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Original Research Article

Investigating the Sleep–Pain Relationship in Youth with Sickle Cell Utilizing mHealth Technology

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Abstract

Objectives The current study utilized mHealth technologies that were objective (e.g., sleep actigraphy and pulse oximetry) and time-sensitive (e.g., ecological momentary assessments [EMAs]) to characterize sleep in youth with sickle cell disease (SCD) and investigate the relationships between sleep variables and pain. It also investigated the influence of age on sleep and the sleep–pain relationship. **Methods** Eighty-eight youth with SCD (aged 8–17 years) were recruited from three regional pediatric SCD clinics. Youth completed twice daily EMAs for up to 4 weeks to assess nighttime subjective sleep quality and daily pain. They also wore a sleep actigraph for 2 weeks to assess sleep duration, sleep efficiency, and sleep latency, and a wrist-worn pulse oximeter for two nights to assess whether they had sleep apnea. Multilevel models were calculated predicting daily SCD pain using the sleep variables, age, and the interaction between age and the sleep variables. **Results** None of the sleep variables were related to one another. Poor subjective sleep quality during the night was related to high pain severity the next day, and high pain was related to poor subjective sleep quality that night. Older age was associated with poorer subjective sleep quality, shorter duration of nighttime sleep, and high sleep latency. Also, findings indicated that as age increased, the strength of the relationship between poor continuous subjective sleep quality and high pain severity increased. **Conclusions** Future research is needed to examine possible mechanisms connecting subjective sleep quality to high pain.

Key words: pain; sickle cell; sleep.

Introduction

Sickle cell disease (SCD) refers to a group of inherited red blood cell disorders characterized by the presence of abnormal red blood cells damaged by an abnormal variant of hemoglobin, HbS. It is estimated that approximately 100 000 individuals in the United States have SCD (Hassell, 2010), and approximately

300 000 infants around the world are born each year with SCD, with this number expected to increase (Piel et al., 2013). Poor sleep is a common occurrence in youth with SCD (Gileles-Hillel, Kheirandish-Gozal, & Gozal, 2015; Valrie, Bromberg, Palermo, & Schanberg, 2013). A study of 66 youth with SCD, aged 10–17 years, found that 91% of the youth reported mild to severe sleep disturbances in the past month and their average global sleep quality score on the Pittsburgh Sleep Quality Index was poor (Graves & Jacob, 2014). Also, youth with SCD evidence a high incidence of sleep disorders (e.g., insomnia, restless leg syndrome, sleep apnea; Hankins et al., 2014). For example, 36% of youth with SCD evidence some form of sleep disordered breathing, including sleep apnea, based on findings from overnight laboratory-based polysomnography studies (Samuels, Stebbens, Davies, Picton-Jones, & Southall, 1992). Also, children and adolescents with SCD evidence more sleep disturbances than demographically similar healthy control samples (Daniel, Grant, Kothare, Dampier, & Barakat, 2010; Valrie et al., 2018).

Notably, poor sleep in youth with SCD has been linked to pain, the most prevalent complication associated with SCD, and also the primary factor leading to poor health outcomes and increased medical costs for this population (Ballas, 2007; Chaturvedi & Debaun, 2016). Sickle cell disease pain varies greatly both between individuals and across the lifespan of individuals, with the likelihood of experiencing pain increasing as the individual with SCD ages (Platt et al., 1991). Evidence indicates a cyclic relationship between poor sleep and high pain severity in youth with SCD, with pain relating to poorer sleep at night and poor sleep relating to high pain the next day (Fisher et al., 2018; Valrie, Gil, Redding-Lallinger, & Daeschner, 2008). These findings are consistent with a Model of the Pain–Sleep Relationship in Pediatric Persistent Pain Populations (Valrie et al., 2013). This model posits that, for youth with persistent pain, there are bidirectional relationships among pain, sleep, physiological/biological factors, and mood, such that high pain, poor sleep (as measured using both subjective and objective assessments), higher disease severity, and negative mood are all risk factors for one another. Additionally, these factors and the relationships between these factors are influenced by a host of biological and sociodemographic factors, such as age. Age has been strongly linked to sleep in healthy youth. Particularly, adolescence is noted as a time of inadequate sleep and poor sleep quality in comparison to childhood (Bartel, Gradisar, & Williamson, 2015). However, most studies examining sleep in youth with persistent pediatric pain fail to examine the influence of age on sleep or the relationship between sleep and pain, which may change as sleep problems escalate across the pediatric years.

