FACTORS THAT INFLUENCE HEALTH-RELATED QUALITY OF LIFE IN ADOLESCENTS WITH SICKLE CELL DISEASE

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ABSTRACT

CHERYL ALLEN BREWER: Factors That Influence Health-Related Quality of Life in Adolescents with Sickle Cell Disease
(Under the direction of Marcia Van Riper, PhD, R.N.)

The chronic course of sickle cell disease (SCD) can be particularly burdensome for adolescents and can have a negative impact on health-related quality of life (HRQOL) during the time of transitioning from childhood to adulthood. Additionally, family functioning has been identified as an important predictor for how well children and adolescents cope with and adapt to SCD. Although there have been major medical advances that have benefited affected individuals, SCD imposes significant demands on affected children and their families. In light of the progress in management and treatment of SCD, and the developmental challenges associated with adolescence, it is an opportune time to assess HRQOL and family functioning in this population. The aims of the research were to: (1) appraise existing research related to family functioning and child outcomes in families of children and adolescents with SCD, (2) identify measures used to assess HRQOL, and (3) describe factors that influence HRQOL in adolescents with SCD. This is a manuscript style dissertation including 3 manuscripts encompassing a single program of research

In manuscript 1, a total of 23 family functioning studies were identified. The findings indicated that families with high levels of family functioning were associated with affected children who had better adaptive outcomes. Low levels of family functioning were associated with children who had poorer adaptive outcomes. Family functioning assessments were

influenced by issues such as number and relationships of informants, study designs, family functioning measures, and coping mechanisms.

A total of seven HRQOL measures were identified among 25 studies in manuscript 2. The PedsQL emerged as the most flexible and useful HRQOL measurement for children and adolescents with SCD.

Finally, in manuscript 3, a secondary data analysis was conducted on 482 adolescents to determine inter-relationships of HRQOL and influencing factors. Findings indicated that factors associated with reduced HRQOL included: (1) female gender compared to male gender, and (2) history of transfusions compared to no history. Factors associated with better HRQOL included: (1) mild disease severity compared to severe, (2) private health insurance compared to Medicaid/Medicare, and (3) other or no health insurance compared to Medicaid/Medicare.

DEDICATION

I dedicate this special accomplishment in my life to those who traveled this journey with me: my parents, Nick and Evelyn Allen; my children, Chantel and Tierre Brewer, my significant other, Senator Floyd Mckissick, Jr., my sisters, Jewel, Ni and Sheilah; Monica Lester, and Dr. Evelyn Wicker, My career-long mentor and inspiration. To all of you and my entire family. I could never have done this without you.

You were my strength when I was weak
You were my voice when I couldn't speak
You were my eyes when I couldn't see
You saw the best there was in me
I'm everything I am
Because you loved me

I also dedicate this to all individuals with sickle cell disease. For the pain and suffering that you endure and the hope that you embrace as we continue to work towards a cure to ease your pain and suffering and improve the quality of your life. I'm with you for the long haul……

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CHAPTER 1

INTRODUCTION

Statement of the Problem

Sickle cell disease (SCD) is an autosomal recessive condition that refers to a group of genetic disorders. Additionally, a growing body of research indicates that SCD is a chronic condition of hemoglobin abnormalities involving inflammatory and coagulation processes that lead to leukocyte and vascular endothelial cell adhesion (Okpala, 2006; Parise, & Telen, 2003; Redding-Lallinger & Knoll, 2006; Rosse, Narla, Petz, & Steinberg, 2000). SCD is characterized by significant morbidities and complications such as bacterial infections, acute chest syndrome, acute multi-organ damage, hemolytic anemia, and jaundice (Pack-Mabien & Hayes, 2009; Mann-Jiles & Morris, 2009; Redding-Lallinger & Knoll, 2006; Rosse, Narla, Petz, & Steinberg, 2000). Frequent, sometimes unpredictable, and often severe vaso-occlusive pain episodes are the number one reason for hospitalizations for children with SCD (Barakat, Lutz, Smith-Whitley, & Ohene-Frempong, 2005; Jacob et al., 2003; Shapiro et al., 1995).

SCD affects millions of people worldwide and 82,079 individuals in the United States (Brousseau, Panepinto, Nimmer, & Hoffmann, 2010). In 2005, there were 31,269 children with SCD in the United States including 28,426 African American children (Amendah, Mvundura, Kavanagh, Sprinz, & Grosse, 2010; National Newborn & Genetics Resource Center, 2005). Total pediatric, SCD-attributable expenditures in 2005, including hospital

admissions, outpatient visits, and prescription drugs were $334,764,427 (Amendah et al., 2010). The chronic treatment course of SCD, along with manifestations of the illness, can be particularly burdensome for children. Even with meticulous, lifelong care management, children with SCD typically require routine visits to health providers and frequent hospitalizations. Complications often lead to changes in physical, emotional, and psychosocial functioning that may have a negative impact on the child's health-related quality of life (HRQOL) and overall well-being (Edwards et al., 2005; Panepinto, O'Mahar, DeBaun, Loberiza, & Scott, 2005).

Health-related quality of life is a multidimensional outcome that provides an assessment of how an illness, its complications, and its treatment affect the patient (Panepinto, 2008). It includes the assessment of children's physical, emotional, and social well-being (Panepinto et al., 2005; Varni, Seid, & Rode, 1999) as reported by the child or caregiver along with major constructs that are necessary to evaluate outcomes in children with chronic diseases (Bonner, 2010). Physical symptoms and illness events contribute to lower HRQOL in children with SCD, and they affect their families as well (McClish et al., 2005; van den Tweel et al., 2008). Children with SCD, along with their parents, tend to report lower HRQOL than their healthy counterparts (Palermo, Schwartz, Drotar, & McGowan, 2002; Panepinto, O'Mahar, DeBaun, Rennie, & Scott, 2004; Panepinto et al., 2005). Many African American families not only experience stressors related to SCD that can significantly impact their quality of life, they also experience stress related to lower socioeconomic status and the stress of being members of an ethnic minority group (Barakat et al., 2006; Boyd-Franklin, Morris, & Bry, 199; Thompson & Gustafson, 1996).

