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An Examination of Family Level Factors and Health-related Psychosocial Concerns in Pediatric Sickle Cell Disease

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AN EXAMINATION OF FAMILY LEVEL FACTORS AND HEALTH-RELATED PSYCHOSOCIAL CONCERNS IN PEDIATRIC SICKLE CELL DISEASE

by

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ABSTRACT

The overall theme of this dissertation is an examination of the relationship between family level factors and health-related psychosocial concerns in pediatric sickle cell disease (SCD). In the first chapter, overviews of SCD, common health-related psychosocial concerns in SCD, and family level factors in pediatric conditions are provided. Rationale is provided for the need to further investigate family level factors in SCD, particularly as it relates to child health-related psychosocial outcomes. Additionally, areas of growth related to assessment, analytic methodology, and intervention are discussed in the context of understanding the relationship between family level factors and health-related psychosocial outcomes in SCD. In the second chapter, I present a study examining family functioning in SCD using the Family Assessment Device (FAD). This study further characterizes family functioning in SCD as assessed by the FAD, elucidates the relationship between family functioning and child health-related psychosocial outcomes in SCD, and describes targets of intervention. In the third chapter, I present a study examining the relationship between child health-related quality of life and parent and child pain catastrophizing in SCD using a novel dyadic analysis. The findings of this study highlight the interrelationship between parent and child pain catastrophizing, the value of multi-informant assessment, the need to incorporate dyadic analyses to examine complex parent-child relationships and perspectives, and the potential benefit of family-based intervention. The fourth chapter consists of a systematic review of interventions for enhancing medication adherence in SCD. This systematic review delineates the extent to which families are included in adherence interventions and the efficacy of such interventions. The final chapter synthesizes how the collection of studies included in this dissertation fits within the extant literature on family functioning pediatric SCD and describes directions for future research.

INDEX WORDS: Pediatric sickle cell disease, Family functioning, Dyadic analysis, Quality of life, Pain catastrophizing, Adherence

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DEDICATION

This work is dedicated to children who are impacted by sickle cell disease, and their families. Thank you for participating in this research and allowing us the privilege of hearing and telling your stories.

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1 INTRODUCTION

1.1 Pediatric Sickle Cell Disease

Pediatric sickle cell disease (SCD) is a genetic, hematological condition characterized by the presence of at least one sickle hemoglobin variation (HbS) in the β-globin gene (Stuart & Nagel, 2004). The prevalence of SCD in the United States is estimated to be 1:365 African American births and 1:16,305 Hispanic births (Hassell, 2010). SCD is thought to differentially impact individuals of African descent due to the adaptive function of the HbS genetic variation to protect against contracting malaria (Stuart & Nagel, 2004). Diagnosis typically occurs at birth through the newborn screening program in the United States, which was designed to identify and treat conditions that can affect a child's long-term health or survival (Vichinsky et al., 1988). As part of this program, SCD is the most commonly identified genetic disease (Brawley et al., 2008; Yusuf et al., 2011).

The four most common genotypes of SCD are sickle cell anemia (Hb SS, 60%), sickle-hemoglobin C disease (Hb SC, 30%), and sickle beta-plus thalassemia ($HbS\beta^{+}$), and sickle beta-zero thalassemia ($HbS\beta^{\circ}$, combined 10%) (Hassell, 2010; Yusuf et al., 2011). Patients with the Hb SS and $HbS\beta^{\circ}$ genotypes tend to have more severe disease pathology than patients with Hb SC and $HbS\beta^{+}$ genotypes (Rees et al., 2010), although all patients are vulnerable to the negative sequelae associated with having a chronic illness, such as SCD. The HbS genetic variation results in the sickling of typically round and flexible red blood cells, which can accumulate and occlude oxygen delivery to vital organs. When this occurs, patients experience painful vaso-occlusive pain episodes. Repeated or prolonged vaso-occlusive pain episodes can lead to tissue death in systems such as the heart, lungs, brain, kidneys, spleen, and bones. Therefore, children with SCD are vulnerable to medical complications such as pulmonary dysfunction, strokes,

infection, and bone infarctions (Rees et al., 2010). Management of SCD is also complex with the need for daily medications and supplements beginning at birth, maintenance of healthy lifestyle behaviors (e.g., good hydration, avoiding extreme temperatures and physical overexertion), frequent medical visits for routine and acute care, and potentially repeated hospitalizations (Rees et al., 2010; Stuart & Nagel, 2004). In addition to these medical complexities and demands, pediatric SCD patients are also vulnerable to health-related psychosocial complications (Anie, 2005; Edwards et al., 2005).

1.1.1 Common Health-Related Psychosocial Concerns in SCD

Children and youth with SCD are at risk of poor health-related psychosocial functioning, such as decreased health related quality of life (HRQOL), pain-related functional disability, and insufficient adherence to recommended medical regimens (Badawy et al., 2018; Gil et al., 2003; Hocking & Lochman, 2005; Sil, Cohen, et al., 2016; Walsh et al., 2014).

HRQOL. HRQOL is defined as an individual's perception of how their health status impacts multiple domains of daily living, such as emotional, social, school, and physical functioning (Ingerski et al., 2010). This broad measure of functioning serves as a widely accepted health outcome measure to assess child well-being in the context of chronic illness (Ingerski et al., 2010). Across pediatric chronic conditions, HQROL is decreased as compared to children without chronic medical concerns (Pinquart, 2020; Varni et al., 2007), and this hold true for patients with SCD as well (Dale et al., 2011; Palermo et al., 2002; Panepinto et al., 2005). In comparing parent-proxy reports of HRQOL in patients with SCD to that of patients with other chronic illnesses, there is evidence that parents of youth with SCD perceive their child to have more impairments in their daily functioning than parents of youth diagnosed with irritable bowel disease, type 1 diabetes, or epilepsy (Ingerski et al., 2010). Youths with SCD themselves

perceive more challenges than youth diagnosed with cystic fibrosis, irritable bowel disease, epilepsy, type 1 diabetes, or renal transplant recipients (Ingerski et al., 2010). Factors associated with decrements in HRQOL in pediatric SCD have included frequency of hospitalizations, acute pain, disease severity, disease related stress in the parent, adherence, internalizing symptoms in the child, priapism, and missed school and work (Panepinto & Bonner, 2012). Furthermore, a recent longitudinal study identified lower baseline HRQOL as a potential risk factor for increased pain intensity, frequency, disability, pain catastrophizing, and inpatient admissions at 2-year follow-up (Sil et al., 2020).

Functional Disability. Functional disability is defined as an individual's perceived difficulty in performing daily activities across various settings due to physical health (Walker & Greene, 1991). Children and youth with SCD report moderate to severe levels of functional disability which has been most commonly attributed to the experience of and complications associated with pain and vaso-occlusive episodes (Gil et al., 2003; Oliver-Carpenter et al., 2011; Palermo et al., 2008; Peterson & Palermo, 2004; Sil, Cohen, et al., 2016). In addition, increased functional disability has been associated with increased parental involvement, though this relationship was correlational and not causal (Oliver-Carpenter et al., 2011). Higher levels of functional disability at baseline have also been related to subsequent increases in pain intensity and frequency (Sil et al., 2021).

Adherence. Children and youth diagnosed with SCD demonstrate poor adherence to prescribed medication regimens (Walsh et al., 2014). Poor adherence in pediatric SCD has been associated with worse clinical outcomes and increased health care utilization, such as more frequent emergency department visits and hospital admissions (Candrilli et al., 2011; Walsh et al., 2014). Furthermore, suboptimal adherence has been found to contribute to poor HRQOL and

increased school absenteeism (Badawy et al., 2017; Fisak et al., 2012; Schwartz et al., 2009; Smaldone et al., 2019). Barriers to adherence in SCD have included deficits in knowledge, forgetting, and difficulties with travel to clinics or pharmacies to receive or fill prescriptions (Badawy et al., 2016; Loiselle et al., 2015; Walsh et al., 2014).

These health-related psychosocial concerns are indicative of adaptation in the context of chronic illness and it is imperative to understand promoters and obstacles to optimal functioning for children with SCD.

1.2 Family level Factors in Pediatric Conditions and SCD

For children both with and without chronic illness, it is well understood that the family context plays a fundamental role in the well-being of the child. Within pediatric research, family level factors have been investigated as drivers of child outcomes, though there is a hypothesized reciprocal relationship (Alderfer, 2017; Canter, 2019; Knafl et al., 2015). One of the most commonly utilized frameworks to understand adjustment and adaption to child chronic illness is Wallander and Varni's risk and resistance model (1995, 1998). Wallander and Varni's (1995, 1998) risk and resistance model of child adjustment to pediatric chronic illness posits that chronic physical disorders are an ongoing stressor for both children and parents, and that a host of risk factors (disease parameters, daily functional abilities, psychosocial stressors) and resistance factors (interpersonal factors, social-ecological factors, and stress-processing factors) play a role in determining child adjustment and adaptation (see Figure 1). This theoretical model is meant to be generic and applicable across pediatric chronic conditions and has been utilized in pediatric SCD research (Sil et al., 2021). It has guided the empirical investigation of specific factors that influence child outcomes and subsequently informed interventions to enhance these outcomes. For the purposes of this dissertation, the specific aspect of this model that is of

greatest interest is the area of social-ecological factors at the family level and their relationship with personal factors and stress processing to confer child adjustment and adaptation (e.g., HRQOL, functional disability, and adherence) in SCD.

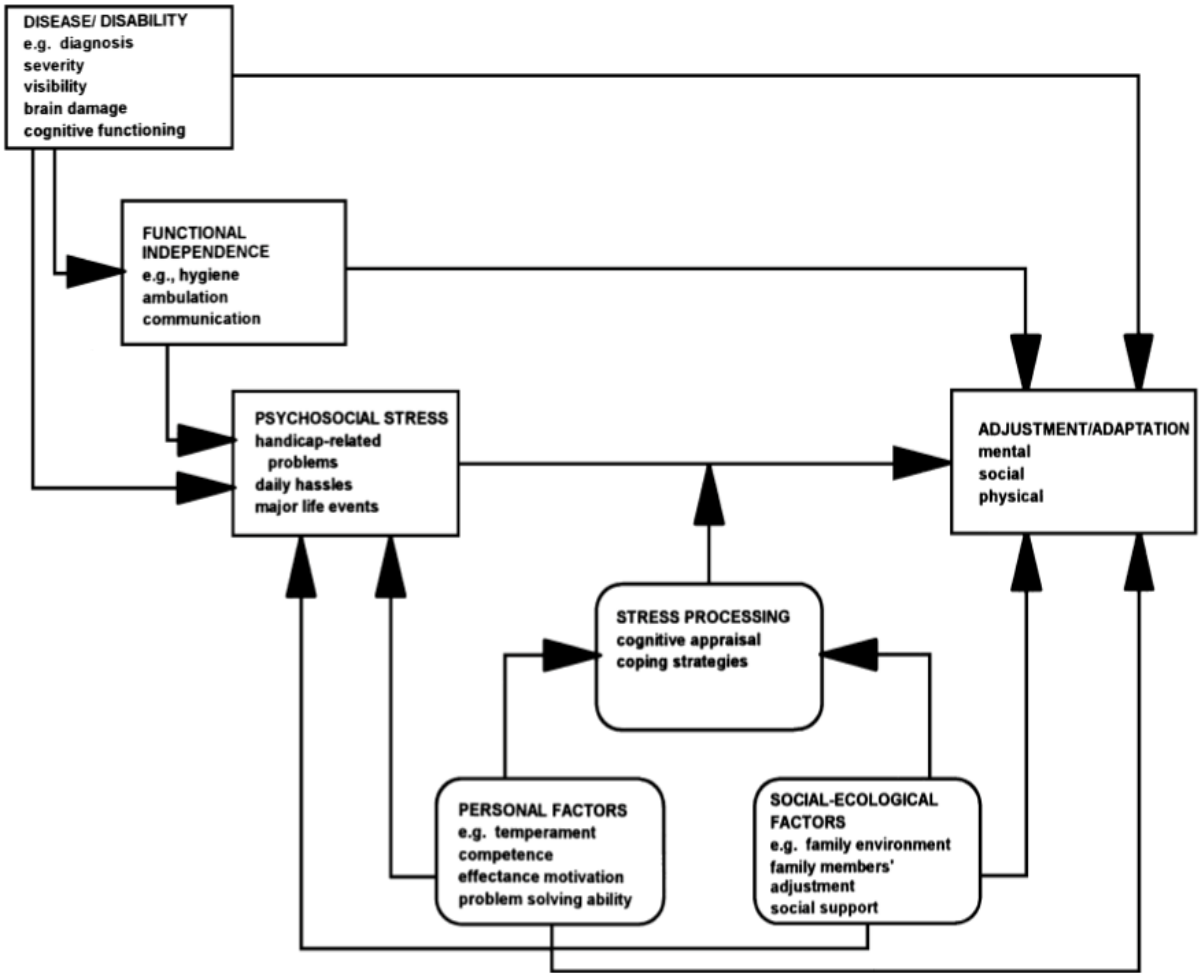

Figure 1. Wallander and Varni (1998) model of child adjustment and adaptation to pediatric chronic illness. Square boxes indicate risk factors; rounded boxes indicate resistance factors.

Family level factors include family functioning and parent-related variables (the term "parent" in this document refers to anyone identifying as a primary caregiver). Family functioning is one of the most frequently assessed family level factors in pediatric research (Barakat & Alderfer, 2011). It can be defined in many ways depending on theoretical orientation

(Hildenbrand et al., 2021), but generally refers to the "social and structural properties of the global family environment" (Lewandowski et al., 2010, p.2). Good family functioning has been characterized as follows, "When families are functioning well, roles are clear, communication is open and straightforward, and affect is well regulated" (Alderfer et al., 2008, pp. 1046-1047). This is contrasted by poor family functioning, where response to stressors happens in a chaotic and unorganized manner, with ineffective communication, and dysregulated affect (Alderfer et al., 2008). In the context of chronic illness, good family functioning lends itself to adequate attendance to daily and acute needs of the child with illness while also maintaining balance and structure in the family unit as a whole (Barakat & Alderfer, 2011). In this way, families necessarily need to have specific tasks clearly delineated to each family member with equal distribution, effective communication so all needs and tasks can be addressed in a timely manner, and appropriate affect that is not overly emotional but is also not under responsive.

Interestingly, on average, children with chronic medical illnesses experience similar levels of family functioning to children without chronic health issues (Herzer et al., 2010; McClellan & Cohen, 2007). However, on a measure with clinically determined cut-offs, families with a child with SCD or obesity were more likely than other chronic conditions to report clinical levels of family dysfunction as compared to healthy populations (Herzer et al., 2010).

Across different pediatric conditions, healthy family functioning has demonstrated greater predicative value than disease severity for health-related psychosocial outcomes in children with chronic medical conditions (McClellan & Cohen, 2007). For example, in pediatric oncology research, family functioning has been found to predict child HRQOL over and above the contribution of treatment intensity (Barakat et al., 2010). In the larger pediatric psychology literature, when children with chronic illness are relieved of family responsibilities and/or there

is poor communication, there has been an association with poorer physical functioning, internalizing problems, and reduced social efficacy (Cipolletta, Marchesin, & Benini, 2015; Leeman et al., 2016).

Previous literature investigating family functioning in pediatric SCD has indicated that family functioning does not demonstrate a direct relationship with pain or healthcare utilization. Specifically, in a longitudinal study of family functioning and health outcomes in SCD, Barakat et al. (2007) did not find significant relationships between family functioning and disease severity, healthcare utilization, average hemoglobin level, or SCD complications (pain episodes). Cross-sectional studies have also corroborated these findings of a non-statistically significant relationship between family functioning and pain features or healthcare utilization (Mitchell et al., 2007; Schlenz et al., 2016, Sil et al., 2021). However, there is more evidence that family functioning may be associated with general behavioral functioning, as well as health-related psychosocial concerns in SCD. Specifically, an increase in family conflict was associated with more behavior problems in a longitudinal study (Thompson et al., 2003), and family cohesion was negatively associated with externalizing problems (Brown et al., 2000). Supportive family relationships have been predictive of better adaptation, characterized by fewer symptoms of anxiety and depression (Burlew et al., 2000), although the relationship between general family functioning and depression was not replicated in a subsequent study (Sil et al., 2021). Additionally, better family functioning has generally demonstrated a positive relationship with child HRQOL (Lutz et al., 2004; Sil et al., 2021), but again, this has also not been consistently shown (Barakat, Lutz, Nicholas, et al., 2005). Only one study to date has investigated the relationship between family functioning and functional disability, and a relationship was not found (Sil et al., 2021). Lastly, family functioning has consistently demonstrated benefit for

adherence in SCD (Barakat et al., 2002; Psihogios et al., 2018). Inconsistencies in findings related to family functioning in SCD might be attributed to variability in assessment of family functioning, as well as outcomes of interest. This suggests there are many areas for growth in better understanding the relationship of family functioning and health-related psychosocial concerns in pediatric SCD.

With regards to parent-related variables and the parent-child relationship, there is evidence that the parent-child relationship is less positive and warm, as well as more demanding and overprotective if a child has a chronic illness as compared to a child without a chronic illness (Pinquart, 2013). A number of different parent factors have been investigated in pediatric research including parent emotional well-being, parenting stress and distress, parent cognitions and behaviors, and parent quality of life (Besier et al., 2011; Cousino & Hazen, 2013; Donnelly et al., 2020; Goldbeck, 2006; Streisand et al., 2001; Lewandowski et al., 2010). The pediatric chronic pain literature in particular has increasingly focused on the unique dyadic, and bidirectional relationship between parent and child cognitive, emotional, and behavioral functioning (Donnelly et al., 2020; Palermo & Chambers, 2005).

One of the most common parent cognition variables assessed in pediatric chronic pain is parent pain catastrophizing (Donnelly et al., 2020; Goubert et al., 2006). Pain catastrophizing is defined as hypervigilance towards pain and a tendency to magnify the threat of pain either in anticipation of or in response to pain (Quartana et al., 2009; Sullivan et al., 2001). Therefore, parent pain catastrophizing is characterized by parents catastrophizing about their child's pain (Goubert et al., 2006). In pediatric chronic pain conditions, parent pain catastrophizing has been associated with poor child outcomes, such as HRQOL, functional disability, pain intensity, and depression; however, questions of directionality persist in this line of study (Donnelley et al.,

2020; Lynch-Jordan et al., 2013). Considering that pain is the hallmark symptom of SCD, it is of interest to determine if dyadic patterns related to pain and functioning observed in other chronic pain conditions are similar to those found in SCD. To date, there have been limited studies of parent pain catastrophizing in SCD (Sil, Dampier, et al., 2016; Goldstein-Leever et al., 2018). These findings indicate that parent pain catastrophizing plays a role in child depression and functional disability. Given the robust literature on this topic in pediatric chronic pain demonstrating a consistent relationship between parent and child pain catastrophizing and child outcomes, it is worth further characterizing this relationship in SCD as well.

Despite indications that family level factors are important to understand in relation to adaptation and adjustment in pediatric chronic conditions, the extant literature on family level factors in pediatric SCD remains relatively limited. As such, it is of value to extend this knowledge base and explore how family level factors, such as family functioning and parent variables, are related to common health-related psychosocial concerns (e.g., HRQOL, functional disability, and adherence) in pediatric SCD. An expanded and more in-depth understanding of these relationships will serve to inform and improve family level intervention in pediatric SCD. Therefore, the first aim of this dissertation is to describe the relationship between family level factors and health-related psychosocial outcomes in pediatric SCD across a collection of studies. However, there is also a need to consider how we assess, analyze, and intervene upon these variables of interest so that we may obtain a more reliable and valid understanding of these relationships.

1.3 Considerations for Assessment, Analysis, and Intervention

1.3.1 Assessment

To examine how the role of these family level factors in the well-being of children with chronic illness, it is necessary to select an appropriate assessment tool. By and large, self-report measures are the most commonly utilized method of assessment for family level factors, though coded observation and interviews are also available (Alderfer et al., 2008; Gerhardt et al., 2017; Hildenbrand et al., 2021). Assessment of family level factors can be utilized to answer a number of research questions, as well as serve clinical purposes. In fact, quality assessment of family functioning has been specifically highlighted as a priority for enhancing understanding of social-ecological factors that place children with chronic illness and their families at risk for poor adjustment and adaption, and to inform intervention development (Barakat & Alderfer, 2011).

