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Sleep Quality and the Prospective Pain-Fatigue Relationship Among Youth With Sickle Cell Disease

Julia D. Johnston

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By

Julia D. Johnston

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Accepted by:

Jeffrey Schatz, Director of Thesis

Nicole Zarrett, Reader

Cheryl L. Addy, Vice Provost and Dean of the Graduate School

ABSTRACT

Youth with sickle cell disease (SCD) are at increased risk for poor psychosocial and functional outcomes due, in part, to disease effects like vaso-occlusive pain crises, fatigue, and poor sleep quality (Brown, 2006). A growing body of literature has examined temporal associations between pain, sleep quality, and mood using daily diary studies (Valrie, Gil, Redding-Lallinger, & Daeschner, 2007a; Valrie et al., 2019). These studies help to identify how symptoms are prospectively related to each other, but they are often limited to small sample sizes and may lack generalizability. Additionally, despite ubiquitous reports of fatigue among sickle cell patients, few studies have examined this construct in youth with SCD. The present study aims to a) replicate findings from prior daily diary studies to increase our understanding of their generalizability and b) examine novel indicators of fatigue among youth with SCD. Daily diaries assessing positive and negative mood, pain severity, fatigue severity, sleep quality, and use of pain medications were collected for eight consecutive weeks among youth. Results indicated significant associations between increased same-day pain and poor prior-night sleep quality, and increased fatigue. Poor sleep quality predicted increases in next-day fatigue levels among youth and moderated the temporal relationship for pain impacting next-day fatigue. Opioid and non-opioid medication use did not significantly affect ratings of next-day fatigue. Overall, most findings from prior daily diary studies were replicated, while a few were not. Future research using larger samples should attempt to elucidate discrepancies

in findings. Novel findings from this study supported that sleep quality plays an important role in predicting fatigue levels and modifies the prospective pain-fatigue relationship. As such, sleep quality may be an important target for intervention. Finally, pain medication use may not substantially contribute to prospective fatigue levels among youth, which decreases concerns about possible iatrogenic effects medication use on sleep quality.

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CHAPTER 1: BACKGROUND AND LITERATURE REVIEW

Sickle cell disease (SCD) describes a group of inherited blood disorders in which recurrent physical complications such as pain, anemia, fatigue, inflammation, and infection negatively impact youth's functioning (Brown, 2006). A growing body of literature has examined temporal associations between variables like pain, mood, and sleep quality through daily diary methods. These studies have examined how symptoms of sickle cell disease are related to one another and affect youth's adjustment. Daily diary studies are valuable by illustrating the direction in which variables are associated, but are often limited to smaller-size samples that may be susceptible to lack of generalizability (Valrie, Gil, Redding-Lallinger, & Daeschner, 2007a; Valrie et al., 2019). Until prior findings can be replicated, it is unclear whether established relationships between pain severity, sleep quality, and mood valence generalize to youth with SCD broadly. Additionally, despite the large body of literature dedicated to understanding physical and psychosocial functioning in youth with SCD, few studies have examined factors that influence youth's fatigue levels (Ameringer & Smith, 2011; Ameringer, Elswick, & Smith, 2014). Because fatigue is a common and debilitating symptom of SCD, this gap in understanding is problematic (Dampier et al., 2010). Given the limitations to the current literature, the goals of the present study are to examine the generalizability of previously established temporal associations between key variables (Ameringer & Smith, 2011; A Ameringer, Elswick, & Smith, 2014; Dampier et al., 2010; Valrie, Gil, Redding

Lallinger, & Daeschner, 2007a; Valrie et al., 2019) and identify novel factors contributing to fatigue levels in youth (Ameringer & Smith, 2011; Ameringer, Elswick, & Smith, 2014). This research is guided by the biobehavioral model of fatigue and biopsychosocial model of pain (Ameringer & Smith, 2011; Grady, 2006; Gatchel, Peng, Peters, Fuchs & Turk, 2007; Brown, 2007).

Sickle cell disease predominantly affects individuals from African descent, accounting for approximately 1 in every 365 African American births in the United States (US) (Hassel, 2010). Sickle cell disease is caused by a mutation in the β-globin gene. This results in polymerization of red blood cells and creation of deoxygenated sickle-shaped blood cells that have a shorter lifespan and a rigid and viscous cell wall. The decreased lifespan of the cell contributes to anemia whereas the shape and properties of the cell walls lead to the clumping of cells, vaso-occlusion, and inflammation of the arterial walls resulting in what is termed vaso-occlusive pain (Reese, Williams & Gladwin, 2010; Quinn, 2016). Other symptoms of sickle cell disease include organ damage, increased risk for infection, cerebrovascular disease, acute chest syndrome, and systemic inflammation (Fuggle et al.,1996; Redding-Lallinger & Knoll, 2006; Serjant & Serjant, 1992).

The severity of SCD and types of complications youth experience vary significantly and are related to specific genotypes and other less understood factors. The most prevalent genotype associated with SCD, accounting for approximately 60% of all SCD patients in the US, is HbSS, commonly known as sickle cell anemia (Dampier, Ely, Brodecki, & O'Neal, 2002). This genotype is considered a severe variant and is associated with greater disease severity (Quinn, 2016; Schlenz, Schatz, & Roberts, 2016).

In contrast, HbSC is associated with moderate disease severity and accounts for 30% of SCD patients in the US (Quinn, 2016; Reese, Williams, & Gladwin, 2010). Beta thalassemia mutations are less common than HbSS and HbSC genotypes but are still seen frequently among patients in the US (Reese et al., 2010). HbSβ^0 (beta thalassemia zero) and HbSβ^+ (beta thalassemia plus) genotypes are considered severe and moderate risk genotypes, respectively (Reese et al., 2010; Quinn, 2016). While genotype is commonly used as a proxy for disease severity, morbidity may vary considerably between individuals with the same genotype (Reese et al., 2010; Quinn, 2016).

Medical interventions (e.g., oral hydroxyurea, transfusion therapy) effectively reduce sickle cell symptom severity, but children and adolescents still suffer from frequent complications that affect day-to-day functioning. Of these symptoms, vaso-occlusive pain is known to be the most prevalent and debilitating complication experienced by youth and has been most extensively studied (Brandow, Zappie, & Stucky, 2017; Stinsor & Naser, 2003). Less is known about how fatigue impacts youth with SCD, although accumulating literature suggests that fatigue is a primary concern and source of significant functional impairment among patients (Ameringer et al., 2014; Anderson et al., 2015; Dampier et al., 2010; While & Mullins, 2004).

The dearth of research exploring fatigue and its relation to other constructs in youth with SCD may be partially explained by the difficulty in defining and measuring the subjective, multidimensional nature of fatigue (Ameringer & Smith 2011; Ameringer et al., 2014; Anderson et al., 2015). Fatigue is generally agreed to consist of "an overwhelming sense of tiredness, lack of energy and feeling of exhaustion, associated with impaired physical and/ or cognitive functioning" (Shen, Barbera, & Shapiro, 2006,

p. 70; Ameringer et al., 2014). 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, Knight, Oaklet, Babl & Anderson, 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). Additionally, preliminary research supports that these constructs are clinically distinct, with Kaynak and colleagues (2006) demonstrating that symptoms of fatigue can occur in the absence of daytime sleepiness in patients with chronic disease and vice versa.

In populations such as those with SCD, clinical fatigue is chronic in nature while acute fatigue, in contrast, is known to occur in healthy individuals after exertion and resolves with rest (Ameringer & Smith, 2010; Shen et al., 2006). Like pain, persistent fatigue is known to be influenced by behavioral, psychological, and physiological factors (Crichton, Knight, Oakley, Babl & Anderson, 2015). The biobehavioral model of fatigue contextualizes these relationships and asserts that person-level, disease-level, and moderating variables interact to produce unique fatigue-related outcomes (Ameringer & Smith, 2010; Hossain et al., 2005; Shen et al., 2006). This model converges with the common conceptualization that fatigue is influenced by primary (disease-level) and secondary factors (person-level) (Ameringer & Smith, 2012; Maughan & Toth, 2014). In SCD, primary factors include inflammation, genotype, age, and anemia (Ameringer et al., 2014; Crichton et al., 2015; Maughan & Toth, 2014) and secondary factors include sleep quality, pain, and mood (Crichton et al., 2015; Ameringer & Smith, 2011).

Among youth and young adults with SCD, cross-sectional research has demonstrated that fatigue is associated with increased school absences, greater internalizing symptoms, more pain, higher stress, impaired cognitive functioning, poor sleep quality, and decreased health-related quality of life (HRQOL) (Ameringer et al., 2014; Anderson, Allen, Thornburg & Bonner, 2015; Dampier et al., 2010). Importantly, fatigue has been shown to be associated with negative psychosocial outcomes while controlling for disease-related variables (Anderson et al., 2015). Along similar lines, Ameringer and colleagues (2014) found that disease severity, age, and specific inflammatory markers (e.g., TNF-α) did not significantly affect subjective fatigue levels among adolescents and young adults with SCD but that sex (female) and anemia severity did. Collectively, these data suggest that fatigue is a unique source of poor adjustment in youth beyond that of disease symptomology and that certain factors play a larger role in influencing the subjective experience of fatigue than others. Of these factors, pain appears to play a large role.