Limitations in HRQOL are even more pronounced in adolescents with SCD as they transition from childhood to adulthood (Barakat, Patterson, Daniel, & Dampier, 2008; Palermo et al., 2002). They must shift from a culture of dependence on others for the care and management of SCD to independence (Pinckney & Stuart, 2004). Among some of the factors that influence HRQOL in adolescents with SCD are sociodemographic factors (Dampier et al., 2010; Palermo et al., 2002), ethnocultural status (Hoff, Palermo, Schluchter, Zebracki, & Drotar, 2006), disease-related factors (Dampier et al., 2010; Fuggle, Shand, Gill, & Davies, 1996; Palermo et al., 2002; Panepinto et al., 2005), and neurobehavioral comorbidities (Brown, Armstrong, & Eckman, 1993; Panepinto et al., 2005). Specifically, delays in growth and sexual maturation may lead to poor self-esteem as well as poor interpersonal functioning in adolescents (Edwards et al., 2005). Symptoms of acute and recurrent pain may also increase as children get older (Petersen, Brulin, & Bergstrom, 2006; Redding-Lallinger & Knoll, 2006). In addition to the developmental challenges faced by adolescents with SCD, these painful events can impact HRQOL and well-being, leading to short-term and long-term consequences such as poor school performance and failure, high absenteeism, and decreased physical and social activities (Brandow, Brousseau, Pajewski, & Panepinto, 2010; Brown et al., 1993; Burlew, Telfair, Colangelo, & Wright, 2000).

Family functioning has also been identified as an important and complex predictor for how well children and adolescents cope with and adapt to SCD (Barakat et al., 2006; Barakat et al., 2007; Thompson et al., 2003). The unpredictable and chronic nature of the SCD illness places significant demands on families and the affected child (Burlew, Evans & Oler, 1989; Kaslow et al., 1996). Barbarin's (1999) model of family functioning proposes that the sociocultural context of the African American family influences how the family functions in

response to having children or adolescents with SCD within it. Adolescents are at a great risk for developing problems related to psychosocial adaptation by virtue of their developmental stage (Barakat, Lash, Lutz, & Nicolaou, 2006, Gil et al., 2001).

The average life expectancy and survival for individuals with SCD are influenced by physical, psychosocial, and environmental factors (Serjeant & Serjeant, 2001). Medical advances including penicillin prophylaxis, pneumococcal vaccines, blood transfusions for stroke prevention, the use of hydroxyurea, and stem cell transplantation have provided great benefits for individuals with SCD (Gaston & Verter, 1990; Hardie, King, Fraser, & Reid, 2009; Redding-Lallinger & Knoll, 2006; Wahl & Quirolo, 2009). The significant progress in prevention and management of SCD illness has improved the average lifespan for individuals with SCD to a median age of 42 years for males and 48 years for females (Bloom, 1995, Platt et al., 1994).

In light of the progress in management of SCD, the extended lifespan, and the developmental challenges associated with adolescence, it is an opportune time to measure HRQOL in adolescents with SCD. Adolescence is also the period within which health behaviors are initiated (Chesney, & Antoni, 2002). Moreover, adolescents and young adults from the ages of 15 and older who transition from pediatric care to adult medical care are at high risk for premature death shortly after the transition to adult medical care (Quinn, Rogers, McCavit, & Buchanan, 2010). The assessment of HRQOL can provide significant insight into the perceived HRQOL stressors related to SCD. Additionally, the construct of HRQOL is useful in describing the health profile and functional status of patients with SCD, in addition to evaluating the effects of condition management and treatments (Palermo et al., 2002; Panepinto et al., 2005).

Despite the acute and chronic stressors associated with SCD in children, there is a paucity of research related to the multidimensional assessment of HRQOL for children with SCD (Palermo et al., 2002) as compared with children who have other chronic conditions (Bonner, 2010). There are even fewer studies on adolescents with SCD's perceptions of HRQOL. Although child and parent proxy reports are extremely useful in fully assessing a child's HRQOL (Eiser & Morse, 2001; Panepinto et al., 2005), as children get older, parents are less accurate in assessing their child's health (Guyatt, Juniper, Griffith, Feeny, & Ferrie, 1997). Self-reported health status has proven to be a valid measure of the physical and emotional dimensions of adolescent well-being (Haas & Fosse, 2008). Moreover, many studies that have assessed HRQOL in children and adolescents with SCD have been limited by measures that have not been validated (Palermo et al., 2002) and samples that do not consistently include demographically matched control groups (Palermo et al., 2002). Finally, there is a direct association between family functioning and adolescent adaptation (Barakat, Smith-Whitley, & Ohene-Frempong, 2002; Burlew et al., 2000). However, understanding and examination of family functioning using culturally appropriate designs and measures over time are lacking (Barakat et al., 2006; Brown & Lambert, 1999).

The World Health Organization (WHO) and United Nations Educational, Scientific and Cultural Organization (UNESCO) have deemed SCD a major public health problem (United Nations Educational, Scientific and Cultural Organization, 2007) due to the significant burdens placed on affected families and the community (WHO, 2006). The WHO adopted a resolution on SCD that called upon affected countries and the secretariat of the WHO to strengthen their responses to hemoglobin disorders such as SCD (WHO, 2006). Among several other commitments, the WHO has committed to promoting and supporting

research to improve quality of life for individuals affected by hemoglobinopathies, including SCD (WHO, 2006). This dissertation research, by identifying factors that influence HRQOL in adolescents with SCD, contributes to the goal set forth by the WHO of establishing research to improve quality of life for individuals affected by SCD.