While preliminary evidence exists for the applicability of the Pain–Sleep Relationship model for understanding the relationship between pain and sleep in youth with SCD, there are significant gaps in this research. Specifically, none have investigated the influence of age on sleep or the influence of age on the relationship between sleep and pain. Also, few studies examining sleep in youth with SCD have utilized time-sensitive or objective assessments of sleep, particularly in the home environment, such as ecological momentary assessment (EMA), actigraphy, and overnight pulse oximetry. Ecological momentary assessment allows for the examination of daily fluctuations in self-reported subjective sleep quality. Whereas, actigraphy, which uses movement to detect sleep and wake patterns, provides more objective indications of sleep summarized over multiple nights (Ancoli-Israel et al., 2015). Lastly, overnight pulse oximetry, which assesses the amount of oxygen in the blood, can be used as a screener for sleep apnea by detecting dips in oxygen levels resulting from significant reductions (i.e., hypopneas) or interruptions (i.e., apneas) in breathing (Dehlink & Tan, 2016).

Only one study has used EMA to examine the relationship between sleep and pain in youth with SCD (Valrie et al., 2008). It focused exclusively on children (aged 8–12 years) and used paper and pencil daily surveys, which are more likely to be influenced by recall bias. Results from the study indicated that poor subjective sleep quality was related to high pain the following day, and that high pain during the day was related to poor subjective sleep quality that night. Also, only one study has examined sleep in youth with SCD utilizing actigraphy data, which it paired with once daily reports of pain (Fisher et al., 2018). Results indicated that worse sleep efficiency was associated with pain occurrence and high pain severity the next day. In addition, high pain severity was associated with worse sleep efficiency and higher wake times after sleep onset. Notably, the age range of the sample was broad (i.e., 8–18 years) and the small sample size of 30 youth did not allow for an examination of possible age differences in the relationships between sleep variables and pain. No studies have used home-based overnight pulse oximetry to examine the sleep–pain relationship. However, studies have consistently linked sleep apnea to higher general pain ratings in individuals with SCD, indicating that lowered oxygen levels due to sleep apnea may lead to increased sickling of red blood cells and subsequently increased vaso-occlusion and pain (Gileles-Hillel et al., 2015). Notably, previous studies have failed to examine the relationship between sleep apnea and SCD pain in the context of other sleep variables. This research is needed to determine the possible comorbidity of sleep apnea with other indicators of poor sleep in

individuals with SCD, and to distinguish the unique relationships between sleep apnea, other sleep variables, and pain.

In conclusion, research is needed to identify what specific sleep variables (e.g., subjective sleep quality, sleep duration, efficiency, latency, and sleep apnea symptoms) are most linked to daily pediatric SCD pain over and above the other variables. Also, the influence of age on sleep in the population and the relationship between sleep and pain needs to be investigated. This would allow for a more rigorous testing and refining of the Model of the Pain–Sleep Relationship in Pediatric Persistent Pain Populations for youth with SCD, which can then be used to both guide future research and the development of targeted interventions for sleep and pain in the population. Thus, the primary aim of the current study is to utilize mHealth technologies that provide both time-sensitive (e.g., EMA) and objective (e.g., sleep actigraphy and pulse oximetry) assessments to (a) more fully characterize sleep in youth with SCD, and (b) investigate the unique relationships between sleep variables as assessed across multiple mHealth technologies and daily SCD pain. It is hypothesized that both subjective and objective sleep variables indicative of poor sleep will be related to higher SCD pain. A secondary aim was to investigate the influence of age on sleep and on the relationships between sleep variables and pain in youth with SCD. It is hypothesized that older youth will exhibit poorer sleep quality than younger youth with SCD, and that the strength of the relationships between sleep variables and daily pain severity will vary based upon age.

Methods

Participants

Participants were recruited as part of a larger study investigating sleep, pain, and related factors in youth with SCD. Youth with SCD and their guardians were recruited from three regional pediatric SCD clinics in the southeastern United States during the youth's scheduled appointments. Inclusion criteria for the larger study included being aged 8 years to 17 years, English speaking, diagnosed with SCD, and having had at least one SCD pain episode in the past year (i.e., at least 20 min of SCD pain). Exclusion criteria included having a comorbid pain condition, neurological impairment that would impede completion of the surveys, a history of extreme noncompliance as indicated by the health-care provider, being on chronic blood transfusions, or currently receiving a sleep intervention (i.e., taking sleep medication or on continuous positive airway pressure therapy). Additional inclusion criteria for the current study was completing at least 2 weeks (24 entries) of daily EMA data.

