Journal of Behavioral Medicine
https://doi.org/10.1007/s10865-022-00368-5

# Sleep and fatigue among youth with sickle cell disease: A daily diary study

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Received: 18 March 2022 / Accepted: 19 September 2022


**Abstract**
Youth with sickle cell disease (SCD) experience disease effects including vaso-occlusive pain crises, poor sleep quality, and fatigue. The present study examines how sleep quality and pain medications impact fatigue in youth with SCD. Daily diaries assessing pain, fatigue, sleep quality, mood, and use of pain medications from 25 youth with SCD ages 11 to 18 years were collected for eight consecutive weeks. Poor sleep quality predicted increases in next-day fatigue levels while controlling for pain and mood. Sleep quality did not moderate the existing temporal relationship between pain and next-day fatigue established by Reinman et al. (2019) as predicted. Non-opioid medications affected ratings of next-day fatigue but opioid medications did not. Sleep quality appears to play an important role in predicting next-day fatigue levels and may be an important target for intervention. Pain medication use did not substantially contribute to prospective fatigue levels among youth, but requires further study.

**Keywords** Sleep quality · Fatigue · Analgesics

## Introduction

Sickle cell disease (SCD) describes a group of inherited blood disorders in which recurrent physical complications such as pain, anemia, fatigue, and infection negatively impact youth's functioning (Brown, 2006). Medical interventions (e.g., oral hydroxyurea, transfusion therapy) reduce symptom severity, but children and adolescents still suffer from complications affecting daily functioning. The frequency of medical complications individuals experience increase with age, making adolescence a particularly challenging time for patients with SCD as they experience greater pain, increased risk for internalizing symptoms, and disruptions to daily life (Rees et al., 2010). Research utilizing daily diary methods have examined prospective relationships between symptoms like pain, mood, and sleep quality to better understand how symptoms influence each other (Valrie et al., 2007a, 2019). These studies have elucidated a cyclic relationship between increased pain and poorer sleep quality (Valrie et al., 2007b; Fisher et al., 2018) and associations between negative mood and increased pain. Daily diary studies are valuable as they demonstrate the strength and direction of associations between symptoms and functioning in youth with SCD. Despite a significant number of daily diary studies conducted among youth with SCD, few studies have examined factors influencing fatigue levels (Ameringer & Smith, 2011; Ameringer et al., 2014).

Accumulating literature suggests fatigue is a primary and common concern among patients with SCD (Ameringer et al., 2014; Anderson et al., 2015; Dampier et al., 2010; While & Mullen, 2004), contributing to significant functional limitations and psychosocial concerns (Dampier et al., 2010). Specifically, nearly 70% of adolescents and young adults with SCD were found to experience moderate fatigue levels (Ameringer et al., 2014) and fatigue has been connected to increased school absences, internalizing symptoms, pain, stress, impaired cognitive functioning, poor sleep, and decreased health-related quality of life (HRQOL) (Ameringer et al., 2014; Anderson et al., 2015; Dampier et al., 2010). Youth have reported fatigue as one of the most difficult and disruptive symptoms to manage (Poku et al., 2020). Among adolescents with SCD, fatigue is

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Published online: 05 November 2022

chronic, characterized by persistent feelings of exhaustion unresolved with rest, and is influenced by behavioral, psychological, and physiological factors (Ameringer & Smith, 2010; Crichton et al., 2015; Shen et al., 2006). Ameringer and Smith (2010) proposed a biobehavioral model of fatigue in patients with SCD, which contextualizes these relationships by asserting that that person-level, disease-level, and moderating variables interact to produce poor outcomes (Ameringer & Smith, 2010; Hossain et al., 2005; Shen et al., 2006). This model converges with the conceptualization that primary (disease-level) and secondary (person-level) factors influence fatigue levels in youths with chronic illnesses (Ameringer & Smith, 2012; Maughan & Toth, 2014). In SCD, primary factors include inflammation, anemia, and overall disease severity, which is often denoted by genotype severity (Ameringer et al., 2014; Crichton et al., 2015; Maughan & Toth, 2014) whereas secondary factors include sleep quality, pain, and mood (Crichton et al., 2015; Ameringer & Smith, 2011). Fatigue has been associated with negative psychosocial outcomes while controlling for effects of disease-related variables (Anderson et al., 2015), suggesting fatigue is a unique source of poor adjustment beyond its correlation with disease symptomology. Among the factors influencing fatigue in SCD pain appears to play a large role and is a focus of the current study.

Increased pain severity was recently shown to predict increased next-day fatigue severity in youth with SCD and increased fatigue was shown to predict increased next-day pain (Reinman, 2019). These data support a cyclic relationship between pain and fatigue in which pain severity accounted for greater variance in next-day fatigue than the alternative, suggesting pain may be the more potent driver of this cycle (Reinman et al., 2019). Fishbain and colleagues (2003) provide additional support for a causal relationship between pain and fatigue in a systematic review of studies across pain populations. Due to high functional impairment in youth experiencing pain and fatigue, behavioral interventions aimed at reducing these symptoms are clinically important. As such, identifying factors that prospectively contribute to fatigue and pain and respond to behavioral change may be significant for future clinical applications.