Reinman (2019) demonstrated that pain severity predicted next-day levels of fatigue among youth with SCD. Specifically, increased pain levels predicted increases in next-day fatigue levels. Fatigue levels, in turn, were found to predict increases in next-day pain, supporting a bidirectional relationship between pain and fatigue (Reinman, 2019). Pain appeared to be the driving force in this relationship, with pain severity accounting for greater variance in next-day fatigue than the alternative. Fishbain and colleagues (2003) also provided compelling support for a causal relationship between pain and fatigue in a review of studies across a range of pain populations. Across reviewed studies, pain and fatigue were invariably related (Fishbain et al., 2003). In

general, these authors found that pain onset preceded fatigue onset and that reductions in pain severity reduced fatigue severity. Prospective studies reviewed provided additional support for a causal relationship between pain and fatigue, with symptoms of fatigue reliably following patients' initial development of pain (Fishbain et al., 2003). In sickle cell disease specifically, the pathophysiology of vaso-occlusive pain may highlight the mechanisms through which this cyclic and reinforcing relationship operates.

Pain experiences in sickle cell patients are thought to result from tissue damage from vaso-occlusion. In addition to the production of pain signals, blood cell adhesion and damage to the endothelium trigger the release of mediating cells and pro-inflammatory cytokines (Redding-Lallinger & Knoll, 2006). Proinflammatory cells result in increased systemic inflammation and are strongly associated with subjective experiences of fatigue (de Oliveira, Sakata, Issy, Gerola & Salomao, 2011; Swain, 2000). Inflammation in sickle cell patients caused by vaso-occlusion subsequently increases risk for further vaso-occlusion and vaso-occlusive pain, suggesting that pain may predict onset of concomitant processes that cause fatigue and in turn, these concomitant fatigue-related processes may contribute to the maintenance and development of pain. Given the nature of this debilitating cycle, interventions aimed at reducing the experience of pain and fatigue in youth are of great importance.

A host of behavioral factors have been shown to influence both feelings of pain and fatigue and may be excellent candidates for improving function in youth. Sleep disorders, including restless leg syndrome, insomnia, and obstructive sleep apnea, a sleep –related breathing disorder, are prevalent among youth with SCD (Valrie, Gil, Redding-Lallinger & Daeschner, 2007b; Samuels, Stebbens, Davies, PictonJones, & Southall,

1992). Sleep quality has been shown to affect pain and fatigue levels in youth with SCD and, as such, is a particularly important factor to evaluate (Ameringer et al., 2014; Valrie et al., 2007b).

The relationship between sleep quality and pain in sickle cell patients has been well-studied. Longitudinal daily diary studies have elucidated a cyclic relationship between pain and sleep quality, with increased pain predicting poor same-night sleep quality and poor sleep quality predicting increased next-day pain (Valrie et al., 2007b; Fisher et al., 2018). This bidirectional relationship is consistent with a well-established model proposed by Lewin and Dalh (1999), which posits that pain interferes with sleep efficiency and quality and that poor sleep increases subjective perception of pain and pain-related interference with functional tasks (Valrie et al., 2007; Bromberg et al., 2013; Jacob et al., 2006; Lewin & Dahl, 1999; Palermo & Kiska, 2005). Pain is thought to disrupt sleep quality and efficiency for two reasons: namely, that the discomfort of pain disrupts sleep latency, quality, and may cause youth to wake at night and that pain can disrupt the internal mechanisms of sleep (Onen, Onen, Courpon & Dubray, 2005; Valrie et al., 2019). In the opposing direction, poor sleep is thought to affect subjective pain severity by precipitating a lower pain threshold and increasing sensitivity to pain (Onen et al., 2005; Bromberg et al., 2013). The authors of these studies have suggested that pain severity, rather than sleep quality, initiates this cyclic relationship (Fisher et al., 2018; Valrie et al., 2007b; Valrie et al., 2019).

While a rich literature describes the relationship between sleep and pain among sickle cell patients, the relationship between sleep quality and fatigue levels is not well characterized. Presently, only a few studies have cross-sectionally examined how sleep

quality is related to fatigue levels in youth with chronic medical conditions. The noteable lack of data regarding this relationship could be explained by two factors. First, ambiguity in differentiating between fatigue and sleepiness due to poor sleep quality (Shen et al., 2006) could prevent researchers from conceptualizing these constructs separately in research studies. Second, it may be that researchers have captured the relationship between sleep and fatigue in current literature but have measured fatigue using a different proxy or related symptom (e.g., functional disability). For example, in a cross-sectional study involving youth with chronic and recurrent pain, disordered sleep was significantly related to increased functional disability (Palermo & Kiska, 2005). Lower levels of functional ability may be explained by high levels of fatigue (Pittion-Vouyovitch et al., 2006), however fatigue as a mediator was not directly measured. These data indirectly suggest that poor sleep may affect fatigue levels in youth with chronic and recurrent pain. This relationship may be common across disease groups.

Preliminary research also supports that sleep quality and fatigue are predictably related. Cross-sectional studies have shown that poor sleep quality and sleep disturbances are associated with increased levels of fatigue in patients with chronic diseases (Butbul Aviel et al., 2011; Crosby, 1991; Kanyak et al., 2006). These findings were replicated in studies involving youth with sickle cell disease (Ameringer et al., 2014). Biomarkers and biochemical responses also suggest that sleep and fatigue are related. Interleukins and TNF-α, which are elevated in patients with high levels of fatigue and pain, have been shown to negatively impact sleep (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). This cascade suggests that the relationship between poor sleep quality and increased levels of fatigue may occur in the presence of pain due to shared mechanisms. In studies examining the relationship between clinical fatigue and sleep, pain was commonly comorbid (Ameringer et al., 2014; Butz Aviel et al., 2011).

Fishbain and colleagues (2003) drew attention to the important role that sleep may play in the pain-fatigue relationship among patients with chronic and recurrent pain. The authors highlighted that many of their reviewed studies failed to control for the effects of sleep when examining the relationship between pain and fatigue and as such, findings related to the relationship between pain and fatigue could be confounded (Fishbain et al., 2003). These authors recommended that future studies control for sleep quality when attempting to characterize the pain-fatigue relationship. However, because sleep is known to influence experiences of pain and fatigue (Ameringer et al., 2014; Valrie et al., 2018) it is important to examine how sleep quality impacts these symptoms rather than simply controlling for its effect. Ameringer and Smith (2011) proposed that disrupted sleep mediates the relationship between pain and fatigue. However, because biological pathways likely underpin this relationship in sickle cell patients and research has shown that pain severity still influences fatigue levels while controlling for sleep quality (Fishbain et al., 2003), it is likely that poor sleep quality interacts with pain severity to influence prospective symptoms of fatigue in youth with SCD.

Finally, when examining how pain severity, sleep quality, and fatigue levels interact over time, researchers must consider the effects of pain medications. Opioids are commonly used to treat sickle cell pain at home and in emergent settings (Stinson & Naser, 2003). Sedation is a potent side effect of pain analgesics and may precipitate the

onset of fatigue-like symptoms (Stinson & Naser, 2003). 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, Norman, DeJardin, & Wallace, 2007) and therefore may contribute to poor sleep quality in youth with pain. In a longitudinal daily diary study, Valrie, Gil, Redding-Lallinger and Daeschner (2007b) demonstrated that the use of pain medication was associated with poor sleep quality, but that use of pain medication dampened the negative effect of pain on sleep quality (Valrie et al., 2007b). It appears that although analgesic pain medications may decrease pain severity and attenuate its impact on sleep quality, biochemical effects of opioids negatively impact sleep (Dimsdale, Norman, DeJardin, & Wallace, 2007; Onen et al., 2005; Valrie et al., 2007b). 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 analgesics impacts daily and prospective levels of fatigue.

