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ORIGINAL ARTICLE

Estimating circadian phase in elementary school children: leveraging advances in physiologically informed models of circadian entrainment and wearable devices

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Abstract

Study Objectives Examine the ability of a physiologically based mathematical model of human circadian rhythms to predict circadian phase, as measured by salivary dim light melatonin onset (DLMO), in children compared to other proxy measurements of circadian phase (bedtime, sleep midpoint, and wake time).

Methods As part of an ongoing clinical trial, a sample of 29 elementary school children (mean age: 7.4 ± .97 years) completed 7 days of wrist actigraphy before a lab visit to assess DLMO. Hourly salivary melatonin samples were collected under dim light conditions (<5 lx). Data from actigraphy were used to generate predictions of circadian phase using both a physiologically based circadian limit cycle oscillator mathematical model (Hannay model), and published regression equations that utilize average sleep onset, midpoint, and offset to predict DLMO. Agreement of proxy predictions with measured DLMO were assessed and compared.

Results DLMO predictions using the Hannay model outperformed DLMO predictions based on children's sleep/wake parameters with a Lin's Concordance Correlation Coefficient (LinCCC) of 0.79 compared to 0.41–0.59 for sleep/wake parameters. The mean absolute error was 31 min for the Hannay model compared to 35–38 min for the sleep/wake variables.

Conclusion Our findings suggest that sleep/wake behaviors were weak proxies of DLMO phase in children, but mathematical models using data collected from wearable data can be used to improve the accuracy of those predictions. Additional research is needed to better adapt these adult models for use in children.

Clinical Trial The i Heart Rhythm Project: Healthy Sleep and Behavioral Rhythms for Obesity Prevention https://clinicaltrials.gov/ct2/show/NCT04445740.

Statement of Significance

Sleep/wake patterns have shown validity as proxies for dim light melatonin onset (DLMO) phase among adolescents aged 9–17. The current study extended these findings to elementary school children ages 5–8 years old to examine agreement between measured DLMO phase and DLMO phase estimated with regression equations using children's objectively measured sleep onset, midpoint, and offset. Estimates of DLMO using sleep/wake behaviors were compared to estimates obtained using a physiological limit cycle oscillator model of circadian rhythms. Findings suggest physiologically informed models of circadian entrainment can facilitate more accurate predictions of children's circadian phase using data collected from wearable devices. Sleep/wake timing proved to be weak proxies of DLMO phase in 5–8-year-old children.

Key words: circadian rhythm; mathematical model; actigraphy; wearable data; children

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Introduction

There is growing awareness of the role of the circadian system in the development of obesity and other physical and mental health conditions [1]. Specifically, desynchronization of the central circadian clock located in the suprachiasmatic nucleus and peripheral clocks disrupts the circadian regulation of metabolism, contributing to weight gain [2] and multiple pathologies including cardiovascular disease [3,4], metabolic disease [5,6], cancer [6], and psychiatric disorders [7,8]. Furthermore, the efficacy of medication regimes and even vaccines have been shown to be affected by an individual's circadian timing [9–11]. As a result, the accurate assessment of circadian rhythm parameters such as circadian phase has become increasingly important for researchers and clinicians.

Circadian rhythms are endogenous rhythms with a cycle of about 24 h which are synchronized with environmental cues allowing organisms (including humans) to easily adapt to their environment (e.g. fluctuations in food availability, temperature changes, presence of predatory animals) [12]. For example, the human body is primed to enter a fasting state during the overnight sleep in which the body transitions to the use of fat reserves and maintains optimal glucose levels even in the absence of carbohydrate input from food [13, 14]. Having accurate assessments of a person's circadian phase enables us to understand the contribution of circadian rhythms in the pathophysiology of disease, which in turn enhances clinical care through the optimal administration of therapeutics [11, 15, 16].

The gold standard assessment of circadian phase is the use of plasma or salivary samples under dim light conditions (dim light melatonin onset, DLMO). This approach requires repeated samples (usually over a period of at least 6 h) to assess the time at which an individual's melatonin secretion increases above a certain threshold [17]. Compared to other markers of endogenous circadian rhythms, such as core body temperature, melatonin is relatively robust [17]. However, the procedure not only requires an in-lab collection of saliva or plasma samples: it also usually requires patients to stay up past their habitual bedtime, resulting in acute sleep restriction. Additionally, these assessments can be cost-prohibitive (not covered by insurance) and thus impose a significant burden on research participants and patients. As such, sleep/wake cycles are often used as proxies for children's circadian phase [18, 19] because they affect an individual's exposure to the light–dark cycle and thus are seen as fundamental to establishing children's circadian rhythms. However, physiological differences such as light sensitivity contribute to substantial inter-individual variability in phase angle of entrainment even when schedules and light–dark patterns are held constant, making sleep/wake parameters such as bedtime, sleep midpoint, and wake time potentially poor indicators of circadian phase [20, 21]. Sleep/wake parameters are also heavily dictated by other external factors, such as school schedules, homework routines, and parental rules, which may mask children's circadian phase and are often associated with error in the prediction of circadian phase [19, 22]. As a result, there is a need to develop more robust and less invasive ways to assess circadian phase in children.