This dissertation research also supports specific goals established by the Healthy People 2020 initiative (United States Department of Health and Human Services, 2010) as far as (a) promoting and monitoring HRQOL, (b) improving care and services for individuals and families with hemoglobinopathies, and (c) addressing health disparities among minorities.

Purpose

The overall purpose of this dissertation was to identify factors that influence HRQOL in adolescents with SCD. Rather than using the traditional dissertation format, a manuscript style format was used. That is, this dissertation consists of a collection of papers that have a cohesive, unitary character. The papers report a single program of research concerning adolescents with SCD and their families, with a major focus on HRQOL. The aims of this dissertation research were to (1) synthesize and appraise existing research related to family functioning and child and adolescent outcomes in families of children and adolescents with SCD, (2) identify measures used to assess HRQOL in children and adolescents with SCD, and (3) describe factors that influence HRQOL in adolescents with SCD.

Dissertation Format

The dissertation consists of five chapters. This chapter included a global introduction and a literature review that linked the three papers together. It also included a statement of the overall problem and will now address the significance and purpose of the global paper

and each individual paper. Chapters 2, 3, and 4 are the three papers that comprise the dissertation. Chapter 5 is the final chapter and includes a synthesis and discussion of the three manuscripts with findings and implications for future research and practice.

The purpose of the integrative review in Chapter 2, "Family Functioning and Child Outcomes in Families of Children and Adolescents With Sickle Cell Disease: An Integrative Literature Review," was to systematically examine existing research in which family functioning and child and adolescent outcomes have been assessed in families of children and adolescents with SCD. The research questions that guided this review were (1) how has family functioning been assessed among families of children and adolescents with SCD in the research literature from 1990 through 2011? (2) what family functioning variables were measured? (3) what are the key findings, and (4) what are the implications for future research? This review extended the literature by synthesizing and appraising research related to the relationship of family functioning and child outcomes in families of children and adolescents with SCD.

Additionally, it contributes to the understanding of family members' significant influences on illness adjustment and adaptation for children with SCD. Thus, recommendations have been offered on specific family-focused interventions that may be developed to improve the care and management of SCD and facilitate optimal adaptation for affected individuals and their families. This paper will be submitted to *The Journal of Family Nursing.*

Chapter 3 is titled "Health-Related Quality of Life Measures Used in Children and Adolescents with Sickle Cell Disease: An Integrative Literature Review." The purposes of this review were to (a) identify measures used in studies to assess HRQOL in children and

adolescents with SCD, (b) describe the general characteristics of each measure, and (c) provide recommendations for future measure development. The research questions that were used to guide this integrative review were: (1) What measures are used to assess HRQOL in children and adolescents with SCD? (2) What are the general characteristics and psychometric properties of the measures? (3) What samples has the tool been used with? (4) What are recommendations for future measure development? Findings from this review expanded the literature by providing an updated, comprehensive and systematic appraisal of the state of the science related to HRQOL measures for children and adolescents with SCD. This will guide health providers in their selection of instruments for fully assessing HRQOL in children and adolescents with SCD. This paper will be submitted to *The Journal for Specialists in Pediatric Nursing.*

Chapter 4 contains the third paper, "Factors That Influence Health-Related Quality of Life in Adolescents with Sickle Cell Disease." The purposes of this study were to describe factors that influence HRQOL in adolescents with SCD and determine interrelationships between adolescent HRQOL and (1) patient-related variables, (2) caregiver-related variables, and (3) combined variables from patients and caregivers. This study was a secondary data analysis of 482 adolescents with SCD. It will be submitted to *Health and Quality of Life Outcomes.*

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CHAPTER 2

FAMILY FUNCTIONING AND CHILD OUTCOMES IN FAMILIES OF CHILDREN AND ADOLESCENTS WITH SICKLE CELL DISEASE: AN INTEGRATIVE LITERATURE REVIEW

Problem Identification

Sickle cell disease (SCD) is a group of genetic disorders involving defective hemoglobin. It is characterized by significant morbidities and complications such as chronic anemia, infections, tissue and organ damage, stroke (Mann-Jiles et al., 209; Pack-Mabien et al, 2009). Vaso-occlusive pain crisis is the hallmark of SCD. The pain is often unpredictable and can vary among individuals as far as the patterns and intensity (Day & Chismark, 2006; Platt et al, 2002).

Family functioning has been identified as an important and complex predictor for how well children and adolescents cope with and adapt to sickle cell disease (SCD; Barakat et al., 2007; Pinckney & Stuart, 2004; Thompson et al., 2003). Moreover, there is evidence in the literature to support relationships between family functioning and child outcomes in children with SCD (Barakat et al., 2007; Burlew, Telfair, Colangelo, & Wright, 2000; Hurtig, 1994; Kell, Kliewer, Erickson, & Ohene-Frempong, 1998; Pinckney & Stuart, 2004; Royal, Headings, Harrell, Ampy, & Hall, 2000). Telfair (1994) reported that a distinct body of literature examines the impact of the presence of a child with a chronic condition on family dynamics and the importance of the family to the child's adjustment. Although study results related to family functioning in families of children with SCD have varied, a consistent body

of evidence supports a strong relationship between family functioning and adaptation to the disease for children with SCD and their caregivers (Brown, Eckman, Baldwin, Buchanan, & Dingle, 1995; Burlew et al., 2000; Kell et al., 1998; Kaslow et al., 2000; Sharpe, Brown, Thompson, & Eckman, 1994; Thompson, Gil, Burbach, Keith, & Kinney, 1993).