Family functioning self-report measures that have been utilized in pediatric SCD research include the FACESII, Family Environment Scale, and the McMaster Family Assessment Device (FAD; Leeman et al., 2016). However, in reviewing the psychometric properties and evidence-base for these assessment tools in pediatric research, the FACESII and the Family Environment Scale were deemed “approaching well-established” while only the McMaster FAD was designated as “well-established” (Alderfer et al., 2008). The FAD is theoretically derived, one of the most widely used measures of family functioning, and has demonstrated good psychometric properties across the domains of internal reliability, test-retest reliability, and construct validity (Epstein et al., 1983; Hamilton & Carr, 2016; Leibach et al., 2017; Miller et al., 1985). The FAD was initially developed and validated with a sample of clinical and nonclinical families and individuals (Epstein et al., 1983). The clinical sample consisted of families with a child in a psychiatric day program, a family member in a stroke rehabilitation program, or a family

member hospitalized in an adult psychiatric hospital (Epstein et al., 1983). A subsequent study investigated the psychometric properties of the FAD with psychiatric and nonclinical families, as well as medical samples, and determined acceptable internal scale reliabilities and factorial validity in each of these groups (Kabacoff et al., 1990).

In addition, clinical cut-offs have been established to identify families with unhealthy family functioning (Miller et al., 1985). The sample utilized to derive clinical cut-offs consisted of adult patients admitted to a psychiatric hospital and their families, as well as adult patients with systemic lupus erythematosus and their families. A comprehensive clinical assessment was completed for each family by an experienced family therapist. Using the clinical interview and previous descriptions of healthy and unhealthy family functioning on dimensions of the McMaster model, the therapist rated the family's functioning, as healthy or unhealthy on each of the model dimensions. Each family also completed a FAD and families rated as having unhealthy functioning by the therapist demonstrated significantly worse functioning on the FAD than those rated by the therapist as having healthy functioning. The clinical cut-off scores were then developed from a combination of theoretical and empirical approaches. Theoretically, having more unhealthy than healthy items endorsed seemed relevant, and thus a cut-off score of 2.0 was considered to meet this criterion based on a likert scale of 1-4. Empirically, therapist interview ratings were utilized as criteria for maximizing sensitivity, such that cut-off values scores accurately captured families that were rated as unhealthy versus unhealthy on each FAD dimension. These theoretical and empirical approaches, in combination with the means of the clinically rated unhealthy families, were utilized to determine cut-off values. Cut-off scores were then used in a non-clinical, community sample and in comparison with the clinical sample, the non-clinical families had significantly higher proportions of healthy scores on all dimensions,

with the exception of behavior control. Therefore, the cut-off scores were determined to accurately identify families with healthy and unhealthy functioning across all dimensions, except for behavior control. These clinical cut-off values were later utilized to identify families "at risk" of significant family dysfunction necessitating therapeutic referral (Akister & Stevenson-Hinde, 1991) and further validated by demonstrating levels of dysfunction above clinical cut-offs in a help-seeking sample versus subclinical scores in a community sample (Mansfield et al., 2015). The FAD consists of six dimensions of functioning, as well as an overall general functioning dimension (Epstein et al., 1983). The factor structure of the FAD has been questioned, due to observed intercorrelations amongst dimensions (Ridenour et al., 1999). In defense of the measure as it stands, Miller et al. (2000) explained that the FAD was developed based on the rational-theoretical method and not on the factor analytic method, such that the dimensions were derived from the McMaster model of family functioning. They further questioned the validity of the factor evaluation by Ridenour et al., given that it was conducted using only the subscale correlations from the original validity study, and not from raw or originally collected data. Therefore, Miller et al. concluded that the FAD should be administered and scored as intended.

In pediatric chronic illness, specific dimensions as well as the general functioning dimension of the FAD have been associated with child psychological health, physical health, and social competence (Leeman et al., 2016). Furthermore, the FAD has been utilized with and validated in Black American samples (Groenenberg et al., 2013; Guada et al., 2010; Leibach & Everhart, 2017). Taken together, the FAD may be a particularly useful research and clinical tool in pediatric SCD.

Furthermore, it is recommended that when examining family level factors, that multi-informant assessment be utilized when possible, given that perspectives may be similar but also

differ across individual members (Alderfer, 2017, Hildenbrand et al., 2021). However, it is not always possible to obtain multiple perspectives in pediatric clinical research when the whole family unit is not present for or interested in participating in research, or when it may be burdensome and taxing for each member of the family to complete all of the same measures. It is recommended that researchers balance participant time expenditure and the incremental value of collecting the same data from multiple informants (Hildenbrand et al., 2021).

1.3.2 Analysis

Along with the question of assessment of family level factors, there is the conundrum of how to analyze the data collected. When there are multiple reporters on the same variable or on different variables, it can be challenging to determine an adequate data analytic plan that accurately captures multiple perspectives and answers the research question. In pediatric psychology research, data of this nature has historically been statistically handled by amalgamating responses from multiple family members to create a sum score for analysis (Hildenbrand et al., 2021; Sayer & Klute, 2005), or by running multiple analyses or models by reporter (e.g., mother, father, child) and comparing and contrasting findings (Hildenbrand et al., 2021; Fuligni, 2014; Lebow & Stroud, 2012). Statistically, these methods assume that reporter data are independent of each other, which may increase the likelihood of biased estimates (Kenny et al., 2006). Conceptually, this approach may obscure important interactions among multiple family members' perspectives and there are missed opportunities to understand the unique processes of dyads or family systems (Hildenbrand et al., 2021; Kenny et al., 2006).

Relatively newer methods of data analysis more accurately capture and analyze data in accordance with our theoretical understanding of how families and parent-child dyads interact (Alderfer, 2017; Kenny, 2011). These methods typically utilize hierarchical linear modeling

(HLM) or structural equation modeling (SEM), which account for the interdependence and shared variance of data. HLM allows for individual predictor data to be nested within hierarchical levels so that variance in the outcome variable can be analyzed between and within levels (Woltman et al., 2012). For example, child data, parent data, and teacher data would each be grouped and hierarchically structured at different levels to analyze their intra- and inter-relationship to the outcome variable. SEM models associations among latent and observed variables, which allows for greater flexibility in testing and expanding theoretical models (Ullman & Bentler, 2013). In addition, dyadic analysis models, such as the Actor-Partner Interdependence Model (APIM) and Common Fate Model, are easily modeled using SEM (Cook & Kenny, 2005; Kenny & Ledermann, 2010; Ledermann & Kenny, 2012). These data analytic methods are complex but provide more statistical and conceptual clarity when examining complex systems and factors, such as family functioning or parent variables.

These analytic methods are increasingly being utilized in pediatric research given the importance of social-ecological variables in child well-being; however, this methodology is still considered novel within the field (Kenny, 2011). Dyadic analyses, such as APIM, have garnered interest due to the emphasis on parent-child dyads in pediatric research (Reed et al., 2013). Pediatric acute and chronic pain research in particular has turned to APIM to test the transactional relationship between parent response and child pain (Birnie et al., 2016; Birnie et al., 2017; Fales et al., 2014; Noel et al., 2017; Palermo & Chambers, 2005). However, application of this analytic methodology has not yet extended to studying the parent-child dyad in pediatric SCD pain research. Within this population, there are numerous research questions for which dyadic analysis would be appropriate and warranted to better understand the experience of families with children diagnosed with SCD.

1.3.3 Intervention

With increased understanding of the experiences of families with children diagnosed with SCD, this allows for improved clinical intervention. Empirically designed intervention studies developed explicitly for pediatric SCD have targeted pain management (Chen et al., 2004; Wihak et al., 2020; Williams & Tanabe, 2016), transition readiness (Melita et al., 2019; Viola et al., 2021), and adherence (Chen et al., 2004). Interventions have varied in their inclusion of caregivers or family members, but it has been strongly recommended (Hocking & Lochman, 2005). Transition readiness interventions have generally included only patients, which may be appropriate considering the goals of transition (Viola et al., 2021). Pain management interventions have been somewhat divided in their inclusion of family members, with one systematic review identifying direct inclusion of parents or caregivers in 6 out of 16 interventions (Williams & Tanabe, 2016). Interventions for pain in SCD have generally consisted of psychoeducation on nonpharmacological pain management strategies (e.g., relaxation) or cognitive behavioral therapy approaches (Chen et al., 2004; Williams & Tanabe, 2016). Interventions that included caregivers and family members largely focused on teaching family members the same coping skills taught to patients in order for caregivers to provide at home support (Barakat et al., 2010), with one study also directly addressing family communication (Kaslow & Brown, 1995). In contrast to family-based interventions in chronic pain, there has been less focus on optimizing how caregivers respond to pain in SCD (Coakley & Wihak, 2017). Specifically, caregivers of children diagnosed with chronic pain are often given guidance on how parental catastrophizing of pain or oversolicitousness may inadvertently reinforce maladaptive child pain responses (Law, Fisher, Fales, Noel, & Eccleston, 2014; Levy et al., 2010). It has been suggested that this is a direct reflection of how research on family systems in pediatric chronic

pain has informed intervention in this population (Coakley & Wihak, 2017). Therefore, the absence of empirically based intervention on parent response to SCD pain may be due to the fact that research on this phenomenon in SCD has been relatively recent (Shneider, 2021; Sil, Dampier, et al., 2016) and intervention may be forthcoming.

In contrast, it is well-established that family level factors are indicated in ensuring satisfactory adherence in pediatric conditions (Dean et al., 2010; Dimatteo, 2004; Kahana et al., 2008; Smith & Shuchman, 2005) including SCD (Beyer & Simmons, 2004; Modi et al., 2009; Platt, 2008; Raphael et al., 2009; Yawn et al., 2014). Recent meta-analytic findings revealed a significant relationship between family functioning and medical adherence across a variety of pediatric conditions (Psihogios et al., 2019). Specific components of family functioning that were associated with better adherence included lower family conflict, greater family cohesion, greater family flexibility, more positive communication, and better family problem-solving (Psihogios et al., 2019). In SCD specifically, better family problem solving was associated with improved medication adherence (Barakat et al., 2002) and higher levels of family efficacy and lower levels of parenting stress were associated with better SCD self-management (Psihogios et al., 2018). These findings indicate the importance of targeting family level factors in SCD adherence intervention; however, the extent to which family functioning is systematically targeted in SCD adherence interventions and the efficacy of such interventions needs to be determined.

1.4 Rationale for Clinical Research in SCD

In considering how these family level factors are associated with SCD health-related psychosocial concerns, it is also necessary to recognize that pediatric SCD is a condition that almost exclusively impacts individuals with a minoritized identity. Due to systemic oppression,

these families are also more likely to experience daily stressors that may be independent of a child's chronic illness (Sheidow et al., 2013). SCD is also an under-researched population, despite affecting approximately 100,000 individuals in the United States (Smith et al., 2006). In comparison to cystic fibrosis, another genetic disorder that impacts multiple organ systems, between 2008 and 2018, SCD received significantly less federal funding for drug development, had lower foundation expenditures for research, and there were fewer published studies in SCD (Farooq et al., 2020). More specifically, the average federal funding per person for cystic fibrosis was $2807, while the average federal funding per person for SCD was $812 (Farooq et al., 2020). The number of research publications followed a similar pattern with 1594 publications identified in cystic fibrosis and 926 publications identified in SCD (Farooq et al., 2020). These statistics emphasize the health disparities experienced by individuals with SCD despite the fact that individuals with SCD experience high rates of morbidity and mortality, reduced life expectancies, and poor psychosocial outcomes, (Piel et al., 2017). With this in mind, it is imperative that the research agenda in SCD be furthered so that clinical intervention may be optimized for families of children with SCD.

1.5 Summary and Purpose

Children with chronic health conditions are at risk of poor health-related psychosocial functioning and it is necessary to determine factors that promote or hinder their well-being. Wallander and Varni's risk and resistance model posits that social-environmental factors, such as family functioning and parent variables, are a vital contributor to functional outcomes in a child with chronic illness. Therefore, there is a need to better understand these family level factors empirically and to inform intervention in pediatric chronic illness.

Pediatric SCD is a chronic, unpredictable condition that requires an involved treatment regimen with the potential to disrupt the routine and schedule of the patient and family. Children diagnosed with SCD experience medical complications, such as recurrent pain, as well as health-related psychosocial challenges, such as decreased HRQOL, functional disability, and suboptimal adherence. The physical and psychosocial sequelae of experiencing SCD necessitates exploration of contributory factors, including those at the family level. Family functioning and parent variables have been identified as potentially relevant factors warranting further investigation. To optimally understand the relationship of these family level factors to health-related psychosocial concerns in pediatric SCD, considerations should be given to how these variables are assessed and analyzed, as well as the extend to which they are included in intervention. Given that SCD is a relatively under-researched chronic condition, there remain many opportunities to initiate empirical efforts in this population. The purpose of this dissertation is to address some of the many gaps in our understanding of family level factors in pediatric SCD.

In summary, systemic factors should be further investigated in the context of pediatric sickle cell disease to gain a more holistic understanding of factors that may promote or hinder the well-being of children diagnosed with SCD. The following manuscripts reflect various inquiries and commentary on family level factors associated with health-related psychosocial outcomes in the context of pediatric SCD. This collection of studies is not meant to be serial, but rather each study provides further insight on the relationship between family level factors and health-related psychosocial concerns in pediatric SCD. Furthermore, they reflect and highlight areas of growth that should be made in assessment, analysis, and intervention of family level factors in pediatric SCD. As such, the goals of this dissertation are primarily to describe the relationship between

family level factors and health-related psychosocial outcomes in pediatric SCD and secondarily to provide commentary on how the field can hone assessment, analytic methodology, and intervention to better understand and address the relationship between family level factors and health-related psychosocial outcomes in pediatric SCD.

The first study characterizes family functioning in pediatric SCD using the McMaster FAD, a well-validated, theory driven assessment tool for family functioning. This study discusses the potential research and clinical benefits in using this measure dimensionally and by clinical categories. Furthermore, the relationship between family functioning and child HRQOL and functional disability are investigated, informing future targets of intervention. The second study presents an investigation of how parent and child pain catastrophizing are uniquely and mutually associated with child HRQOL using a novel dyadic analysis. This study contributes to the limited literature on parent pain catastrophizing in pediatric SCD, and also highlights the use of dyadic analyses for examining multi-informant data and multiple perspectives. The third study is a systematic review of psychological interventions for improving adherence in SCD. This review addresses the extent to which family-based intervention for adherence in pediatric SCD have been conducted and the efficacy of such interventions. In the final chapter, conclusions drawn from these studies are collated, and additional factors are discussed to inform future directions within the field of clinical research in pediatric SCD.

2 ARTICLE 1: FAMILY FUNCTIONING IN PEDIATRIC SICKLE CELL DISEASE: CHARACTERIZING THE FAMILY ASSESSMENT DEVICE

2.1 Abstract

Objective: Data indicate that families of children with sickle cell disease (SCD) are at greater risk for unhealthy functioning. Previous studies utilizing the Family Assessment Device (FAD) have reported on general functioning, though individual dimensions may provide better insight into the impact of chronic illness and targets of intervention. This study aimed to characterize family functioning in SCD using the FAD, examine the FAD dimensionally, and to explore the relationship between clinical categories of family functioning ("healthy" vs "unhealthy") and health-related psychosocial outcomes.

Method: 93 12- to 18-year-olds with SCD and their caregivers were enrolled. Caregivers completed a measure assessing family functioning and youth completed self-report measures of health-related quality of life (HRQOL) and functional disability. Descriptive analyses and analyses of relationships between FAD dimensions and sociodemographic variables were conducted. T-tests were utilized to determine differences between families determined to have "healthy" vs. "unhealthy" functioning and psychosocial outcomes.

Results: Group means on all FAD dimensions fell in the "healthy functioning" range, with greatest impairments reported in affective involvement, roles, general functioning, and problem solving. A negative relationship was found between family income and the role dimension. Families categorized as having any dimension of "unhealthy" functioning demonstrated worse HRQOL and functional disability with specific relationships found for the roles dimension.

Conclusions: Families of children with SCD show impairments in functioning. Results did not replicate previous research in level of dysfunction for SCD families specifically, but percentage of families reporting dysfunction across dimensions were comparable to other previously studied chronic illness groups. Data supports that dysfunction in role responsibility may be most related to psychosocial outcomes, suggesting targets of intervention include addressing social determinants of health.

2.2 Introduction

Pediatric chronic illness can impact how a family functions by altering routines, parental demands, and overall familial dynamics (Knafl et al., 2015). In turn, poor family functioning might affect successful management of pediatric conditions and child well-being (Alderfer & Stanley, 2012; Wallander & Varni, 1998). As such, family functioning plays a vital role in understanding the promoters and barriers of well-being in children with chronic conditions.

A commonly utilized framework for conceptualizing family functioning in pediatric illness is the McMaster approach to families model. This model posits that how a family functions determines how successful it is at completing necessary tasks (Epstein et al., 1983). In the approach to families model, the foundational dimensions of family functioning consist of problem-solving, communication, roles, affective responsiveness, affective involvement, and behavior control (Miller et al., 2000). These dimensions are reflected in the McMaster Family Assessment Device (FAD; Epstein et al., 1983). The authors argue that assessing each of these dimensions provides a more holistic understanding of the family unit. The problem-solving dimension is defined as how effectively a family resolves concerns without disrupting family functioning. The communication dimension is defined as how clearly and directly verbal information is exchanged within a family. The roles dimension is defined as how family

members fulfill family tasks and functions. The affective responsiveness dimension is defined as the quality and quantity of appropriate emotional responses. Affective involvement is defined as how much family members engage in and value the activities and interests of each other. Behavior control is defined as how behavior is managed in accordance with family-based standards and rules. The FAD assessment instrument maps onto these dimensions and includes an additional general functioning dimension that reflects overall family functioning. The FAD is a commonly used tool in pediatric psychology research and is considered a "well established" measure of family functioning and has been validated and used with racially and ethnically diverse samples (Alderfer et al., 2008).

Previous literature has used the FAD to compare family functioning in pediatric conditions and children without chronic health conditions (Herzer et al., 2010). Families of children with sickle cell disease (SCD) have been identified as being at greater risk than other conditions for unhealthy family functioning (Herzer et al., 2010). SCD is a common, inherited hematological condition that primarily affects families of African descent (Hassell, 2010). SCD is characterized by abnormally shaped red blood cells that can occlude blood flow. This results in vaso-occlusive pain episodes that require pharmacological pain management and can necessitate emergency department visits or hospitalizations (Brousseau et al., 2010). At worst, vaso-occlusion can also lead to acute pulmonary dysfunction or stroke (Piel et al., 2017). To prevent the likelihood of vaso-occlusive episodes, patients take daily medications and are instructed to engage in regular hydration and healthy eating, as well as avoidance of extreme temperatures or physical overexertion (Driscoll, 2007). As a result, SCD is a particularly complex and demanding pediatric condition that has been described as a chronic, progressive, and life-

shortening disease with recurrent exacerbations and an intricate treatment regimen that necessarily impacts and involves the family (Herzer et al., 2010).

Herzer et al. (2010) found that for families of patients with SCD (*n*=44), the average scores on all dimensions of the FAD were in the "healthy" functioning range; however, a percentage of families fell in the "unhealthy" family functioning range on general functioning (32%), problem solving (16%), communication (25%), roles (41%), affective responsiveness (23%), affective involvement (45%), and behavior control (30%). In group analyses examining the relationship between FAD dimensions and sociodemographic variables across all pediatric conditions, older child age was associated with greater problems in the dimensions of communication, affective responsiveness, and general functioning, while better communication and general functioning were associated with more children in the home. Further, lower household income was associated with higher levels of difficulty on the roles and affective involvement dimensions. No differences were found for child gender, child minority status, or caregiver marital status. In studies of family functioning in SCD using the FAD, families with higher socioeconomic status reported significantly better general functioning in one study (Barakat et al., 2005), but this relationship was not replicated in a subsequent study (Bills et al., 2020). Relationships to other sociodemographic differences were not found, and additional dimensions were not included in analyses.