Sleep quality influences both pain and fatigue and is particularly important for youth with SCD because sleep disorders, including restless leg syndrome, insomnia, and obstructive sleep apnea, are highly prevalent and many of these disorders can be alleviated with behavioral interventions (Rosen et al., 2014; Valrie et al., 2007b). Whereas the relationship between pain and sleep quality in SCD has been a prominent focus of research, the relationship between sleep and fatigue is not well understood. This may be partially explained by the difficulty defining and measuring the subjective, multidimensional nature of fatigue (Ameringer et al., 2014; Anderson et al., 2015). Even less research has examined the relationship between fatigue and sleep, which may be due to confusion surrounding the distinction between constructs. Sleep medicine has attempted to distinguish fatigue from daytime sleepiness or sleep propensity, defined as "one's tendency to fall asleep" (Shen et al., 2006, p. 64). However, many researchers and clinicians continue to use these terms interchangeably (Crichton et al., 2015; Shen et al., 2006). An important distinction between sleepiness and fatigue is that while restorative sleep improves symptoms of sleepiness, it does not improve symptoms of fatigue (Shen et al., 2006; Hossain et al., 2005). Fatigue is further characterized by the presence of physical weakness, rest without reprieve of symptoms, cognitive symptoms such as memory and attention difficulties, and reduced motivation (Anderson et al., 2015; Shen et al., 2006). Of note, sleepiness is also characterized by some cognitive impairment, although research with youth with SCD has shown fatigue to more strongly impact neurocognitive and academic functioning compared to poor sleep quality (Rogers & Lance, 2017).

Presently, only a few studies have cross-sectionally examined how sleep quality is related to fatigue severity in youth with chronic medical conditions. Poor sleep quality and sleep disturbances were associated with increased levels of fatigue in several studies (Butbul Aviel et al., 2011; Crosby 1991; Kanyak et al., 2006) and these findings were replicated in one cross-sectional study of youth with SCD (Ameringer et al., 2014). Biomarkers and biochemical responses present in SCD provide theoretical support for the relationship between sleep and fatigue. Inflammatory cytokines (i.e., specific interleukins and TNF-α), which are elevated in patients with high levels of fatigue and pain, have been shown to negatively impact sleep in patients with SCD, highlighting underlying mechanisms through which these symptoms may be associated (Ameringer & Smith, 2010; Klimas et al., 2012). In addition, inflammatory responses that mediate vaso-occlusive injury and are associated with symptoms of fatigue have been shown to relate to poor sleep quality (Ameringer et al., 2014). Pain was commonly comorbid in studies examining the relationship between fatigue and sleep, providing support for shared physiological mechanisms across these constructs (Ameringer et al., 2014; Butz Aviel et al., 2011). Studies showing inter-relationships among fatigue, increased pain and poor sleep quality indicate several important points for youth with SCD: Whereas Ameringer & Smith (2011) proposed that disrupted sleep mediates the relationship between pain and fatigue, research on SCD pathophysiology suggests it is more likely that poor sleep quality interacts with pain severity to influence prospective symptoms of fatigue in youth with SCD. This is because biological pathways underpin these relationship in sickle cell disease,

with increased inflammation from pain and poor sleep likely exerting multiplicative effects on fatigue severity (Klimas et al., 2012; Butz Aviel et al., 2011). Further, research has shown that pain severity still influences fatigue levels while controlling for sleep quality, reducing the likelihood of a mediating relationship (Fishbain et al., 2003). Because mood has been shown to influence pain, fatigue, and sleep, this is an important factor that should be controlled for to understand the specifity of relationships.

Researchers must also consider the effects of pain medications when examining how pain severity, sleep quality, and fatigue levels interact over time. Opioids are commonly used to treat sickle cell pain at home and in emergent settings (Stinson & Naser, 2003) and sedation is a potent side effect of analgesics, which may precipitate the onset of fatigue-like symptoms. As emphasized by other authors, studies exploring the association between pain and fatigue often fail to account for the effects of pain medications in data analyses and thus may report inflated or skewed levels of fatigue (Ameringer et al., 2014; Dampier et al., 2010; Fishbain et al., 2005). In addition, research has shown that opioids alter sleep structure (Dimsdale, 2007) and therefore may contribute to poor sleep quality in youth with pain. In a longitudinal daily diary study, Valrie and colleagues (2007b) demonstrated use of pain medication was associated with poor sleep, but pain medication dampened the negative effect of pain on sleep quality (Valrie et al., 2007a). It appears that while analgesic pain medications may decrease pain severity and attenuate pain's impact on sleep quality, biochemical effects of opioids negatively impact sleep (Dimsdale, 2007; Onen et al., 2005; Valrie et al., 2007a). Based on current literature, it is unlikely non-opioid pain medications would impact fatigue levels as side effects of these medications are typically restricted to renal, gastrointestinal, and cardiovascular complications (Harirforoosh et al., 2013). While researchers investigating the pain-sleep relationship frequently control for use of medication (Fisher et al., 2018; Valrie et al., 2019), it is equally important to explore how the use of opioid and non-opioid analgesics impacts daily and prospective fatigue severity.