Family functioning is a multifaceted concept that encompasses several social and structural constructs related to the global family environment (Lewandowski, Palermo, Stinson, Handley, & Chambers, 2010; McClellan & Cohen, 2007). Variables that are useful in assessing family functioning and interactions may be negative or positive and include constructs such as cohesion, conflict, communication, adaptability, social competence, family relationships, and parent–child relationships (Barakat, Patterson, Daniel & Dampier, 2002; Devine, Brown, Lambert, Donesgan, & Eckman, 1998; Kell et al., 1998; Lewandowski et al., 2010; Pritchett et al., 2011). A recent systematic review of the literature was conducted by Pritchett et al. (2011) to identify all existing questionnaire measures of family functioning for use in primary care and research. More than 100 self-report measures of family functioning were identified, categorized, and deemed suitable for continued use. The large number of measures and wide variety of constructs speaks to the complexity of family functioning assessment in general.

Challenges related to SCD include lifelong management of the illness, consistent utilization of health-care resources and significant burdens placed on the general functioning and well-being of affected children and their families (Boekaerts & Roder, 1999; Kinney & Ware, 1996; Palermo, Schwartz, Drotar, & McGowan, 2002; Pinckney & Stuart, 2004). The management of SCD complications and utilization of resources and health-care services often require active and impromptu involvement from the caregivers of affected children

(Kaslow et al., 2000). Additionally, caregivers must deal with their own emotional and financial issues related to their child's SCD and complications experienced by the child (Treadwell, Gold, Weissman, Barnes, & Vichinsky, 1995). Because SCD is a hereditary condition, the biological parents and/or siblings of children with SCD may carry the SCD trait or also have the condition, thereby increasing the family's overall burden.

Findings from numerous studies have revealed a significant relationship between family cohesion and child outcomes (Kell et al., 1998; Pinckney & Stuart, 2004; Royal et al., 2000). The child outcomes assessed in these studies have varied. However, in the majority, greater psychosocial challenges such as adjustment difficulties, learning disabilities, and behavioral problems were associated with less family cohesion for children and adolescents with SCD (Brown et al., 1993; Brown & Lambert, 1999; Burlew et al., 2000; Hurtig & Park, 1989; Kell et al., 1998; Pinckney & Stuart, 2004; Royal et al., 2000).

On the other hand, poor perceived family relationships involving family values and support were reported to lead to greater independence in adolescents with SCD (Newland, 2008). Findings from this study suggested that poor family relationships forced adolescents with SCD to become more independent in terms of taking charge of their condition. Additionally, studies have concluded that family functioning was not correlated with behavioral, adaptive, or cognitive functioning in children with SCD (Barbarin et al., 2004; Brown et al., 1995; Brown et al., 2000; Devine et al., 1998; Noll et al., 1994; Schuman et al., 1993).

Risk and resistance models have been proposed to identify and integrate psychosocial variables related to family functioning and adjustment in childhood chronic illnesses (Kell et al., 1998). Risk and resistance models provide a useful guide for predicting psychosocial

adaptation in children and adolescents with SCD. Although these models are useful in characterizing patterns of family functioning and advancing the understanding of adaptation in children with chronic illnesses, they have unique limitations relevant to the population under study. For example, the Transactional Stress and Coping Model (TSC) has been used in several studies involving children and adolescents with SCD and their mother. In this model, psychosocial factors contribute more to adjustment and functioning rather than biomedical factors (Thompson & Gustafson, 1996). Concerns related to the TSC center around the premise that family functioning is proposed to influence maternal adjustment which will subsequently influence child adjustment (Thompson & Gustafson, 1996). However, studies support that child adjustment is directly influenced by family functioning in families with children who are affected by SCD (Burlew et al, 2000; Thompson et al, 2003). Social support is also a significant component for consideration in African American families with children who are affected with SCD. Social support is not included as one of the psychosocial components in the TSC model. This poses a major disadvantage since social support has been linked to positive adjustment in children with SCD. The TSC model also lacks components related to child adaptive living skills, competence, and general functioning. The lack of such components limits the use of the TSC model in families with SCD unless the model is expanded or modified accordingly (Gold, Treadwell et al., 2008).

Purpose

Despite the growing body of research exploring the relationship between family functioning and outcomes for children and adolescents with SCD, there are no known integrative reviews of these studies. Therefore, the purpose of this integrative review was to systematically review the existing research in which family functioning and child and

adolescent outcomes are assessed in families of children and adolescents with SCD.

The research questions that guided this review were (1) how has family functioning been assessed among families of children and adolescents with SCD in the research literature from 1990–2011?, (2) what family functioning variables were measured?, (3) what are the key findings related to adjustment? And (4) what are the implications for future research ? This integrative review will contribute to the understanding of family members' significant influences on illness adjustment and adaptation for children with SCD. Thus, recommendations will be offered on specific family-focused interventions that may be developed to improve family functioning and facilitate optimal adaptation to the disease for affected individuals and their families.

Description of the Framework

The guiding framework employed for this research was the updated integrative review methodology described by Whittemore and Knafl (2005), and they contend that an integrative literature review is a review method that provides a summary of combined empirical or theoretical literature from the past in order to explain a phenomenon. According to Whittemore & Knafl,

> "the integrative review method is an approach that allows for the inclusion of diverse methodologies (i.e. experimental and non-experimental research) and has the potential to play a greater role in evidence-based practice for nursing" (Whittemore & Knafl, 2005, p. 546).

The stages of this review method are (a) problem identification, (b) literature search, (c) data evaluation, (d) data analysis, and (e) presentation.