Previous studies that have examined health-related outcomes and family functioning in SCD using the FAD have demonstrated equivocal findings. The general functioning dimension individually has not demonstrated a relationship with SCD pain or pain related outcomes (Schlenz et al., 2007; Sil et al., 2021). Mitchell et al. (2007) also found no significant relationship between FAD dimensions and disease severity or healthcare utilization (e.g., pain days, number

of hospitalizations, emergency department visits). With regards to health-related psychosocial outcomes, only general functioning dimension was used in a recent study and it did not demonstrate a relationship with functional disability (Sil et al., 2021). Similarly, in investigating the relationship between health-related quality of life (HRQOL) and family functioning using only the general functioning dimension, studies have not consistently demonstrated a significant association (Barakat et al., 2005; Lutz et al., 2004; Sil et al., 2021). The inconsistent relationship between family functioning and HRQOL is surprising given that both family functioning and HRQOL are known to be impaired in SCD and family functioning has been identified as essential to child well-being (Herzer et al., 2010; Hocking & Lochman, 2005; Ingerski et al., 2010). However, in meta-analytic studies of pediatric conditions in general, the specific FAD dimension of roles was associated with HRQOL, such that better role fulfillment was related to improved HRQOL, but there was no relationship to general functioning (Leeman et al., 2016). This suggests that there may be increased utility and specificity in examining the FAD dimensionally, instead of relying solely on the general functioning dimension.

Therefore, the purpose of the current study is to (1) characterize family functioning in SCD using the FAD, including describing relationships with sociodemographic variables, and (2) examine the FAD dimensionally and using clinical categories (e.g., healthy vs. unhealthy functioning) to explore the relationship between clinical categories and health-related psychosocial outcomes (i.e., HRQOL, functional disability). It is hypothesized that the FAD will demonstrate a similar profile to previous findings, such that overall averages will be below clinical range, but a percentage of families will exhibit clinically unhealthy functioning. With regards to sociodemographic differences, we except to find similar relationships as in previous studies. The general functioning dimension has typically been utilized in previous studies as a

global measure of family well-being. However, it is also worthwhile to consider the unique contribution of each individual dimension, given that they are theoretically related but not necessarily the same (Miller et al., 2000). Furthermore, there may be increased clinical utility in examining health-related psychosocial outcomes by clinically determined levels of impairment. Therefore, it is hypothesized that families demonstrating any unhealthy dimensions of family functioning will exhibit worse HRQOL and increased functional disability as compared to families with healthy levels of family functioning.

2.3 Method

2.3.1 Participants

Participants were recruited from a children's hospital system in the Southeast region of the United States between 2015-2016. Inclusion criteria included English proficiency and a diagnosis of SCD. Exclusion criteria included cognitive or developmental delays prohibiting completion of study procedures. Participants were 93 adolescents between the ages of 12- to 18-years old (*M* = 15.23 years, *SD* = 1.97 years, Female = 52.7%) and diagnosed with SCD (HbSS 68.8%, HbSC 8.6%, HbSβ° 4.3%, HbSβ$^+$ 18.3%), as well as their caregiver (*M* = 43.62 years, *SD* = 8.43 years). Caregivers were predominantly mothers (86%), with some fathers participating (14%). Approximately half of caregivers identified as Married or Partnered (52.7%), followed by Single (22.6%), Divorced (11.8%), Separated (7.5%), and Widowed (3.2%). The average family income fell in the $50,001-60,000 range with at least 20.5% of the sample falling below the 2015 poverty guideline for a 4-person family ($24,250). See Table 1 for additional demographic data.

2.3.2 Measures

Demographics. Caregivers reported their own and their child's demographic and SCD-related information by completing the Background Information Form. Information about the

caregiver's relationship to the adolescent (i.e. mother, father, or grandparent), age, marital status, as well as the family's income and number of siblings in the home were gathered. Caregivers also provided information about their adolescent's age, gender, race, and SCD genotype (i.e. HbSS, HbSC, HbSβ°, HbSβ^{+}).

Family Functioning. Family functioning was measured by the Family Assessment Device (FAD; Epstein et al., 1983) and was completed by the caregivers. The FAD assesses family functioning across seven dimensions, as described earlier in this manuscript. The FAD contains 60 items that are rated on a 4-point Likert scale, with lower scores corresponding to better family functioning. The FAD has been used widely to evaluate family functioning among pediatric samples (Alderfer et al., 2008) and families of youth with SCD (Barakat et al., 2005; Bills et al., 2020). In addition, the general functioning dimension has been utilized in studies with Black and African American samples (Groenenberg et al., 2013; Leibach & Everhart, 2017). Cronbach's alpha for all dimension subscales in the current sample were in the acceptable to good range ($a > 0.61$), which aligns with previous reliability scores for general medical (Kabacoff et al., 1990) and pediatric (Alderfer et al., 2008) populations. Clinical cut-off scores are used to differentiate "healthy" vs. "unhealthy" family functioning (Miller et al., 1985).

Quality of Life. Adolescents' quality of life was measured by the Pediatric Quality of Life Inventory (PedsQL 4.0 Generic Core Scale; Varni et al., 2001) and was completed by the adolescents. The PedsQL evaluates health-related quality of life across four domains including physical, emotional, social, and school functioning. This measure contains 23 items, rated on a 5-poin Likert scale, that were reverse-scored and transformed to standard scores. Higher total scores indicate better quality of life. The PedsQL has been demonstrated to be a reliable and

valid measure of health-related quality of life in youth with SCD (McClellan et al., 2008). Cronbach's alpha for the current sample indicated good internal reliability (α =.93).

Functional Disability. The Functional Disability Inventory (FDI; Walker & Greene, 1991) was used to measure adolescents' perceptions of their ability to engage in common, physical, day-to-day activities over the past two weeks, while considering their physical health. Adolescents completed the 15-item self-report measure. Item responses were on a 5-point scale, with higher scores indicating greater functional disability. The FDI has been demonstrated to be a reliable and valid measure of functioning in pediatric populations and adolescents with chronic pain (Cohen et al., 2010; Palermo et al., 2008). Reliability in the current sample was good as demonstrated by Cronbach's alpha (α =.94).

2.3.3 Procedure

Participants were enrolled in a larger study investigating risk and resilience factors in SCD. Participants either completed paper and pencil measures or online via REDCap survey.

Eligible families were approached and consented by trained research assistants during a clinic visit. Surveys were completed by both adolescents and their caregivers and completion time averaged 30-45 minutes. Families were compensated for their time with a $5 gift card.

2.3.4 Data Analyses Plan

Descriptive analyses were conducted for the sample, sociodemographic variables, FAD dimensions, and health-related psychosocial variables. Pearson correlations were used to examine relations between FAD dimensions and sociodemographic variables such as child age, number of children in the home, and family income. Independent *t*-tests and ANOVA were used to examine group differences on FAD dimensions based on the categorical sociodemographic variables of child gender, SCD genotype, and caregiver marital status. Families were categorized

as having either "healthy" or "unhealthy" levels of functioning on each FAD dimension based on clinical cut-offs (Miller et al., 1985). Families with any dimensions in the "unhealthy" classification were differentiated from families with no dimensions in the "unhealthy" classification to create dichotomous groups. *T*-tests were used to examine any group differences between "unhealthy" and "healthy" functioning groups on sociodemographic variables and health-related psychosocial variables (HRQOL, functional disability). Pearson correlations were conducted to describe the relationship between FAD dimensions and health-related psychosocial variables (HRQOL, functional disability). To reduce Type I error due to repeated comparisons, a Bonferroni correction was applied (.05/9) and p-value was set at .005. Statistically significant correlations were further explored by examining unhealthy vs. healthy functioning group differences on health-related psychosocial variables.

2.4 **Results**

2.4.1 Descriptive Analyses

The group means on all FAD dimensions fell below the established cutoffs for "unhealthy" functioning. However, when looking at the family level, 15.7-33.3% of families fell in the "unhealthy" functioning range on individual FAD dimensions (see Table 2). Specifically, Affective Involvement (33.3%), Roles (30.1%), General Functioning (26.8%), and Problem Solving (24.4%) demonstrated the highest percentage of "unhealthy" functioning, followed by Behavioral Control (19.3%), Communication (18.8%), and Affective Responsiveness (15.7%). In addition, 55.7% of families had at least one FAD dimension in the unhealthy functioning range (see Table 3). Descriptive statistics on health-related psychosocial variables were as follows: HRQOL (M = 72.41, SD = 18.50) and functional disability (M = 10.79, SD = 12.10).

2.4.2 Relationship to Sociodemographic Variables

FAD dimensions were not significantly associated with child age, child gender, or number of children in the home. There was a statistically significant, negative relationship between family income and the role dimension, such that lower family income was associated with higher levels of dysfunction in family roles (r = -.26, p = .024). When the role dimension was explored at the item level, a statistically significant relationship was found between lower family income and more challenges with meeting bills (r = -.45, p<.001), running out of needed items (r = -.45, p<.001), transportation (r = -.31, p = .006), having to check behind others for task completion (r = -.27, p = .015), and reduced time to explore personal interests (r = .26, p = .023). There was a statistically significant difference in affective responsiveness between SCD genotype groups as determined by a one-way ANOVA (F(3, 79) = 2.88, p = .041). However, Tukey's HSD posthoc test did not reveal statistically significant differences between SCD genotype groups. There was a statistically significant difference in role between caregiver marital status groups as determined by a one-way ANOVA (F(4, 77) = 2.52, p = .048). However, Games-Howell posthoc test did not reveal statistically significant differences between caregiver marital status groups. When the sample was split by families with any FAD dimension in the "unhealthy" classification (n = 39, 55.7%) versus no FAD dimension elevations (n = 31, 44.3%), no group differences were found on sociodemographic variables.

2.4.3 Relationship to Health-Related Psychosocial Variables

Family income was not correlated with HRQOL or functional disability (p >.05). Families categorized as having any dimensions with unhealthy functioning (M = 68.75, SD = 20.92) demonstrated worse HRQOL than families with healthy functioning (M = 78.13, SD = 14.51), t(64.95) = 2.17, p=.034. Families categorized as having unhealthy functioning (M =

14.89, *SD* = 14.82) demonstrated worse functional disability than families with healthy functioning (*M* =7.34, *SD* = 7.79), *t*(58.53) = -2.69, *p*=.009.

Pearson correlations revealed statistically significant relationships between the role dimension and HRQOL (*r*=-.35, *p*=.002) and functional disability (*r*=-.36, *p*=.001; see Table 4). Based on these results, group differences on HRQOL and functional disability were examined between unhealthy and healthy functioning groups in the role dimensions. Families categorized as having unhealthy role functioning (*M* = 62.38, *SD* = 19.56) demonstrated worse HRQOL than families with healthy role functioning (*M* = 77.53, *SD* = 16.95), *t*(75) = 3.43, *p* <.001. Families categorized as having unhealthy role functioning (*M* = 16.29, *SD* = 15.11) demonstrated worse functional disability than families with healthy role functioning (*M* = 8.37, *SD* = 9.76), *t*(76) = -2.77, *p*=.007).

2.5 Discussion

The purpose of this study was to characterize family functioning in pediatric SCD using the FAD and to explore relationships with sociodemographic variables. The FAD was examined dimensionally and clinical categories were used to explore the relationship between “healthy” vs. “unhealthy” functioning and health-related psychosocial outcomes (i.e., HRQOL, functional disability).

In line with hypotheses, the FAD scores demonstrated a similar profile to previous findings (Herzer et al., 2010), such that overall averages were below clinical range, but a percentage of families did report clinically unhealthy functioning. The percentages of families in each dimension who exhibited scores above cut-off were lower than those found in the previous study for all dimensions, except for problem solving, with more families in our study reporting challenges with being able to effectively solve problems (Herzer et al., 2010; Mitchell et al.,

2007). It is unclear why families in our study showed "healthier" functioning than previously reported SCD samples as Mitchell et al.'s (2007) patient sample was also predominantly from an urban, low SES community. One potential explanation is that our sample was older than the sample in the previous study and it is possible that as children enter adolescence and gain greater independence, perceptions of family functions on the whole improve, while problem-solving may become more difficult as adolescents strive for autonomy (Bihum et al., 2004). Of note, based on Mitchell et al.'s results, Herzer et al. concluded that families with SCD were at greater risk for unhealthy functioning. However, our results support that families with SCD generally show similar percentages of families who meet clinical cut-offs across dimensions to other illness groups (i.e., IBD, Epilepsy). Additionally, similar to Herzer et al.'s findings, the pattern of areas of dysfunction were consistent, with the dimensions with the highest percentage of families falling in "unhealthy" functioning including affective involvement, roles, general functioning, and problem solving.

With regards to sociodemographic differences, our data did not support hypotheses that higher income, younger child age, or more children in the home were associated with better general functioning. We did replicate previous findings that lower family income was associated with higher levels of dysfunction in the roles dimension. Our lack of findings with income data may be attributed to limited range representation in our sample and differences in analysis. Herzer et al. (2010) classified families based on income in two categories (i.e., above or below $50,000), while this study utilized categorical ranges and assessed income-functioning relations continuously. Although there was a range in reported income, our sample came predominantly from lower SES backgrounds, while living in an urban area undergoing significant gentrification, urban development, and subsequent increased cost of living (Immergluck & Balan, 2018). It is

possible that even participants reporting higher income faced financial challenges that impact family life. Or, it is also possible that participants feel the strain of income on ability to fulfill family roles (e.g., meeting bills, providing transportation, addressing needs), but have resilient factors that protect them from having income-related stress impact other areas of family functioning.

Age and number of children in the home did not appear to impact family functioning generally or in specific domains. As mentioned above, our sample was limited to adolescents, while previous research reported from samples where average patient age was around 10-years-old. This restriction of range may have limited opportunity to detect an age-functioning relationship. Herzer et al. (2010) suggested that families with more children develop better family functions out of necessity. The lack of relationship in our sample may be due to the overall higher functioning reported across domains. Additionally, as SCD is a genetic disease, it is possible that some families had multiple children facing this chronic condition. So though there may have been benefits to having more children, they also may have been susceptible to more illness-related stress. We were not able to investigate this directly in our study.

Finally, when examining psychosocial outcomes, our results supported that families who reported any unhealthy dimension of family functioning exhibited worse HRQOL and worse functional disability. Further analyses suggested that role dysfunction was related to worse HRQOL and functional disability. When looking only at general functioning, this relationship was not significant and emphasizes the utility of using the FAD dimensionally. The relationships between “unhealthy functioning” and HRQOL and functional disability are consistent with hypotheses and previous literature. A previous meta-analysis found that unhealthy functioning in several domains were associated with poorer child psychological health across all pediatric

conditions (Leeman et al., 2016). When looking specifically at the roles dimension, similar to our findings, better role fulfillment was associated with improved QOL (Leeman et al., 2016).

Generally, our findings suggest that family functioning is related to health-related psychosocial functioning. Role fulfillment appears to be a specifically salient family functioning dimension. However, the relationship between poverty and role fulfillment cannot be overlooked. Our results suggested that several of the items within this dimension were strongly related to low income. Previous studies have identified that families with low-income have a high degree of disruption in the roles dimension (Banovcinova et al., 2014; Mansfield et al., 2013). It has been suggested that pediatric chronic conditions that have periods of pain, flare-ups, or exacerbations, like SCD, may cause for frequent role shifts as family members manage the complex needs (Herzer et al., 2010). This would suggest that family functioning and related outcomes (i.e., HRQOL, functional disability) could be improved with intervention around role negotiation during crises or times of heightened health needs (DiMatteo, 2004; Kazak, 2001). Race is intrinsically tied to SCD and Black and African-American adolescents are disproportionately represented among those living in poverty (Choe, 2000) due to systemic inequities and systematic prohibitive economic practices that continue to perpetuate in our country. Although family functioning interventions can be beneficial, if social determinants of health like food, housing, electricity, and transportation security are not also targeted and improved, families will likely continue to struggle. Poverty, apart from the direct impact on individual family members, endangers the functioning of the family system as a whole and systemic interventions are needed to best intervene on downstream effects.

The findings from our study should be interpreted within the context of some limitations. First, our study was cross-sectional in design, thus the direction of relationship between family

functioning and health-related psychosocial outcomes is unclear. It is possible that "unhealthy" family functioning contributes to lower HRQOL and functional disability, but it is also likely that having a teenager with low HRQOL and increased functional disability increases the risk for greater family dysfunction. Longitudinal study designs would help clarify directionality of relationships. Additionally, the FAD is a self-report measure of family functioning, thus is subjective in nature. Additionally, we relied on parent report to limit adolescent burden. Parent report provides valuable insight into family functioning, but previous research has evidenced that parent report often provides a more positive picture of family functioning than adolescent responses (Sawyer et al., 1988). Additionally, child functioning likely impacts how parents perceive the family system and how they shape the family environment (Alderfer et al., 2008). Future research examining family functioning may benefit from multi-informant approaches or utilizing behavioral coding of family interactions. This would also allow for more sophisticated statistical analyses to examine these complex perspectives and relationships.

In summary, data from the current study builds upon the extant literature in several ways. This study supports that examining individual dimensions of family functioning may provide greater insight into the impact of chronic illness and isolate targets of intervention. Additionally, this study supports that families with SCD are generally functioning well, but the number of families who are experiencing some area of "unhealthy" functioning is consistent with other chronic illness groups both in frequency and dimensional areas impacted. The consistency across illness groups in family functioning dimensions indicates that specific dimensions may be at greater risk for impairment due to illness management. Pediatric psychologists across illness specialty groups may benefit from developing targeted interventions in these areas (e.g.,

affective involvement, roles, and problem solving) that can be implemented both preventatively and as need arises.

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Table 1. Participant Demographic Information (*N*=93 patients)

Factor	*M* (*SD*)	*n* (%)
Child Age	15.23 (1.97)	
Parent Age	43.62 (8.43)	
Child Gender		
Female		49 (52.7%)
Male		44 (47.3%)
Child Race		
Black/African American		92 (98.9%)
Mixed		1 (1.1%)
Caregiver Relation		
Mother		80 (86%)
Father		12 (14.6%)
Marital Status		
Single		21 (22.6%)
Married/Partnered		49 (52.7%)
Separated		7 (7.5%)
Divorced		11 (11.8%)
Widowed		3 (3.2%)
Other Children in the Home		
None		21 (22.6%)
1		32 (34.4%)
2		23 (24.7%)
3		7 (7.5%)
4 to 7		5 (5.7%)
Family Income		
Up to $10,000		5 (5.4%)
$10,001 to $20,000		14 (15.1%)
$20,001 to 40,000		15 (16.1%)
$40,001 to 50,000		9 (9.7%)
$50,001 to 60,000		3 (3.2%)
$60,001 to 70,000		6 (6.5%)
$70,001 to 80,000		4 (4.3%)
$80,001 to 90,000		9 (9.7%)
Above $90,000		16 (17.2%)
Child SCD Genotype		
HbSS		64 (68.8%)
HbSC		8 (8.6%)
HbSβ°		4 (4.3%)
HbSβ^{+}		17 (18.3%)

Table 2. Family Assessment Device (FAD) – Means, SD, Unhealthy Functioning (%)

FAD Dimensions	*M* (*SD*)	*Clinical Cut-Off**	*Unhealthy Functioning (%)*
General Functioning	1.63 (.38)	2.00	26.8%
Problem Solving	1.90 (.42)	2.20	24.4%
Communication	1.94 (.38)	2.20	18.8%
Roles	2.12 (.38)	2.30	30.1%
Affective Responsiveness	1.82 (.43)	2.20	15.7%
Affective Involvement	1.91 (.44)	2.10	33.3%
Behavioral Control	1.59 (.38)	1.90	19.3%

Note. *Derived from Miller et al. (1985)

Table 3. Total Number of Unhealthy Dimensions – n, Dimension Means and SD

Number of Dimensions in Unhealthy Range	*n* (%)	*GF*	*PS*	*C*	*R*	*AR*	*AI*	*BH*
0	31 (44.3%)	1.39 (.26)	1.66 (.30)	1.88 (.32)	1.88 (.32)	1.60 (.35)	1.65 (.26)	1.34 (.28)
1	13 (18.6%)	1.37 (.18)	1.77 (.38)	2.08 (.30)	2.08 (.30)	1.68 (.43)	1.75 (.36)	1.44 (.36)
2	10 (14.3%)	1.80 (.24)	2.14 (.21)	2.18 (.28)	2.18 (.28)	1.85 (.36)	1.94 (.23)	1.76 (.27)
3	4 (5.7%)	2.00 (.25)	1.95 (.10)	2.21 (.28)	2.22 (.28)	2.29 (.28)	2.21 (.53)	1.72 (.21)
4	4 (5.7%)	2.08 (.18)	2.10 (.20)	2.17 (.14)	2.75 (.23)	2.21 (.16)	2.64 (.34)	1.92 (.14)
5	6 (8.6%)	2.01 (.21)	1.93 (.50)	2.25 (.23)	2.50 (.11)	2.42 (.23)	2.45 (.47)	2.15 (.34)
6	1 (1.4%)	2.08	2.20	2.17	2.50	2.33	2.71	2.00
7	1 (1.4%)	2.58	2.80	3.00	2.63	2.50	2.71	2.00

Note. GF = General Functioning, PS = Problem Solving, C = Communication, R = Role, AR = Affective Responsiveness, AI = Affective Involvement, BH = Behavior Control

Table 4. Correlations Among Study Variables

Variable	PedsQL	FDI
1. General Functioning	-.26	.22
2. Problem Solving	-.06	.06
3. Communication	-.07	.03
4. Roles	-.35*	.36*
5. Affective Responsiveness	-.15	.23
6. Affective Involvement	-.13	.19
7. Behavioral Control	-.21	.29

Note. $*p < .005$.