1.1 The present study

In general, research has shown that pain severity, sleep quality, fatigue, and mood valence are temporally related in specific directions (Ameringer et al., 2014; Valrie et al., 2007a; Valrie et al., 2019). While this research is meaningful, at present, it is unknown whether these findings generalize to most youth with SCD. Additionally, although symptoms like pain, fatigue, and poor sleep quality have been shown to negatively impact youth's functioning (Dampier et al., 2010), it is unclear how these symptoms are

temporally related to each other. Empirical and theoretical evidence suggests that symptoms of pain, disrupted sleep, and fatigue may interact to produce synergistic negative effects for youth (Ameringer & Smith, 2010; Ameringer et al., 2014; Dampier et al., 2010; Lewin & Dahl, 1999). Because fatigue is a common and debilitating symptom of sickle cell disease, identifying novel factors that predict fatigue in youth is important for future clinical interventions. The goal of this thesis is to enhance understanding of generaliziability of prior findings and examine novel indicators of fatigue in youth with sickle cell disease. Specifically, this thesis aims to: (a) replicate interrelations observed among sleep, fatigue, pain, and mood, in previous studies (b) examine how sleep quality affects the prospective pain-fatigue relationship, and (c) determine how the use of pain medications affects next-day fatigue levels among youth with sickle cell disease through daily diary methods.

1.2 Objectives and Hypotheses

The first objective of this thesis is to replicate findings from prior daily diary studies to support their generalizability to youth with SCD. Specifically, replication of associations and causal pathways between variables of sleep, mood, fatigue, and pain will be tested.

- Hypothesis 1a: Daily levels of pain intensity will be significantly related to same-day reduced sleep quality, increased negative mood, and increased levels of fatigue (Ameringer et al., 2014; Valrie, Gil, Redding-Lallinger & Daeschner, 2007a).
- Hypothesis 1b: Daily pain levels will predict poor same-night sleep quality (Valrie et al., 2007b; Valrie et al., 2019) and poor sleep quality will predict

increases in next-day pain (Valerie et al., 2019; Valrie et al., 2007a; Jacob et al., 2006).

The second objective is to examine the effects of sleep quality on fatigue levels in youth with SCD. Specifically, the effect of sleep on prospective fatigue levels and the prospective pain-fatigue relationship will be examined.

- Hypothesis 2a: Poor sleep quality will predict next-day fatigue.
- Hypothesis 2b: Poor subjective sleep quality will moderate the relationship between pain severity and next-day fatigue levels.

The third objective of this study is to examine how pain medications affect prospective fatigue levels among youth with SCD.

- Hypothesis 3: Use of analgesic pain medications will predict increases in next-day fatigue levels. Non-opioid medications (e.g., ibuprofen, Tylenol) will not predict next-day fatigue levels.

CHAPTER 2: METHODS

2.1 Participants

30 youth (M_{age} = 14.44, *SD*= 2.03, 53% = male) between the ages of 11 and 18 with a clinical diagnosis of sickle cell disease were recruited from Prisma Health Children's Center for Cancer and Blood Disorders (CCBD) following IRB approval from the University of South Carolina and Prisma Hospital. Eligible youth were identified through review of medical records, neuropsychological assessment reports, and consultation with the CCBD hematologist. Additional inclusion criteria required English fluency and daily access to the internet. Participants who were experiencing a medical crisis (e.g., surgery) at the time of recruitment that would affect their ability to participate were excluded from the study. Youth with major developmental disorders or significant cognitive impairments (e.g., those who had experienced an overt stroke) were also 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 in order for researchers to draw sound inferences from longitudinal data.

2.2 Procedure

Participants were recruited as part of a larger study through the Children's Center for Cancer and Blood Disorders at Prisma Health Children's Hospital after their routine healthcare appointment. 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 of pain and fatigue. The use of daily health diaries has been established as a valid methodology among youth with chronic illnesses (Gil et al., 2000). Previous studies involving youth with SCD have utilized daily health diaries to study temporal relationships between variables of interest (Butz & Alexander, 1991; Gil et al., 1997; Valrie et al., 2007). Therefore, this design was adopted for the present study. Additional baseline measures were completed for descriptive purposes as part of a larger study. These measures are not included in the present study as they are not relevant to its purpose. Participants then received instructions on daily health diary completion. Participants were instructed to complete their diary at the same time each day for eight consecutive weeks during the academic school year. Each daily diary survey was expected to take between 10-15 minutes to complete and were completed using SurveyGizmo, an online survey generator. Participants received an email from researchers at midday (between 1:00-2:00pm) containing a unique URL code that would take them to their daily survey. Surveys could be accessed and completed on any electronic device with internet (e.g., tablet, computer, or smartphone). Reminder texts were sent to participants' mobile phone if they had not completed their daily diary survey by 5:00pm. For every 10 diaries completed, participants would receive $10.00. Follow-up contacts were made if participants had not completed diaries for three consecutive days. After seven weeks, participants were contacted to set up an appointment to complete follow-up measures at the Children's Center for Cancer and Blood Disorders Clinic. Participants received $10.00 at baseline and $10.00 at follow-up.

2.3 Data management

Data were collected using SurveyGizmo, a platform with a secure interface. Each participant was given a unique identifier used in the daily diary study to ensure responses from the daily diary study could not be linked to protected health information. Principal investigators had access to a confidential document where study identifiers were connected to participant names. Data analysis was conducted using R statistical software. Data entries were connected using participants' unique study identifier to ensure anonymity. All documents and data were stored and analyzed on computers that were firewall and password protected to ensure confidentiality.

2.4 Measures

Pain: Daily pain was measured with two items. Pain was rated on an 11-point numeric rating scale (NRS) anchored by zero "no pain whatsoever" and 10 "worst pain imaginable". Visual-analog scales are frequently used to assess pain intensity and have been established to yield reliable and valid measurements of pain (Breivik et al., 2008; Wong & Baker, 1998). A second item assessed whether a) participants they taken any medications for pain and b) whether this medication was an opioid (e.g., codeine, morphine) or a non-opioid (e.g., ibuprofen, Tylenol) pain medication.

Fatigue: Daily fatigue was assessed using 3 items. Participants rated the 1) severity, 2) bother, and 3) interference of their fatigue on a scale from 0-10. This three-item measure, known as the Daily Fatigue Report Form, was developed by Erickson et al. (2010) and used in a sample of youth receiving chemotherapy. Similar measures have been used to measure daily fatigue in other disease populations (Ream et al., 2006; Schwartz, 2000).

Sleep Quality: Sleep quality was measured with one-item. Participants rated the quality of their previous nights' sleep on a 0-10 numeric rating scale (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 a reliable and valid measure (Bromberg, Gil & Schanberg, 2012; Valrie et al., 2007b).

Mood: Mood was assessed using the *Positive and Negative Affect Schedule for Children (PANAS-C)*. This 27-item scale was developed based on personality dimensions of extraversion and neuroticism and measures positive affect (PA) and negative affect (NA). This scale has been shown to strongly relate to internalizing symptoms in youth and is a widely used measure of mood valence (Watson, Clark & Tellegan, 1998). It has demonstrated strong reliability and utility in populations of youth with chronic illness (Zempsky et al., 2013).

2.5 Planned Statistical Analyses

Data will be analyzed using R statistical software. Data from participants who completed fewer than 9 daily diaries will be excluded. Preliminary bivariate correlations will be run to identify the strengths of intercorrelation among variables. Multilevel modeling analyses (MLM) will be run to evaluate the temporal relationship between variables of sleep quality, pain, use of pain medication, and fatigue levels. MLM analyses will be modeled after previous daily diary research studies having occurred within the past 5 years in the Pediatric Health and Neuropsychology lab (Schlenz et al., 2015; Reinman, 2019 <unpublished>). Specifically, models will be run in three steps. First, an error structure will be fitted. Second, initial analyses will be run to determine inclusion of

potential covariates (e.g., age, sex, genotype, mood). Finally, predictors will be added to the model. Each model included a 'Day' and person-level variable to statistically correct for serial dependency of sequential days and individual differences, respectively. Comparative null models were run with 'Day' variables. R^2 comparing null and alternative models will be computed using the following formula:

1 – ((SD of intercept for full model + SD of residual for full model) / ((SD of intercept for null model + SD of residual for null model))

Multilevel modeling assumptions will be evaluated using L-ratios by comparing fixed versus fixed and random intercepts. Normality and linearity assumptions will be visually evaluated by plotting scatterplots and histograms of standardized residuals from the models. Given the variable nature of sickle cell disease symptoms, kurtosis and skew in histogram plots are expected. No data will be transformed due to associated challenges interpreting such data. Any significant violations of assumptions warrant explanation of why assumptions could be violated, and results should be cautiously interpreted. Effect sizes were calculated.

Addressing Hypotheses:

H1a: Pain will be significantly related to poor sleep quality, negative mood, and increased levels of fatigue (Ameringer et al., 2014; Valrie et al., 2007b). To address this hypothesis, a multilevel model will be run looking at same-day associations between pain and poor sleep quality, negative mood, and fatigue level.

H1b: Same-day pain will predict same-night sleep quality scores (Valerie et al., 2019; Valrie et al., 2007b; Jacob et al., 2006). Specifically, increased pain scores will predict poor same-night sleep quality. This hypothesis was tested using a model that

controls for mood, sex, age, and genotype and focuses on the association between pain scores and sleep quality that night.