Literature Search

This review included research conducted from 1990 through 2011. This period was significant as it was the time frame within which universal screening for hemoglobinopathies, including SCD, was included in all newborn screening programs across the United States. There was also an increase in the appropriation of funds for hemoglobinopathies and the establishment of SCD treatment centers nationally. These advances, in addition to continuously changing family patterns and relationships, racially and ethnically diverse populations, and the inclusion of the family in family medicine, shifted the paradigm for family research and led to new challenges for contemporary family assessment (Carlson, 2001).

Numerous search strategies were employed to retrieve the most relevant literature. A comprehensive and exhaustive search was conducted using the following computerized data bases: the Cochrane Library, the Cumulative Index of Nursing and Allied Health Literature, EMBASE, Health Source: Nursing/Academic Edition, PubMed, PSYCHINFO, Race Relations Abstracts, and the Web of Science Citation Manager.

The key search terms and major subject headings were *sickle cell disease; sickle cell anemia; anemia, sickle cell; family functioning; parental functioning; family adaptation; family adjustment; family coping; family health; adaptation psychological; adolescent; child;* and *youth.* The terms were searched until no new studies could be found. Furthermore, a medical librarian was consulted to maximize the search efforts and make sure the search terms and strategies were appropriate.

The Sample

Searches were restricted to the period from 1990 to 2011. Additional inclusion criteria were that studies (a) were published in English, (b) included at least one family-level variable designed to assess family functioning, (c) included at least one child-outcome variable, (d) were about families of children with SCD under the age of 18 years, (e) were in peer-reviewed journals.

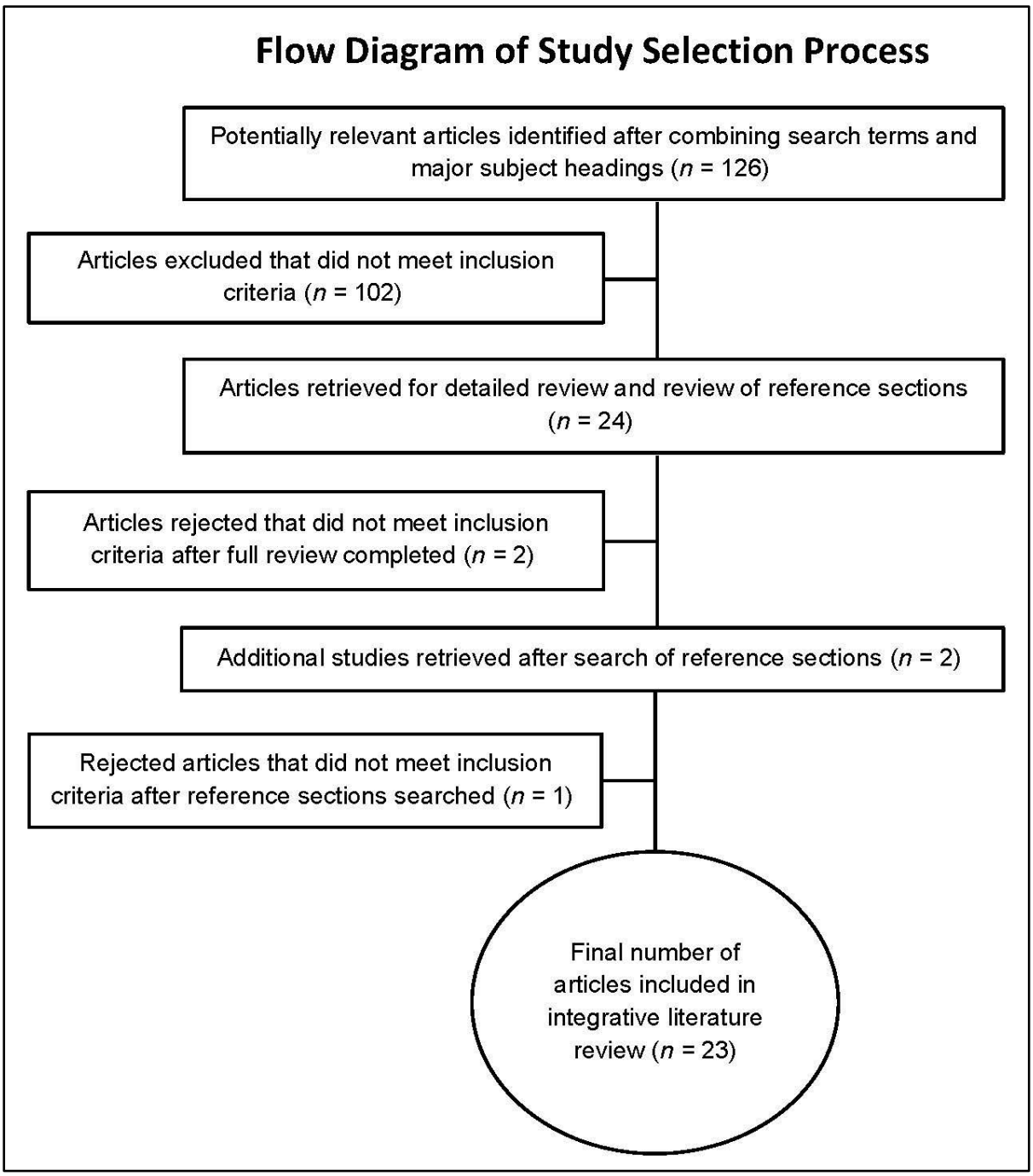

Figure 2.1. Flow diagram of study selection process.