The final sample for the current study consisted of 88 youth aged 8 years to 17 years ($M = 11.66$, standard deviation [SD] = 2.99) out of the total 123 youth who participated in the larger study (72% of the total sample). The majority of the final sample was female ($n = 52$, 59%), and was currently prescribed hydroxyurea ($n = 46$, 54%). Also, the majority had sickle cell genotype HbSS ($n = 44$, 50%), 27 had HbSC (31%), 12 had HbSβ^+ (14%), 3 had HbSβ^0 (3%), and 2 had another SCD genotype (2%). The final sample of youth did not significantly differ in relation to age, sex, SCD genotype severity, or whether they were currently prescribed hydroxyurea when compared with the youth in the larger study.

Procedure

The study procedure was approved and monitored by the primary and secondary sites' institutional review boards. Written informed consent and assent were obtained from the guardians and youth, respectively, prior to beginning data collection. First, the youth and their guardians were administered measures, which included assessments of demographic and disease information. Medical chart reviews were conducted at a separate time to confirm and gather additional disease information. After completing the measures, the youth were asked to complete the daily EMA, which consisted of brief surveys administered via an app twice a day (i.e., in the morning and evening), for up to 4 weeks on either an Apple or Android device they owned or that was provided to them as part of the study. The morning survey assessed youth's sleep the night before and the evening survey assessed their pain and mood during the day. The youth, with consultation from their guardians, determined preselected times to set an alarm every morning and evening on the devices to remind them to complete the surveys. Study staff contacted the youth once a week via phone and mail to provide feedback on compliance, provide encouragement to complete the EMAs, and problem solve technical and other issues.

Also, youth were asked to wear a sleep actigraph for the first 2 weeks of the survey period, and a wrist-worn pulse oximeter for the first two nights of the survey period. At least five nights of actigraph data is designated as the minimum to produce reliable sleep variable estimates (Acebo et al., 1999); thus, 2-week assessment periods were chosen to maximize the chances of collecting five nights of usable actigraph data. In addition, overnight pulse oximetry is usually conducted over one night; however, a recent study indicated there is substantial variability in overnight pulse oximetry assessments over sequential nights (Burke et al., 2016). Thus, a one-night assessment period may underestimate rates of sleep apnea, and a two-night assessment period for overnight pulse oximetry was

chosen to increase accuracy of assessment while not overly burdening participants. Guardians and youth received $20 Walmart Gift Cards for completing the initial assessments, and the youth received up to an additional $40 for completing daily EMAs and wearing the sleep actigraph and pulse oximeter.

Measures

Demographic and Disease Information

Guardians reported on the youths' age, sex (0 = male and 1 = female), and SCD genotype. For the primary analyses, SCD genotype was coded as 1 for severe genotypes (e.g., HbSS and HbS/β^0), and 0 for moderate genotypes (e.g., HbSC and HbSβ+, or other). Medical chart reviews were done to confirm SCD genotypes, and to assess whether the youth were currently prescribed hydroxyurea.

EMA of Daily Mood

As part of the evening survey of the daily EMA completed for up to 4 weeks, youth were asked to complete 10 items from the Positive and Negative Affect Schedule for Children (PANAS-C; Laurent et al., 1999). The PANAS-C is a 20-item self-report measure that assesses levels of positive and negative affect. Youth are asked to rate how much of each emotion they were feeling today using a scale ranging from 1 (*very slightly or not at all*) to 5 (*extremely*). The items chosen included five assessing negative affect and five assessing positive affect, and the five items in each area were then summed to produce a number between 5 and 25. The items have been found to be valid and reliable for children and adolescents with juvenile arthritis in a daily diary format (Connelly et al., 2012).

Actigraph

The youth wore the Motionlogger Micro Actigraphs (Ambulatory Monitoring, Inc., Ardsley, NY, USA), which are the size of wrist-watches and worn on their nondominant wrists, for up to 2 weeks. Actigraphs are designed to electronically monitor movement, which is then recorded in 1 min epochs. Actigraphic data are compared with the EMA data to screen for potential artifacts, such as removal of the actigraph watch. Then the data are converted into relevant sleep variables using the Analysis Software Program (ActionW2), which features reliable and well-validated sleep and wake algorithms developed by Sadeh, Sharkey, and Carskadon (1994). Each youth's average scores for all nights studied were used to calculate the following sleep variables: sleep duration (i.e., total time between sleep onset and sleep offset), sleep efficiency (i.e., the percent of time asleep versus in bed), and sleep latency (i.e., the length of time between first attempting to sleep and sleep onset). At least five nights of actigraph data have been established as the minimum to ensure reliability of the data (Acebo et al., 1999). Thus, actigraph data from youth with less than five nights were excluded from analyses.