Hypothesis2a: Poor sleep quality will predict next-day fatigue. This hypothesis will be addressed using a lagged model focusing on the association between sleep quality scores and next-day fatigue levels.

H2b: Poor subjective sleep quality will moderate the relationship between pain and next-day fatigue. For this hypothesis, an interaction term between mean-centered pain severity scores and mean-centered sleep quality scores will be computed. A lagged model will be run to examine how associations between the interaction term and next-day fatigue scores.

H3: Use of analgesic pain medications will predict increases in next-day fatigue levels. Non-opioid medications (e.g., ibuprofen, Tylenol) will not predict next-day fatigue levels. For this analysis, a lagged model will first examine the effects of use of analgesic pain medication (coded as 1) on next-day fatigue scores. Second, a lagged model will then examine the effects of non-opioid pain medication (coded as 2) on next-day fatigue scores.

Table 2. 1 Sample Demographics

Variable Name	Total Sample	Diary Completer	Diary Non-Completer
Gender (*n, %*)			
Male	16 (53.3)	14 (60.9)	2 (28.6)
Female	14 (46.7)	9 (39.1)	5 (71.4)
Age (*M*, SD)	14.44 (2.03)	14.27 (1.88)	14.98 (2.57)
Age Category (*n, %*)			
Child (11-12 years)	8 (26.7)	6 (26.1)	2 (28.6)
Teen (13-18 years)	22 (73.3)	17 (73.9)	5 (71.4)
Disease Severity			
Genotype (*n, %*)			
HbSS	20 (66.7)	14 (60.9)	6 (85.7)
HbSC	4 (13.3)	4 (17.4)	0 (0)
$HbS\beta^{+}$	4 (13.3)	3 (13.0)	1 (14.3)
$HbS\beta^{0}$	2 (6.7)	2 (8.7)	0 (0)
Other	0 (0)	0 (0)	0 (0)
On Hydroxyurea (*n, %*)	22 (73.3)	16 (69.6)	6 (85.7)
Race/Ethnicity (*n, %*)			
Black/African American	30 (100)	23 (100)	7 (100)
Multiracial	1 (3.3)	1 (3.3)	0 (0)
Insurance (*n, %*)			
Medicaid	21 (70)	15 (65.2)	6 (85.7)
Military	4 (13.3)	3 (13.0)	1 (14.3)
Private	5 (16.7)	5 (21.7)	0 (0)

CHAPTER 3: RESULTS

Of the original 30 youth recruited in the present study, 23 youth (M_{age} = 14.27, *SD*= 1.88, 61% = male) between the ages of 11 and 18 with a clinical diagnosis of sickle cell disease completed 9 or more diaries. Youth who completed diaries differed from youth who did not complete diaries on several baseline characteristics. Specifically, diary completers reporter greater baseline fatigue levels than non-completers and diary non-completers reported higher baseline anxiety sensitivity than diary non-completers (Reinman, 2019). Of the 23 youth included in the final sample data analysis, 6 were children (11-12 years old) and 17 were adolescents (13-18 years old). Additional demograpics of the sample (e.g., race/ ethnicity, genotype) can be found in Table 2.1 and same-day associations between variables can be found in Table 3.2.

Multilevel models were run to address all hypotheses. Prior to running these analyses, model assumptions were checked and met (p<.0001). The distribution of residuals can be found in Appendix A and are represented in scatterplots and histograms for each multilevel model tested. Results are organized sequentially by hypothesis.

First, prior research findings were tested for replication using data from the present study. Hypothesis 1a predicted that pain would be significantly related to poor sleep quality, negative mood, and increased levels of fatigue (Ameringer et al., 2014; Valrie et al., 2007b). The overall model used to test this hypothesis was statistically significant χ^2 = 63.734, p < .0001, R^2= .2761 (Table 1.1). The model revealed that poor

prior-night sleep quality $t(1, 593) = -2.02$, $p = .043$, greater fatigue levels $t(1, 593) = 4.34$, $p < .001$, effect size r =.18 and positive mood $t(1, 593) = -2.63$, $p < .001$ significantly predicted increased levels of same-day pain. These data partially supported the hypothesis. Unexpectedly, negative mood did not significantly predict same-day pain levels $t(1, 593) = -0.75$, $p = .45$, while positive mood was significantly associated with decreased pain severity.

The temporal relationship between pain and sleep quality was then tested for replication. Hypothesis 1b posited that same-day pain would predict same-night sleep quality scores (Valerie et al., 2019; Valrie et al., 2007b; Jacob et al., 2006). More specifically, increased pain scores were hypothesized to predict poor same-night sleep quality. The overall model for this hypothesis was statistically significant $\chi^2 = 67.46$, $p < .001$, $R^2 = .503$ (Table 1.2). However, contrary to expectations and prior research findings, same-day pain $t(1, 591) = -0.42$, $p = .68$, did not predict sleep quality scores while controlling for fatigue levels and positive and negative affect. These findings suggest that controlling for the effect of fatigue levels and mood may change our understanding of this relationship.

Second, novel associations between sleep quality and fatigue were examined. Hypothesis 2a asserted that poor sleep quality would predict next-day fatigue. The overall model for this hypothesis was statistically significant, $\chi^2 = 90.28$, $p < .001$, $R^2 = .25$ (Table 2.1). Poor previous night's sleep quality $t(1, 593) = -3.64$, $p < .001$, greater same-day pain severity $t(1, 593) = 5.33$, $p < .001$, and same-day negative affect $t(1, 593) = 3.45$, $p < .00$ predicted increased levels of fatigue in youth.

Collectively, these data revealed that sleep quality was not affected by same-day pain ratings, but that poor sleep quality predicted increased levels of fatigue. Next, hypothesis 2b was tested, which stated that poor subjective sleep quality would moderate the relationship between pain and next-day fatigue. The overall model for this hypothesis was statistically significant, $\chi^2 = 71.52$, $p < .001$, $R^2 = .35$ (Table 2.2). Specifically, the interaction between previous night's sleep quality and pain severity $t(1, 593) = -1.99$, $p < .05$, effect size r=0.08 predicted greater fatigue levels, while controlling for prior night's sleep quality (1, 593) = -4.13, $p < .001$, pain severity $t(1, 593) = 3.31$ $p < .001$, and prior day fatigue levels $t(1, 593) = 5.56$, $p < .001$ (Figure 1). These findings reveal that poor sleep quality moderates the prospective pain-fatigue relationship among youth with SCD.

Finally, the effects of pain medications on fatigue levels were examined. Hypothesis 3 predicted that the 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 hypothesis was statistically significant $\chi^2 = 62.27$, $p < .001$, $R^2 = .44$ (Table 2.3). However, both opioid $t(1, 593) = 0.58$, $p = .22$ and non-opioid medications $t(1, 593) = .51$, $p = .10$ did not significantly predict next day fatigue levels.

Table 3. 1 Descriptives

	M	MDN	SD	R	F
Variable	–				
Fatigue	1.104	0	1.983	11	
Pain	0.841	0	1.778	11	
Sleep Quality	7.321	8	2.546	11	
Positive Affect	36.413	36	15.913	48	
Negative Affect	17.902	15	5.129	37	
Opioid Pain Medication					0.035 (3.5%)
Non-opioid Pain Medication					0.064 (6.4%)

M=mean, MDN=median, SD=standard deviation, R=range, F=frequency

Table 3. 2 Simple correlations

	1.	2.	3.	4.	5.	6.
1. Pain Intensity	–					
2. Sleep Quality	d = -0.187** r = -.093**					
3. Fatigue Severity	d = 0.222** r = .110**	d = 0.247** r = .122**				
4. Positive Mood	d = -0.377** r = -.185**	d = 0.601** r = .288**	d = -0.375 r = .184			
5. Negative Mood	d = 0.086 r = .043	d = -0.230** r = .114**	d = 0.331** r = .163**	d = -0.333** r = -.164**		
6. Opioid Medication Use	d = 2.339** r = .760**	d = -0.308** r = .152**	d = 1.448** r = .586**	d = -0.387** r = -.190**	d = 0.149 r = .074	
7. Non-opioid Pain Medication Use	d = 0.948** r = .428**	d = -0.336* r = .166*	d = 0.175 r = .087	d = -0.103 r = -.051	d = 0.100 r = .050	d = -.104** r = -.052**

**p>.01, *p>.05, (N = 623)

Table 3. 3 Same day relations between sleep quality, pain, fatigue, & mood

	B	***SE***	***95% CI***	***t***	***p***
Variable					
Pain Severity					
Intercept	2.17	.27	1.63, 2.71	7.93***	<.001
Day	-.02	.01	-.00, -.01	-4.10***	<.001
Person-Level Pain	2.29	.34	1.51, 3.09	6.01***	<.001
Sleep Quality (C)	-.15	.07	-.30, -.00	-2.02*	<.05
Fatigue Severity (C)	.32	.07	.18, .47	4.34***	<.001
Positive Affect	-.31	.12	-.55, -.08	-2.63***	<.001
Negative Affect	-.10	.14	-.38, .17	-.75	0.45