After using various combinations of relevant search terms and major subject headings, a total of 126 articles were initially retrieved (Figure 2.1). Of these articles, 24 met the inclusion criteria and 102 were excluded. The articles that were excluded included articles that were (a) focused on adults with SCD, (b) reviews, (c) commentaries, (d) articles related to family functioning in children with chronic diseases other than SCD, and (e) articles in which family functioning was assessed at the individual or parental level rather than the family level. Of the remaining 24 articles, a detailed review was conducted on each which included a manual hand search of the reference section of each article. Two articles were rejected after the full review because they did not completely meet inclusion criteria. Two additional articles were identified during the detailed hand search of the reference sections of each article. Only 1 of these articles was eliminated based on inclusion criteria. The final sample for this integrative literature review was 23 articles.

Data Evaluation

Quality Assessment

Quality evaluation of primary sources can be complex in integrative reviews depending on the sampling frame (Whittemore & Knafl, 2005). In as much as all of the studies in this review are from peer-reviewed journals and all have also met the inclusion and exclusion criteria, some form of quality assessment has been satisfied for each study. Primary data were extracted from qualifying studies using a data abstraction form and included the following: author, year, age range of children with SCD, sample respondents and size, family functioning measure(s) and scales, and key findings. Results of the extracted data are depicted in Table 2.1.

Table 2.1

Family Functioning Study Information and Key Findings

Author(s)	**Year**	**Age Range of Children**	**Sample Size**	**Family Functioning Measure(s) or Method/ (Scales Used)**	**Key Findings**
Barakat, Lutz, Nicolaou, et al.	2005	6 months–11 years	31 children, 31 caregivers	FAD (general functioning scale)	General family functioning was not associated with child HRQOL. Caregivers with high internal locus of control reported better general family functioning.
Barakat, Patterson, Weinberger, et al.	2007	12–19 years	41 adolescents, 41caregivers, 15 healthy siblings	FES (full scale)	When caregivers experienced greater distress and caregivers and teens reported lower family functioning, poorer adolescent health outcomes were reported
Barakat, Smith-Whitley, & Ohene-Frempong	2002	4 months–18 years	24 children, 73 caregivers	FAD (full scale)	Better family problem solving was associated with better child treatment adherence.
Barbarin	1999	5–18 years	77 children, 28 siblings, 74 control children	FRS* (full scale), Semi-structured Interviews	When parents received high levels of family support from their families, had strong emotional ties to friends and kin, had low psychological distress, and when illness led to fewer life changes for the ill children, there were fewer internal and external behaviors.

Author(s)	Year	Age Range of Children	Sample Size	Family Functioning Measure(s) or Method/ (Scales Used)	Key Findings
Barbarin, Whitten, & Bonds	1994	4–17 years	327 children, 327 parents	Structured interviews (family issues related to financial needs & resources, family impact of illness, and general family functioning)	Family functioning was not significantly associated with psychosocial problems for urban and poor children with SCD
Brown, & Lambert	1999	7–17 years	38 children, 38 caregivers	FACES-II (full scale)	When children and caregivers rated family cohesion low, depression was more frequent in children. When family cohesion was high or low by either group alone, depression did not occur in children.
Brown, Eckman, Baldwin, et al.	1995	2–16 years	61 children	FACES-III (full scale)	Adaptive family functioning was unrelated to any child behavioral competencies. Family cohesion was only moderately and insignificantly related to child adaptive competence.
Brown, Kaslow, Doepke, et al.	1993	6–17 years	61 youth, 61 families with 15 non-diseased sibling controls	FACES III (full scale)	Families with greater adaptability and role flexibility have children with internalizing behavioral symptoms. Families with lower levels of adaptability and role flexibility have children who employ disengagement coping. Less cohesive families have SCD youth with more depressive symptoms.

Author(s)	Year	Age Range of Children	Sample Size	Family Functioning Measure(s) or Method/ (Scales Used)	Key Findings
Brown, Lambert, Devine, et al.	2000	5–16 years	55 children, 55 primary caregivers	FACES-II (full scale), FSS (helpfulness index), FRS (full scale), FILE (full scale)	Family cohesion accounted for less than 4% of the variance in child adjustment.
Burlew, Telfair, Colangelo, et al.	2000	14–19 years	90 adolescents, 90 caregivers	FES (full scale), FRI (abbreviated version- shortened scales of FES conflict, cohesion & expressiveness)	Better family relations and greater self-esteem were associated with fewer child depressive symptoms.
Casey, Brown, & Bakeman	2000	5–18 years	118 children, 118 caregivers	FACES II (full scale)	Family cohesion and adaptability were not significantly associated with child disability stress.
Devine, Brown Lambert, et al.	1998	5-17 years	74 children and caregivers	FACES II (full scale)	Family environment did not predict behavioral or cognitive functioning.

Author(s)	Year	Age Range of Children	Sample Size	Family Functioning Measure(s) or Method/ (Scales Used)	Key Findings
Ievers, Brown, Lambert, et al.	1998	5–17 years	67 caregivers	FACES-II (full scale), FRS (helpfulness index), FSS (full scale)	Higher levels of cohesion and adaptive family functioning buffered the potential detrimental effects of caring for children perceived as difficult to manage.
Kell, Kliewer, Erikson, et al.	1998	*M* = 14.4 years	80 adolescents, 80 caregivers	SFI (health/competence scale)	Higher family competence was associated with fewer internalizing and externalizing behaviors, especially for younger adolescents and for girls.
Kliewer, & Lewis	1995	7–16 years	39 children, 39 caregivers	FES (cohesion scale)	Family cohesion was positively related to active child coping.
Lutz, Barakat, Smith-Whitley, et al.	2004	Birth – 18years	23 children, 73 caregivers	FAD (general family functioning scale)	Children's active coping strategies were associated with better family functioning.
Midence, McManus, Fuggle, & Davies	1996	6-16 years	39 children, 24 control children	FES (full scale)	Children with SCD demonstrated more behavioral problems than controls, even though children with SCD were from families with more cohesion and less conflict.