Advances in wearable technology and mathematical modeling of human circadian entrainment offer potential opportunities to improve the estimation of children's circadian phase to facilitate the study of circadian phase in larger populations [23]. Light and rest/activity data collected from wrist activity can be used to generate estimations of circadian phase using mathematical models of circadian entrainment [24–26]. These models have been evaluated in shift workers who experience extreme circadian disruption [27, 28]. In a head-to-head comparison of various models of circadian rhythms, the Hannay model stands out for being a circadian model derived from physiology as opposed to one adapted from the van der Pol oscillator to match circadian phenomena [26]. It estimates DLMO via a correction of core body temperature minimum as the primary model output [29]. It has been shown to provide a more accurate estimate of DLMO phase using ambient light exposure and activity collected from wearables than DLMO predictions estimated based on sleep/wake parameters in adults [29]. However, due to physiological differences in children's circadian physiology such as their sensitivity to evening light [30], it is unclear to what extent a model developed based on adult physiology and responsiveness to light will be able to accurately predict children's circadian phase. The purpose of the current study was to compare the ability of the Hannay model to predict children's DLMO phase during the school year with other proxies of circadian phase (e.g. bedtime, sleep midpoint, and wake time).

Methods

Study design

The data included in these analyses were collected as part of a baseline assessment of an ongoing clinical trial (NCT04445740) aimed at examining the feasibility of an obesity prevention intervention. Data were collected between April and mid-June 2021 during the school year in Houston, TX.

Participants

A sample of 5–8-year-old children was recruited from a volunteer database, flyers distributed online through elementary schools to parents, and via Facebook advertisements. Children had to be between the ages of 5 and 8 years old and enrolled in kindergarten through second grade. Because children were participating in a study focused on the prevention of obesity, inclusion was limited to children with a BMI percentile above the 50th percentile. Exclusion criteria included having a chronic medical condition affecting sleep, eating behaviors, weight status, or behavioral rhythms (e.g. obstructive sleep apnea, attention deficit hyperactivity disorder, autism) and having participated in an obesity prevention or treatment program within the last 6 months. Due to the SARs-COV-2 pandemic, parents completed an online screening form. Parents were provided with a YouTube video that instructed them on how to measure their child's height and weight at home. A follow-up screening visit was conducted via Zoom to provide parents and children with informed consent and assent and to confirm eligibility. Parental consent forms were signed electronically. The Institutional Review Board at Baylor College of Medicine approved the study protocol (H-47369).

Procedures

Actigraphs were mailed to the child's home. A link to an online instructional video demonstrated proper wear and how to avoid

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covering the accelerometer with clothing (https://www.youtube.com/watch?v=8o9rN9J63j4). Children wore Actigraphs (GT3X-BT, Pensacola, FL) on the wrist of their non-dominant hand to assess their sleep, activity, and ambient light exposure for 7 days and 8 nights during the school year. Children slept according to a "self-selected" schedule, though in this age group bedtimes were likely heavily influenced by parents and the school year schedule. The Actigraph GT3X-BT is a tri-axial microelectromechanical systems accelerometer. The monitor digitized acceleration data using a 12-bit analog to a digital converter with a sampling rate of 30 Hz. Data were downloaded using the Actigraph's digital pass filter with a bandwidth of 25Hz–2.5 Hz, designed to detect normal human behavior. Wear time data were also collected by the GT3X-BT monitor. The photocell contained in the Actigraph GT3X-BT (capable of measuring 0–5000 lx) measured ambient light exposure. Lux data were binned in 60-s epochs. Parents documented their child's sleep patterns daily in an electronic survey that was emailed to parents every morning. Parents were also provided with a paper copy for note-taking purposes.