3 ARTICLE 2: A DYADIC ANALYSIS OF PAIN CATASTROPHIZING AND HRQOL IN PEDIATRIC SICKLE CELL DISEASE

3.1 Abstract

Objective: To examine the dyadic and individual level effects of parent- and child-pain catastrophizing on child health-related quality of life (HRQOL) in pediatric sickle cell disease (SCD) using dyadic analyses.

Method: Questionnaires assessing child HRQOL, child and parent pain catastrophizing, and child pain frequency were completed by youth with SCD and their primary caregiver. A Common Fate Model (CFM) was estimated to test the dyadic level relationship between parent and child pain catastrophizing and child HRQOL. An Actor-Partner-Common Fate Model hybrid (AP-CFM) was estimated to test the relationship between child HRQOL and individual-level child pain catastrophizing and parent pain catastrophizing, respectively. In each model child HRQOL was modelled as a dyadic variable by factoring parent and child ratings.

Results: Patients (N = 100, M_{age} = 13.5 years, 61% female) and their caregivers (M_{age} = 41.8 years, 86% mothers) participated. Pain frequency was controlled for in each model. Dyad-level pain catastrophizing was negatively associated with child HRQOL, demonstrating a large effect (β = -0.809). Individual-level parent and child pain catastrophizing were each uniquely negatively associated with child HRQOL, demonstrating small to medium effects (β = -0.309, β = -0.270). Individual level effects were net of same-rater bias, which was significant for both parents and children.

Conclusions: When examining parent-child dyads, both the unique and overlapping aspects of parent and child pain catastrophizing are significant contributors to associations with child HRQOL, such that higher levels of pain catastrophizing are associated with worse child

HRQOL. The large effect demonstrated at the dyad level highlights the strong relationship of the shared relationship between parent and child pain catastrophizing on HRQOL. Notwithstanding, the strong dyad effect, significant unique relationships at the individual levels indicate important child- and parent-specific factors. Findings suggest the need for multi-pronged intervention targeting factors common to parent-child dyads and factors unique to parents and children respectively. Findings also support the utility of statistical analyses developed for dyad-level data.

3.2 Introduction

Sickle cell disease (SCD) is an inherited blood disorder that is present in approximately 1 of every 365 births of African descent in the United States (Hassell, 2010). SCD is characterized by abnormally shaped hemoglobin in red blood cells, which can lead to serious medical complications such as painful vaso-occlusive episodes, organ failure, cerebrovascular stroke, pulmonary events, and infection (Ware et al., 2017). In comparison to other children with and without chronic illnesses, health-related quality of life (HRQOL) is more severely impaired in children with SCD (Dale et al., 2011; Panepinto & Bonner, 2012). According to Wallander and Varni's model of child adjustment to pediatric chronic conditions (1998), SCD can be conceptualized as an ongoing stressor for children and their families that places children at risk for poor adjustment, including decreased HRQOL. Adjustment is determined by modifiable risk factors, such as disease severity or psychosocial stress, and resistance factors, such as child cognitive appraisals and parent adjustment. In line with this theory, reduced HRQOL in pediatric SCD has been attributed to more severe disease or frequent pain from vaso-occlusive episodes (Barakat et al., 2008; Dampier et al., 2010; Palermo et al., 2002; Panepinto et al., 2005), as well as the psychological sequelae of experiencing the unpredictable nature of pain (Bakshi et al.,

2018, Graves et al., 2016). However, less is known about the relationship between cognitive components of the pain experience, namely pain catastrophizing, and HRQOL in SCD. Furthermore, parent factors and perspectives have demonstrated a contributory role in determining child outcomes in SCD and warrant further investigation (Sil, Dampier et al., 2016).

Pain catastrophizing is conceptualized as a cognitive schema that increases the propensity to exaggerate the threat of pain either in anticipation of or in response to pain due to amplified, biased attention towards pain (Quartana et al., 2009; Sullivan et al., 2001). Therefore, individuals who catastrophize about pain are likely to ruminate about the potential of pain, magnify the experience of pain, and feel more helpless about coping with pain. Considering this, it is not surprising that in the general chronic pain population, pain catastrophizing is a robust predictor of heightened pain experience and poor HRQOL (Miller et al., 2018; Lame et al., 2005; Quartana et al., 2009; Sullivan et al., 2001). Within pediatric SCD, level of pain catastrophizing does not significantly differ across chronic and episodic SCD pain groups, suggesting that just the mere presence of pain is associated with moderate levels of catastrophizing (Sil, Dampier et al. 2016). In adults and youth with SCD, higher levels of pain catastrophizing have been associated with poorer HRQOL (Bakshi et al., 2018; Citero et al., 2007; Hollins et al., 2012; Mathur et al., 2016). However, consistent with Wallander and Varni's model of child adjustment to pediatric chronic conditions (1998), parent factors are also implicated in determining child outcomes.

It is well established in the pediatric chronic pain literature that parent factors impact the child's pain and functioning, such that higher levels of parental distress and parent pain catastrophizing are associated with poorer child outcomes (Lynch-Jordan et al., 2013; Palermo et al., 2014; Peterson & Palermo, 2004). Parent pain catastrophizing is the tendency for parents to catastrophize about their child's pain (Goubert et al., 2006). Parent pain catastrophizing often

leads to solicitous parent pain behavior (e.g., accommodation, reinforcement of activity avoidance), which can further impinge upon child functioning (Palermo et al., 2014). In youth with SCD, parent pain catastrophizing has been found to predict clinical levels of depressive symptoms (Goldstein-Leever et al., 2018), and it has been shown to mediate the relationship between pain frequency and HRQOL in youth with SCD (Barakat et al., 2008). Furthermore, daily parent pain catastrophizing was associated with increased odds of administering opioids for child pain management (Stone et al., 2020).

When examining both parent and child pain catastrophizing concurrently in pediatric SCD, high levels of parent catastrophizing appear to contribute to child functional disability despite low levels of child catastrophizing (Sil, Dampier et al., 2016). In addition, low parent catastrophizing was not protective for functional outcomes in the presence of high child catastrophizing (Sil, Dampier et al., 2016). Overall, this indicates that there is an interrelated relationship between parent and child catastrophizing to determine child outcomes, but the nature of this relationship is not known for HRQOL in pediatric SCD.

Previous studies examining the effects of child- and parent- pain catastrophizing on child outcomes in SCD have examined pain catastrophizing at the individual level. That is, these studies examined the unique contributions of child- or parent-pain catastrophizing to child outcomes without analyzing the shared variance of child- and parent- pain catastrophizing within dyads. Numerous studies examining coping and emotion regulation constructs have demonstrated within dyad interdependence between parent-and child-levels of these constructs (Valdes et al., 2016) including pain catastrophizing in pediatric acute and chronic pain samples (Birnie et al., 2016; Dougherty et al., 2021; Pielech et al., 2014; Examining the effects of this mutual influence on outcomes is important, given the theorized nature of coping within parent-

child dyads (bidirectional influences, sharing common traits; Burk & Laursen, 2010; Palermo et al., 2014). Mutual influence models of parent-and child coping and emotional regulation constructs, interactions between child and parent pain catastrophizing, and strong overlap between child and parent pain catastrophizing, suggest a benefit from considering catastrophizing at the dyadic level in addition to examining individual level effects.

When analyzing both individual level and dyadic level effects at the level of predictor variables, it is beneficial to obtain both parent and child ratings of outcome variables to account for shared rater variance (Burk & Laursen, 2010; Laursen et al., 2008). To evaluate child outcomes such as HRQOL, it is necessary to consider how parents and children may have unique but also shared perspectives (Panepinto et al., 2005), which is evidenced by moderate correlations between parent proxy-report and child self-report of HRQOL (Panepinto et al., 2013; Varni et al., 2007). When dyads report on the same variable, there is inherently shared variance in their reporting, as well as variance unique to the individual. When these types of dyadic data are presumed to be independent, conclusions drawn about the relationship between variables may be overinflated or misinterpreted. To ameliorate this issue, dyadic analyses consider the nonindependence of the data and disentangle dyadic correlations from individual correlations (Burk et al., 2010; Kenny et al., 2006).

Given what is known about the interplay between parent and child factors, it was important to include both parent and child perspectives in this study to understand how parent and child pain catastrophizing impact child HRQOL within a familial context. Therefore, this study utilized dyadic analyses to determine how parent pain catastrophizing and child pain catastrophizing are each uniquely and interdependently related to child HRQOL by using an integrated model. We expected to find a significant and unique association between child pain

catastrophizing and shared, dyadic perspectives on child HRQOL. Similarly, we expected to find a significant and unique association between parent pain catastrophizing and shared, dyadic perspectives on child HRQOL. Furthermore, we hypothesized that the overlapping variance between parent and child pain catastrophizing would account for a larger proportion of the variance in shared dyadic perspectives of child HRQOL than the unique parent and child pain catastrophizing associations. The results of this study will contribute to our understanding of parent and child pain catastrophizing and HRQOL in pediatric SCD, appropriate assessment of constructs in families, demonstrate the utility of dyadic analysis, and determine points of intervention for improving HRQOL in pediatric SCD.

3.3 Method

3.3.1 Recruitment

Children and adolescents with SCD and their parents were recruited from an urban children's hospital during comprehensive sickle cell clinic visits. Participants were recruited across 3 campus locations between 2014-2015. Youth were eligible for the study if they had a confirmed medical diagnosis of SCD and were between 8 to 18 years of age. Youth were excluded from the study if they were non-English speaking or had significant cognitive or developmental disabilities (e.g., overt stroke history, severe cognitive impairment) documented in the medical chart or based on parent or physician report. An intentional stratified sample targeted youth with SCD who experienced disease-related pain in the past month (n=80) and a concurrent subset of patients with SCD without disease-related pain in the past month (n=20) to capture a full range of pain frequency (0-31 pain days/month). Stratification was based on patient response to one question about their pain frequency in the past month during the screening process. Patients were recruited consecutively until monthly enrollment goals were achieved. A

total of 180 patients were screened for eligibility of which 70 patients were deemed ineligible. Of the 110 patients who were deemed eligible and approached for further screening, 7 patients (6.4%) were not interested in study participation and 3 patients (2.7%) were confirmed ineligible due to significant cognitive impairment, resulting in a 90.9% enrollment rate.

3.3.2 Procedure

Institutional Review Board approval was obtained prior to study initiation. Trained research coordinators reviewed clinic appointment lists and collaborated with hematologists and/or nurse practitioners to screen patients for eligibility. Potentially eligible patients were introduced to the study and coordinators assessed eligibility. For families who expressed interest, additional study details were provided. Caregivers provided written consent and children and adolescents provided written or verbal assent. Children and caregivers were provided the option to complete all measures electronically (using Research Electronic Data Capture, REDCap) or with paper-and-pencil forms during their outpatient visit and received a monetary compensation for their time and participation.

3.3.3 Measures

Demographic and clinical characteristics. Parents reported on parent and child demographics, such as age, sex, race, and ethnicity. Parents were asked if they had a diagnosis of SCD. Medical information related to the child, such as SCD genotype and common disease-modifying SCD treatments (i.e., hydroxyurea, chronic transfusions), were obtained through electronic medical chart review.

Pain frequency. Youth and parents reported on youth pain frequency to quantify the total number of pain days experienced over the past month (0-31).

Pain catastrophizing. The Pain Catastrophizing Scale Child-Report (PCS-C) and Parent-Report (PCS-P) are 13-item questionnaires that assess child's and parent's beliefs and perceptions of their own negative thinking about the child's pain. Items are rated on a 5-point Likert scale (0=mildly to 4=extremely). Total scores range from 0 to 52, such that higher scores are indicative of greater catastrophic thinking about child's pain. Both parent- and child-report measures are commonly used in pediatric pain research and are well-validated in samples of youth with pain and their parents (Crombez et al., 2003; Goubert et al., 2006; Lynch-Jordan et al., 2013; Pielech et al., 2014). Cronbach's alphas for the current sample were 0.92 for child-report and 0.90 for parent-report.

Health-related quality of life (HRQOL). Children and parents completed the Pediatric Quality of Life Sickle Cell Disease Module (PedsQL-SCD Child-Report and Parent-Report), a well-validated 42-item measure that assesses 9 dimensions of the child's quality of life related to SCD (Panepinto et al., 2013). Items are rated on a 5-point Likert scale (0=never to 4=almost always) and transformed on a scale from 0 to 100. Total scale scores were used in analyses, where higher scores are indicative of better child quality of life. Cronbach's alphas in the sample were 0.96 for child-report and 0.96 for parent proxy report.

3.3.4 Statistical Analyses

Methods for analyzing dyadic data are designed to account for the non-independence among observations within dyads. The methods differ in the assumed nature of the non-independence. Two of the most frequently used models are the Actor-Partner Interdependence Model (APIM; Kenny & Ledermann, 2010) and the Common Fate Model (CFM; Ledermann & Kenny, 2012). Within the APIM conceptualization, the examined dependence between outcome variables is due to partner effects (effects of each individual predictor variable on respective

partner outcomes), net of actor effects (effects of each individual predictor variable on respective self outcomes) (Ledermann & Kenny, 2012). Other dependencies are left unexamined and are reflected in a covariance between error terms. In contrast, the CFM conceptualization assumes that non-independence is the result of an underlying source or latent influence that is common to both dyad members (Ledermann & Kenny, 2012; Ledermann & Macho, 2009). CFM is most often associated with dyad-level variables conceptualized to exist at the level of the relationship, such as relationship quality (Galovan, Holmes, & Proulx, 2017). However, CFM conceptualizations can be appropriate for incorporating proxy ratings (e.g., parent- and adolescent- reports of adolescent behavior problems; Burk & Laursen, 2010) and for modeling mixed-level variables in which there is a strong intra-dyad component, reflected by a robust intraclass correlation coefficient (ICC; ICC > .20).

3.3.5 Analysis plan.

For the current study we expected several sources of interdependence. We expected that the between-dyad variation in pain catastrophizing would represent a substantial portion of the total variation in pain catastrophizing and significantly predict HRQOL. To examine this hypothesis, we estimated a CFM in which both pain catastrophizing and HRQOL are considered common fate variables and the structural dyad-to-dyad level effect of regressing HRQOL on pain catastrophizing is estimated.

Given findings from previous studies, we also expected that both child- and parent-pain catastrophizing would uniquely predict HRQOL (as measured by both parents and children). To examine this hypothesis, we utilized an Actor-Partner-Common Fate Model hybrid (AP-CFM) model. In this model, the predictor variables are modelled as individual-level variables, as in an APIM conceptualization, and the outcome variable, HRQOL, is modelled as a common fate

variable. This allows for examination of an actor effect (child pain catastrophizing on child HRQOL) and a partner effect (parent pain catastrophizing on child HRQOL, net of child catastrophizing).

Pain frequency was included as a covariate in both models. We created a pain frequency factor utilizing parent and child-reports of pain frequency and saved the values for use as a covariate.

3.4 Results

3.4.1 Sample Characteristics

Participants were 100 children and adolescents with SCD aged 8 to 18 years (*M* = 13.53, *SD* = 2.8) and their caregivers (*M* = 41.82, *SD* = 6.5). Children were primarily Black or African-American (94%), female (61%), and had hemoglobin type HbSS (77%). Caregivers were primarily mothers (86%), Black or African American (93%), and married (42%) (see *Table 1*). Approximately 19% of parents also had a diagnosis of SCD, which was not significantly associated with HRQOL or pain catastrophizing. Patients reported moderate levels of average pain intensity (*M* = 4.15, *SD* = 2.8, range= 0-10). Average pain frequency as reported by patients was 11 days (*SD* = 10.08, range 0-31) of pain in the past month, and parents reported an average of 9 days (*SD* = 8.94, range 0-30) of child pain in the past month. Of the total sample, 60% were prescribed hydroxyurea and 16% received chronic transfusion therapy. There were no significant differences in patient or parent demographic or clinical characteristics based on hospital campus location.

3.4.2 Correlations

The ICCs for pain catastrophizing and HRQOL were 41% and 58%, respectively. These robust correlations, suggest that, for both constructs, a high proportion of the total variance in

responses is due to shared, dyad-level influence. However, the relatively lower ICC for pain catastrophizing also suggests a potential benefit to considering pain catastrophizing at the individual level. The four actor-partner correlations were robust and of the same direction (negative relationship between pain catastrophizing and HRQOL). The actor correlations ($r_{\text{Actor child}}$ = -.596; $r_{\text{Actor parent}}$ = -.618) were relatively larger than the partner correlations ($r_{\text{Partner child}}$ = -.429; $r_{\text{Partner parent}}$ -.418).

3.4.3 Common Fate Model (CFM)

The pure CFM, in which all covariances are at the dyadic level, assumes that all actor-partner correlations are equal. The relatively stronger actor correlations in this sample suggested a violation of this assumption. Indeed, the pure CFM was not able to be estimated due to a non-positive definite covariance matrix. Therefore, a standard CFM model, in which error variances at the individual level (pain catastrophizing$_{\text{child}}$ with HRQOL$_{\text{child}}$; pain catastrophizing$_{\text{parent}}$ with HRQOL$_{\text{parent}}$) are allowed to covary, was estimated.

The dyad-level effect from pain catastrophizing to HRQOL was negative and statistically significant, b = -1.483, SE = 0.248, $p < .001$. The effect size was large, β = -0.809, SE = 0.085, $p < 0.001$. A standard unit increase in dyad-level catastrophizing corresponded to a 0.809 standard unit decrease in the HRQOL factor.

3.4.4 AP-CFM model

Similar to the CFM, the pure AP-CFM model, with no direct effects from individual pain catastrophizing to individual HRQOL, was a poor fit. Therefore, a standard model, with direct paths from each dyad member's pain catastrophizing to their respective HRQOL rating were added. The direct paths likely represent same-rater bias.

The unique effect of child pain catastrophizing on the HRQOL factor, holding parent pain catastrophizing constant, was negative and statistically significant, b = -0.251, SE = 0.102, p = .014. The effect size was small to medium (β = -0.270). Similarly, the unique effect of parent pain catastrophizing on the HRQOL factor, holding child pain catastrophizing constant, was negative and statistically significant b = -0.316, SE = 0.138, p = .022, with a small to medium effect size (β = -0.309). Both of the effects were net of same-rater bias. The two effects did not differ significantly. A Wald Test revealed that allowing the two coefficients to freely vary did not significantly improve the fit of the model relative to equating the two coefficients, χ^2 (1) = 0.425, p = 0.515.

3.4.5 Summary

The results of the dyadic analyses suggest that pain catastrophizing (by both parents and children) has a significant negative impact on child HRQOL in pediatric SCD patients. Moreover, the analyses indicate that the way in which parent-child systems (dyads) impact HRQOL is complex, with both dyad-level and individual-level effects.

Within the Common Fate model, the large pain catastrophizing dyad-level effect suggests that the between-dyad variation in the aspects of pain catastrophizing shared by parent-child pairs is a strong determinant of child HRQOL. This interrelationship in pain catastrophizing could represent a bidirectional- or unidirectional-relationship between parents and children within dyads, a shared common trait (a common vulnerability), or some combination of these factors. The covariances between the error terms of pain catastrophizing and HRQOL for parent children respectively, indicated important individual level effects.