Author(s)	Year	Age Range of Children	Sample Size	Family Functioning Measure(s) or Method/ (Scales Used)	Key Findings
Mitchell, Lemanek, Palermo, Crosby, Nichols, & Powers	2007	7-13 years	48 children and 53 caregivers	FAD (full scale) Focus group session	Family functioning was not related to health care utilization factors.
Sharpe, Brown, Thompson, et al.	1994	3–16 years	55 children, 55 mothers	FACES-III (full scale)	Healthy family functioning is predictive of child sickle cell disease adjustment.
Thompson, Armstrong, Kronenberger, et al.	1999A	5–15 years	289 children, 289 mothers	FES (full scale)	Family functioning characterized as conflicted was related to mother-reported behavioral problems in children with SCD.
Thompson, Armstrong, Link, et al.	2003	7–17 years, 5–15 at start	222 children	FES (full scale)	An increase in child behavioral problems was associated with increased family conflict. Poor child adjustment was related to higher levels of family functioning.

Author(s)	Year	Age Range of Children	Sample Size	Family Functioning Measure(s) or Method/ (Scales Used)	Key Findings
Thompson, Gustafson, Gil, Kinney, & Spock	1999B	7-16 years at Time 1	50 children and their mothers	FES (full scale)	High levels of family control contributed to significant increments in child psychological adjustment. Consistency in child adjustment was 31-32% for child self-report & 66% for mother-reported child behavioral problems.
Treadwell, Alkon, Quirolo, et al.	2010	5–8 years	38 children, 38 caregivers	FILE (full scale)	Children with SCD and classic ANS in cognitive and emotion domains were most vulnerable to the effects of stress, with more functional impairment and injuries when family stress was high, controlling for age, sex, and parent education.

Note. ANS = autonomic nervous system, FACES = The Family Adaptability and Cohesion Scales, FAD = Family Assessment Device, FES = Family Environment Scale, FILE = Family Inventory of Life Events & Changes, FRI = Family Relations Index, FRS = Family Resource Scale, FSS = Family Support Scale, HRQOL = Health-related quality of life, *M* = median, SCD = sickle cell disease, SFI = Self-Report Family Inventory.

Data Analysis

The results will be presented and categorized based on the research questions.

Question 1

How is family functioning assessed among families of children and adolescents with SCD in the research literature from 1990 – 2011?

The sample sizes varied across many of the studies and included 23 – 327 children with SCD and 31 – 327 caregivers. Siblings were also included in some of the studies (*n=3*) as well as control children (*n=1*). The ages for the children with SCD ranged from birth to 18 years and the majority of the study designs were cross-sectional studies (*n=19*), with 3 longitudinal studies.

Several studies in this review (39%) included family conceptual or theoretical frameworks that were useful in guiding the research (*n = 9*). The guiding frameworks that were included were the: (a) Risk and Resistance Adaptation Model (*n=2*), (b) Barbarin's Model of Illness, Family Functioning and Development (*n=1*), (c) Disability-Stress-Coping Model (*n=3*), (d) Transactional Stress and Coping Model with Modified Variables (*n=1*), (e) Transactional Stress & Coping Model Combined with Disability Stress-Coping Model (*n=1*), and (f) Integration of the Transactional Stress and Coping Model of Adaptation with Elskys Process of Model of Parenting (*n=1*).

Question 2

What family functioning variables were measured?

Of the 23 studies identified in this review, 10 different quantitative measures were used to assess family functioning. One study employed structured interviews and two studies

included approaches for mixed-methods which included a quantitative measure and qualitative measure (Table 2.2).

Table 2.2

Family Functioning Measures

Family Functioning Measurement	**Year**	**Author(s)**	**Scales**	**Number of Items**	**Reliability Per Scale Author(s)**	**Validity Per Scale Author(s)**	**Respondent**
Family Adaptability and Cohesion Scale II (FACES-II)	1982	Olson, Portner, & Bell	flexibility/adaptability and cohesion	30	cronbach's alpha = .70 for adaptability scale, .78 for cohesion scale	psychometric properties have ranged from "adequate" to "excellent"	self-report
Family Adaptability and Cohesion Scale III (FACES-III)	1985	Olson, Portner, & Lavee	flexibility/adaptability and cohesion	40	has demonstrated high reliability	has demonstrated "high" validity	self-report
Family Assessment Device (FAD)	1983	Epstein, Baldwin, & Bishop	problem-solving, communication, roles, affective responsiveness, affective involvement, behavioral control, general functioning	53	cronbach's Alpha for all scales except "roles", ranged from .72 to .92	concurrent, discriminant, and predictive validity	self-report

	Family Environment Scale (FES)	1986	Moos & Moos	cohesion, expressiveness, conflict, independence, achievement, orientation, intellectual-cultural orientation, active-recreational orientation, moral-religious emphasis, organization, control	90	Cronbach's alpha = .61 - .78	construct, face, and content validity	self-report
	Family Inventory of Life Events and Changes (FILE)	1996	McCubbin, Thompson, & McCubbin	Intra-family strains, marital strains, pregnancy and childbearing strains, financial and business strains, work–family transitions and strains, illness and family care strains, losses, transitions in and out, legal	71	cronbach's alpha = .72–.82; test–retest = .66–.84	construct validity, convergent validity	self-report
	Family Relations Scale (FRS*)	1996	Barbarin	support, emotional expressiveness, conflict	40	cronbach's alpha = 0.76 - 0.86	construct, discriminant, convergent	self-report