Table 3. 4 Temporal relations between sleep quality & pain severity

	B	***SE***	***95% CI***	***t***	***p***
Variable					
Sleep Quality					
Intercept	7.09	.24	6.62, 7.56	29.43***	<.001
Day	0.00	.00	-.00, .02	1.36	.17
Person Level Sleep Quality	1.63	.16	1.31, 1.95	10.43***	<.001
Sleep Quality (C)	0.86	.10	.66, 1.06	8.57***	<.001
Pain Score (C)	-.03	.08	-.19, .12	-.41	.68
Fatigue Severity (C)	-.02	.09	-.20, .17	-.20	.84
Positive Affect	0.13	.13	-.11, .38	1.08	.28
Negative Affect	-.10	.14	-.38, .18	-.68	.50

Table 3. 5 Temporal Relations between sleep quality & fatigue severity

	B	***SE***	***95% CI***	***t***	***p***
Variable					
Fatigue Severity					
Intercept	1.78	.33	1.13, 2.43	5.38***	<.001
Day	-.02	.01	-.03, -.01	-3.26**	<.001
Person-Level Fatigue	2.60	.57	-14, 3.78	4.52***	<.001
Sleep Quality (C)	-.31	.09	-.48, -.14	-3.64***	<.001
Pain Severity (C)	.42	.08	.26, .56	5.33***	<.001
Positive Affect	-.17	.14	-.45, .112	-1.18	.24
Negative Affect	.55	.16	.24, .87	3.45**	<.001

Table 3. 6 Moderating influence of sleep quality on pain-fatigue relationship

	B	***SE***	***95% CI***	***t***	***p***
Variable					
Next-Day Fatigue Severity					
Intercept	2.18	.18	1.92, 2.64	12.61***	<.001
Day	-.01	.00	-.03, -.01	-3.68**	<.001
Person-Level Fatigue	2.75	.42	1.87, 3.64	6.46***	<.001
Fatigue Severity (C)	0.50	.09	.36, .68	5.56***	<.001
Previous Night's Sleep Quality (C)	-.32	.08	-.47, -.17	-4.13***	<.001
Pain Severity (C)	.26	.08	.11, .42	3.31**	<0.01
Sleep (C) X Pain (C)	-.12	.06	-.24, -.00	-1.99*	<0.05

Table 3. 7 Temporal relations between pain medication & next-day fatigue

	B	***SE***	***95% CI***	***t***	
Variable					
Fatigue Severity					
Intercept	2.19	.16	1.88, 2.49	14.05***	<.001
Day	-.02	.00	-.03, -.01	-4.09***	<.001
Person-Level Fatigue	2.50	.32	1.89, 3.12	7.94***	<.001
Fatigue Severity (C)	.62	.09	0.44, .81	6.71***	<.001
Pain Severity (C)	.22	.09	.04, .40	2.41*	<.05
Opioid Medication	.58	.47	-.34, 1.49	1.24	.22
Non-opioid Medication	.51	.31	-.10, 1.12	1.63	.10

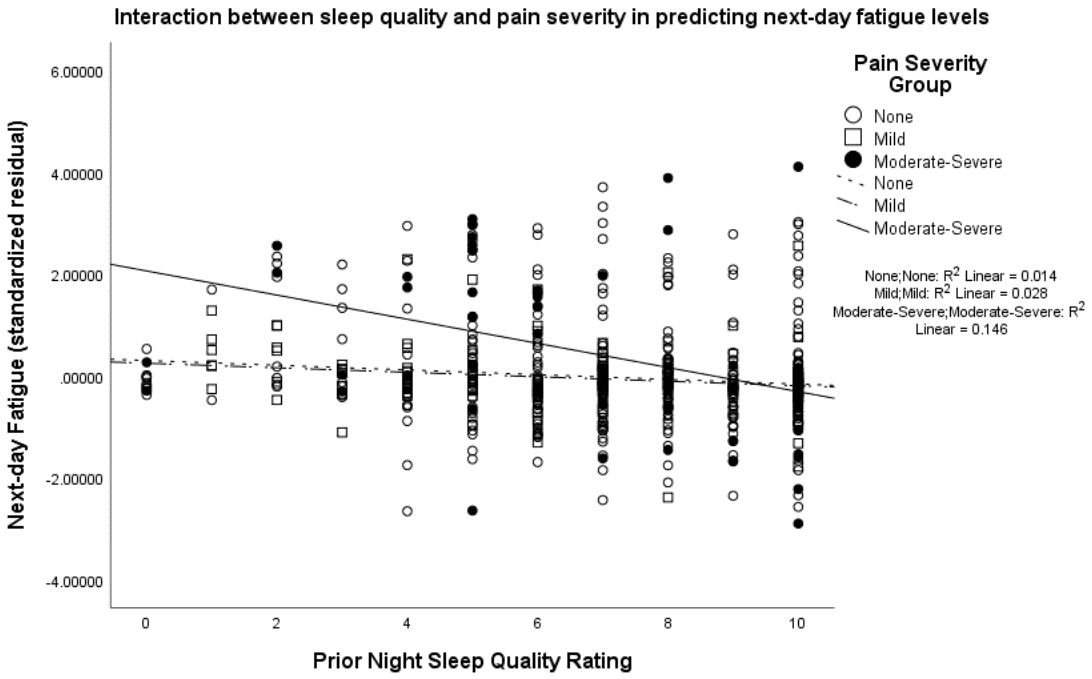

Figure 3. 1 Interaction between sleep quality and pain severity

CHAPTER 4: DISCUSSION

Adolescents with sickle cell disease experience frequent disease complications and increased risk for internalizing symptoms (Brown, 2007). In particular, youth are likely to expeirnce acute pain crises, fatigue, and disrupted sleep quality, all of which exert negative effects on functional ability and adjustment (Dampier et al., 2010; Valrie et al., 2007). To date, little research has examined whether previously established relationships between sleep quality, mood valence, and pain severity hold true for most youth with SCD. Additionally, unique predictors of fatigue in youth with SCD and how pain, sleep quality, and fatigue are temporally related are largely undetermined (Ameringer & Smith, 2011). Aligned with a biopsychocial model of pain and biobehavioral model of fatigue, this thesis aimed to enhance understanding of the generalizability of previously established relationships between biopsychosocial variables and identify novel indictors of fatigue. To this end, interrelations among key biopsychosocial variables were tested for replication, unique and moderating effects of sleep quality were examined, and the effect of pain medications on prospective fatigue levels were explored through daily diary methods.

In general, a majority of same-day associations between variables of mood, pain severity, sleep quality, and fatigue demonstrated in previous research were successfully replicated. In line with previous research, decreased pain was associated with greater

same-day positive mood. Conceptually, positive mood is thought to attenuate the severity of clinical pain experiences by increasing feelings of well-being and lowering negative affective reactivity to pain experiences (Finan & Garland, 2015). As such, our are consistent with empirical and conceptual models of positive affect and pain. Also in line with prior research, greater levels of pain were associated with increased same-day levels of fatigue and poor prior night sleep quality (Ameringer et al., 2014; Valrie et al., 2007; Valrie et al., 2007b). The significant same-day association observed between pain severity and fatigue levels converges with previous findings from cross-sectional studies (Ameringer et al., 2014; Dampier et al., 2020; Gold, Mahrer, Yee, & Palermo, 2009) and expected relations posited by the biobehavioral model of fatigue (Ameringer & Smith, 2011). Consistent findings across studies support that symptoms of fatigue and pain are predictably related and should be better understood through future research efforts. Additionally, these data contribute to now four daily diary studies that have demonstrated the negative effect of poor sleep quality on next-day pain ratings among youth with sickle cell disease (Fisher et al., 2018; Valrie et al., 2007a; Valrie et al., 2007b). These data underscore the important role that sleep plays in predicting symptoms of pain and suggest that sleep quality may be an important target for pain management interventions.

Collectively, these findings provide additional support for empirical and theoretical associations between symptoms of fatigue, pain, poor sleep quality, and positive mood among sickle cell patients. Replicated associations support that previously established relationships likely generalize across youth with SCD. These findings are particularly compelling by demonstrating that expected associations between variables were maintained while controlling for individual differences and other key variables.

Contrary to prior research findings and expected associations, however, pain severity was not significantly related to same-day negative mood in this sample (Gil et al., 2003; Porter, Gil, Carson, Anthony, & Ready, 2000; Valrie et al., 2007b).The reason for this result is less clear as same-day associations between pain severity and negative mood have been demonstrated in both adolescents and young adults with sickle cell disease (Valrie et al., 2007b; Porter et al., 2000). Nonetheless, several factors may explain why negative mood was not significantly associated with same-day ratings of pain in the present study. One of these factors involves differences in participants' age and developmental stage.