The AP-CFM model further confirmed significant individual level effects. Moreover, by continuing to model child HRQOL as a dyad-level variable (factoring parent and child ratings)

the model was able to estimate the effects of same-rater bias. This proved important, as the same rater-biases were significant for both parents and children. After accounting for these, the unique individual level effects of parent and child catastrophizing were both significant predictors of child HRQOL.

3.5 Discussion

In adults with SCD, higher levels of pain catastrophizing are associated with poorer HRQOL (Mathur et al., 2016), and there is initial evidence of a similar relationship in pediatric SCD (Bakshi et al., 2018). However, the role of parent pain catastrophizing on child HRQOL has not been explored in the context of SCD. Therefore, the purpose of this study was to use dyadic analyses to determine how parent pain catastrophizing and child pain catastrophizing are each uniquely and interdependently related to child HRQOL in SCD. Child HRQOL was rated by both child self-report and parent proxy-report and a latent variable termed "HRQOL" was used to model the shared, dyadic perspective on child HRQOL. This allowed for the estimation of the dyad level effect, apart from individual level variance, using a CFM. It also allowed for the accounting of same-rater variance when estimating the unique individual level effects using an AP-CFM model.

Consistent with expected findings, controlling for pain frequency, results of the AP-CFM analyses revealed statistically significant, negative relationships between parent pain catastrophizing and child pain catastrophizing with HRQOL. A small to medium effect was found for each individual level to dyad level relationship. As hypothesized, controlling for pain frequency, the shared variance between parent and child pain catastrophizing also demonstrated a statistically significant, negative association with HRQOL, as evidenced by the CFM analysis. There was a large effect observed for this dyad level to dyad level relationship, supporting our

hypothesis that the overlapping variance between parent and child pain catastrophizing would account for a larger proportion of the variance in shared dyadic perspectives of child HRQOL than the unique parent and child pain catastrophizing associations.

These findings contribute to our understanding of parent and child pain catastrophizing in SCD, as well as their relationship with child HRQOL. Specifically, the research on pain catastrophizing in pediatric SCD is still in the nascent stages, with evidence that youth with SCD demonstrate similar or higher levels of pain catastrophizing as compared to youth with other chronic pain conditions, and that higher levels of child pain catastrophizing contribute to poorer functional outcomes (Sil, Dampier, et al., 2016) and lower HRQOL (Bakshi et al., 2018). The findings of this study provide further support for the relationship between child pain catastrophizing and child HRQOL in children with SCD, even when controlling for pain frequency. Although specific mechanisms were not assessed in this study, it is hypothesized that pain catastrophizing is maladaptive for HRQOL because exaggerated fear of or worry about pain may lead to disproportionate avoidance of activity and subsequent deconditioning, pain, isolation, and distress (Miller et al., 2018; Tran et al., 2015).

Additionally, these findings extend the literature on pain catastrophizing in SCD by identifying parent pain catastrophizing as a unique contributor to child HRQOL. This effect may be due to how parents respond when a child is experiencing pain or in how pain is managed. For example, parent solicitous or protective tendencies may manifest as decisions about opioid administration or emergency department visits during acute pain experiences (i.e., vaso-occlusive episodes), which may impact overall child functioning by contributing to school absences and activity restriction (Caes et al., 2011; Logan et al., 2012; Mitchell et al., 2007). Furthermore, these parental responses may communicate that a high level of activation around

pain is necessary, which in turn could reduce child self-efficacy in managing and coping with pain. Decreased parent involvement in SCD management tasks has been shown to improve child use of adaptive coping strategies, but in contrast, when more parental involvement is present, children demonstrate lower levels of functioning (Oliver-Carpenter et al., 2011). Although directionality cannot be determined, giving children a sense of control over a generally unpredictable disease may be an empowering practice.

Perhaps the most interesting finding of this study is that beyond the individual effects of parent and child pain catastrophizing, the complex, shared variance between parent and child pain catastrophizing significantly contributed to child HRQOL. This supports the notion that there is indeed some type of mutual, bidirectional relationship between parent and child pain catastrophizing. As alluded to above, it may be that through social learning and emotion socialization, children of parents with higher levels of pain catastrophizing internalize more extreme messages about pain (Boerner et al., 2017; Hajal & Paley, 2020; Seddon et al., 2020). An additional possibility is that through the communal model of coping, child pain catastrophizing encourages children to seek support from caregivers by demonstrating high need behaviors (Sullivan et al., 2001). In exchange, parents develop a heightened awareness of their child's pain and respond accordingly. Another potential explanatory approach that has recently gained more attention is that of underlying trait or genetic factors (Aaron et al., 2020; Koechlin et al., 2018). Specifically, pain catastrophizing has been theorized as a form of emotion dysregulation (Petrini & Arendt-Nielsen, 2020) and emotion dysregulation has been found to have moderate levels of heritability (Hawn et al., 2015). Therefore, the significant overlap in parent and child pain catastrophizing could be attributed to a genetic vulnerability. In all probability, it is a combination of genetic and environmental factors that determine this mutual

relationship in parent and child pain catastrophizing. Regardless of mechanism for the overlap, the findings of this study suggest that when parent-child dyads share this same preponderance to catastrophize about child pain, child HRQOL suffers in the context of SCD.

To our knowledge, this is the first study to utilize dyadic analyses to examine parent-child relations in pediatric SCD. It is recommended that statistical analyses that account for the interdependence of parent-child data and handle multi-informant data be utilized in pediatric research, though this is still a burgeoning area of practice (Hildenbrand et al., 2021). By using multi-informant assessment and dyadic analytic methods, the individual and dyadic effects could be more accurately modeled, which is consistent with our theoretical understanding of the parent-child dynamic and the social nature of pain catastrophizing. Another benefit of dyadic analyses is that they account for same rater bias, which is notable given that typical practice usually involves separate parent and child models of self-reported data. Furthermore, there has been debate over measures of HRQOL and how to handle parent-proxy report and child self-report of HRQOL, given moderate levels of correlation between reporters (Panepinto et al., 2013). Utilizing dyadic analyses that account for this correlation and parse out same-rater bias within the same model could serve as a potential solution.

With regards to clinical implications, these findings suggest that interventions addressing parent functioning and cognitive factors are warranted. Parents of children with SCD experience stress and poor psychosocial functioning that has demonstrated relationships with poorer child functioning (Sil et al., 2021). It may even be helpful for intervention to be delivered in a family therapy format so dyads can learn more helpful ways to mutually de-escalate when catastrophic thinking and associated behavior is identified. Additionally, strengths-based factors, specifically

the modifiable one of pain acceptance, may play an important role for youth HRQOL in the context of SCD pain (Wright et al., 2021)

These findings should be considered in light of its limitations. As with all cross-sectional data, directionality cannot be determined though we posit there are likely multiple influences in determining parent and child pain catastrophizing, as well as HRQOL. Longitudinal studies examining additional sources of influence should be conducted. This may include additional intrapersonal and interpersonal factors, which may contribute to ratings of pain catastrophizing. For example, in pediatric chronic pain conditions, overall family functioning has been related to parent and child report of catastrophizing about child pain (Jastrowski Mano et al., 2011), and in SCD, parent problem solving has been associated with HRQOL (Baraket et al., 2014). Measures of emotional functioning, such as anxiety and depression, were not included in these analyses, though there is a known relationship between emotional well-being and both pain catastrophizing and HRQOL. A more robust model could be determined with the inclusion of these variables. Mechanisms of the relationship between pain catastrophizing and HRQOL were surmised, but it may be of value to quantify the exact behaviors of both parent and child that are contributory. Consistent with this, direct observation of parent and child interactions in the context of SCD pain would be of interest in future studies. As this study enrolled youth aged 8-18 years, it would also be of interest to investigate these relationships in young childhood; previous studies that increased age is associated with higher levels of pain catastrophizing in other chronic pain conditions (Miller et al., 2018). Longitudinal data may provide further insight on the trajectory of pain catastrophizing in parents and children, as well its relationship to HRQOL. Examining these constructs within a wide age range may be particularly applicable in SCD given that pain is a part of the disease course beginning at a young age. As is common in many pediatric studies,

predominantly mothers participated in our study, but having the perspective of additional caregivers would enrich our understanding of how social-ecological factors contribute to child adjustment.

In conclusion, parent and child pain catastrophizing both uniquely and interrelatedly contribute to child HRQOL within the context of pediatric SCD. Dyadic analyses are beneficial for examining the complex, bidirectional relationship between parent and child factors.

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Table 5. Sample Characteristics

Child (*n* = 100)	
Mean age (SD), range	13.53 (2.73), 8.65-18.63
Sex, Female (%)	61
Race and Ethnicity (%)	
Black or African American	94
Hemoglobin Type (%)	
HbSS	77
HbSC	15
HBS beta plus thalassemia	5
HbS beta zero thalassemia	3
SCD treatments (%)	
Hydroxyurea	60
Chronic transfusions	16
Pain frequency, child report (M, SD, range)	11.01 (10.08), 0-31
Pain frequency, parent report (M, SD, range)	9.38 (8.94), 0-30
Average pain intensity (M, SD, range)	4.15 (2.80), 0-10
Parent/Caregiver (*n* = 100)	
Mean age (SD), range	41.82 (6.54), 27.64-62.79
Relationship to Child (%)	
Mother/Stepmother	86
Father/stepfather	13
Grandmother	1
Race and Ethnicity (%)	
Black or African American	93
Biracial/multiracial	2
Hispanic	1
American Indian/Alaskan Native	1
Prefer not to answer	3
Marital Status (%)	
Married	42
Single	37
Divorced/Separated	17
Widowed	4
Parent SCD Diagnosis	
Presence	19.5
Absence	77.9
Missing	2.6

Table 6. Common Fate Model (CFM)

Parameter Estimates			
	b	SE	*p*
Standardized loadings			
PedsQL CR	.755	0.052	< 0.001
PedsQL PR	.720	0.055	< 0.001
PCS-C	.613	0.065	< 0.001
PCS-P	.664	0.071	< 0.001
Regression coefficients			
HRQOL on Catastrophizing	-1.483	0.248	< 0.001

Table 7. Actor Partner Common Fate Model Hybrid (AP-CFM)

Parameter Estimates			
	b	SE	*p*
Standardized loadings			
PedsQL CR	.608	0.063	< 0.001
PedsQL PR	.579	0.065	< 0.001
Regression coefficients			
HRQOL on PCS-C	-0.251	0.102	0.014
HRQOL on PCS-P	-0.316	0.138	0.022
PedsQL CR on PCS-C	-0.461	0.133	0.001
PedsQL PR on PCS-P	-0.570	0.158	< 0.001

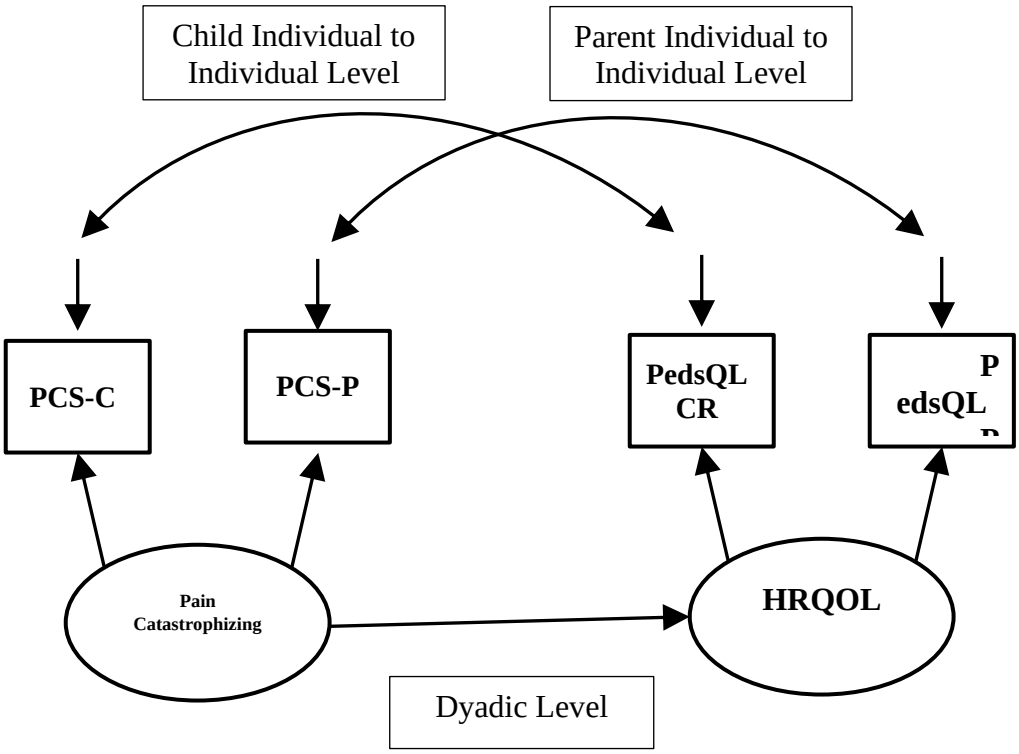

Figure 2. Theoretical Common Fate Model

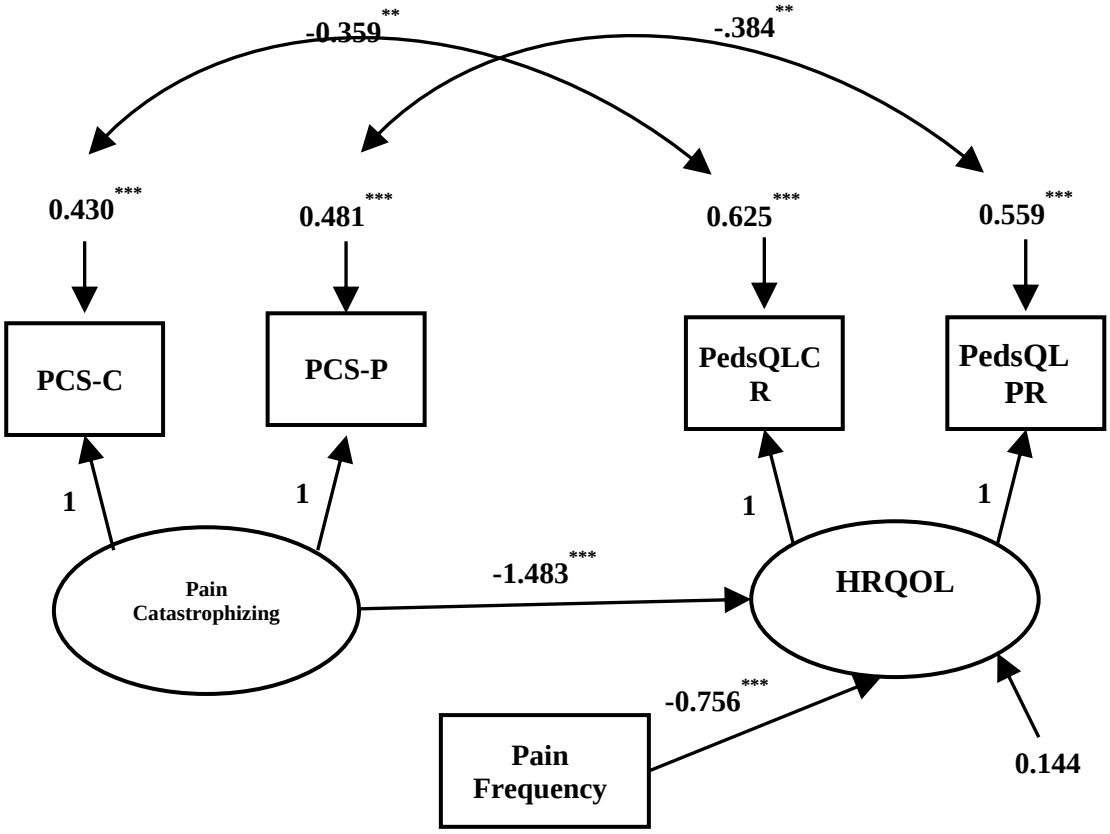

Figure 3. Common Fate Model

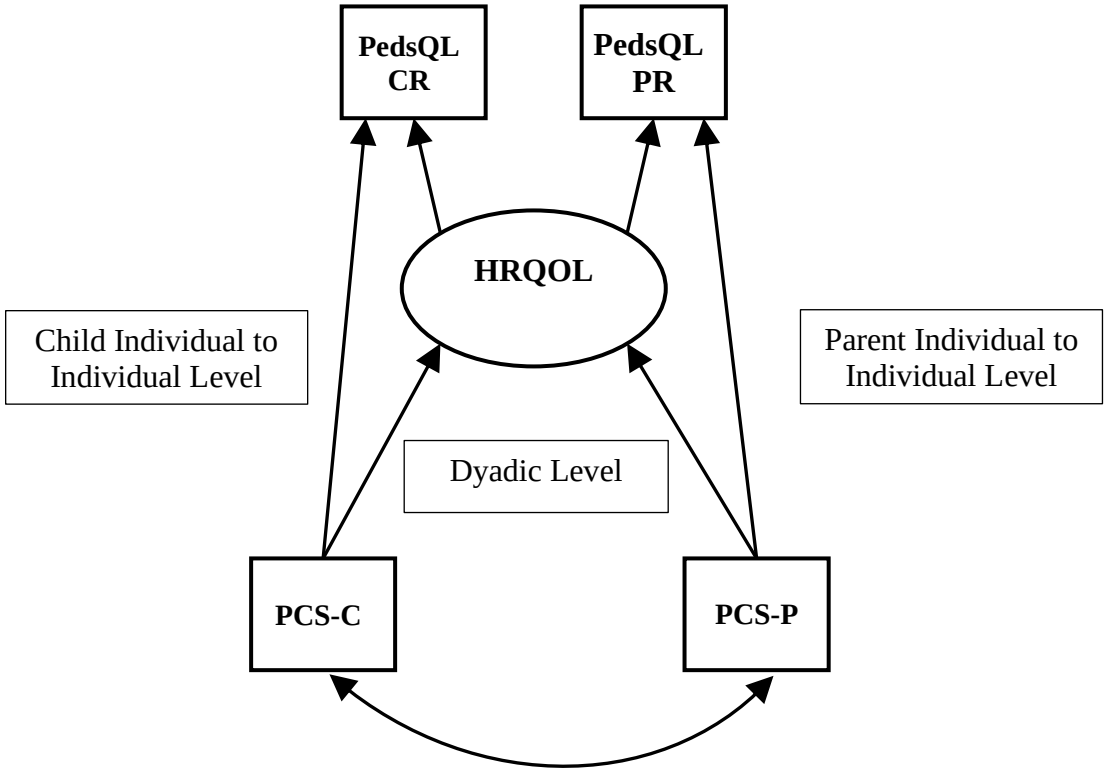

Figure 4. Theoretical AP-CFM Model

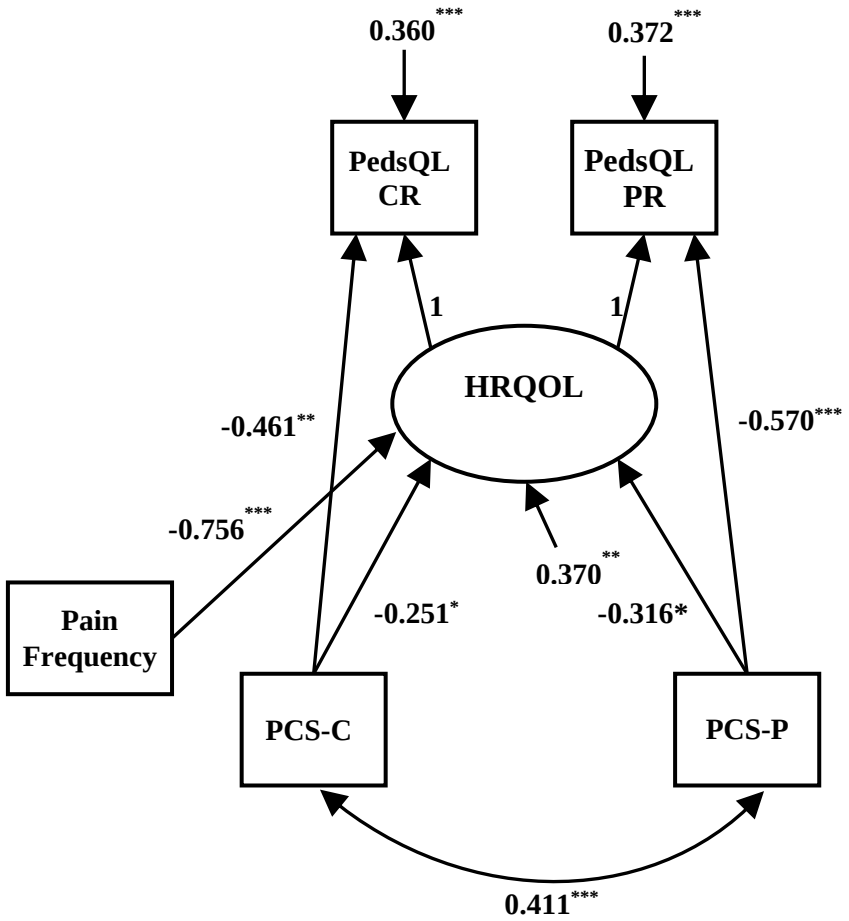

Figure 5. AP-CFM Model

4 ARTICLE 3: A SYSTEMATIC REVIEW OF MEDICATION ADHERENCE INTERVENTIONS IN PEDIATRIC SICKLE CELL DISEASE

4.1 Abstract

Objective: Adherence to medication regimens is of critical importance in sickle cell disease (SCD). Most notably, data indicate that hydroxyurea, penicillin, and iron chelators increase life expectancy and decrease comorbid medical problems (e.g., strokes). However, average pediatric SCD adherence rates are only 55-74%. Studies have introduced interventions for pediatric SCD adherence, but no review has synthesized these data.