At the end of the week, DLMO was assessed in the lab. On the day of the lab visit, participants were asked to avoid intake of caffeine, chocolate, nonsteroidal anti-inflammatory drugs (NSAIDs), and CBD products. Saliva (~1 mL) samples were collected using untreated Salivettes (Starstedt, Germany) every hour beginning 5 h before and ending 1 h following typical bedtime in dim light (<5 lx). Before the samples, children were seated for 10 min to minimize postural effects on melatonin concentration. If participants ate or drank before the sample, they gently brushed their teeth with a soft-bristled toothbrush and water. Saliva samples were centrifuged and frozen until analyzed for melatonin measurement using radioimmunoassay (RIA) test kits (NovoLytiX GmbH, Switzerland) at SolidPhase, Inc. in Portland, ME. The lower limit of detection of the assay was 0.2 pg/mL.

Circadian phase and sleep/wake measures

DLMO phase was determined using linear interpolation across the time points before and after melatonin concentration increased to and remained above 4 pg/mL [31, 32].

The Sadeh algorithm was used to score epochs as sleep or wake [33, 34]. According to the established protocols, each sleep episode reported in the parent diary was inspected in the activity data starting 15 min before and 15 min after the reported bedtime and wake time, respectively [35–37]. If epochs of low activity existed outside of the scoring interval or if nonwear time occurred during the interval, a consensus was reached by the research team. Nights were considered valid if the participant provided 20 min of wear time before sleep onset. Nonwear time in the hour before bedtime had to be less than 60 min unless confirmed by the wear log, or unless ambient light data were available to confirm bedtime. Sleep onset was defined as the first three consecutive epochs scored as sleep. Sleep offset was defined as the last five consecutive minutes of sleep occurring before 15 min after the reported wake-up. Sleep midpoint was defined as the midpoint between sleep onset and offset.

Circadian phase prediction

Previous studies have suggested that activity data can be used with mathematical models for the prediction of circadian phase [27, 29]. Light data collected by wrist-worn devices may not be representative of the light received by the eye due to placement on the wrist and not close to the eye [38], the potential of being covered by clothing, or to limitations of the device themselves. Due to the limited data regarding the accuracy of light measurements with wrist-worn GT3X-BT devices [39], a visual inspection of plots of activity and light data across subjects was conducted (see Supplementary file). Additionally, the fraction of 6-minute bins (interval used for passing the data into the model) coded as awake in which detected ambient light levels were <1.0 lx and activity levels were > 0 steps was calculated. In our actigraphy data, 54% of the intervals had lux values that were likely underestimated or missing (e.g. obstructed by clothing) during wake time. For comparison, we applied the same procedures to publicly available actigraphy and ambient light data collected from the Hispanic Community Health Study/Study of Latinos (in the Sueño ancillary study; n = 2252; 18–74 years old). Using the same operationalization of missing data collected under similar conditions (Philips Actiwatch worn for 1-week [40–42]), the percentage of intervals that were underestimated or missing was 22%. Due to the substantial amounts of missing light data during periods of daytime activity, we conducted additional testing of the light monitor (see Supplementary file). As a result of the significant percentage of intervals with missing/underestimated light data and additional testing of the light sensor, we chose to use the activity data as a proxy for light exposure. All available data were used for each subject.

Model simulations of the Hannay model were conducted using Runge–Kutta 45 numerical integration written in Python. Code to run these models on Actiwatch data is provided at https://github.com/khannay/Circadian-DLMO-Prediction. Briefly, the Actigraph time series data were binned into 6-minute intervals. Activity measurements were summed within each 6-minute bin, and the total lux exposure was estimated as 10.0 times these activity levels in each bin. These data were linearly interpolated and used as the light input to the Hannay model. Model initial conditions were chosen to match the expected state for an entrained subject with 16 h of light from 0800 to 0000 and an eight-hour dark period. For all subjects in the study, the choice of initial condition did not have any significant effect on the prediction accuracy. Phase estimates for the DLMO were calculated as the time the model phase crossed the threshold $5\pi/12$ on the day the experimental measurement was taken.

Statistical analyses

Descriptive analyses were conducted using analysis of variance to assess for differences between males and females across children's sleep/wake and circadian parameters. To assess for agreement between estimates of DLMO, DLMO was approximated using regression equations for estimating DLMO phase based on sleep times developed in a sample of adolescents [19]. The phase angle for mid-sleep was calculated by taking the midpoint of the phase angle for sleep onset and offset. The mean absolute error and percentage of participants with a predicted DLMO within 1 h of measured DLMO were calculated, a standard for the accuracy of mathematical models [29]. The range of estimated DLMO was compared to the range of measured DLMOs to determine the percentage of true DLMOs captured within the