Despite comparable sample sizes across daily diary studies examining negative mood and pain, measurement indices and participant ages differed (Porter et al., 2000; Valrie et al., 2008). It is possible that the relationship between negative mood and pain differs among younger children, aged 8-12, and adults. However, it is more likely that the effect of negative affect on pain severity is consistently small, rather than varied across developmental stages. For example, although Porter and colleagues (2000) demonstrated a significant same-day association between negative mood and increased pain severity among a group of 15 adult participants between the ages of 25 and 54, the association became non-significant when controlling for stress and positive affect (Porter et al., 2000). As such, negative affect did not exert an indepdent effect on same-day pain ratings did not examine this association while controlling for covariates. Additionally, this study's main contribution to the literature demonstrated that negative mood partially mediated the relationship between pain severity and poor sleep quality and poor sleep quality and subsequent pain (Valrie et al., 2007b). In summary, methodological

differences between studies, the effect of fatigue, or a non-significant independent effect of negative affect on pain could account for inconsistent findings. The association between negative affect and pain severity may be indirect or accounted for by other factors.

Measurement instrumentation could also contribute to inconsistent findings across studies. Specifically, some authors quantified mood dimensionally with visual analog scale scores falling between 0 and 1 (Valrie et al., 2007b). Other authors (Gil et al., 2003; Porter et al., 2000) indexed positive and negative mood separately, consistent with our measurement, but utilized significantly fewer items (e.g., 8 and 13). Quantifying positive and negative affect on the same measure when they are conceptually distinct could contribute to differential findings (Diener & Emmons, 1984). Future research should establish a gold standard measure of positive and negative affect for daily diary studies that yields valid and reliable findings among youth with SCD.

Finally, it is also possible that a significant association between negative mood and fatigue could account for the non-significant finding between negative mood and pain. Theoretical models and empirical research support a strong relationship between negative mood and increased levels of fatigue (Ahmadi, Poormansouri, Beiranvand, & Sedighie, 2018; Ameringer & Smith, 2011; Ameringer et al., 2014; Lyon et al., 2014). In this study, negative mood was shown to influence fatigue levels at nearly the same strength as sleep quality. The significant relationship between negative mood and fatigue and non-significant relationship between negative mood and pain severity suggests that symptoms of fatigue could attenuate or partially account for negative mood's effect on pain severity. The biobehavioral model of fatigue posits that depressed mood

independently affects pain severity and fatigue levels (Ameringer & Smith, 2011). However, research has shown strong interrelation between these variables, which may render the predicted isolated effects of one construct on another conceptually unsound. Finally, it is important to consider that limitations to the current study, including a relatively small sample size and restricted age group, may also explain these findings. It may be that negative affect did not affect pain ratings among the youth in our sample due to an artifact or another unknown reason.

As a whole, most previously established relationships tested in the first hypothesis were replicated. After replicating a significant effect of prior night's sleep quality on next-day pain severity ratings, this thesis sought to examine whether pain severity predicted poor same-night sleep quality in the current sample. Contrary to hypothesis 1b, pain severity did not predict same-night sleep quality in this sample while controlling for the effects of fatigue and mood. These data oppose findings from several studies conducted with youth diagnosed with SCD, wherein poor sleep quality and increased pain temporally predicted the other (Fisher et al., 2018; Valrie et al., 2008; Valrie et al., 2007; Valrie et al., 2018). Given these data, two lines of reasoning could explain conflicting findings. First, although two prior studies that produced findings contrary to ours controlled for the effects of mood on sleep quality (Valrie et al., 2008; Valrie et al., 2018), the inclusion of fatigue in our model could possibly change the observed effect of pain severity on sleep quality. Second, methodological differences, such as differences in measurement instrumentation across studies, could contribute to differential findings. Before exploring these possibilities, it is important to note that the literature examining the impact of pain severity on sleep quality among youth with persistent pain conditions

is mixed. While studies involving youth with SCD have consistently demonstrated a significant relationship between pain and same-night sleep quality, multiple studies have failed to demonstrate a predictive effect of pain on same-night sleep quality among youth with chronic pain or pain-related illnesses (Bromberg et al., 2012; Lewandowski et al., 2010). Given this literature, it is likely that both methodological differences and an omitted effect of fatigue are involved in producing mixed findings across literatures.

First, the addition of fatigue in our model predicting sleep quality could have rendered the effect of pain non-significant. While sleep quality is not included in the biobehavioral model of fatigue (Ameringer & Smith, 2011), Ameringer and colleagues (2014) demonstrated significant associations between disrupted or poor sleep and increased levels of fatigue. Additionally, the pathophysiology of fatigue and pain involve overlapping mechanisms and appear to reinforce the other. Therefore, pain and fatigue may interact or mutually influence sleep quality of youth with SCD (Butz Aviel et al., 2011). Among cancer patients, sleep quality has been hypothesized to influence fatigue levels, but the reverse relationship is unclear (Ancoli-Israel, Moore, & Jones, 2001). Moreover, non-significant findings between pain and same-night sleep quality among youth with chronic pain and arthritis suggest pain intensity may be important to consider when exploring causal relationships (Bromberg et al., 2012; Lewandowski et al., 2010). It could be that severe pain disrupts sleep quality whereas mild or moderate pain does not. However, disentangling the effects of pain and use of pain medications on sleep quality remains challenging (Ancoli-Israel et al., 2001; Stinson & Naser, 2003). The relationship between sleep, pain, and fatigue is complex and difficult to characterize.

Second, methodological differences could account for conflicting findings. Specifically, differences in sample characteristics (age ranges) could affect observed results. For instance, it is possible that pain's effect on sleep quality depends on the developmental stage of the youth involved (Valrie et al., 2007, 2008). There is little evidence to support this line of reasoning, however. Pain's effect on sleep quality was replicated in an actigraphy study including same-aged participants by Valrie and colleageues (2018), suggesting that other methodological differences are important to consider. Valrie et al., (2007, 2008, 2018) quantified pain and sleep quality on a 10mm visual-analog scale whereas we, along with other authors (Bromberg et al., 2012; Lewandowski et al., 2010) utilized an 11-point numeric rating scale. Research has shown that, while ratings of pain on visual analog scales and numeric ratings scales reliably correlate with one another, ratings on these measures are distinct (Myvrik et al., 2015). Specifically, one study conducted with youth with SCD demonstrated that VAS and NRS produced similar ratings at high levels of pain but variability between pain ratings on these scales increased at lower levels of pain (Myrvik et al., 2015). Given that acute pain episodes among youth with sickle cell are variable and relatively infrequent, it is possible that these two methods of measuring pain and sleep differentially captured genuine experiences and thus, different findings could be due to measurement errors. Of note, Lewandowski et al. (2010) and Bromberg et al., (2012) reported a nonsignificant effect of pain on same-night sleep quality among youth with chronic pain using eleven-point rating scales to quantify pain and subjective sleep quality. Future research is needed to better elucidate the relationship between variables.

The second overall goal of this thesis was to examine novel indicators of fatigue levels in youth with SCD. As such, we examined associations between youth's sleep quality, use of pain medication, and fatigue levels. Hypothesis 2a, which posited that sleep quality would predict next-day fatigue (above and beyond prior-day fatigue levels), was supported. Specifically, poor sleep quality predicted increased levels of fatigue among youth. Same-day pain severity and negative affect also contributed to fatigue levels in a positive direction, but positive affect did not. These data extend prior cross-sectional research, which had demonstrated associations between sleep and fatigue levels, by identifying a temporal relationship among constructs (Ameringer et al., 2014; Rogers & Lance, 2017). Of note, the biobehavioral model of fatigue presently does not include sleep quality (Ameringer & Smith, 2011). Revisions to this model may be 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). Research supports that inflammation resulting from increased levels of IL-6 may mediate the effect of poor sleep on subjective feelings of fatigue (Rohleder, Aringer & Boentert, 2012; Thomas, Motivala, Olmstead, & Irwin, 2010). For patients with elevated levels of baseline inflammation, poor sleep may exert a multiplicative effect on inflammatory pathways, making these patients particularly vulnerable to the effects of poor sleep on fatigue levels (Gutstein, 2001). Importantly, the effect of prior night's sleep quality on fatigue levels was nearly identical to the effect of negative affect, which has long been theorized and empirically validated to influence fatigue levels across a multitude of studies and disease populations (Ahmadi, Poormansouri, Beiranvand, & Sedighie, 2018; Ameringer & Smith, 2011; Ameringer et al., 2014; Lyon et al., 2014). As

such, sleep quality and negative affect may be equally significant in determining symptoms of fatigue. The influence of sleep quality on prospective fatigue levels among youth with SCD is likely underappreciated. Sickle cell patients demonstrate a high prevalence of sleep disorders (Samuels et al., 1992) anemia, and hypoxia, all of which confer increased risk for fatigue (Brown, 2006; Gutstein, 2001). 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).