Pulse Oximetry

Youth were asked to wear a mobile, wrist oximeter (WristOx 3100 or 3150, Nonin Medic, Inc.) on their dominant wrist for two nights to assess continuous levels of oxygen saturation (SaO_2), specifically examining for sleep apnea symptoms. The pulse oximeter consists of a finger sensor attached to a minicomputer the size of a wrist watch and attached to the wrist. Youth were trained to put the pulse oximeter on, and the interviewer preset the device to turn on and off when attached to a finger and to record in 1-min epochs prior to giving it to the youth. Raw data were downloaded and movement-related artifacts were removed. Then Nonin's nVision Data Management Software was used to analyze the data. Criteria for detecting sleep apnea in youth includes an apnea-hypopnea index (AHI) of one or more, which is indicative of an average of one or more apneas or hypopneas per hour across the night (Dehlink & Tan, 2016). Across the two nights, the AHI was calculated based upon the number of dips (<4% from baseline) in oxygenation per hour associated with acute pulse rate rises, which is a pattern suggestive of apneas-hypopneas (Kirkham et al., 2001). Youth in the current study were then categorized using the following criteria: <1 AHI = no sleep apnea, 1≤ AHI ≥5 = mild apnea, 5≥ AHI = moderate to severe, which is consistent with how the majority of sleep centers classify apnea symptoms in youth (Dehlink & Tan, 2016). Pulse oximetry data from youth with less than 2 hr of data were excluded from analyses.

EMA of Daily Sleep

As part of the morning survey of the daily EMA completed for up to 4 weeks, youth were asked to rate their sleep quality on a visual analog scale (VAS) consisting of a 100 mm line anchored at "did not sleep well" (0 mm) to "slept very well" (100 mm) with instructions to "please move the marker on the line to show how well you slept last night." They were also asked to report what time they went to bed and woke up, which was used to clean the actigraph data. Research views daily diary assessments as the "gold standard" for assessing sleep (Wolfson et al., 2003), and studies have provided support for the reliability and validity of child completed daily sleep logs (Gaina, Sekine, Chen, Hamanishi, & Kagamimori, 2004; Sadeh, Raviv, & Gruber, 2000).

EMA of Daily Pain

As part of the evening survey of the daily EMA completed for up to 4 weeks, youth were asked to report

whether they experienced any SCD pain during the day. If so, the youth were asked to rate their average pain severity that day on a 100 mm horizontal VAS ranging from "not hurting at all" (0 mm) to "hurting a whole lot" (100 mm). If the youth indicated no pain on that day, their pain severity rating was automatically coded as 0. Research has provided support for the reliability and validity of the VAS in assessing daily SCD pain in children and adolescents (Gil et al., 2003; Valrie, Gil, Redding-Lallinger, & Daeschner, 2007).

Data Analysis Plan

Statistical analyses were conducted using SAS/STAT® software, Version 9.4 of the SAS System for Windows (SAS/STAT, 2013). First, descriptives of the demographic, disease characteristics, daily mood and pain, and sleep variables derived from the EMAs, actigraphs, and pulse oximeters were calculated. Pearson product correlations were calculated to examine the relations among age, the continuous sleep variables, and pain. *T*-tests were calculated to examine group differences based on sex and sleep apnea status for age, the other sleep variables, and pain. To investigate the unique relationships between sleep variables and daily SCD pain, multilevel models (MLMs) were calculated using SAS PROC MIXED using restricted maximum likelihood estimation and an unstructured between-person error structure. A continuous-time autoregressive within-person error structure was used to control for time by regressing current observations on more recent observations, which takes into account that observations which are more proximate are more correlated than measures that are more distant. The random effects components of these models consist of the individuals' intercepts, which allows for the modeling of relationships between the dependent and independent variables when individuals randomly vary in relation to their individual mean level of the dependent variable. For EMA data, the between-person variability was represented by person-centered means, and the within-person variability was represented by the person's daily report. All of the models controlled for daily reports of positive and negative mood at the within-person level, and controlled for the following variables at the between-person level: sex, SCD genotype, whether the youth was currently prescribed hydroxyurea, and person-centered means of the positive and negative mood EMA data. Specific models are detailed below.

To investigate the predictive value of different sleep variables on daily SCD pain, models were calculated predicting daily SCD pain severity using sleep variables: within-person variables consisted of the daily EMA subjective sleep quality rating, and between-person variables included person-centered EMA subjective sleep quality ratings, actigraphy data (sleep duration, efficiency, and latency), and sleep apnea status (AHI $<1=0$ and AHI $\geq 1=1$). To investigate the bidirectional nature of sleep–pain relationship, a MLM predicting daily EMA subjective sleep quality was calculated using daily pain severity from the previous day.