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range of the predicted DLMO. Lin's Concordance Correlation Coefficient (LinCCC) was used to assess agreement between predicted DLMO (novel assessment) and in-lab DLMO (gold standard measurement). LinCCC is a rigorous assessment because it compares deviation from perfect agreement (i.e. line-of-slope-one) [43] as opposed to a regression line that allows for bias (i.e. line-of-best-fit). In accordance with Cohen's guidelines on strength of agreement, weak, moderate, and strong agreement was determined with a LinCCC 0.0–0.59 (weak), 0.6–0.79 (moderate), 0.8–1.0 (strong). LinCCC was computed using a publicly available SPSS macro https://doi.org/10.1371/journal.pone.0239931.s002 and compared to the linear association of variables calculated using bivariate regression. The Bland–Altman method was used to evaluate bias between the methods and to estimate an agreement interval within which 95% of the differences fall [44]. Sensitivity analyses were conducted to determine whether the accuracy of Hannay model predictions differed according to children's age, sex, or race/non-Hispanic ethnicity. Analyses were conducted using SPSS software version 28 (2021, IBM Corp., Armonk, NY) and Prism version 9.2.0 (2021, GraphPad Software, LLC, San Diego, CA).

Results

Descriptive analyses

A total of 33 children were recruited in year one of the clinical trial which began in 2021. Four children were excluded due to indeterminable timing of DLMO (n = 2) and Actigraph technical errors (n = 2), resulting in 29 children being included in the current analyses (14 females) with a mean age of 7.4 years (SD =.97, range: 5.4–8.6). The sample was representative of the Houston area demographics (17% Non-Hispanic Black, 28% Non-Hispanic White, 3.5% Non-Hispanic American Indian, 3.5% Pacific Islander, 10% Hispanic Black, 38% Hispanic White or Native American). According to parent report, 83% of children attended in-person school while 17% participated virtually during spring 2021. Children's sleep/wake and circadian parameters are presented in Tables 1 and 2. There were no significant differences in the sleep/wake and circadian parameters by sex.

Examination of agreement between DLMO phase and its proxies

DLMO estimates based on sleep onset ranged between 7:46 pm and 9:18 pm and captured 59% of the true values of measured DLMO (Table 3). The average mean absolute error was 38 min with 86% of predictions falling within ± 1 hour of the observed DLMO. The LinCCC was 41 indicating weak agreement (lowest agreement for all the DLMO proxies) (Figure 1A). The Bland–Altman plot revealed an average bias of 0.17 ± 0.9 h with a wide range of 95% limits of agreement from –1.5 to 1.9 (Figure 2A). The plot of the difference vs. the average of the measures reveals a positive trend with consistent spread across the regression line, suggesting an inability to identify DLMO at the extremes: early DLMOs are not estimated as early enough, while late DLMOs are not estimated as late enough.

DLMO estimates based on sleep midpoint ranged from 7:32 pm to 10:01 pm and captured 83% of the true values of measured DLMO. The average mean absolute error was 35 min, with 90% of predictions falling within ± 1 h of the observed DLMO. The LinCCC was 59, indicating weak–moderate agreement, but the best agreement of the sleep variables (Figure 1B). The Bland–Altman plot for mid-sleep revealed an average bias of 0.07 ± 0.8 and a range of 95% agreement from –1.5 to 1.6 (Figure 2B). The plot of the difference vs. the average of the measures reveals a positive trend with a consistent spread from the regression line, again suggesting poor descriptive ability at the extreme DLMO values.

DLMO estimates based on sleep offset ranged from 7:47 pm to 9:58 pm and captured 63% of the true values of measured DLMO. The average mean absolute error was 38 min, with 69% of predictions falling within ± 1 h of the observed DLMO. The LinCCC was 0.52 indicating weak agreement (Figure 1C). The Bland–Altman plot revealed a bias level of 0.03 ± 1.1 (the lowest of all the DLMO proxies) and a range of 95% agreement from –1.6 to 1.6 (Figure 2C). The plot of the difference vs the average of the measures again reveals a bias.

DLMO estimates based on the Hannay model ranged from 7:18 pm to 10:36 pm and captured 93% of the true values of measured DLMO. The average mean absolute error was 31 min (the lowest of all the DLMO proxies) with 93% of predictions falling within ± 1 h of the observed DLMO. Predictions from the Hannay

Table 1. Descriptives of children's sleep/wake behaviors

	Mean	SD[1]	Minimum	Maximum
Sleep onset (24-h time)				
Sex				
Male	21:53	46	20:27	23:07
Female	22:14	53	21:04	23:55
Total	22:03	50	20:27	23:55
Sleep midpoint (24-h time)				
Sex				
Male	2:23	40	1:06	3:39
Female	2:48	48	1:49	4:39
Total	2:35	45	1:06	4:39
Sleep offset (24-h time)				
Sex				
Male	6:53	41	5:45	8:13
Female	7:23	49	6:32	9:22
Total	7:08	46	5:45	9:22

[1]Minutes.