Method: We conducted a systematic review of interventions for enhancing medication adherence in pediatric SCD. There were 9 studies that met inclusion and exclusion criteria. The Pediatric Self-Management Model provided a framework for organizing the modifiable factors targeted by existing interventions.

Results: The 9 studies had high risk of bias levels and most targeted hydroxyurea. All studies used multiple measures of adherence, the interventions were multicomponent, and most included behavioral or technological interventions. There was variability in terms of whether the intervention targeted the individual, family, community, or healthcare system.

Conclusions: Consistent with the broader adherence literature, knowledge alone was insufficient in increasing adherence. Findings suggest that reminders and targeting self-efficacy were key to success. In addition, addressing multiple domains in an intervention yielded larger effects on adherence. Although these results are promising, this review highlights several limitations of the extant literature, including a paucity of intervention studies and several methodological weaknesses, such as small sample sizes, few randomized controlled trials, and

variable measures of adherence. Recommendations for advancing scientific understanding of adherence promoting interventions in pediatric sickle cell disease are provided.

Keywords: sickle cell disease; adherence; systematic review

4.2 Introduction

4.2.1 Overview of Sickle Cell Disease

Sickle cell disease (SCD) is a group of inherited blood disorders characterized by at least one sickle hemoglobin variation (HbS) in the β-globin gene (Stuart & Nagel, 2004). This variant causes red blood cells to become sickled, or crescent shape, rather than round and flexible. The most common medical complication of SCD is acute vaso-occlusive pain episodes, which occur when rigid, sickled red blood cells become interlocked and occlude veins. Chronic vaso-occlusive pain episodes can lead to tissue death in vital body systems, including in the heart, lungs, brain, kidneys, spleen, and bones. Children with SCD are more susceptible to bacterial infection due to the effects of SCD on the spleen. An addition concern is the prevalence of silent stroke in pediatric SCD (21.8%), and overt stroke (11%) (Kwiatkowski et al., 2009).

4.2.2 Common Medications

Multiple medications have been developed in the past three decades to prevent or reduce the complications of pediatric SCD. Hydroxyurea reduces the number of sickled red blood cells in the body, thereby decreasing frequency or intensity of vaso-occlusive episodes (Strouse & Heeney, 2012). Clinical trials of hydroxyurea in children with SCD have demonstrated efficacy for improving hematological variables, reducing complications, and minimizing hospitalizations (Ferster et al., 1996; Jayabose et al., 1996; Kinney et al., 1999; Ware et al., 2002). Penicillin is prescribed to infants and young children as a prophylactic for infection. Researchers have found an 84% reduction in infections with penicillin treatment and it is considered standard

prophylactic treatment for children under age 5 (Cober & Phelps, 2010; Gaston et al., 1986). To address the risk of iron toxicity associated with receiving chronic blood transfusions for stroke prevention, iron chelators are prescribed to excise excess iron.

These three medications – hydroxyurea, penicillin, and iron chelators – are commonly prescribed as a daily regimen and are frequently utilized treatments for many patients with SCD (Ware, de Montalembert, Tshilolo, & Abboud, 2017). Since the introduction of these medications, an approximately 24%-68% reduction in mortality of pediatric patients has been observed (Lanzkron, Carroll, & Haywood, 2013; Prabhakar, Haywood, & Molokie, 2010). In contrast, poor adherence to medications is associated with increased health care utilization, such as more frequent emergency department visits and hospital admissions (Candrilli et al., 2011; Walsh et al., 2014). In addition, poor adherence to hydroxyurea has been associated with poor health related quality of life and school absenteeism (Badawy et al., 2017; Fisak, Belkin, von Lehe, & Bansal, 2012; Smaldone, Manwani, & Green, 2019).

4.2.3 Medication Adherence and the Pediatric Self-Management Model

The value of pharmaceutical treatments is clear; however, a review found average medication adherence rates in pediatric SCD to be 55-74% (Loiselle et al., 2015). This indicates a need for additional research on interventions to promote adherence. Theoretical frameworks or models are valuable for organizing complex phenomena and guiding intervention approaches (e.g., Drotar, 2009). To date, only one child-adolescent specific model of adherence or self-management has been developed. The Pediatric Self-Management Model is an adaptation of the Social Ecological Model and proposes that multilevel influences occur at the individual, family, community, and healthcare system levels that facilitate or impede self-management behaviors (Modi et al., 2012). Within each level or domain, there are modifiable and non-modifiable

influences that are rooted in underlying cognitive, emotional, and social processes. Examples of modifiable factors include knowledge, parental monitoring, peer support, and patient-provider communication. Non-modifiable factors are more difficult to alter and examples include cognitive functioning, income level, and neighborhood. As expected, these factors are interrelated, dynamic, and reciprocal at multiple levels, so theoretically, intervening on any of the modifiable factors within a domain should lead to changes in self-management or adherence behavior.

Existing research on adherence in pediatric SCD has identified both modifiable and non-modifiable factors across all domains. At the *individual* level, older age is associated with poorer adherence in pediatric SCD, which is also common in other pediatric conditions, (Loiselle et al., 2015). Knowledge deficits are also common in adolescents who are transitioning to more independent self-management; however, forgetting is the most common association with poor adherence (Badawy, Thompson, & Liem, 2016; Modi et al., 2009; Smaldone et al., 2019). Lastly, for a portion of children, especially younger ones, difficulty swallowing pills may present a barrier to medication adherence (Bekele et al., 2014).

At the *family* level, knowledge deficits in caregivers are a frequently cited reason for poor adherence and can manifest in a number of different forms such as concern about medication side effects, prematurely stopping medication administration because symptoms are not apparent, uncertainty about effectiveness, and incorrect dosing (Brandow & Panepinto, 2010; Loiselle et al., 2015; Oyeku et al., 2013; Walsh et al., 2014). Other risk factors for poor adherence include stress related to disease and poor family functioning (Barakat, Smith-Whitley, & Ohene-Frempong, 2002). These findings suggest that family factors such as stable daily family routines and effective family communication may be protective for medication adherence (Klitzman,

Carmody, Belkin, & Janicke, 2018). Logistical barriers to adherence include challenges in reliable transportation for accessing clinics and pharmacies (Brandow & Panepinto, 2010).

At the *community* level, patients with poor adherence have reported higher rates of perceived social isolation, which may represent a lack of support from peers for promoting self-management (Badawy et al., 2017). Similarly, families have identified social support as a facilitator of regular hydroxyurea administration (Thornburg, Calatroni, Telen, & Kemper, 2010).

At the *systems* level, perceived judgment or negative provider interactions may also contribute to variability in medication adherence, such that patients may be hesitant to communicate concerns about taking medications or may not feel aligned with their provider (Haywood et al., 2009).

The Pediatric Self-Management Model has been utilized to develop and evaluate adherence interventions in other chronic conditions, such as asthma and diabetes (Gray et al., 2018; Hilliard, Powell, & Anderson, 2017); it should be beneficial to understanding adherence factors in pediatric SCD and coordinating intervention efforts.

There is strong evidence for the benefits of daily medications for pediatric SCD; however, adherence is variable. Unfortunately, the current state of the research on interventions for medication adherence in pediatric SCD is unknown (Savage et al., 2015). The aims of this systematic review were to (1) describe, synthesize, and evaluate the extant intervention literature for medication adherence in pediatric SCD; and (2) report effectiveness of interventions within the Pediatric Self-Management Model.

4.3 Methods

4.3.1 Literature Search Strategy

The electronic databases CINHAL, PubMed, and PsycINFO were searched using the BOOLEAN operator "OR" and the key terms: "intervention or treatment or therapy," "sickle cell," "pediatrics or child or children or teen or teenagers or adolescents," "adherence or compliance or nonadherence or noncompliance or treatment adherence or treatment compliance." Results were restricted for the dates January 1970 – December 2018 and for English language. Hand searching of reference lists was also conducted. Gray literature, such as unpublished theses and dissertations, was included.

4.3.2 Study Selection

Only original research articles were eligible for this review; commentaries and book chapters were excluded. Studies were included if they met the following criteria: (1) participants were diagnosed with SCD, (2) were ≤ 21 years old, (3) intervention for medication adherence was reported in detail, (4) primary or secondary outcome included medication adherence, and (5) studies were in English language.

The initial search identified 455 records. After duplicates were removed, 361 records remained and each abstract was reviewed for exclusionary criteria. Of those, 340 records were excluded for failure to meet eligibility. Subsequently, 21 full-text articles were thoroughly assessed for inclusion. Following review, 12 records were removed. Therefore, 9 papers were included in the final review. For details, see the PRISMA flow diagram in the supplementary files, Figure 1.

4.3.3 Data Extraction

The following data were extracted from each of the articles – author(s) and year of publication, sample size, sample age, medication targeted, description of intervention, intervention components, self-management domains, comparison group, study period, measures of medication adherence, and key adherence findings including effect sizes or information to calculate effect size. The principal summary measure – effect sizes – were calculated with guidance from Hozo, Djulbegovic, and Hozo (2005), Lakens (2013), and Thalheimer and Cook (2002). A summary of these variables is displayed in Table 1.

4.3.4 Risk of Bias Analysis

A risk of bias analysis is essential for evaluating sources of bias in individual studies that may threaten the validity of observed intervention effects and subsequently impact conclusions drawn in a systematic review. In this review, risk of bias was assessed using the Cochrane Collaboration tool, which includes evaluations for selection bias, performance bias, detection bias, attrition bias, and reporting bias (Higgins et al., 2011). For each category, a study can demonstrate low, high, or indeterminate levels of risk. In this review, studies were downgraded to high-risk for selection bias if a control group was not included or if sequence generation and allocation concealment were not utilized. Studies that lacked blinding from group assignment were also downgraded for performance bias. If outcome assessors were not blind to intervention assignment, this constituted a downgrade for detection bias. Studies that failed to include or report on participants who did not complete the study were downgraded for attrition bias. Lastly, selective reporting of intervention findings rendered a study vulnerable to reporting bias.

4.4 Results

For the nine studies included in the final review, publication date ranged from 1998 to 2018 with the majority (n = 6) published after 2013. One unpublished dissertation was included in the qualitative integration (Reed, 2016). Sample size ranged from 11 to 55. Sample mean age ranged from 37 months to 14.5 years. Caregivers were specifically included in five intervention studies, and the remaining four studies directly targeted adolescents. The most frequently targeted medication was hydroxyurea (n = 6), followed by iron chelator (n = 2), and penicillin (n = 1). Studies were conducted over 8 weeks to 2 years. Two studies were randomized controlled trials while the remaining seven studies used a pre-post, within-subjects design. Three articles were feasibility or pilot studies (Creary et al., 2014; Green et al., 2017; Inoue et al., 2016). Given the high variability in methodology across the small number of available studies, we decided that a meta-analysis was inappropriate.

4.4.1 Description of Studies

The first aim of the current review was to systematically describe, synthesize, and evaluate the extant literature on interventions for medication adherence in pediatric SCD. Study-level risk of bias analysis is presented first, as this should guide the interpretability of the results. Then, the various measures of medication adherence utilized in these nine studies are discussed. Finally, descriptions of the intervention characteristics are provided. Table 1 provides a summary of study characteristics and findings.

4.4.1.1 Risk of bias analysis.

A randomized, controlled study design was used in two studies, but only one was rated as having low risk of selection bias. Green et al. (2017) reported a 2:1 randomized allocation sequence with assistance from a computerized random number generator. Berkovitch et al.

(1998) did not specify randomization procedure; therefore, risk of selection bias was rated as indeterminate. Lack of a control group caused all other studies to be downgraded to high risk for selection bias. In regards to performance bias, all studies were rated at high risk. However, it should be noted that it is not always possible for participants to be blinded to condition in psychosocial interventions. Similarly, detection bias is typical in psychosocial interventions, particularly when a control condition is not present. As such, all within-subjects studies were downgraded to high risk. The two studies that did use a control condition did not specify if outcome assessors were blinded to condition so they were rated as indeterminate level of detection bias. In terms of attrition bias, one study did not report attrition rates and only reported on study completers (Reed, 2016). Three studies did not provide analyses of any differences between completers and non-completers; however, reasons for attrition were explicitly reported so they were rated as having indeterminate level of attrition bias. The remaining studies were rated as having low risk of attrition bias because they reported attrition rates, reason for attrition, and either analyzed differences in completion groups statistically or descriptively. Lastly, five studies were rated as having low risk of reporting bias as they reported on both statistically significant and non-significant outcomes while also adhering to proposed statistical analyses. Two studies were rated as having indeterminate levels of reporting bias for excluding statistical analyses due to small sample sizes and lack of power analysis (Inoue et al., 2016; Treadwell & Weissman, 2001). Two studies were downgraded for conducting post-hoc analyses that were not proposed a priori. No studies were rated as having low risk of bias in all categories, though the studies with randomized control conditions each only had one category rated at high risk. Several studies were rated as having concerning levels of validity threats in multiple categories. For a summary, see supplementary files, figure 2.

4.4.1.2 Measures of adherence.

All studies used multiple methods of adherence assessment. *Subjective methods* included self- or parent-report questionnaires, interviews, and daily diaries if direct monitoring was not possible. Six of nine (66.67%) studies utilized a subjective measure of medication adherence. However, all studies varied in their use of specific subjective measures; for example, each study that utilized the Morisky Medication Adherence Scale used a different form of the measure (Creary et al., 2014; Green et al., 2017; Reed, 2016).

Objective methods included Medication Possession Ratio (MPR; ratio of days medication was prescribed to days medication was available), medical record review, and electronic or direct monitoring. With six studies reporting MPR, it was the most common form of medication adherence assessment (Anderson et al., 2018; Creary et al., 2014; Estepp et al., 2014; Green et al., 2017; Inoue et al., 2016; Leonard et al., 2017). In both studies that utilized electronic monitoring (pill bottles with specialized caps that monitor the frequency and/or timing of bottle openings), participants experienced technological difficulties characterized by bottles breaking, patients opening bottles without actually ingesting medication, and liquid forms of medication interfering with accurate dosing (Berkovitch et al., 1998; Inoue et al., 2016). Three studies used a form of technology-based direct monitoring. Anderson et al. (2018) and Leonard et al. (2017) both used the same phone application to deliver intervention and to track adherence through a daily “selfie” or video of at-home medication administration. However, in both studies, participants experienced technological failures that prevented them from recording or submitting evidence of administration for direct monitoring. Therefore, both studies also provided the option of subjective reporting by manually logging daily administration within the application. Creary

et al. (2014) also utilized a technology-based direct monitoring system that required participants to submit a daily video of medication administration.

Lastly, *biological parameters* were collected for seven studies and used as a primary or secondary measure of medication adherence (Anderson et al., 2018; Creary et al., 2014; Estepp et al., 2014; Green et al., 2017; Inoue et al., 2016; Leonard et al., 2017; Reed, 2016; Treadwell & Weissman, 2001). For studies targeting hydroxyurea adherence, bioassays were obtained for hematological values, such as hemoglobin (Hg), mean corpuscular volume (MCV), white blood count (WBC), absolute neutrophil count (ANC), absolute reticulocyte count (ARC), and fetal hemoglobin (HgF). For studies targeting iron chelator adherence, serum ferritin was used as a biomarker. Although biological parameters were a common measure of adherence, they did not consistently correlate with other measures of adherence. For example, in Anderson et al. (2018), no statistical difference in Hb, MCV, or ARC was observed despite a significant difference in MPR from pre- to post-intervention. In contrast, Estepp et al. (2014) found no significant difference in MPR from pre- to post-intervention despite statistical differences in multiple hematological parameters.

In summary, all studies utilized multi-method assessment of medication adherence. However, across modalities, many different challenges were presented that limit interpretability of the results. For example, within subjective measures, multiple versions of the Morisky Adherence Scale were used, which may make it challenging to compare results across studies. Within objective methods, MPR was the most common form of assessment and appeared to present fewer challenges. However, electronic and direct monitoring devices and applications suffered from numerous technological difficulties. Although direct monitoring may provide the most accurate measure of adherence, it may not be consistently feasible or reliable. Within

biological measures of adherence, multiple different biological values were utilized for measuring hydroxyurea effect across studies. This suggests potential lack of specificity in utilizing biological parameters for validly assessing hydroxyurea adherence or a lack of consensus across providers of how adherence should be measured. However, serum ferritin was consistently utilized as a measure of compliance with iron chelation therapy. Furthermore, agreement between measurement modalities within studies was variable. In particular, biologic parameters were not consistently associated with MPR, the two most common modalities utilized.

4.4.1.3 Intervention characteristics.

All interventions were multicomponent and utilized a combination of behavioral, educational, family-based, human support, technology, and social support element. Almost all studies (n = 8) included a behavioral component. Six studies included an educational component. Five studies included a family-based component. Six studies included human support, which consisted of receiving feedback from study staff. Technology, such as phone applications or text message reminders, was included in five studies. Lastly, only one study included social support as a component of the intervention.

4.4.2 Adherence Outcomes within the Pediatric Self-Management Model

Individual domain. Seven studies fell within the individual domain with targeted modifiable factors including knowledge, self-monitoring, and self-efficacy. The effect of intervention on adherence outcomes ranged from small to large and significant increases in adherence were found for three studies. Anderson et al. (2018) utilized the Intensive Training Program (ITP), a phone application intervention that provided educational videos, remote daily monitoring of medication compliance, and weekly study staff feedback. Multiple measures of

hydroxyurea adherence were obtained and there was a moderate effect of intervention on MPR (d = 0.75), such that MPR significantly increased from pre-intervention (M=0.57) to post-intervention (M=0.74) (p = 0.001). Participants in the study were predominantly adolescents (M_{age} = 13.0). The modifiable factors targeted were knowledge, self-efficacy, and self-monitoring, although only disease knowledge was measured. The intervention included behavioral, educational, human support, and technology-based components. Leonard et al. (2017) utilized the same ITP intervention to increase daily administration of iron chelators; however, only a small effect was found for increasing MPR (d = 0.25). Similar to Anderson et al. (2018), only the modifiable factor of disease knowledge was measured. Creary et al. (2014) utilized Electronic Directly Observed Therapy (DOT) to increase hydroxyurea adherence in mostly adolescents (M_{age} = 13.7). DOT is a web-based platform where patients can receive daily alert messages, upload videos of medication adherence, receive feedback from study staff, and incentives ($1/day if ≥90% adherence was maintained for a 30-day period). DOT was the only intervention to specifically include incentives but more generally included behavioral, human support, and technology-based components. Modifiable factors targeted were self-efficacy and self-monitoring, but they were not measured. Small to large effects of the intervention were found, such that median MPR significantly improved from baseline (0.75) to end of study (0.91) (p = 0.02, d = 0.89), two biological parameters also significantly increased (MCV, p = 0.009, d=0.50; HbF, p = 0.03, d = 0.25), and self-reported adherence also significantly increased (MMAS-4, p = 0.004). Notably, this was the only study to report concordance of positive outcomes between multiple measures of adherence. To increase hydroxyurea adherence in adolescents (M_{age} = 13.9), Estepp et al. (2014) used Scheduled Instant Messaging Over the Network (SIMON), an intervention containing behavioral and technology components targeting

self-efficacy and self-monitoring. These modifiable factors were not measured. SIMON allowed participants to customize the text message reminder they received by selecting the content, delivery time, frequency, and duration of the text messages. There was no effect of intervention on MPR; however, small to moderate effects were found for change in biological parameters. Of nine biological parameters that were collected, an initial significant difference was found for MCV (p = <0.001), ARC (p =0.005), and bilirubin (p = 0.003). However, sustained effects were not consistently observed for these biological measures with only ARC and bilirubin maintaining significantly lower values a year post-intervention and HbF significantly increasing (p = 0.002). The authors concluded that this represented improved medication adherence and a sustained response to the intervention.