To investigate whether age influenced the relationships between sleep variables and daily pain, age was treated as a between-person level moderator for the sleep–pain relationship. To do this, age was included as a between-person variable and the interactions between age and the predictor factors (e.g., sleep variables in the model predicting daily pain severity and pain in the model predicting sleep) were included in all of the models. Interactions were created by multiplying age by the predictor factors. To decrease collinearity between the variables and interaction terms, age, the sleep variables, and the pain variables were centered prior to calculating the interaction terms. Specifically, age and all of person-level variables were grand-mean centered, and the within-person variables were person-mean centered. Significant interactions were probed using the online interactive calculator for probing interactions developed by Preacher, Curran, and Bauer (2006) and based on techniques discussed in Bauer and Curran (2005). Specifically, the calculator was used to calculate simple intercepts and slopes for the predictors variables at varying levels of age (i.e., mean and ± 1 *SD* of the mean), and to test whether the simple intercepts and slopes were significantly different from 0.

Missing Data

Youth completed an average of 81.87% of possible EMA entries (*SD* = 16.00%, range = 30.36–100%). This resulted in youth completing an average of 51 EMA entries each, which is equivalent to 3.64 weeks (*SD* = 15.18 entries, range = 28–108 entries). This included an average of 25 morning entries (range = 12–54 entries) and 25 evening entries (range = 10–54 entries). In addition, 14 of the 88 youth (16%) had less than five nights of sleep actigraphy data, with the remaining averaging 12.73 nights of usable information (*SD* = 2.63 nights, range = 5–15 nights). Seventeen of the 88 youth (19%) had less than 2 hr of pulse oximetry data, with the remaining averaging 8.55 hr of usable data (*SD* = 4.52 hr, range = 2.4–23.5 hr). Missing data were handled using listwise deletion for the *t*-tests, chi-squares, and correlations detailed below. In the MLM analyses, missing data were handled using full information maximum likelihood (Enders, 2010). Information on the number of youth and data points used for each analysis are detailed in the *Results* section.

Results

Descriptive statistics for age, sleep, and pain data are summarized in Table I. Using EMA, youth reported

high average person-centered mean subjective sleep quality ($M = 74.66$). The actigraphy data indicated that youth had overall good sleep quality as evidenced by low average sleep latency ($M = 7.27$ min) and high average sleep efficiency ($M = 91.79\%$). The average AHI was 2.18, which is in the mild sleep apnea range for pediatric populations (Dehlink & Tan, 2016). Based on AHI, 25.35% of the youth evidenced no sleep apnea, 74.65% evidenced sleep apnea (AHI ≥ 1), and 5.63% evidenced moderate to severe sleep apnea (AHI > 5).

Pearson product correlations were calculated to examine relations between the continuous sleep variables assessed via different methodologies as well as the sleep variables relations to age and pain severity (see Table II). For these analyses, the person-centered means of the EMA data were used. None of the sleep variables were correlated with each other. However, age was negatively correlated with EMA sleep quality ratings and sleep actigraphy sleep duration, as well as being positively correlated with sleep latency. This indicates that older age was related to poorer subjective sleep quality, shorter duration of nighttime sleep, and high sleep latency. As for relations between pain severity, age, and sleep variables, high pain severity was related to low EMA subjective sleep quality and high actigraphy sleep latency. *T*-tests were calculated to examine differences in age, sleep variables, and pain based on sex and sleep apnea status, and no significant differences were found.

Table I. *Descriptives Statistics for Pain and Sleep Data (N = 88)*

	M	*SD*	Range
Age (years)	11.66	2.99	8–17
EMA data			
Percentage of pain days	22.40	26.70	0–100
Pain severity	13.50	18.82	0–88.39
Sleep quality	74.66	16.59	22.07–99.94
Actigraphy data			
Sleep duration (hr)	8.03	0.94	5.27–10.92
Sleep efficiency (%)	91.79	5.39	70.59–99.43
Sleep latency (min)	7.27	2.55	4.36–25.57
Pulse oximetry data			
AHI	2.18	2.55	0–18.5

Note. EMA data presented are based on person-centered means. AHI = apnea-hypopnea index; EMA = ecological momentary assessment; *SD* = standard deviation.

MLM Predicting Daily EMA Pain Severity Using Age and Sleep Variables

Low EMA sleep quality the night before ($t = -3.37$, $p < .01$) predicted high pain severity the next day (Table III). This means that for a 1 point change in sleep quality the model predicts a 0.09 change in pain severity the next day. In addition, the interaction between age and the person-centered EMA subjective sleep quality ratings predicted pain severity. Thus, the relationship between person-centered sleep quality and pain severity was examined at varying ages (i.e., 1 *SD* below the mean age, at the mean age, and above the mean age; see Table III). While none of the simple intercepts and simple slopes were significantly different from 0, the pattern of findings suggests that as age increases, poorer mean sleep quality was more strongly related to high SCD pain severity.