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Table 2. Descriptives of children's predicted and measured circadian parameters

	Mean	SD[1]	Minimum	Maximum
DLMO phase (24-h time)				
Sex				
Male	20:20	50	19:08	22:09
Female	20:59	76	19:33	23:31
Total	20:39	65	19:08	23:31
Hannay model predicted DLMO (24-h time)				
Sex				
Male	20:29	39	19:18	21:48
Female	20:43	61	19:18	22:36
Total	20:36	51	19:18	22:36
DLMO phase to sleep onset (mins)				
Sex				
Male	93	37	30	139
Female	74	57	-71	149
Total	84	48	-71	149
DLMO phase to sleep midpoint (mins)				
Sex				
Male	363	38	295	412
Female	349	49	237	416
Total	356	43	237	416
DLMO phase to sleep offset (mins)				
Sex				
Male	633	44	536	690
Female	624	48	525	696
Total	629	45	525	696

[1]Minutes.

Table 3. Comparison of DLMO proxy predictions across models

DLMO Proxy	Range of Predicted DLMO		Mean Absolute Error (min)	% of DLMOs Falling within Range of Proxy	% within 1h of Measured DLMO	LinCCC*	Bias (SD)	Bland Altman 95% Limits of Agreement		Limits of Agreement Distance
	From	To						From	To	
Onset[1]	19:46	21:18	38	59	86	0.41	0.17 (0.9)	-1.5	1.9	3.4
Offset[1]	19:47	21:58	38	69	83	0.52	0.03 (0.8)	-1.6	1.6	3.2
Midpoint[1]	19:32	22:01	35	83	90	0.59	0.07 (0.8)	-1.5	1.6	3.1
Hannay Model	19:18	22:36	31	93	93	0.79	0.05 (0.6)	-1.2	1.3	2.5

*Presented in ascending order of Lin's CCC. Hannay model Lin's lower one-sided 95% CL = 0.65.
[1]DLMO calculated using formulas developed to predict DLMO phase based on sleep wake variables among Adolescents (Crowley et al., 2006).

model produced the highest LinCCC (ρ_c = 0.79; lower one-sided 95% CL = 0.652, Figure 1D), suggesting moderately strong agreement with measured DLMO [43] as opposed to the models using sleep/wake proxies that produced weaker agreement (onset ρ_c =0.41, offset ρ_c = 0.52, and midpoint ρ_c = 0.59). According to the Bland–Altman analysis, the Hannay model had a similar average bias (0.05 ± 0.6), but the smallest range of 95% agreement (–1.2 to 1.3, Figure 2D). The plot of the difference vs. the average of the measures reveals a positive trend, though one which is markedly weaker than the other proxies.

Sensitivity analysis

Errors in prediction of DLMO were not explained by child age, sex, race/ethnicity, or virtual vs. in-person schooling; however, there was a significant difference in the mean absolute error of DLMO predicted by sleep onset and midpoint depending on the number of scorable nights ($F(2, 26) = 8.63$, $p = .001$, $\eta^2 = 0.40$; 95% CI: 0.9 to 0.6 and $F(2, 26) = 4.26$, $p = .025$, $\eta^2 = 0.24$; 95% CI: 0.0–0.5). Post hoc analysis revealed that DLMO predictions using sleep onset and midpoint were poorer when using four nights of actigraphy (mean for sleep onset 2.0 and offset 1.4) compared to six (mean for sleep onset 0.3 and offset 0.4), and seven (mean for sleep onset 0.5 and offset 0.5) nights of actigraphy.

Examination of agreement with the line of best fit

To facilitate comparison with previous studies conducted among youth [19], we examined the bivariate linear association between DLMO phase and DLMO proxies. The percentage of the variance in DLMO phase explained by sleep onset, midpoint, offset and the Hannay model was 47%, 56%, 52%, and 67%, respectively.

Discussion

Sleep/wake patterns have shown validity as proxies for DLMO phase among adolescents aged [9–17, 19]; however, an overreliance on sleep/wake parameters may mask