Small to large effects were found for interventions in the individual domain. The three studies that reported significant increases in hydroxyurea medication adherence targeted the modifiable variables of self-efficacy and self-monitoring within the individual domain and predominantly for adolescents. When knowledge deficits were a target of intervention, it was the only modifiable variable measured. They all utilized a behavioral and technology-based component in their intervention package but the study that reported multiple significant outcomes also specifically included incentives. In addition, these studies utilized a pre-post, within subjects design and a control condition was not included.

Family domain. Five studies fell within the family domain with targeted modifiable factors including knowledge, caregiver-efficacy, caregiver-monitoring, and task/responsibility division. These studies included parents/caregivers but not siblings or other family members. Two studies targeted parents/caregivers due to enrolling young patients, one study included only parents but not patients, and two studies included parent-child dyads. Although statistical

differences were not found, interventions yielded small to large effects on adherence. Reed (2016) provided parents with an educational video for improving daily hydroxyurea administration, which yielded only a small effect on HgF levels. Parent health literacy was assessed prior to the intervention in order to ensure health literacy would not be a barrier. In comparison to a control group, parents who received education, weekly phone consultation, and a behavioral plan showed moderate increases on an objective measure of penicillin adherence immediately after intervention (d = 0.49) and at four-month follow-up (d = 0.53; Berkovitch et al., 1998). The only modifiable factor measured was knowledge. Two studies reportedly addressed division of tasks/responsibility between parent and patient, with one study evidencing no effect on adherence (Treadwell & Weissman, 2001, see Community Domain) and the other demonstrating small to large effects (Green et al., 2017; see Healthcare system domain). Notably, family functioning was not specifically targeted in any of these studies.

Community domain. One study fell within the community domain and targeted the modifiable factor of social support. Treadwell and Weissman (2001) utilized an intervention that included an iron chelation day camp, with the intention of building peer support for participants. The modifiable variable of perceived social support was measured. Statistical analyses were not conducted and there was no effect of intervention on iron chelation adherence at one-year post-intervention (d=0.16).

Healthcare system domain. Only one study fell within the health system domain and targeted the modifiable factors of language preference and access to providers. However, it should be noted that this study also fell within the individual and family domains. In Green et al. (2017), the authors included community healthcare workers who visited family homes monthly to provide education and identify which hydroxyurea adherence habit to modify in the

intervention. The adherence habit was targeted via text message reminders. Families were then able to select the language and time of day they wanted to receive the reminder. Families were allowed to contact and communicate with community health care workers for any medical need, such as arranging visits, scheduling follow-up appointments, and urgent medical concerns. In this way, the intervention attempted to enhance patient access to the healthcare system, both from a language and ease of interface perspective. Although no significant differences between the intervention and control condition were found, there was a large effect of intervention on HbF at four-months (d = 0.93) and a moderate effect at six-months (d = 0.64).

4.5 Discussion

The current body of literature on psychosocial interventions for medication adherence in pediatric SCD is markedly small with only nine studies included in this review and with the majority of interventions for hydroxyurea. Studies had generally high levels of validity threat across areas of bias, likely owing to the use of predominantly pre-post, within subjects study designs and relatively small sample sizes. In addition, all studies used multimethod assessment of adherence outcomes with MPR and bioassay being the most frequently utilized. Similarly, interventions were characterized by packages consisting of multiple components with behavioral, educational, and human support features being the most common. Interventions were also generally developed for adolescents, which is consistent with data indicating that teens are most vulnerable to poor medication adherence (Taddeo, Egedy, & Frappier, 2008).

Across studies, the study period varied from 90 days to 2 years. This does present an additional barrier to comparing outcomes across studies for different time points. In previous review studies of adherence enhancing interventions in pediatrics, effects were only sustained for up to 6 months following intervention completion with effects continuing to diminish over time

(Kahana et al., 2008). This review similarly revealed that immediate effects often do not persist to 1-year follow up. An additional consideration is the utility of using incentives to increase adherence. Only one study (Creary et al., 2014) provided incentives for directly observed therapy and large effects on adherence were observed. However, long-term follow-up was not conducted in this study and incentivizing adherence has also been associated with diminished effects once the incentive is removed (DeFulio & Silverman, 2012). Both of these issues present questions about the generalizability and sustainability of these interventions.

The Pediatric Self-Management Model provided a framework for examining multilevel influences on adherence. It was challenging to draw conclusions across studies due to variable assessment methodologies for adherence outcomes and limited statistical analyses. In general, small to large effects on adherence were found for interventions at the individual, family, and health system levels. The two studies that utilized a randomized control study design both demonstrated relatively fewer risks of bias and also evidenced small to large effects (Berkovitch, 1998; Green et al., 2017). While both of these interventions targeted interventions at the family domain level, Green et al. also addressed the individual and the health care domains and demonstrated more robust findings. This suggests that interventions that target multiple domains and utilize a more sensitive study design may have a greater effect on adherence. In addition, three studies did report statistically significant positive increases in adherence following intervention delivery. These studies all fell within the Individual Domain of the Pediatric Self-Management Model and targeted the modifiable factors of self-efficacy and self-monitoring. These factors were impacted by interventions that contained technological components (i.e., text messaging, smartphone applications, and web-based platform) and behavioral components (i.e., receiving reminders, tracking adherence daily, and receiving feedback from study staff).

Therefore, this review tentatively concludes that medication adherence can be enhanced by targeting self-efficacy and self-monitoring at the individual level using inventions with behavioral and technological components.

Moreover, interventions that only provided reminders and no education for adolescents demonstrated small to large effects on increasing adherence (Creary et al., 2014; Estepp et al., 2014). This suggests that cues to action, such as reminders, paired with self-efficacy are key to behavior change. This is consistent with adolescent patients reporting "forgetting" as the primary barrier to regular regimen maintenance (Badawy et al., 2016). Interestingly, despite being a common barrier to adherence in pediatric SCD, addressing knowledge deficits in caregivers yielded small effects (Reed, 2016) but when combined with efforts to increase caregiver monitoring and self-efficacy, there were moderate effects on adherence (Berkovitch et al., 1998). This may reflect how psychoeducation alone is limited in promoting behavior change (Murphy, Rayman, & Skinner, 2006; Nieuwlaat et al., 2014). No interventions directed addressed access issues, which reflects a lack of systemic or health care level change. Lastly, pill-swallowing interventions were not found in the literature, despite being a reported barrier to adherence.

Future Directions. This review significantly contributes to the literature by exhibiting both *what* modifiable factors have been successfully targeted and *how* they were targeted. In addition, it also highlights what work remains to be done. Notably, multiple measures of medication adherence were utilized in this study, which limited the interpretability of the results. Although multimethod assessment of adherence is recommended (Dolezal, Mellins, Brackis-Cott, & Abrams, 2003), subjective versus objective reports of medication adherence often do not correlate due to inflated subjective self-report (Hommel, Davis, & Baldassano, 2009). Therefore, a major consideration for future research would be to better understand why different modalities

of measurement vary so widely and to determine if an integrative composite could be of use as suggested by Thornburg et al. (2010). Furthermore, it is worthwhile to consider the value of tying medication adherence to clinical outcomes, which could also assist in determining meaningful cut-offs for measures of adherence amongst and between measures. It is likely unreasonable to expect patients to maintain 100% adherence, therefore establishing acceptable thresholds for adherence levels that are also characterized by objective measures may provide more clinical utility and research clarity.

In addition, interventions included in this review were predominantly within the Individual Domain of the Pediatric Self-Management Model, which leaves ample opportunity for further invention development in other domains. For example, despite strong evidence for the relationship between positive family functioning and better medical adherence in other medical populations, few interventions have specifically targeted family functioning in pediatric SCD (Psihogios, Fellmeth, Schwartz, & Barakat, 2018). This is surprising considering the genetic etiology of the condition, which means that parents themselves or other family members often also have SCD. In line with Social Learning Theory, it is likely that attitudes and behaviors towards SCD medication adherence are modeled within the family environment and learned by children. This suggests that by having a family based intervention, there may be benefits for multiple individuals within the system, not just the intended patient. In addition, positive parent and child communication has been associated with better adherence, likely due to more collaborative efforts to incorporate medication administration into the daily routine, including aiding in reminders, as well as providing support in problem solving (Mellins, Brackis-Cott, Dolezal, & Abrams, 2004; Miller & Drotar, 2007). Therefore a major consideration for future

research would be to develop family based interventions. Other systemic approaches to intervention development should also be considered.

In addition to the major considerations for future directions identified above, some minor suggestions to guide future intervention research are provided. Specific measurement of the modifiable factors targeted in these interventions would support the mechanistic theory underlying the Pediatric Self-Management Model. Although some of the included studies did measure modifiable variables (e.g., knowledge), this should be considered for all targeted variables and in all future intervention studies. This would ensure that change in supposed mechanisms are responsible for change in adherence behavior. For example, mapping change in self-efficacy to change in adherence levels. Moreover, future studies should investigate moderating variables, such as age, gender, socioeconomic status, disease severity, and health beliefs about disease susceptibility, disease severity and attitudes towards traditional medication versus holistic treatments. In addition, all reported barriers to adherence were not addressed by the interventions reviewed, suggesting a need for more research directed towards ameliorating these barriers. It is also unclear if the effects of these interventions are sustained over time and this should be addressed in future study designs. Lastly, it is important to remember that patients who elect to participate in an intervention are likely not representative of all patients who could benefit from adherence interventions. In addition, given the risk of comorbid executive functioning and attentional deficits in pediatric SCD that may interfere with successful self-management, future research should examine how intervention can be targeted to varying levels of cognitive functioning (Hijmans et a., 2011). Therefore, additional efforts should be undertaken to include the most vulnerable patients in these intervention studies.

It is worth addressing that intervention studies for medication adherence in other chronic illness populations have been well studied but they are severely lacking in pediatric SCD. Historically, patients with SCD have been understudied and underserved due to discriminatory practices (Prabhakar et al., 2010; Smith, Oyeku, Homer, & Zuckerman, 2006). In considering the publication dates of the papers included in this review, the majority of findings were published within the past 5 years, which suggests a positive trend towards prioritizing SCD in both research and clinical initiatives. However, the dearth of literature in this area remains concerning and attention should be geared towards maximizing research opportunities and interest within this underserved population.

Limitations. Although this review highlights many important points of consideration, there are limitations that should be mentioned. First, only nine studies were included, which prohibits definitive conclusions to be made. This may be due to overly stringent inclusion criteria or restricted search terms. Furthermore, only two studies were randomized controlled trials, which limits conclusions that can be made about causality. Additionally, the studies included also contained pilot and feasibility studies and/or reported small sample sizes. This reduced the statistical power to conduct advanced analyses and detect smaller effects in individual studies. Moreover, studies utilized multiple measures of adherence and variable study periods so any significant findings were considered evidence for effectiveness. However, this may be a liberal interpretation of the data. As additional intervention research is published, an updated review should be conducted with quantitative approaches to assess overall effect sizes.

Conclusion. This review is the first to systematically integrate and assess the extant literature on interventions for enhancing medication adherence in pediatric SCD. Although the body of literature is still in the nascent stage, the results of the present study suggest that utilizing

behavioral and technological intervention components to target self-efficacy and self-monitoring behaviors may enhance medication adherence in adolescents with SCD. Targeting multiple domains simultaneously may also yield larger effects on adherence. Furthermore, the Pediatric Self-Management Model offers an effective framework for developing and studying adherence interventions in pediatrics. Lastly, this review also revealed a dearth of quality adherence intervention studies in pediatric SCD. Despite increasing interest, research and clinical efforts within this underserved population continues to be inadequate. Interventions on mechanisms and factors that are known to improve quality of life and minimize morbidity and mortality in pediatric SCD need to remain a priority on clinical research agendas.

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Table 8. Table 4.9 Summary of Study Characteristics and Findings for Studies Included (n = 9)

Author, Year	*n*	Sample Age	Target Medication	Intervention Description	Intervention Components[1]	Self-Management Domain: *Modifiable Factor Targeted*[2]	Comparison Group	Study Period	Measurement of Adherence[3]	Key Adherence findings[4]
Anderson et al., (2018)	32	13.0 ± 3.33	Hydroxyurea	Intensive Training Program (ITP) App: Education sessions, Remote daily monitoring of medication compliance (selfie video or log), Study staff weekly feedback	B, E, H, T	Individual Domain: *Knowledge^, Self-Efficacy, Self-Monitoring*	Pre-post, within subjects	90 days	1. ITP App Entries (S, O) 2. MPR (O) 3. Med Record Review (O) 4. Hg (B) 5. MCV (B) 6. ARC (B)	1. X, 42% 2. +*, p=0.001, d=0.75 3. + 4. = 5. = 6. = Moderate effect of intervention. Statistically significant increase in adherence (MPR) immediately post-intervention. No change across biological measures.
Berkovitch et al., (1998)	45	37m. ± 19m.	Penicillin	Education, Weekly phone calls by SW, Behavioral calendar	B, E, F, H	Family Domain: *Knowledge^, Caregiver-Efficacy, Caregiver-Monitoring*	No Education	6 months	1. Medication Event Monitoring System (O)	1. + d=0.49 (2m.) d=0.53 (6m. follow-up) Moderate effect of intervention immediately post-intervention and maintained at follow-up. No statistically significant difference between groups.

Creary et al., (2014)	15	13.7 ± 6.3	Hydroxyurea	Electronic directly observed therapy (DOT): Reminders, Remote daily monitoring of medication complication (Videos), Feedback, Incentives	B, H, T	Individual Domain: *Self-Efficacy*, *Self-Monitoring*	Pre-post, within subjects	6 months	1. Video Observation (O) 2. Morisky Medication Adherence Scale (MMAS-4) (S) 3. MPR (O) 4. MCV (B) 5. HbF (B)	1. X, 93.3% 2. +*, p=0.004 3. +*, p=0.02, d=0.89 4. +*, p=0.009, d=0.50 5. +*, p=0.03, d=0.25 Statistically significant increase in adherence with small to large effect of intervention on adherence across subjective, objective, and biological measures at study completion.
Estepp et al., (2014)	55	13.9	Hydroxyurea	Scheduled Instant Messaging Over the Network (SIMON): Customizable text messages (content, delivery time, frequency, duration)	B, T	Individual Domain: *Self-Efficacy*, *Self-Monitoring*	Pre-post, within subjects	2 years	1. MPR (O) 2. Hg (B) 3. HgF (B) 4. MCV (B) 5. ARC (B) 6. WBC (B) 7. Absolute neutrophil (B) 8. Platelet (B) 9. Bilirubin (B) 10. Lactate dehydrogenase (B)	1. -, d=0.13 2. =, d=0.06 3. +*, p=0.002, d=0.13 4. +*, p<0.001, d=0.23 5. +*, p<0.001, d=0.69 6. =, d=0.11 7. =, d=0.03 8. =, d=0.10 9. +*, p=0.003, d=0.16 10. =, d=0.03 Small to moderate effects of intervention on biological measures of adherence. Statistically significant differences in biological measures found immediately post-intervention, not maintained at 1-year follow-up.

Green et al. (2017)	28	14.5±2.7	Hydroxyurea	HABIT study: Community health care workers (CHW) visited home monthly, Education provided, Target behavior identified, Text messages tailored to the preferences of family (language, time of day, reminder based on identified behavior), mutual contact by telephone or text message with CHW	B, E, F, H, T	Individual Domain: *Knowledge* Family Doman: *Knowledge, Division of tasks/responsibilities* Health System Domain: *language preference, access to providers*	Educational brochure	6 months	1. Decrease from HbF Personal Best (B) 2. MPR (O) 3. Modified Morisky Medication Adherence Scale (MMAS-4) (S)	1. +, *d*=0.93 (4m.) *d*=0.64 (6m.) 2. +, *d*=0.35 3. = Large and moderate effect of intervention on biological measure of adherence at 4 months and 6 months, respectively. Small effect on MPR. No statistically significant differences between groups.
Inoue et al. (2016)	19	6.5±10.4	Hydroxyurea	GlowCap: Electronic cap on medication bottle. Flashes light if patient is late, then sounds chimes if patient is still late, phone call if cap is not opened within 2 hours	B, F, H	Individual Domain (older pt. age): *Self-monitoring* Family Domain (younger pt. age): *Self-monitoring*	Pre-post, within subjects	1 year	1. MPR (O) 2. GlowCap Electronic Monitoring (O) 3. Hg (B) 4. MCV (B) 5. WBC (B) 6. ANC (B) 7. ARC (B) 8. HbF (B)	1. X, 86% 2. X, 78% 3. X, + 4. X, + 5. X, + 6. X, + 7. X, + 8. X, + Indeterminate effect.

Leonard et al. (2017)	11	12.4±3.8	Iron Chelator	Intensive Training Program (ITP) App: Education sessions, Remote daily monitoring of medication compliance (selfie video or log), Study staff weekly feedback	B, E, H, T	Individual Domain: *Knowledge^*, *Self-Efficacy*, *Self-Monitoring*	Pre-post, within subjects	6 months	1. ITP App Entries (S, O) 2. MPR (O) 3. Serum Ferritin (B)	1. X, 80% 2. +, *d*=0.25 3. + Small effect of intervention on adherence (MPR).
Reed (2016)	22	9.5±3.02; 37.5±6.77	Hydroxyurea	Educational Video for Parents	E, F	Family Domain: *Knowledge*	Pre-post, within subjects	8 weeks	1. Morisky Medication Adherence Scale-8 (MMAS-8) (S) 2. MCV (B) 3. HgF (B)	1. =, *d*=.09 2. =, *d*=.15 3. =, *d*=.28 Small effect of intervention on adherence (HgF).

Treadwell & Weissman (2001)	20	11.6±4.6	Iron Chelator	Desferal Day Camp:	B, E, F, S	Individual Domain: *Knowledge^, Self-efficacy, Self-monitoring* Family Domain: *Division of tasks/responsibilities^* Community Domain: *Social Support^*	Pre-post, within subjects	2 years	1. 24 hour recall interview of medications administration (S) 2. Serum ferritin	1. X, 1 yr post-intervention = 83%, *d*=0.16; 2 yr post-intervention = 73% 2. X, = Minimal to no effect of intervention on adherence.

Note. [1]B = behavioral, E = educational, F = family based, H = human support S = social support, T = technology; [2] ^ = modifiable factor measured; [3]O = Objective, S = Subjective, B = Biological; [4]+ = Positive change in adherence, * = Statistically significant change, = = No change in adherence, - = Negative change in adherence, X = no stats done, effect size (*d*) presented if sufficient information available.

5 CONCLUSIONS

5.1 Summary of Findings and Implications

Children exist within the context of their family system, and family level factors should be taken into consideration when investigating child outcomes. Within the pediatric SCD literature, family level factors have been under-investigated, and the extant research on how family factors are related to child health-related psychosocial concerns is limited. Therefore, the primary goal of this dissertation was to describe the relationship between family level factors and health-related psychosocial outcomes in pediatric SCD. Secondarily, each of these studies addressed issues of assessment, analysis, and intervention, albeit to varying extents and emphases. The primary findings from each study are first summarized and then integrated across the three foci.