MLM Predicting Daily EMA Sleep Quality Using Age and Pain Severity

Poor EMA sleep quality that night was predicted by older age ($t = -2.49$, $p = .02$), being male ($t = 2.06$, $p = .04$), and higher pain severity the day before ($t = -0.06$, $p = .02$; see Table IV). This means that for a 1 year change in age, the model predicts a 1.42 point change in sleep quality. Being male was related to a 6.74 point reduction in sleep quality. Also, this means that for a 1 point change in pain severity, the model predicts a 0.06 point change in sleep quality the following night. The interactions between age and the pain variables were not significant.

Discussion

The current study focused on rigorously testing aspects of the Model of Pain–Sleep Relationships in Pediatric Persistent Pain Populations (Valrie et al.,

Table II. *Correlations Between Age, Sleep, and Pain Variables*

	1	2	3	4	5	6	7
1. Age	–						
2. EMA—sleep quality mean	−0.32**	–					
3. Actigraphy—sleep duration	−0.36**	0.22	–				
4. Actigraphy—sleep efficiency	−0.22	0.04	−0.11	–			
5. Actigraphy—sleep latency	0.26*	−0.12	−0.06	−0.22	–		
6. Pulse oximeter—AHI	−0.13	0.14	0.03	−0.22		–	
7. EMA—pain severity mean	0.07	−0.23*	0.10	−0.20	0.29*	0.11	–

Note. EMA variables used are all person-centered means. Due to missing data, sample sizes ranged from 58 to 88 participants.
AHI = apnea-hypopnea index; EMA = ecological momentary assessment.
*$p < .05$; **$p < .01$.

Table III. *Multilevel Model Predicting Daily Ecological Momentary Assessment Pain Severity (N = 58 with 1268 Observations)*

	B	SE	*t*	*P*
Level 2: between-person variables				
Age (years)	−1.67	1.87	−0.89	.38
Sex	6.03	5.52	1.09	.28
EMA—sleep quality mean	−0.17	0.19	−0.88	.39
Actigraphy—sleep duration	0.00	0.05	0.05	.96
Actigraphy—sleep efficiency	−0.59	0.56	−1.05	.30
Actigraphy—sleep latency	1.76	1.27	1.38	.18
Pulse oximeter—sleep apnea status	10.83	5.88	1.84	.07
Level 1: within-person variable				
EMA—sleep quality the night before	−0.09	0.03	−3.37	<.00**
Interactions				
Age×EMA—sleep quality mean	−0.12	0.06	−2.07	.04*
Age×EMA—sleep quality the night before	−0.01	0.01	−0.68	.50
Age×actigraphy—sleep duration	0.02	0.02	1.30	.20
Age×actigraphy—sleep efficiency	−0.00	0.16	−0.01	1.00
Age×actigraphy—sleep latency	−0.12	0.27	−0.43	.67
Age×pulse oximeter—sleep apnea status	0.17	2.06	0.09	.93

Conditional relationships of mean EMA sleep quality mean on pain severity at varying levels of age

	Simple intercept	*z*	Simple slope	*z*
Younger age (−1 *SD* below age)	−3.16	−0.18	0.20	0.83
Mean age	−8.16	−0.48	−0.17	−0.88
Older age (+1 *SD* above age)	−13.15	−0.71	−0.54	−1.95

Note. The model controls for SCD genotype, current hydroxyurea prescription, and positive and negative mood. Level 2 EMA variables are all person-centered means. Level 1 EMA subjective sleep quality variable is from the morning report referencing the previous night. EMA = ecological momentary assessment; SCD = sickle cell disease; SE = standard error.
*$p < .05$; **$p < .01$.

Table IV. *Multilevel Model Predicting Daily Ecological Momentary Assessment Subjective Sleep Quality (N = 87 with 1772 observations)*

	β	SE	*t*	*p*
Level 2: between-person variables				
Age	−1.42	0.57	−2.49	.02*
Sex	6.74	3.27	2.06	.04*
EMA—pain severity mean	−0.01	0.10	−0.10	.92
Level 1: within-person variables				
EMA—pain severity previous day	−0.06	0.02	−2.27	.02*
Interactions				
Age×EMA—pain severity mean	−0.02	0.03	−0.83	.41
Age×EMA—pain severity previous day	−0.01	0.01	−1.52	.13

Note. The model controls for SCD genotype, current hydroxyurea prescription, and positive and negative mood. Level 2 EMA variables are all person-centered means. Level 1 EMA pain severity variable is from the evening report referencing pain the previous day. EMA = ecological momentary assessment; SCD = sickle cell disease; SE = standard error.
*$p < .05$.