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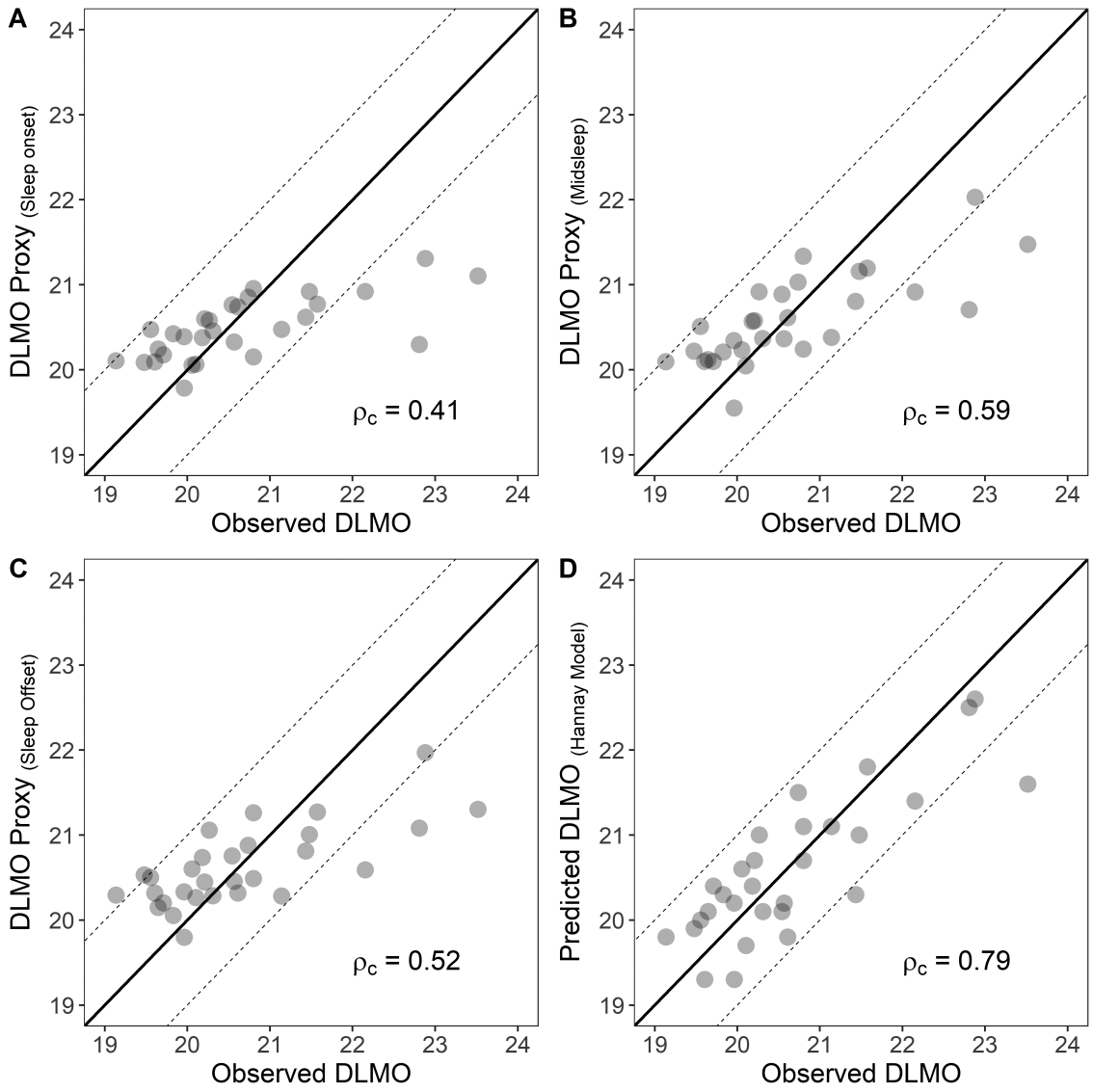

Figure 1. Comparison of DLMO Predictions using sleep timing and the Hannay Model.

inter-individual differences in light sensitivity and the endogenous pacemaker [20,21]. The regression equations developed by Crowley et al. were originally developed to predict adolescents' DLMO phase using self-reported sleep times. The current study extended these findings to elementary school children ages 5–8 years old to examine agreement between measured DLMO phase and DLMO phase estimated using the Crowley regression equations. In the current study, children's sleep onset, midpoint, and offset were assessed by wrist actigraphy instead of self-reported sleep. In addition, the current study leveraged advances in wearable technology and mathematical modeling of human circadian entrainment to examine the ability of a physiologically based circadian limit cycle oscillator model (i.e. Hannay model) to improve upon traditional sleep/wake parameters in the prediction of DLMO phase [29].

Similar to the results obtained with adolescents, the regression equations using children's sleep onset, midpoint, and offset estimated 86%, 90%, and 83% within ±1 h of measured DLMO. While the regression coefficients for DLMO predicted using sleep/wake behaviors were stronger in the child sample compared to the adolescent sample, the same general pattern was observed with sleep midpoint explaining the greatest variance (56%) in measured DLMO. The Hannay model improved predictions, estimating 93% within ±1 h of measured DLMO and explained 67% of the variance in DLMO phase.