The present study aims to extend current findings by identifying how sleep and use of pain medications contribute to prospective fatigue severity in adolescents with SCD (Ameringer & Smith, 2011; Ameringer et al., 2014) while controlling for effects of mood. Poor sleep quality and the use of opioid pain medications are expected to predict increased next-day fatigue wheras use of non-opioid medications (e.g., ibuprofen, Tylenol) is not. Sleep quality is hypothesized to moderate the relationship between pain severity and next-day fatigue severity.

## Methods

### Participants

Thirty two youths between the ages of 11 and 18 with a clinical diagnosis of sickle cell disease by a hematologist (confirmed by chart review) and a primary caregiver were recruited from a Center for Cancer and Blood Disorders (CCBD) at a children's hospital in the southeastern US after IRB approval. Additional inclusion criteria required English fluency and daily access to the internet. Youth with acute medical complications (e.g., admission for surgery), or those with major developmental disorders (i.e., autism spectrum disorders, intellectual disability) or significant cognitive impairments (e.g., those who had experienced an overt stroke) were excluded due to possible limitations in their ability to provide accurate and valid self-report data. Final inclusion criteria required youth to complete 9 or more daily diaries and consecutive diaries such that youth contributed data to both same-day and lagged analyses, resulting in 25 participants included in the final analyses.

### Procedure

Participants were recruited after their routine healthcare appointment as part of a larger study occurring before the COVID-19 pandemic (Reinman, 2019). Researchers met with eligible participants and their caregivers to discuss the purpose and methodology of the study. Following written participant assent and caregiver informed consent, parents and youth completed baseline measures as part of the larger study. Measures collected at baseline will not be described in detail as they are not central to the present study. Daily health diaries, which have been established as a valid methodology among youth with chronic illnesses (Gil et al., 2000) and utilized in previous studies involving youth with SCD (Valrie et al., 2007a) were used to collect longitudinal data. Participants received instructions on how to complete the diary and were asked to complete their daily diary at the same time after school for eight consecutive weeks during the academic school year. Daily diaries were expected to take between 10 and 15 min to complete using an online survey generator estimate; however, most youth completed diaries within five minutes. Participants received an email from researchers between 1:00–2:00pm and would click a unique URL code (e.g., tablet, computer, or smartphone) to complete the diary. Reminder texts were sent to participants' cell phones if they had not completed their daily diary survey by 5:00pm. For every 10 diaries completed, participants received a $10.00 gift card. Follow-up contacts were made via text, phone, or email if participants had not completed

diaries for three consecutive days. Data were collected via an online survey platform with a secure interface.

## Measures

Demographic information including participant age, sex, and genotype was collected via the *Psychosocial Assessment Tool 2.0 (PAT 2.0)*, a caregiver report measure commonly used among patients with chronic medical conditions such as cancer and sickle cell disease (Karlson et al., 2012). Baseline characteristics of pain, fatigue, depression, and anxiety were measuring using a pain history interview with the caregiver (Schlenz et al., 2016), the Pediatic Quality of Life Inventory Multidimensional Fatigue Scale (PedsQL MFS) (Anderson et al., 2015), the Child Depression Inventory, 2nd edition (CDI-2) (Kovacs & Staff, 2003), and the Multidimensional Anxiety Scale for Children, 2nd edition (MASC-2) (Baldwin & Dadds, 2007). These measures were collected at the time of study enrollment.

**Pain & Pain Medication** Daily pain and use of medication were indexed with two items. Participants rated daily pain on an 11-point numeric rating scale (NRS) anchored by 0 "no pain whatsoever" and 10 "worst pain imaginable". Numeric rating scales have been established to yield reliable and valid measurements of pain (Breivik et al., 2008; Wong & Baker, 1988). A second item assessed whether (a) participants had taken any medications for pain and (b) whether this medication was an opioid (e.g., codeine, morphine) or a non-opioid (e.g., ibuprofen, acetaminophen) pain medication.

**Fatigue**: Daily fatigue was measured with 3 items assessing fatigue's (1) severity, (2) bother, and (3) interference on a 0–10 NR. This 3-item measure, (Daily Fatigue Report Form), was developed by Erickson et al., (2010) and used among youth with cancer. Similar measures have been used to measure daily fatigue in other disease populations (Ream et al., 2006; Schwartz, 2000). In the present study, fatigue severity was used in multi-level model analyses for several reasons: (1) empirical support for use of single item measures of fatigue (Berger & Higginbotham, 2000), (2) Erikson et al.'s (2010) finding strong correlations between these three characteristics of fatigue with fatigue severity emerging as the most sensitive indicator of change over time, and (3) the greater influence of other psychological constructs on ratings of bother and interference. Youth were provided with a definition of fatigue as part of completing the baseline PedsQL Multdimensional Fatigue measure. No participants posed questions about the construct of fatigue during the study.

