance with sleep feature extraction resulting from the original publication resulting from this data set; and Adam Gillum for creating the data visualizations.

FUNDING INFORMATION

This study was supported in part by the Texas Children's Hospital Pediatric Pilot Research Fund and the Texas, USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, and has been funded in part with federal funds from the USDA/ARS under Cooperative Agreement No. 58-3092-5-001. Dr. Moreno also receives research support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (R00HD0913s96). Philip Cheng is funded by the National Heart, Lung, and Blood Institute (K23HL138166, R01HL159180, R41HL163783). Kevin Hannay was partially supported by the National Science Foundation (DMS-1853506). The funding sources played no role in the study design; collection, analysis, or interpretation of data; the writing of the manuscript; or the decision to submit for publication.

CONFLICT OF INTEREST

Olivia Walch is the CEO of Arcascope, a company that makes circadian rhythms software. She has done consulting for Unilever, MetroNaps, and Gideon Health. Kevin Hannay is the Chief Technology Officer of Arcascope. Models used in this paper have been released as open source. Philip Cheng was funded through an NIH Small Business Technology Transfer award (R41HL163783) in conjunction with Arcascope. The other authors declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

ORCID

Jennette P. Moreno https://orcid.org/0000-0002-9372-6104
Philip Cheng https://orcid.org/0000-0002-2874-658X

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How to cite this article: Moreno JP, Hannay KM, Goetz AR, Walch O, Cheng P. Validation of the Entrainment Signal Regularity Index and associations with children's changes in BMI. *Obesity (Silver Spring)*. 2023;31(3):642-651. doi:10.1002/oby.23641