The effect of sleep quality on prospective fatigue levels is also meaningful in that it provides support for the distinction between the two constructs (Kanyak et al., 2006; Shen et al., 2006). Had sleep quality demonstrated a large predictive effect on next-day fatigue levels, the interpretation of findings would likely be that the constructs are confounded. However, because the effect of sleep quality was relatively small and equal to those of negative affect, these data support that sleep quality plays an important but not all-encompassing role in affecting youth's fatigue. Further distinguishing conceptual and practical characteristics between these constructs is warranted. It is important to note that our findings are limited in that they 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). Future research should examine how poor sleep quality cumulatively affects fatigue levels among youth with SCD.

The relationships between pain severity, negative affect, and fatigue levels that emerged in this model fall in line with the biobehavioral model of fatigue (Ameringer &

Smith, 2011). Interestingly, significant associations between mood valence and fatigue found in our study are opposite of those in pain severity. Specifically, while negative mood and not positive mood affected fatigue levels, positive mood, but not negative mood, affected pain severity. These data suggest that despite a causal relationship between pain and fatigue, mood differentially impacts these symptoms.

Of particular interest to the present study was the relationship between sleep quality, fatigue, and pain severity among youth with SCD. Specifically, the temporal relationship between pain severity and next-day fatigue levels coupled with significant associaitons between these constructs and sleep spurred the examination of the moderating effect of sleep quality. Consistent with hypothesis 2b, sleep quality moderated the impact of pain on next day fatigue levels in youth. Poor sleep quality exacerbated the effect of pain on next-day fatigue such that youth reporting pain and poor sleep quality endorsed higher levels of next-day fatigue than those who reported pain but adequate sleep quality. Importantly, sleep quality appeared to most strongly affect next-day fatigue levels at moderate levels of pain severity. Sleep quality did not appear to strongly affect fatigue levels when youth experienced no pain or mild pain the day prior. Of note, Ameringer and Smith (2011) had proposed that sleep might mediate the relationship between pain and fatigue. Findings from the current study and limited research supporting a causal impact of pain on subjective sleep quality support that sleep instead interacts with pain to exert a synergistic effect on fatigue levels. These findings are further supported by the pathophysiology of sickle cell disease. Specifically, vaso-occlusive pain and poor sleep quality activate shared inflammatory pathways and

systemic inflammation, likely contributing to increased levels of fatigue among patients (Gutstein, 2001; Reese et al., 2010).

These results underscore the importance of intervening with youth who demonstrate high levels of pain and poor sleep quality. While both of these factors predict increased fatigue in youth, the combination of these factors leads to even greater levels of fatigue, which subsequently put youth at risk for functional disability, poor QOL, and challenges in school (Anderson, et al. 2015; Dampier et al., 2010; Rogers & Lance, 2017). For youth reporting high levels of fatigue, providers should thoroughly assess patients' pain management strategies and sleep habits. Behavioral and pharmacological interventions that target pain management and sleep hygiene may produce ameliorative effects on fatigue levels and restore youth's functional ability.

Finally, in line with the goal to identify novel predictors of fatigue in youth with SCD, the effect of pain medication on prospective fatigue levels was examined. This aim was particularly important for two reasons: the dearth of literature examining the effects of pain medications on fatigue levels among youth with chronic illness and the widespread failure for prior research studies to account for the effects of pain medications. As expected, use of non-opioid pain medications did not predict increases in next-day fatigue levels. However, contrary to hypothesis 3c, opioid pain medications also did not predict increases in prospective fatigue levels. Non-opioid pain medications include non-steroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics (acetaminophen), and topical medications (Okpala & Tawil, 2002). Side effects of these medications are typically restricted to renal, gastrointestinal, and cardiovascular complications and, as such, should not significantly affect fatigue levels in patients with

sickle cell disease (Harirforoosh, Asghar, & Jamali, 2013). Opioid medications, however, exert a powerful sedative effect. Their association with fatigue levels among patients with significant pain disorders remains unclear (Ameringer et al., 2014; Fishbain et al., 2005; Valrie et al., 2007). Delays between high plasma concentration of opioids and perceived effects can last up to an hour (Lotsch, 2005). Additionally, the half-lives of long-acting opioids may last up to seven hours and short acting opioids commonly used to treat pediatric sickle cell pain (Ballas, 2011) have half-lives of three to four hours (Lotsch, 2005). Sedative effects of opioids used to treat pain crises, therefore, could persist for a duration that spans multiple days. However, in a review of medications proposed to affect fatigue levels among patients, opioids were not thought to significantly contribute to persistent levels of fatigue (Zlyott & Byrne, 2010). Because the timeframe under which opioids affect fatigue levels may be restricted, it is possible that researchers are instead interested in how other drugs, whose side effects may include anemia, affect fatigue levels among patients. However, based on the half-life of opioid pain medications, it seems plausible that opioids taken for pain management could affect next-day levels of fatigue.

Evidence supporting opioids' potentially long-acting sedative effects suggest that our findings could be explained by measurement error or study limitations. Specifically, few participants reported days in which they experienced severe pain and took opioid medications. Our study could be underpowered to detect a significant effect of these medications on prospective fatigue levels. Additionally, participants did not specify which type of opioid they took. Controlling for differences in dosage, potency, and the half-life of the drug may be important when examining the effects of these drugs. Finally,

participants were only given three options which specified whether they took non-opioid, opioid, or no medication daily. It is possible that some patients reported taking non-opioid drugs when they instead took both non-opioid and opioid drugs, which is the recommended sequence for managing sickle cell pain (Ballas, 2011). Alternatively, it could be that short half-lives mitigate persistent sedative effects of opioid pain medications. Future researchers should carefully examine next-day effects of opioid use on fatigue levels, functional disability, and mood among sickle cell patients.

Limitations are important to consider when evaluating findings from the present study. Daily diary studies typically involve small sample sizes and although studies may be adequately powered to detect clinically meaningful associations between constructs, findings may not generalize to the broader population. These limitations, in part, explain why replication of prior findings are important and necessary to extend the research literature. 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 days and diary information. Although participants who completed few diary entries were excluded from the present study, it is likely that some patients did not complete diaries on days with meaningful data, such as high levels of pain. It is possible that effect sizes and associations between variables may be underestimated. Researchers should identify effective strategies to boost adherence rates for diary completion and recommend standardized procedures that can be used for daily diary studies. Along these lines, at present, there is limited understanding of how diary completers may differ from diary non-completers as well as how participants might differ from patients that chose not to participate in these studies. Until

researchers can elucidate these differences or lack thereof, conservative estimates of the generalizability of findings from daily diary studies are warranted. Another limitation to the present study was the use of self-report data. While our primary interests were concerned with subjective ratings of fatigue, sleep quality, and pain severity, including additional objective measures of these constructs is important. Alternatively, collecting parent ratings of youth's pain, fatigue, and sleep quality could provide useful information for researchers. 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 work to 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, these data supported the generalizability of prior research findings and countered generalizability of others regarding relationships between pain, mood, fatigue, and sleep. The relationship or lack thereof between negative affect and pain severity should be better characterized by future research. Additionally, future research should attempt to replicate analyses from the present study while addressing methodological inconsistencies in order to better characterize associations between these variables. This thesis also identified novel relations among variables of sleep, pain, fatigue, and use of pain medications. Specifically, sleep was found to independently predict fatigue and interact with moderate levels of pain to predict prospective fatigue levels among youth. While significant effects of opioid and non-opioid medications were not found in the current sample, future research should attempt to elucidate the ways in which pain medications affect sickle cell patients. Taken together, these findings can help

inform future research efforts devoted to developing effective interventions to promote adaptive outcomes for youth with sickle cell disease.