**Sleep quality** Sleep quality was measured with one item. Participants rated the quality of their prior nights' sleep on a 0–10 NRS with 0 indicating "poor" sleep and 10 indicating "ideal" sleep quality. This method of assessing sleep quality has been used in a number of studies including youth with SCD and is established as reliable and valid (Bromberg et al., 2012; Valrie et al., 2007b).

**Mood** Mood was assessed using the *Positive and Negative Affect Schedule for Children (PANAS-C)*, a 27-item scale was developed based on personality dimensions of extraversion and neuroticism and measures positive affect (PA) and negative affect (NA). Participants rate items on a 1–5 likert scale to yield total scores for positive and negative affect, measured by 12 and 15 items, respectively. This scale has been shown to strongly relate to internalizing symptoms in youth and is a widely used measure of mood valence (Watson et al., 1988). It has demonstrated strong reliability and utility in youth with chronic illnesses (Zempsky et al., 2013).

## Planned statistical analyses

Data were analyzed using R statistical software (version 4.1.2). Preliminary intraclass correlations were run to identify the strength of intercorrelation among variables and assess for concerns about multicollinearity. Multilevel modeling analyses (MLM) were run to evaluate the temporal relationship between variables of sleep quality, pain, use of pain medication, and fatigue levels. MLM analyses were modeled after previous daily diary research studies (Gil et al., 2003; 2004; Schatz et al., 2015; Valrie et al., 2007; 2008). A three-step approach was taken for the analyses: (a) fitting an error structure to correct for serial dependency, (b) modeling age (child, adolescent), gender (male, female) and sickle cell genotype, which can indicate disease severity (moderate [HbSC, HbSβThal$^{+}$] severe [HbSS, HbSβ$^{0}$]), to determine their inclusion as covariates, and (c) adding the predictors. As part of fitting an error structure, a "Day" variable was included, in order to correct for serial dependency by days in the study. For the error structure, an auto-regressive, moving average (ARMA) was used. A person-level predictor of each dependent variable was added to control for between-person effects, consistent with similar studies using multilevel modeling in SCD (Gil et al., 2003; 2004; Valrie et al., 2007; 2008).

The appropriateness of the MLM analyses was tested in each statistical model through one-way analysis of variance (ANOVA) to test for significant between groups variance and random coefficient regression models to test for a significant pooled within groups slope and significant variance

**Table 1** Sample demographics and daily diary descriptive information

| Variable | N | M ± SD | MDN | R | F |
|---|---|---|---|---|---|
| Age (years) | - | 14.3 ± 1.9 | 14.2 | 11.3–18.5 | |
| Gender | 15 (60%) | - | | - | |
| Male | 10 (40%) | | | | |
| Female) | | | | | |
| Genotype | 16 (64%) | - | | - | |
| Severe: HbSS | 2 (8%) | - | | - | |
| $HbS\beta thal^0$ | 4 (16%) | - | | - | |
| Moderate: HbSC | 3 (12%) | - | | - | |
| $HbS\beta thal^+$ | | | | | |
| *Baseline Variables* | | | | | |
| Pain episodes over prior 12 months* | 25 | 0.9 ± 1.4 | 0 | 0–5 | |
| Lasting more than 4 h + medical visit | 25 | 3.9 ± 9.9 | 1 | 0–50 | |
| Lasting more than 4 h + no medical visit | 25 | 0.6 ± 1.2 | 0 | 0–5 | |
| Lasting less than 4 h | | | | | |
| Multidimensional Fatigue – General (possible scores (0-100) | 25 | 60.5 ± 16.8 | 62.5 | 12.5–87.5 | |
| CDI – norm referenced T-score | 25 | 57.0 ± 10.6 | 57 | 40.0–84.0 | |
| MASC – norm referenced T-score | 25 | 58.0 ± 11.6 | 57 | 40.0–75.0 | |
| *Daily Diary Features* | | | | | |
| Number of diaries | 819 | 32.0 ± 17.0 | 31 | 9.0–56.0 | |
| Number of diaries with any pain | 243 (30%) | | | | |
| Pain intensity on days with pain (range 1–10) | | 2.9 ± 2.3 | 2 | 1.0–10.0 | |
| Number of diaries with any fatigue | 260 (32%) | | | | |
| Fatigue intensity on days with fatigue (range 1–10) | | 3.0 ± 3.4 | 2 | 1.0–10.0 | |
| Days with non-opioid pain medicine use | 57 (7%) | | | | |
| Days with opioid pain medicine use | 27 (3%) | | | | |
| *Daily Diary Variables (possible scores)* | | | | | |
| Fatigue (0–10 scale) | | 1.2 ± 2.1 | 0 | 0–10 | |
| Pain (0–10 scale) | | 0.9 ± 1.8 | 0 | 0–10 | |
| Sleep Quality (0–10 scale) | | 7.3 ± 2.6 | 8 | 0–10 | |
| Positive Affect (12–60 scale) | | 36.3 ± 15.9 | 36 | 12–60 | |
| Negative Affect (15–75 scale) | | 18.0 ± 5.3 | 15 | 15–54 | |
| Opioid medication use (yes/no) | | | | | 42 (7%) |
| Non-opioid medication use (yes/no) | | | | | 22 (3%) |