2018) for youth with SCD by utilizing multiple mHealth technologies to provide both objective and time-sensitive assessments of sleep. In relation to characterizing sleep, youth reported primarily high sleep quality on the EMAs, which is consistent with a previous study of children with SCD (Valrie et al., 2008). Good sleep quality was also evidenced by low sleep latency (<30 min), and high sleep efficiency, with the majority of youth reporting >90% sleep efficiency. The previous study using actigraphs in youth with SCD (Fisher et al., 2018) also found high sleep efficiency (i.e., mean sleep efficiency of 86.42%), though the current study's mean of 91.79% is higher. Notably, using overnight pulse oximetry, the majority of youth (74.65%) evidenced sleep apnea, with an average AHI of 2, which is indicative of mild sleep apnea for pediatric populations (Dehlink & Tan, 2016). This is consistent with research indicating a high rate of sleep apnea in individuals with SCD, but was much higher than current prevalence estimates, that indicate about 36% of youth with SCD evidence sleep disordered breathing, including sleep apnea (Samuels et al., 1992). However, overnight pulse oximetry findings, though considered a good initial screener for sleep apnea symptoms in youth, need to be confirmed by a full overnight polysomnography study to definitively diagnose sleep apnea (Dehlink & Tan, 2016). Thus, the use of pulse oximetry in the current study may have led to an overestimation of sleep apnea symptoms.

As hypothesized and consistent with the Pain–Sleep model and previous pediatric SCD research

(Fisher et al., 2018; Valrie et al., 2008), subjective sleep quality and pain severity did evidence a bidirectional relationship. Specifically, poor subjective sleep quality during the night was related to higher pain the next day, and high pain during the day was related to poor subjective sleep quality that night. The changes in subjective sleep quality and pain severity were related to relatively small subsequent daily changes in the other variable; however, the effects were significant and over and above the influences of other variables linked to SCD pain (i.e., SCD genotype, hydroxyurea use, and changes in positive and negative mood). Contrary to hypotheses, only EMA sleep quality was related to daily EMA pain severity, and none of the objective sleep variables were related. It could be that subjective sleep quality is based on different sleep variables than the objectively measured sleep variables used in the current study. This is consistent with the lack of relations between the sleep variables in the current study, as each of the assessments focused on unique aspects of sleep. EMA provided a subjective assessment of sleep quality, sleep actigraphy focused on characterizing sleep patterns based on movement, and overnight pulse oximetry focused on evidence of sleep apnea as indicated by oxygen saturation levels.

Notably, the lack of a relationship between actigraphy sleep variables and pain severity in the current study was inconsistent with a previous study of youth with SCD (Fisher et al., 2018). One key difference between the studies is that the previous research team matched up daily actigraphy records with the daily pain reports, which is a novel way of using actigraph data as actigraph data are usually summarized across several days (Acebo et al., 1999). Thus, the lack of a relation between the objective sleep variables and daily pain severity in the current study may be due to the data being summarized versus being connected to daily pain fluctuations. Notably, the accuracy and reliability of single night actigraph assessments of sleep variables has not been established for youth. Previous studies indicate that when compared with polysomnography, current actigraphs demonstrate poor specificity in relation to wake agreement, which would significantly impact single night estimates of sleep duration and sleep efficiency (Galland, Meredith-Jones, Terrill, & Taylor, 2014). Thus, current actigraph guidelines recommend assessing sleep across multiple nights to ensure accurate sleep estimates (Acebo et al., 1999; Ancoli-Israel et al., 2015). There is a need for future research into the accuracy of single night actigraph sleep assessments, particularly as sleep actigraphy technology continues to evolve.

Another significant aspect of the Pain–Sleep relationship model was the influence of age on sleep variables and the relations between sleep variables and pain in youth. As hypothesized and consistent with sleep of healthy youth (Hirshkowitz et al., 2015), older age was associated with poor subjective sleep quality, shorter duration of nighttime sleep, and high sleep latency. Also as hypothesized, findings indicated that age influenced the relationship between mean levels of subjective sleep quality and SCD pain severity. Specifically, findings suggested that as age increased, the strength of the relationship between poor person-centered mean levels of EMA subjective sleep quality and high pain severity increased. It may be that the impact of consistently poor subjective sleep quality on pain severity becomes exacerbated over time. Specifically, consistently poor subjective sleep quality early in childhood may be due to a host of factors, but as youth with SCD age, it may become more related to youth experiencing increased inflammation, which is also linked to increased pain (Ameringer & Smith, 2011). Thus, as youth age, the relation between continuously poor subjective sleep quality and pain severity may become strengthened through the connection between poor subjective sleep quality and inflammation. In conclusion, findings indicate that the relation between subjective sleep quality and pain in youth with SCD may be influenced by age. However, research is needed to validate these findings, to further examine how the relation between subjective sleep quality and pain severity may change as individuals age, including during individuals' transitions from childhood to adulthood, and to see if changes in the sleep–pain relationship as individuals' age are related to underlying inflammation processes.