The first study characterized family functioning in pediatric SCD using the Family Assessment Device (FAD; Epstein et al., 1983) dimensionally and with clinical categories of dysfunction. The FAD is one of the most widely used measures of family functioning and is consider to a be a well-established assessment tool (Alderfer et al., 2008). Although the measure consists of seven dimensions in total, the extant research has typically only utilized the general functioning dimension of the FAD. In doing so, the exact nature of a family's dysfunction may not be thoroughly assessed or captured. Furthermore, the relationship between the general functioning dimension of the FAD and health-related psychosocial outcomes, such as HRQOL and functional disability, has been inconsistently demonstrated in pediatric SCD. Findings from this study indicate that in contrast to a previous study (Herzer et al. 2010), the frequency and dimensions of poor family functioning in pediatric SCD were similar to those found in other pediatric chronic conditions. Therefore, families with children diagnosed with SCD may not

experience disproportionately higher levels of family dysfunction within the context of pediatric chronic illness, which has been suggested in the literature (e.g., Herzer et al., 2010). However, having any dimension in the clinically elevated range was associated with poorer HRQOL and greater functional disability. Furthermore, a negative relationship was found between the role dimension of family functioning and child HRQOL and functional ability. Specific items on the role dimension were associated with family income, such that lower income was correlated with higher levels of difficulty in instrumental areas of functioning (i.e., reliable transportation, meeting bills on time, obtaining needed items). This points to the need to attend to social determinants of health in this population. Therefore, by assessing family functioning dimensionally, its relationship with child health-related psychosocial outcomes was more specifically described and this suggests that using a global marker of functioning may obscure the identification of an important target of intervention at the family level.

The second study examined the unique and mutual contribution of parent and child pain catastrophizing on child HRQOL in pediatric SCD. This study utilized the common fate framework to model the relationship between the shared variance in parent and child pain catastrophizing and the shared perspective between parent and child in child HRQOL. A significant, negative relationship and a large effect were demonstrated, such that an increase in dyad level pain catastrophizing was associated with a decrease in shared dyadic perspectives on child HRQOL. Additionally, when using an actor-partner common fate model hybrid to examine the unique relationship between child HRQOL and child pain catastrophizing and parent pain catastrophizing, respectively, there was also a significant, negative relationship with a small to medium effect for both parent and child pain catastrophizing. In totality, these findings indicate that there is interdependence between parent and child pain catastrophizing and that both are

uniquely and mutually associated with child HRQOL. Therefore, parent pain catastrophizing, in addition to child pain catastrophizing, should be incorporated as a target in intervention. Additionally, these types of dyadic analyses more closely align with theoretically assumptions that parents and children exist within the same context and are therefore not entirely independent in their influences. Moreover, parents and children have shared and unique perspectives, but when there is a high degree of concordance between perspectives, it may be worthwhile to examine both perspectives in an integrated manner. For example, it is recommended that both child self-report and parent-proxy report be collected but when both child self-report and parent-proxy report of child HRQOL are collected, ratings tend to demonstrate moderate correlations (Panepinto et al., 2013). Dyadic analyses provide an opportunity to analyze the data collected in a cohesive manner such that both shared and unique perspectives can be examined. The findings of this study contribute to the limited research on parent and child pain catastrophizing in pediatric SCD and also present how dyadic analyses can be utilized to analyze the parent-child relationship in a manner consistent with our theoretical understanding of this complex dynamic.

The third study was a systematic review of interventions for enhancing medication adherence in pediatric SCD. The findings of this review were organized using the pediatric self-management model, which posits that there are individual, family, community, and healthcare system level influences that promote or hinder adherence behaviors (Modi et al., 2012). At each of these levels, there are modifiable factors that should be targeted in intervention. Existing research in pediatric SCD medication adherence has pointed to a number of family level modifiable factors that should be targeted in intervention. These have included caregiver knowledge deficits, poor family functioning, unstable daily family routines, ineffective family communication, and logistical challenges related to obtaining medications (Barakat et al., 2002;

Brandow & Panepinto, 2010; Klitzman et al., 2018; Loiselle et al., 2015; Oyeku et al., 2013; Walsh et al., 2014). A total of nine studies were identified in the systematic review with five studies falling in the family level domain of intervention; however, only two studies included parent-child dyads. Interventions at the family level targeted the modifiable factors of caregiver knowledge, caregiver-efficacy, caregiver-monitoring, and task-responsibility division. Interventions within this domain demonstrated small to large effects on adherence, though this should be interpreted with caution due to high risk of bias in study design. The study which demonstrated a large effect on adherence addressed caregiver knowledge and division of tasks/responsibilities, as well as larger systemic concerns, such as increasing patient access to providers and providing intervention in the family's desired language (Green et al., 2017). However, family functioning, family routine, family communication, and instrumental support were not directly addressed in these studies. A brief review was conducted for pediatric SCD medication intervention studies published since December 2018 to assess for any additional studies since this systematic review was completed. Additional interventions targeting these modifiable factors were not found. In sum, medication adherence interventions that directly involve the child's family and parents demonstrate initial efficacy for increasing medication adherence. Family-based interventions should be enhanced to address additional modifiable factors, including those that are related to social determinants of health.

In considering how the findings across these three studies can be further integrated, there are potential implications for understanding factors associated with adherence and HRQOL in pediatric SCD. Previous research has indicated that family level barriers to adherence in pediatric SCD consist of family dysfunction (e.g., division of tasks/responsibilities, poor communication, chaotic routines) and structural difficulties (e.g., unreliable transportation; Barakat et al., 2002;

Brandow & Panepinto, 2010; Klitzman et al., 2018; Loiselle et al., 2015; Walsh et al., 2014). Results of the first study in this dissertation suggest that in addition to adherence, one specific aspect of family functioning, role fulfillment, is associated with worse HRQOL and that other factors, like problem-solving and affective involvement, may be less related than previously thought. Previous research has evidenced that barriers to adherence (e.g., transportation problems, insurance or financial problems, difficulty getting medication, and time constraints) mediate the relationship between poor adherence and low child HRQOL in pediatric SCD (Fisak et al., 2012). Therefore, it's possible that through addressing challenges with family functioning in the area of instrumental role fulfillment (e.g., meeting bills, obtaining needed resources, establishing reliable transportation), there could be improvements in both adherence and HRQOL. Furthermore, improved family functioning has been associated with lower levels of both parent and child pain catastrophizing in a sample of youth with chronic pain (Jastrowski Mano et al., 2011), which indicates that there could be value in concurrent investigation of family functioning and pain catastrophizing in pediatric SCD, as both were shown to be associated with HRQOL across the first and second studies in this dissertation.

Additionally, the role of parent pain catastrophizing in pediatric SCD medication adherence warrants further exploration. In a general child sample without chronic illness, parent pain catastrophizing was associated with greater utilization of pharmacological techniques for child pain alleviation (Gorodzinsky et al., 2013). Similarly, in pediatric SCD, parent pain catastrophizing has been associated with increased odds of opiate administration for at-home youth acute pain management (Stone et al., 2020). However, the association between parent pain catastrophizing and utilization of daily, non-acute medication adherence in pediatric SCD is unknown. It stands to reason that if a parent is concerned about their child experiencing pain, all

efforts would be made to prevent the child from experiencing pain. Although pain catastrophizing has been shown to lead to over solicitous and impairing parental behaviors in other pediatric chronic pain conditions (Palermo et al., 2014), it may be somewhat adaptive in pediatric SCD as daily medications are thought to reduce the potential for pain episodes (Rees et al., 2010)), and adherence may be improved. It is of interest to investigate the relationship between parent pain catastrophizing and medication adherence in pediatric SCD, particularly to assess if increased levels of parent pain catastrophizing leads to hypervigilance and actions to prevent pain episodes, including improved adherence. Furthermore, incorporating family functioning into this examination might garner additional insights and mediators. Specifically, there is a potential that in families with clear and equally distributed roles that are consistently fulfilled, medication adherence is optimal. This may also be associated with reduced parental anxiety and worry about pain episodes and lead to overall improved child HRQOL.

Implications. Our understanding of why some children with SCD do better or worse than others is incomplete. Perhaps one reason for this knowledge gap is the relative dearth of literature investigating the role of family level factors. The findings of these three studies suggest that our understanding of child health-related psychosocial concerns in pediatric SCD can be expanded by examining their relationship to family level factors. Across studies, the relationship between family level factors and child outcomes were significant and in the expected direction. Study results were consistent with Wallander and Varni's (1998) risk and resistance model and these findings emphasize the need to include a more family systems-based lens to our research and clinical efforts in pediatric SCD.

There are a few major take-aways from these studies, including suggestions for how to move the field forward in family-based assessment, analysis, and intervention in pediatric SCD.

Specifically, to have a holistic understanding of family functioning, general measures may not capture specific areas of dysfunction that are related to outcomes in pediatric SCD and multiple perspectives should be included. Additionally, dyadic analyses offer a statistical methodology that more closely maps onto our theoretical understanding of the parent-child relationship. If thorough assessment and analytic methods are used jointly and consistently, these methods could inform intervention at a more sophisticated level. Also, family-based interventions to improve child HRQOL should consider addressing role fulfillment in the family, providing instrumental and logistical support (e.g., access to reliable transportation and social services), and targeting parent cognitive factors, such as catastrophizing about their child's pain. Relatedly, social determinants of health, such as reliable transportation, economic stability, and access to quality and supportive health care should be targeted in tandem with psychological intervention to optimize outcomes for the child with SCD and the family unit overall. Preliminary evidence indicates that child medication adherence in pediatric SCD can be enhanced with family-based intervention, although there are additional modifiable factors that have not been addressed in intervention. Not only can multi-informant assessment and dyadic analyses inform intervention, but they can also be utilized to monitor response to intervention (Braithwaite & Fincham, 2011; Cook & Snyder et al., 2005; Hayes et al., 2018). Taken together, an example of a future study directly informed by these implications may consist of baseline parent and child report on dimensions of family functioning, dyadic analysis of these reports, and assessment of other instrumental areas in need of support. Given that dimensions of family functioning are considered modifiable factors, intervention could be tailored to address specific areas of family dysfunction as identified by the dyad. Care coordination and case management could also be integrated into the study design to provide referrals to service agencies and resources to address

social determinants of health. Outcomes of interest could include child HRQOL, functional ability, and adherence. The efficacy of such interventions could be evaluated through reassessment and dyadic analysis, including examination of longitudinal effects.

It is also important to acknowledge the limitations of the current 3-study project. First, various constructs were investigated across studies; although, study 1 and study 2 both examined child HRQOL as an outcome, and study 1 and study 3 both addressed family functioning, and all studies were conducted to ultimately inform intervention. The specificity of the conclusions drawn from this dissertation could have been improved by examining a more uniform set of constructs in a serial manner. Second, the methodology across studies was variable and increased correspondence amongst studies could have strengthened the points made with regards to assessment and analysis. More specifically, study 2 presented rationale for using multi-informant data and applying dyadic analyses to examine the interrelationship between parent-child factors and perspectives. Study 1 would have benefitted from both of these practices. That said, contrasting the 2 studies highlights the value of parent and child perspectives as well as advanced dyadic analyses. Third, I could have included several additional or different variables that would have strengthened each study and resulted in more consistent conclusions. To address some of these limitations and provide additional considerations more broadly across the field, future directions are outlined below.

5.2 Future Directions

5.2.1 Acknowledgement of Racism and Structural Violence

As stated throughout this dissertation, SCD is an under researched population despite a host of medical comorbidities, decreased psychosocial functioning, and reduced lifespan (Piel et al., 2017; Smith et al., 2006). Health disparities in clinical care experienced by individuals with

SCD have also been well documented (Lee et al., 2019). The extent of the discrepancy between funding and published research in pediatric SCD and other disorders is significant (e.g., Farooq et al., 2020). Moreover, improvement in the availability of effective, empirically-based intervention to address poor child outcomes in the broader pediatric chronic pain population has been attributed to considerable research efforts to inform those interventions (Donnelly et al., 2020). Unfortunately, this pattern of practice has not been emulated in pediatric SCD specifically, despite the ubiquitous experience of pain in this population and similar challenges in other domains of functioning. We might expect that decreased research funding is the reason for hinderances in clinical advancement, but an alternative explanation is that there is an underlying, mutual process affecting both reduced research prominence and clinical care.

It is hypothesized that the health disparities observed between SCD and other chronic conditions are the result of structural violence, or the societal and systemic manner in which certain groups are harmed or exploited (Bahr & Song, 2015; Bailey et al., 2017). Despite being a developed, resource-rich nation, the United States has presented reduced funding opportunities for SCD research, a condition that predominantly impacts individuals of African descent and individuals from lower socioeconomic status (Palermo et al., 2008). This lies in stark contrast to the well-funded and fruitful research in other pediatric chronic illnesses that predominantly impact individuals of European descent (e.g., cystic fibrosis) and where study samples are largely White (e.g., chronic pain). In short, the issues of racial inequity and privilege are more than likely to account for these differences (Bahr & Song, 2015).

Racism and structural violence impact access to and delivery of healthcare, as well as patient outcomes (Bailey et al., 2017; Beck et al., 2020). Therefore, beyond just increasing the quantity of funding and research efforts, these historical and systemic issues of racism should be

directly considered in our research from conceptualization, method, and interpretation of data in pediatric SCD. For example, social determinants of health were identified as relevant factors in the collection of studies in this dissertation and has also been documented as relevant in the adult literature (Lubeck et al., 2019). Instead of setting income as a covariate in our analyses, perhaps we should include this data point in a more meaningful way and recognize how inequity in these variables is derived from systemic oppression (Cheng & Goodman, 2015; Bahr & Song, 2015). For example, perhaps there is an additive impact of economic and structural (e.g., housing and transportation) instability to child health outcomes, beyond just disease-specific factors. Economic and structural instability are also a family level concern, which emphasizes that when examining the family unit, these social determinants of health should be included.

Furthermore, the recruitment of families with children diagnosed with SCD may be impacted by similar structural challenges, as well as mistrust of healthcare providers and clinical research borne from a history of discrimination and exploitation in treatment and research of Black and African American patients (Ellis et al., 2021; Raphael et al., 2017; Stevens et al., 2017; Winter et al., 2018). Particularly when researchers are coming from academic and medical institutions that are disproportionately White and reflect educational privilege. Even when families do engage in research, the nature of the questions asked tend to be sensitive and personal. This may be an uncomfortable situation for participants and how the information will be used should be clearly explained. There is also evidence that when parents and caregivers are required to actively participate in research, recruitment of minoritized patients is particularly challenging (Cui et al., 2015). This may also account for why family level factors and family-based interventions have been more limited in pediatric SCD research. However, recent research suggests that persistence and flexibility in recruitment of Black, Indigenous, and People of Color

(BIPOC) can result in increased recruitment and is perceived to be acceptable by participants (Ellis et al., 2021). In addition, training study personnel in cultural competency and sensitivity during recruitment procedures (Crosby et al., 2021) or partnering with patient advocates and community networks (Grape et al., 2018; Hartlieb et al., 2015; Nicholson et al., 2011) may promote increased trust.

Racism exists within and external to the healthcare setting and incorporating sociopolitical context should be regularly conducted in research (Bailey et al., 2017), including pediatric SCD. An addition that could be made to Wallander and Varni's (1998) risk and resistance model would be to include sociopolitical context. For that matter, racism could be conceptualized as a chronic stressor, much like chronic illness (Bailey et al., 2017), and the impact of racism across physical and mental health are also marked (Paradies et al., 2015). Our study results should be viewed in light of structural and institutional racism and discrimination. Pertinent to SCD in particular is the experience of pain. Research in adult SCD has evidenced frequent discrimination from healthcare providers and difficulty convincing healthcare providers about pain (Haywood et al., 2014), as well as increased experiences of pain (Mathur et al., 2016). For example, patients with SCD have been accused of feigning their pain in pursuit of opiates and this discriminatory treatment contributes to negative attitudes towards medical treatment and subsequent avoidance of health care (Power-Hays & McGann, 2020; Stanton et al., 2010). Furthermore, experiencing discrimination has been correlated with poorer adherence in Black and African American adults (Williams & Mohammed, 2009). Youth with SCD experience racism both within medical settings and in day-to-day life, which is associated with poorer HRQOL and greater pain burden (Mougianis et al., 2020; Wakefield et al., 2017). Within the context of the studies included in this dissertation, these variables could have been assessed in

relation to HRQOL and adherence. In addition, studies of pain related phenomena should also consider the influence of these discriminatory practices. For example, it would be valuable to understand how pain catastrophizing is maintained in pediatric SCD and whether experiences of discrimination and racism contribute to child amplified worry about pain and/or parental concern about their child's pain. Furthermore, an

An additional layer of sociopolitical context that is relevant for individuals with SCD is the stigma associated with chronic illness and privilege for able-bodied individuals (Amundson, 2013). As individuals with SCD are likely to experience both racism and ableism, these factors should be further considered in our research. Without acknowledging these factors, our scope of understanding the lived experience of individuals with SCD is limited and biased.

5.2.2 The Family: Definitions and Inclusion

What constitutes a family system in the United States has moved beyond what is considered a traditional nuclear family (Walsh, 2003). Families may consist of single-parent households, grandparents or other extended relatives, same-sex relationships, blended families, foster families, or non-biological kin (Hildenbrand et al., 2021; Teachman et al., 2013; Widiss, 2016). Therefore, families should be characterized by how family is defined within the child's individual family unit. Considering the relationship between family role fulfillment and child HRQOL and functional disability in pediatric SCD identified in study 1 of this dissertation, clarifying family members and their role in the system may be particularly relevant.

Additionally, to date, research on family perspectives should probably be more appropriately deemed "maternal perspectives" given that mothers are disproportionately represented in pediatric research (Phares et al., 2005). This was also true of the studies included in this dissertation, and greater efforts could have been made to incorporate additional caregiver

perspectives, as appropriate. If additional caregivers are identified by the patient and family, attempts should be made to include these perspectives. For example, paternal perspectives may be important to assess but fathers are infrequently represented in pediatric research (Phares et al., 2005). In one study, when fathers were asked about barriers to participation in child health research, they attributed their underrepresentation to not being asked to participate by researchers (Davidson et al., 2017). Non-White fathers also recommended recruitment venues outside of doctors' offices, including advertisement on public transportation, playgrounds, and barber shops. In this study, fathers indicated greater willingness to participate in research when a clear benefit to the child or family was communicated and the organization was perceived as credible. Therefore, alternative routes to recruitment, clear communication of direct benefit, and a trusting relationship are all strategies to undertake in increasing inclusion of fathers in pediatric research. Relatedly, healthy siblings of children with SCD may have unique perspectives on family level factors and they also report poor psychosocial adjustment (Gold et al., 2011; Guite et al., 2004). This may become even more relevant as hematopoietic stem cell transplantation from matched sibling donors increases in frequency and multiple members of the family become directly involved in medical treatment (Packman et al., 2010; Sinha et al., 2020). Additionally, given the genetic etiology of SCD, siblings and additional family members with SCD should be assessed in research to clarify the cumulative impact of chronic illness on the family unit. Greater emphasis on the family unit should be incorporated in the risk and resilience model to account for this context. To examine shared and unique perspectives and experiences within a family unit, multi-informant assessment is necessary. Additionally, to analyze these multiple perspectives in an integrated manner, a common fate model or hybrid model could be utilized as these statistical models permit incorporation of more than two informants.

To further investigate family level factors and familial dynamics in pediatric SCD, qualitative approaches should be also considered. Qualitative methodology is designed to capture multiple perspectives, develop insight on nuanced or complex processes, and explore new or less commonly researched phenomena (Wu et al., 2016). Moreover, in qualitative work, individualized experiences and contexts are meant to be represented, which allows for narratives that may not fit just one mold (Popp et al., 2014; Wu et al., 2016). This has clear applicability to research related to child adaptation to chronic illness, which along with family-based functioning is nuanced and an evolving, ongoing process.

5.3 Conclusion

The studies in this dissertation expand the research on the relationship between family level factors and health-related psychosocial concerns, indicate social determinants of health as a relevant area to address, and suggest ways of furthering the literature through more thorough assessment, dyadic analysis of the data, and targeting modifiable family factors in intervention. Thorough assessment and advanced analyses can inform specific targets of intervention, and also be utilized to monitor change and efficacy over the course of intervention. In addition, this dissertation highlights the need to continue engaging in research efforts in pediatric SCD due to systemic and institutionalized racism that have limited research and clinical advancement to date. Including sociopolitical context in future studies in pediatric SCD will provide a more holistic picture of factors that contribute to child outcomes. Furthermore, family research should integrate perspectives from more family members to provide a more accurate depiction of family level factors and processes and utilize methods that allow for nuance and individualized experiences to be recognized and honored.

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