Notes: M = mean, MDN = median, SD = standard deviation, R = range, F = frequency of "yes" responses, *Pain history was from caregiver report at enrollment with emergency department or inpatient medical visits counting as a medical visit, CDI = Children's Depression Inventory, 2nd edition; MASC = Multidimensional Anxiety Inventory for Children, 2nd edition

in intercepts and slopes. To test the statistical significance of the multi-level regression models we used a likelihood ratio test that compared the −2 log likelihood of the model with the full set of predictors to a model model with only the "Day" variable included as predictor. The effect size of associations within the regression models are reported using Cohen's *d*. The assumptions of linearity, homogeneity of variance, and normally distributed residuals were examined through visual inspection of graphs plotting: the model residuals versus each predictor variable, fitted values versus residuals, and a histogram of the residuals, respectively. Given the dearth of studies in this area, a test-wise alpha level of 0.05 was chosen to interpret the hypotheses.

## Results

### Preliminary analyses

Of the original 32 youth recruited in the present study, 25 youth ($M_{age}$ = 14.3, *SD* = 1.9, 60% = male) between the ages of 11 and 18 with a clinical diagnosis of sickle cell disease completed 9 or more diaries, including consecutive diaries, and were included in the final study data set. Because all analyses involved lagged variables, diaries that had missing values for next-day variables (N = 175) were excluded, resulting in a final data set with 644 diaries of the total 819 diary entries completed by participants (Table 1). The 644 diaries included 191 days with pain, 62 days with

**Table 2** Effects of prior-night sleep quality and pain medication use on next-day fatigue levels

| | *B* | *SE* | *95% CI* | *t* | *p* |
|---|---|---|---|---|---|
| **Variable** | | | | | |
| *Fatigue Severity* | | | | | |
| Intercept | 1.57 | 0.44 | 0.71, 2.44 | 3.56*** | < 0.001 |
| Day | − 0.02 | 0.01 | − 0.03, − 0.02 | -4.03*** | < 0.001 |
| Person-Level Fatigue (C) | 1.73 | 0.31 | 1.09, 2.37 | 5.60*** | < 0.001 |
| Fatigue Severity (C) | 0.42 | 0.09 | 0.24, 0.60 | 4.60*** | < 0.001 |
| Sleep Quality (C) | − 0.37 | 0.09 | − 0.55, − 0.20 | -4.12*** | < 0.001 |
| Pain Severity (C) | 0.29 | 0.08 | 0.13, 0.44 | 3.58*** | < 0.001 |
| Positive Affect (C) | − 0.01 | 0.01 | − 0.02, 0.01 | -0.77 | 0.440 |
| Negative Affect (C) | 0.04 | 0.02 | 0.01, 0.07 | 2.72** | 0.007 |
| Opioid Pain Medication | 0.66 | 0.44 | − 0.21, 1.54 | 1.50 | 0.135 |
| Non-Opioid Pain Medication | 0.66 | 0.30 | 0.07, 1.25 | 2.21* | 0.027 |

Notes: (C) denotes variables were centered

moderate-to-severe pain (pain scores of ≥ 4), 260 days with fatigue, 84 days with moderate-to-severe fatigue (fatigue scores of ≥ 4) and 64 days with medication use (42 non-opioid, 22 opioid). Youth who met inclusion criteria for daily diaries did not differ from youth who did not complete diaries on baseline characteristics. Baseline characteristics for depressive symptoms, anxiety, and general fatigue can be found in Table 1 and indicate youth in this sample experience a high number of fatigue symptoms and generally report average to high average internalizing symptoms. Of the 25 youth included in the final data set, seven were children (11–12 years old) and eighteen were adolescents (13–18 years old). Additional demograpic (e.g., race/ethnicity, genotype) and descriptive statistics can be found in Table 1.

Examination of intra-class correlations among the independent and dependent variables indicated very-small-to-medium associations (range 0.043 – 0.586) among variables except for the association of pain severity and use of opioid pain medication, $r = .760$, which is high enough to raise concerns about multicollinearity for the analyses including opioid pain medication use. Follow-up diagnostics for these statistical models indicated the variance inflation factor (VIF) scores for all variables were less than two, which is not indicative of multicollinearity concerns.