While the current study addresses a number of gaps in the literature, it also has a number of limitations that may have impacted the findings. First, though the overall sample size of the project was large in comparison to other pediatric SCD projects, missing data limited the sample sizes for specific analyses. Notably, the high number of observations per participant and across participants increased the power for the MLM analyses. Also, though we sampled a wide age range of youth and the EMAs allowed for a brief longitudinal aspect to the study, the current study design did not allow for a full examination of the influence of age on sleep in youth with SCD. Specifically, the negative correlation between age and subjective sleep quality may indicate that subjective sleep quality declines across the pediatric years for youth with SCD. Longitudinal research to examine trends in subjective sleep quality and other sleep variables for youth with SCD and related factors may help to identify key transitions points and biopsychosocial factors that would help with creating effective sleep interventions for this population.

Another limitation was the varying lengths of the different sleep assessments. While youth completed

the EMAs for up to 4 weeks, they were only asked to wear the actigraphs for 2 weeks, and the pulse oximeters for two nights. Though these assessment periods were chosen based on current standards for collecting reliable sleep data, they may have exacerbated differences between the sleep variables as they represented different sleep periods. Future research should consider having overlapping sleep assessment periods. Lastly, overnight pulse oximetry was used to assess sleep apnea symptoms. As mentioned previously, this may have led to an overestimation of sleep apnea symptoms. In addition, the use of overnight pulse oximetry does not allow for the determination of which of the different types of sleep apnea, such as obstructive sleep apnea (OSA) and central sleep apnea (CSA), is present. While OSA is due to obstruction of airflow in the throat area, CSA is due to the brain not properly regulating muscles that control breathing (White, 2005). Thus, they are related to different mechanisms and may be differently related to SCD pain and inflammation processing. Future research should focus on distinguishing these types of sleep apnea within the pediatric SCD population and understanding how they may relate to pain.

Beyond the limitations detailed above, the current study highlights areas for future directions and clinical implications. An important implication of the current findings is that the pediatric years is an important time for screening for and addressing sleep problems in individuals with SCD. Given that our findings indicate a cyclic relationship between poor subjective sleep and high pain severity throughout the pediatric years, identifying and addressing sleep problems during this period may both help to reduce the risk of future poor sleep and reduce pain severity or escalation over time. Also, the current study highlights the importance of subjective sleep quality in investigating the pain–sleep relationship. However, the lack of relation between subjective sleep quality and the objective sleep variables points to the need for future research to identify what underlying sleep processes may be linked to subjective sleep quality, and thus, need to be targeted in future interventions. Lastly, our findings and the work of Fisher and colleagues (2018) highlight the importance of collecting time-varying data that can be matched up on a daily basis. As previously noted, there is a need for research to validate single night actigraph sleep assessments; however, advances in eHealth technology should allow for better integration of EMA and actigraphy data. For example, there are a number of actigraphs currently on the market that allow individuals to answer brief, repeated daily surveys. Also, the lack of relations between EMA sleep variables and more objective sleep variables provides support for the unique contributions of each methodology and speak to the need to use multimethod assessments as part of both research and clinical trials focused on gathering accurate, time-sensitive brief assessments of sleep, particularly in pediatric pain populations.

In conclusion, the current study addressed gaps in the previous literature exploring the pain–sleep relationship in youth with SCD by utilizing mHealth technologies to provide objective and time-sensitive assessments of sleep. It also tested and refined specific aspects of the Model of Pain–Sleep Relationships in Pediatric Persistent Pain Populations (Valrie et al., 2018) for youth with SCD by investigating which sleep variables are related to daily SCD pain, and the influence of age on sleep and the sleep–pain relationship. Across the different mHealth methodologies, EMA sleep assessments were related to daily SCD pain severity, such that poor subjective sleep quality at night was related to high pain severity the next day, and high pain severity during the day was related to poor subjective sleep quality that night. Also, age influenced the sleep–pain relationship, such that the relationship between continuously poor subjective sleep and high pain severity was strengthened as age increased. Future research is needed to validate the current findings and examine possible mechanisms connecting subjective sleep quality to high pain severity. In addition, the current findings support that the need for systematic sleep assessments as part of comprehensive care in youth with SCD as well as targeting of poor subjective sleep quality as either a possible precursor to SCD pain or potential outcome.

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