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APPENDIX A: VISUAL REPRESNTATIONS OF MODELING ASSUMPTIONS

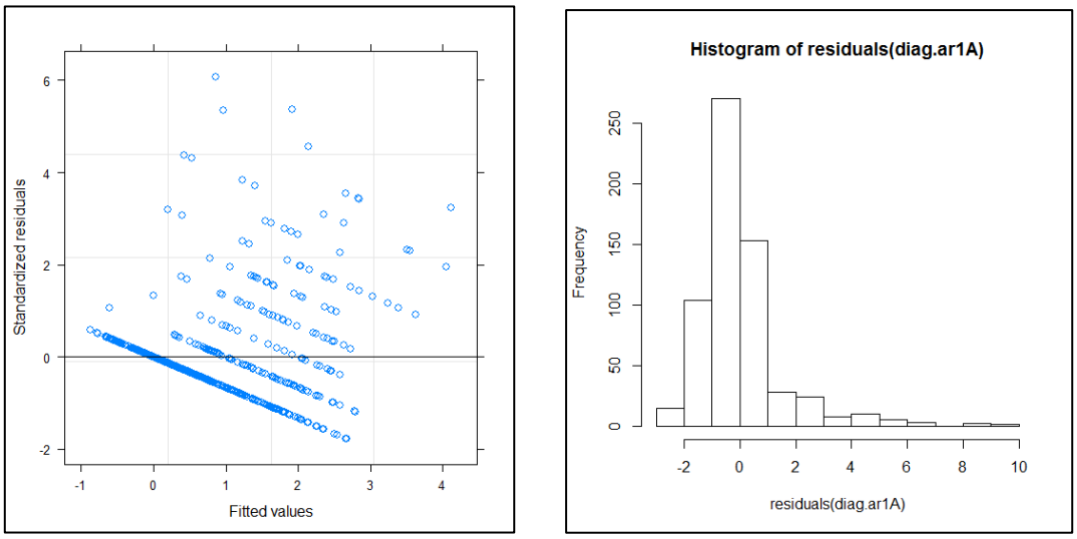


Figure A. 1 Model assumptions for H1A

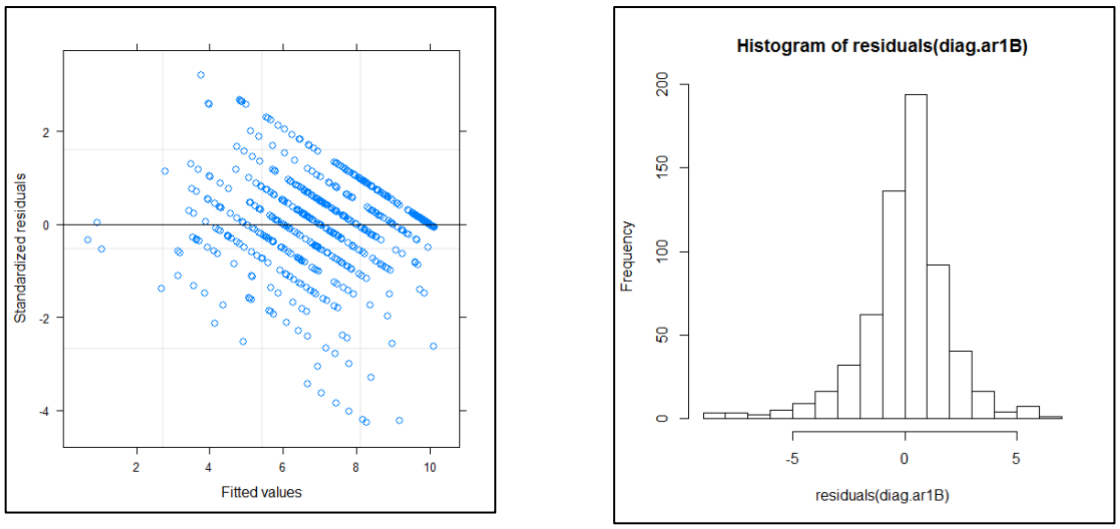


Figure A. 2 Model assumptions for H1B

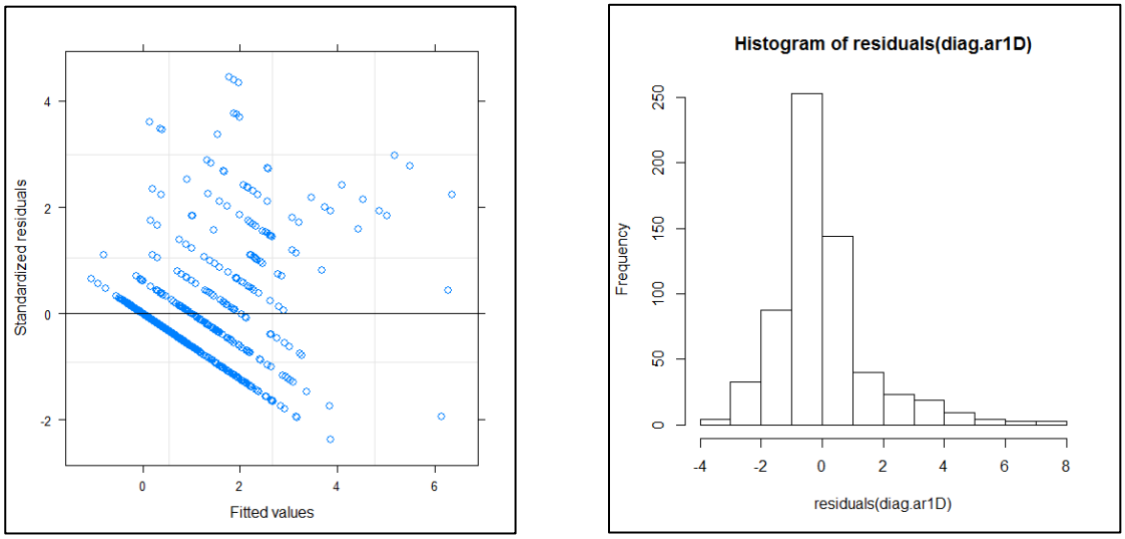
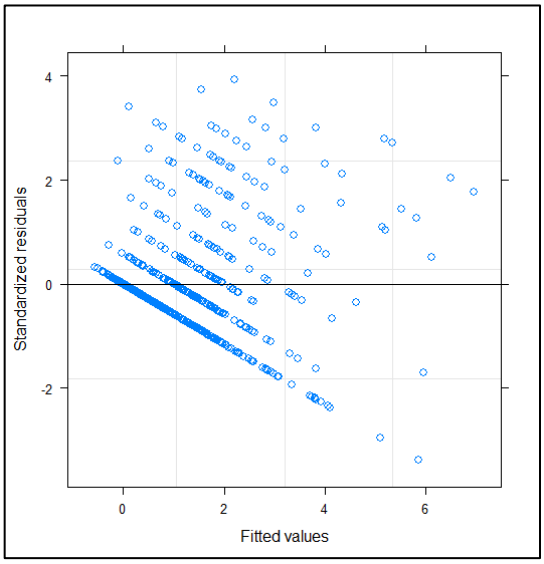


Figure A. 3 Model assumptions for H2A



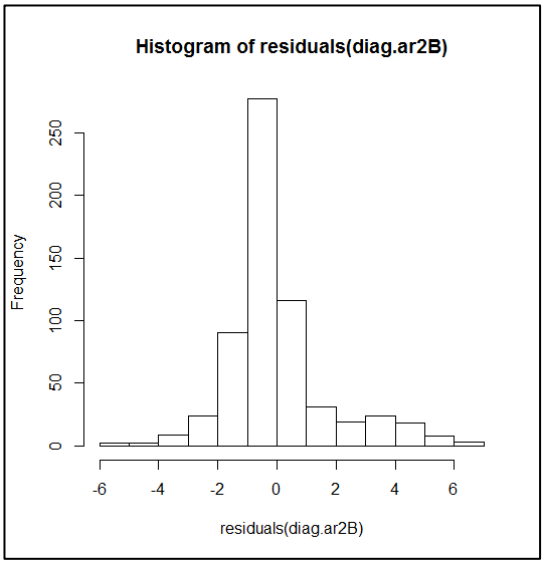
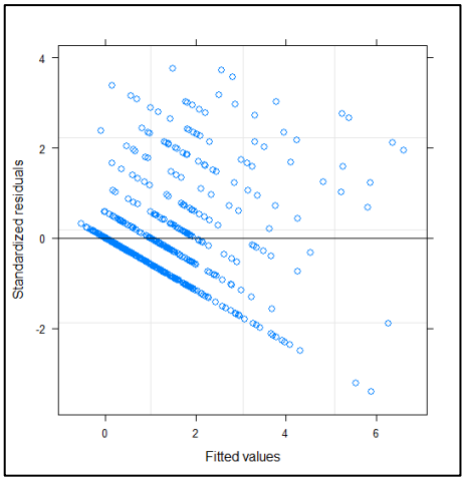


Figure A. 4 Model assumptions for H2B



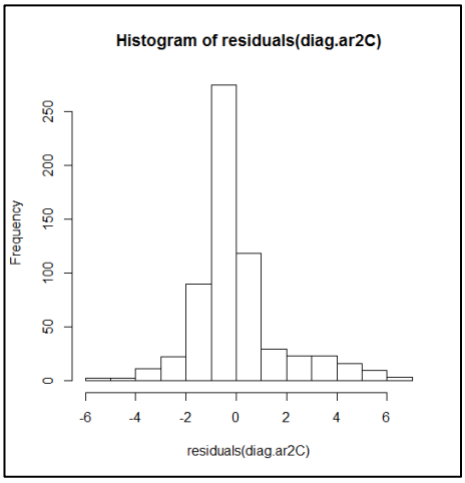


Figure A. 5 Model assumptions for H3