For all analyses of study hypotheses we tested the impact of our decision to drop participants with few diary entries ($n = 7$) from the final data set and determined these choices did not bias the study outcomes. We compared MLM models including data from all 32 participants versus the final data set. Analyses conducted with all 32 participants and the final 25 participants produced the same the outcomes for study analyses based on p-levels and similar strengths of associations between variables, though the excluded participants contributed modest data to impact the findings.

All MLM models met the assumptions as described in the planned statistical analyses, above. All tests of the impact of level 2 variables (i.e., age group, gender, sickle cell genotype severity) did not indicate they were related to the dependent variable and therefore they were not included as covariates.

## Study hypotheses

The associations between use of prior-day pain medication, prior-night sleep quality and next-day fatigue were examined while controlling for the effects of prior-day affect and fatigue (Model 1). It was predicted that the poor prior-night sleep quality and use of analgesic pain medications would predict increases in next-day fatigue levels and that non-opioid medications (e.g., ibuprofen, Tylenol) would not affect next-day fatigue levels. The overall model for this regression was statistically significant, $\chi^2 = 101.66$, $p < .001$, $R^2 = 0.38$ (see Table 2). Poor prior night's sleep quality $t(611) = -4.121$, $p < .001$, $d = 0.33$, greater prior-day pain severity $t(611) = 3.58$, $p < .001$, $d = 0.29$, and use of non-opioid pain medication from the previous day $t(611) = 2.21$, $p = .03$, $d = 0.18$, predicted increased levels of next-day fatigue in youth while controlling for effects of the prior day's fatigue levels $t(611) = 4.60$, $p < .001$, $d = 0.37$, negative affect $t(611) = 2.72$, $p < .01$, $d = 0.22$, and positive affect $t(611) = -0.77$, $p = .44$, $d = 0.06$.

Next, the moderating effect of prior-night sleep quality on the relationship between prior-day pain and next-day fatigue was examined (Model 2). The overall model for this regression was statistically significant, $\chi^2 = 89.65$, $p < .001$, $R^2 = 0.39$ (see Table 3). However, the interaction between prior night's sleep quality and prior-day pain severity $t(614) = -0.81$, $p = .42$, $d = 0.07$, did not predict greater next-day fatigue severity, while controlling for prior night's sleep quality $t(614) = -5.97$, $p < .001$, $d = 0.48$, pain severity $t(614) = 2.80$ $p < .001$, $d = 0.23$, and prior day fatigue levels $t(614) = 5.55$, $p < .001$, $d = 0.45$.

**Table 3** Moderating influence of sleep quality on pain-fatigue relationship

| | *B* | *SE* | *95% CI* | *t* | *p* |
|---|---|---|---|---|---|
| **Variable** | | | | | |
| *Next-Day Fatigue Severity* | | | | | |
| Intercept | 2.31 | 0.17 | 1.98, 2.65 | 13.51*** | < 0.001 |
| Day | − 0.02 | 0.01 | − 0.03, − 0.01 | -4.37** | < 0.001 |
| Person-Level Fatigue (C) | 2.03 | 0.30 | 1.41, 2.64 | 6.88*** | < 0.001 |
| Fatigue Severity (C) | 0.50 | 0.09 | 0.32, 0.68 | 5.55*** | < 0.001 |
| Previous Night's Sleep Quality (C) | − 0.48 | 0.08 | − 0.64, − 0.32 | -5.97*** | < 0.001 |
| Pain Severity (C) | 0.23 | 0.08 | 0.07, 0.39 | 2.80** | 0.005 |
| Sleep Quality (C) X Pain (C) | − 0.05 | 0.06 | − 0.17, 0.07 | -0.81 | 0.418 |

Notes: (C) denotes variables were centered

## Post hoc analyses

The daily diary variables for fatigue intensity, pain severity, and sleep demonstrated skew with significantly more data points at the low end of the scale for fatigue and pain and at the high end of the scale for sleep quality. Although there were no outliers detected, we evaluated the impact of this skewness on Model 1 by recoding the 11-point scales to four-point ordinal scales (for pain and fatigue: 0 vs. 1,2,3 vs. 4, 5, 6 vs. 7, 8, 9,10; for sleep: 10 vs. 7,8,9 vs. 4,5,6, vs. 0,1,2,3). This resulted in at least 21 data points at all levels of these variables. We sequentially tested the impact of using a four-point scale for each of these variables while keeping the others in their original scaling in testing the outcomes shown in Table 2. In each of these analyses the model predicting next-day fatigue levels showed attenuated associations related to the truncated variable, but the *p*–levels for pain, sleep quality, and negative affect still surpassed the study alpha as significant predictors of next-day fatigue.