One of the limitations of examining agreement using regression coefficients is that regression examines the deviation of data points from the line of best fit rather than the deviation from perfect agreement with the gold standard [29]. Calculating the LinCCC is one way to address this limitation [43]. When examining deviation from perfect agreement, the DLMO predictions obtained using sleep onset, offset, and midpoint demonstrated weak agreement with true DLMO (LinCCCs: 0.41, 0.52, and 0.59), while the DLMO predictions by the Hannay model demonstrated moderately strong agreement (LinCCC = 0.79)[43]. Indeed, the LinCCCs for the other sleep/wake proxies fell below the lower bound of the one-sided 95% confidence interval for the Hannay model (0.65), suggesting that the differences in magnitude are reliable. The results for the Hannay model are similar to those obtained for other DLMO predictions made by mathematical

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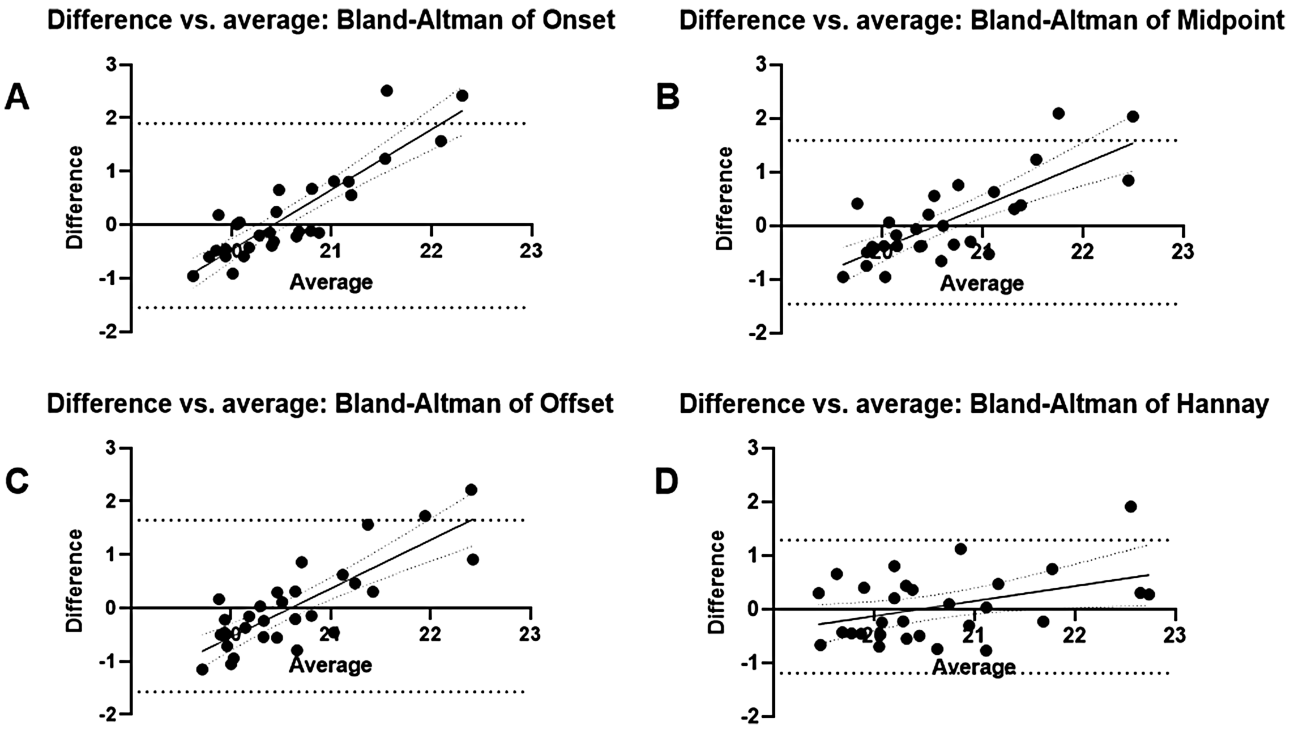

Figure 2. Bland Altman plots of agreement between DLMO phase and its proxies.

models across different adult samples [27, 29]. The similarity in agreement across populations is surprising given the fact that the Hannay model was entirely fit to adult data. Indeed, one potential explanation for the lack of higher agreement among a child population is that this model was developed based on adult physiology and phase response curves [26, 30, 45]. Specifically, there is evidence that children may differ in important ways from adults. For example, the effect of evening light exposure among elementary school-age children has been shown to be twice that of adults in terms of the magnitude of their melatonin suppression, possibly due to having larger pupil sizes and clearer lenses relative to adults [30]. However, the impact of this increased sensitivity on the circadian timing of young children is unknown. Other factors that may affect the accuracy of adult models for children include potential developmental changes in circadian period and homeostatic drive to sleep. For example, there is evidence that adolescents experience changes in their homeostatic drive that facilitate a circadian phase delay in adolescents [46–48]. The extent to which development affects the circadian and homeostatic processes among elementary school children is understudied. A better understanding of circadian entrainment and response to light across the circadian clock may help to further improve DLMO predictions among children.