## Discussion

The present study aimed to elucidate prospective relationships between sleep quality, pain medications, and fatigue levels among youth with sickle cell disease while controlling for effects of mood. Our first hypothesis, which posited prior-night sleep quality and opioid (but not non-opioid) medications would predict fatigue (Model 1) was partially supported. Specifically, poor prior-night sleep quality predicted increased levels of next-day fatigue among youth while controlling for prior-day fatigue, pain severity, negative affect, and positive affect. Increased prior-day pain and negative affect also contributed to fatigue levels in a positive direction consistent with prior research. These data provide converging evidence for prior cross-sectional studies showing an association of sleep and fatigue by using measures of these constructs collected in a more naturalistic setting and less reliant on retrospective memory (Ameringer et al., 2014; Rogers & Lance, 2017). Although we assessed prior night sleep quality and fatigue in a manner that suggests a temporal association, participants would have reported these two variables within the same diary. Thus, there is a strong suggestion of a temporal order for these variables but it is possible that participant's current fatigue level biased their report of prior-night sleep quality.

The effects of pain medications on next-day fatigue were examined for two reasons: the limited literature examining effects of pain medications on fatigue levels among youths with chronic illness and the widespread limitation in prior research studies to account for the effects of pain medications in understanding fatigue. Contrary to expectations, use of opioid pain medications did not predict increases in next-day fatigue levels and non-opioid pain medications predicted increases in prospective fatigue levels. Non-opioid pain medications used by participants in this study included non-steroidal anti-inflammatory drugs (NSAIDs) and non-opioid analgesics (acetaminophen). The reason for this significant finding is unclear. Given NSAIDs decrease inflammation, which typically accompanies fatigue, it is unlikely non-opioid analgesic medications account for increased fatigue levels. A notable feature of our data was that the frequency of using non-opioid medication on days with pain was much lower than reported in prior studies of home-based pain management using daily diary methods. For example, Dampier et al., (2002) reported youth using non-opioid pain medication on 71% of days with pain and using opioid medications on 14% of days with pain whereas our sample reported using non-opioid pain medication on 23% of days with pain and opioid medications on 10% of days with pain. Given the relatively low use of non-opioid pain medication on days with pain, it is possible that use of non-opioid pain medication acted as a proxy for some other factor that we did not evaluate in our study. Why opioid medications were not found to influence fatigue levels is also unclear, but is consistent with the lack of consensus regarding the general association between opioids and fatigue levels among patients with pain disorders (Ameringer et al., 2014; Fishbain et al., 2005; Valrie et al., 2007a, b). In a review of medications proposed to affect fatigue, opioids

did not significantly contribute to persistent levels of fatigue (Zlyott & Byrne, 2010). However, significant evidence supports opioids should produce fatigue given delays between plasma concentration of opioids and perceived effects (Lotsch, 2005) and half-lives of long-acting opioids used to treat pediatric sickle cell pain lasting up to seven hours (Ballas et al., 2012). Our study may have been limited in its ability to detect these types of relationships due to the low number of days with reported use of opioid medications.

The expected relationship outlined in our second hypothesis between prior-night sleep quality, pain severity, and next-day fatigue examined in Model 2 was not supported. Specifically, sleep did not moderate the impact of prior-day pain on next-day fatigue levels in youth. Several reasons that could explain these findings. First, variability of pain severity scores reported across daily diary studies completed at home is typically limited. Although the number of days in which youth reported pain was consistent with prior daily diay studies (Dampier et al., 2002), there were relatively few days with moderate-to-severe levels of pain ($n = 76$, 9% of diaries) and not all participants had diary days with moderate-to-severe pain. This could reduce the statistical power and generalizability of our observed null interaction effect. As such, future research should examine this relationship in other samples involving youth reporting a greater number of days with moderate-to-severe pain. Ameringer & Smith (2011) had proposed sleep may mediate the relationship between pain and fatigue. While this relationship is feasible, we believed sleep would exert a moderating effect given vaso-occlusive pain and poor sleep quality activate shared inflammatory pathways that likely contribute to increased fatigue (Gutstein, 2001; Reese et al., 2010). We did not examine a mediating effect of sleep because our data did not show a significant relationship between pain severity and sleep quality, in contrast to prior research (Valrie et al., 2008; Valrie et al., 2007b; Valrie et al., 2018). These findings are notable and could be explained by the novel inclusion of fatigue in our model, which may change the observed effect of pain severity on sleep quality. Third, methodological differences, such as the use of different measures assessing constructs of sleep and pain (e.g., NRS vs. VAS, brief vs. full inventories) across studies, could contribute to differential findings. In summary, it is possible that methodogical factors led to our null finding for an interaction between pain and sleep quality or that sleep and pain exert independent effects on next-day fatigue levels.

Although the interaction effect was not observed as predicted for our second hypothesis, this analysis also provides support that prior-night sleep quality is related to prospective fatigue levels. This temporal association is meaningful in that it provides support for the distinction between the the constructs of sleep quality and fatigue (Kanyak et al., 2006; Shen et al., 2006) while controlling for effects of prior-day fatigue and mood. Had sleep quality demonstrated an unusually large predictive effect on next-day fatigue levels, an interpretation of findings could be that the constructs were treated as synonymous by the participants. Because the symptoms of these constructs do overlap, further distinguishing conceptual and practical characteristics between these constructs is warranted (Shen et al., 2006). It is important to note that our findings do not capture the cumulative impact of poor sleep quality over multiple nights on youth's fatigue levels. Poor sleep quality across an extended period of time may differentially predict fatigue levels among youth with chronic illnesses (Dawson & McCulloch, 2005) and is an important future direction. Researchers should make efforts to examine how poor sleep quality cumulatively affects fatigue levels among youth with SCD, especially given that sleepiness can be distinguished from fatigue.

The biobehavioral model of fatigue presently does not include sleep quality (Ameringer & Smith, 2011). Revisions to this model are warranted, as findings from the present study align with the conceptualization that poor sleep quality contributes to increased fatigue among patients with chronic diseases (Ancoli-Israel et al., 2001). The magnitude of our effects suggested sleep quality may be more robust than pain in accounting for symptoms of fatigue, likely due to the prevalence of lower sleep quality and fatigue occurring in the absence of pain. The influence of sleep quality on prospective fatigue severity among youth with SCD is likely underappreciated. Sickle cell patients demonstrate a high prevalence of sleep disorders, anemia, and inflammation, all of which confer increased risk for fatigue (Brown, 2006; Gutstein, 2001; Rosen et al., 2014). Sleep quality and fatigue, therefore, are important targets for clinical interventions given fatigue has a negative impact on psychosocial functioning, QOL, and academic success (Anderson et al., 2015; Dampier et al., 2010; Rogers & Lance, 2017). Medical treatments are available that can address sleep disorders such as sleep apnea and improve sleep quality in SCD (Farrell et al., 2018). Cognitive and behavioral interventions including sleep hygiene education, relaxation strategies (e.g., mindfulness, imagery), bedtime restriction, and cognitive restructuring have been shown to improve sleep quality among youth with sleep difficulties and cognitive behavioral therapy has shown reductions in clinical fatigue among youth with chronic medical conditions (Åslund et al., 2018; Boonstra et al., 2019).

Limitations are important to consider when evaluating findings from the present study. First, self-reported sleep quality and self-reported fatigue may have been at least partially conflated by participants, given that these constructs have nuanced distinctions. Despite efforts made to distinguish between constructs of sleep and fatigue, the predictive

effect of sleep on fatigue observed in this study could be inflated. Efforts made in the current study to minimize the overlap between sleep and fatigue included providing youth with a definition and list of fatigue symptoms in baseline questionnaires and controlling for effects of prior-day fatigue in models. Future studies measuring both fatigue and sleep quality should consider additional efforts to operationalize sleepiness and fatigue for youth to help them distinguish between these constructs. Further, it could be beneficial to include a measure of daytime sleepiness when measuring daytime fatigue to control for this effect.

Second, daily diary studies typically involve small sample sizes and findings may not generalize to the broader population. Based on the benchmarks suggested by Cohen (1988), the present study was able to detect small effect sizes and therefore appeared to have adequate in statistical power. Future studies should attempt to replicate research findings with larger samples including sickle cell patients of varying age, genotype, and location within the US. Additionally, most participants provided data with missing diary days, consistent with prior daily diary studies with this population. Researchers should identify effective strategies to boost adherence rates for diary completion and recommend standardized procedures that can be used for daily diary studies. Finally, although we used a daily measure of fatigue that was similar to measures used in previous research (Ream et al., 2006; Schwartz, 2000), the reliability and validity of our measure of daily fatigue should be explored. Researchers and clinicians should develop an agreed-upon definition of fatigue among sickle cell patients to aid in advancing understanding of this construct and its effects on patients.

In summary, sleep was found to independently predict prospective fatigue severity among youth, but did not moderate the pain-fatigue relationship. No significant effects of opioid medications on fatigue were noted, though we observed significant effects of non-opioid medications on prospective fatigue levels that were unexpected and likely represent a methodological artefact. Future research should attempt to elucidate the ways in which pain medications affect fatigue levels in sickle cell patients. Taken together, these findings suggest sleep hygiene and other interventions to improve sleep are important for improving the functioning of youth because adequate sleep quality may attenuate a negative cascade of symptoms which includes fatigue. Future research efforts devoted to developing effective interventions to promote adaptive outcomes for youth with sickle cell disease are needed.

**Funding** This publication was made possible in part by Grant Number T32-GM081740 from NIH-NIGMS. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIGMS or NIH.

**Availability of data and material** Available upon request.

**Code Availability** Available upon request.

**Conflict of interest** None.

**Ethics approval** Approved by university and hospital IRB systems.

**Consent to participate** Written assent and consent obtained.

**Consent for publication** Written assent and consent obtained.

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