The Bland–Altman plots revealed a similar level of bias across the DLMO proxies and illustrated that all proxies struggled to accurately predict the DLMO phase of children with later DLMOs. This is likely because parents are socialized to avoid later bedtimes in young children. However, the Hannay model had a tighter range of agreement suggesting higher agreement. One reason that the Hannay model may produce more robust predictions is that it takes activity and light as inputs into the circadian system as opposed to using sleep/wake timing as a proxy of the system. While activity and light are both subject to external factors, they are still integrated into the human circadian system to influence the physiological outputs (e.g. DLMO and core body temperature minimum). In contrast, while sleep/wake timing is an output of the circadian system, it is complicated by multiple factors that further modulate the occurrence of these events such as physiological differences in light sensitivity which can be accounted for by mathematical models [20, 21]. As such, it is not surprising that there is more noise when using sleep/wake timing as proxies for circadian phase. Furthermore, the error associated with sleep/wake timing as a proxy for circadian phase is not uniform as parents are more likely to enforce a bedtime before DLMO, especially for children with later chronotypes.

Strengths of the study include the use of objectively assessed sleep and gold standard assessment of circadian phase collected within spring of the same year, limiting potential impact of variation in the solar day on the findings. Limitations of the current study include this being a secondary analysis of data being collected as part of an ongoing clinical trial. As such, this study has a limited sample size (n = 29), though the statistics used to assess concordance are robust to deal with sample sizes as small as 10 [43]. Regardless, the small sample size makes it challenging to examine differences in sleep and circadian parameters by sex, race/ethnicity, and age and to explore factors associated with error. In the current study, there were no differences in sleep and circadian phase found across demographics, though others have observed sex differences in these variables among adolescents [19]. Additionally, the Hannay model was intended to be used with light as the input to the model; however, there is evidence that activity data can yield more accurate predictions when used as the input, possibly because activity is not only an input to the circadian system but also due to the limitations of using light measured by wrist-worn devices [27, 29]. As a result, the activity data were used as a proxy for light in the Hannay model. Another source of potential error is in the method used to estimate DLMO from saliva samples. Because linear interpolation was used to

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estimate the time at which melatonin rose above 4 pg/mL, it assumes a steady rise in melatonin between samples. Furthermore, hourly saliva samples were used in the current study instead of 30-minute sampling which may introduce error in the estimation of "true DLMO." An additional limitation is that while mathematical models hold promise to improve predictions of DLMO phase, they can be nontrivial to set up and run (though they operate directly on actigraphy data and require no manual sleep scoring from actigraphy and sleep diaries). On the other hand, the use of sleep/wake regression equations requires scoring of actigraphy data which is time-intensive. If the only goal of the actigraphy data is to estimate circadian phase, these results suggest that efforts should be focused on the preparation of the data and code for running the mathematical model rather than the scoring of sleep/wake timing.

Conclusions

Overall, these results suggest that physiologically informed models of circadian entrainment can facilitate more accurate predictions of children's circadian phase using data collected from wearable devices than sleep/wake behaviors. Physiologically informed models can be used to identify and account for inter-individual physiological differences in factors such as light sensitivity and intrinsic period thereby improving prediction of circadian phase [23]. Accurate predictions of circadian parameters derived from wearable devices offer promise for future studies seeking to assess circadian parameters in children and significantly reduce participant burden associated with more invasive, burdensome, and time-intensive methods of assessing circadian parameters.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Author Contributions

Concept, design, and interpretation by Moreno, Hannay, Walch, and Cheng. Analysis by Moreno and Hannay. Funding obtained by Moreno. Supervision of data collection and study management: Moreno, Bacha, Dadabhoy. Data collection by Dadabhoy, Christian, El-Mubasher, Grant, and Park. Actigraphy scoring and extraction of sleep parameters: Moreno, Christian, Puyau. Application of the Hannay Model by Hannay. Drafting of the manuscript: Moreno. Critical intellectual input and revision of the manuscript: Hannay, Walch, Cheng, El-Mubasher, and Bacha. All authors approved the final version of the manuscript.

Data Availability

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

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