Family Resources Scale (FRS)	1987	Dunst, & Leet	food and shelter, financial well-being, time for family, extrafamilial support, child care, specialized child resources, luxuries	30	cronbach's alpha = .92 - .97; test–retest over an interval of 2–3 months = .52	the FRS has been demonstrated to be a valid instrument for economically disadvantaged groups.	self-report
Family Support Scale (FSS)	1984	Dunst, Jenkins, & Trivette	helpfulness of informal kinship, spouse/partner support, social organizations, formal kinship, professional services	18	alpha = .79; test–retest = .91 for a 1-month retest and .50 for administrations 1–2 years apart		self-report
Self-Report Family Inventory (SFI)	1990	Beavers, Hampson & Hulgus	Family health/competence, conflict, cohesion, directive leadership, & expressiveness	36	cronbach's alpha for scale = .84 - .88, test–retest = .85	No data on validity with minority families. Minorities were involved in development process.	self-report

Note. FACES = Family Adaptability and Cohesion Scale, FES = Family Environment Scale, FILE = Family Inventory of Life Events and Changes, FRI = Family Relations Index, FRS = Family Resources Scale, FSS = Family Support Scale, Family Assessment Device (FAD), SFI = Self-Report Family Inventory.

General measures of family functioning were used in many studies to assess global family functioning and specific aspects of family functioning relevant to having a child with SCD in the family. Family functioning was assessed by the Family Environment Scale (FES; Moos & Moos, 1981) in the majority of the studies that were included in this review (*n = 6*). The FES was used to assess the social climate of the family including interpersonal relationships, and personal growth. Variables such as cohesion, expressiveness and conflict were used for FES assessments. The FES was also used to assess the impact of the family environment in relation to family coping processes. The McMaster Family Assessment Device (FAD; Epstein, Baldwin, & Bishop, 1983) was used in four studies to assess general family functioning as well as problem solving, and coping strategies. Studies using The Family Adaptability and Cohesion Scales (FACES II, Olson et al., 1983 and FACES III, Olson et al., 1985) to assess family functioning had variable results related to child behavioral problems, social competence, and coping (FACES II, *n=5*; FACES III, *n=3*). Variables assessed by the FACES scales included flexibility, adaptability, and cohesion. The Beavers Self-Report Family Inventory (SFI, Beavers & Hampson, 1990) was used to assess health and competence in one study (Kell et al., 1998), while the Family Inventory of Life Events and Changes (FILE, McCubbin, Thompson & McCubbin, 1996) assessed past and recent family stressors (*n=1*).

Four measures were used to examine family support systems. The Family Relations Scale (FRS*, Bloom, 1985) was used to assess support, emotional expressiveness, and family conflict in one study. The Family Resource Scale (FRS, Dunst & Leet, 1987) was helpful in evaluating financial well-being and extra-familial support (*n=2*). The Family Support Scale (FSS; Dunst et al., 1984) was used in two studies to determine the helpfulness of formal and

informal kinship. An abbreviated version of the Family Relationships Index (FRI, Holahan & Moos, 1981) was used in one study to measure family relationships and supportiveness.

Qualitative assessments of family functioning were used in two studies (Barbarin, 1999; Barbarin et al., 1994). Structured interviews were used to assess problems of family adjustment related to parent, child, and sibling fears in the study conducted by Barbarin et al. (1994). A mixed methods approach using a quantitative measure (FRS*) and semi-structured interviews that assessed the role of the child in the family, family strategies for managing medical care, the impact of the illness, illness-related events, coping styles, social support and relationships was used in the study conducted by Barbarin (1999).

Question 3

What are the key findings?

The key findings are organized according to the following categories: (a) behavioral problems, (b) social competence, (c) coping processes, (d) moderator and mediator effects of family functioning, and (e) sociodemographic factors.

Behavioral problems. Negative associations existed between cohesive family environments and child behavioral problems as well as family competence and child behavioral problems (Brown et al., 1993; Brown & Lambert, 1999; Burlew et al., 2000; Kell et al., 1998). Additionally, families with high levels of family conflict reported having children with more behavioral problems (Thompson et al., 1999A; Thompson et al., 2003). Family assessments indicated that psychological disorders classified as internalizing behavioral conditions such as anxiety and depression were negatively associated with adaptation and adjustment in children and adolescents with SCD (Brown et al., 1993; Brown & Lambert, 1999; Burlew et al, 2000; Kell et al., 1998; Thompson et al., 1999B; Thompson

et al., 2003). However, behavioral problems were reported in a study involving a group of British children with SCD, compared to controls, even though children with SCD demonstrated more cohesion and less conflict than controls (Midence et al., 1996). Internalizing and externalizing behavioral problems were less likely to occur when families were less distressed and had strong social support systems and when child illnesses were associated with fewer life changes and better family relations for the affected children (Barbarin, 1999; Burlew et al., 2000).

Conversely, adaptive family functioning was unrelated to child behavioral competencies in studies conducted by Barbarin et al., (1994) and Brown et al. (1995). Additionally, family cohesion was not significantly related to child adjustment or health-related quality of life (Barakat et al., 2005; Brown et al., 2000). Finally, the family environment, as assessed by FACES II, did not predict behavioral or cognitive functioning (Devine et al., 1998). In a study conducted by Treadwell et al. (2010), family stress was associated with child functional impairment controlling for autonomic nervous system reactivity.

Social competence. Children's perception of high levels of maternal support, parental religiosity, and low levels of family conflict were associated with better social competence in children with SCD (Barbarin, 1999). In a study conducted by Brown et al. (1993), children with SCD reported lower self-esteem, greater academic challenges and greater social challenges related to acceptance by their peers, when compared to healthy siblings.

Coping processes. The impact of the family environment and specific aspects of family functioning also influenced child coping processes. Using the FACES III

measurement, families with lower adaptability and flexibility were reported as having more disengagement coping in children with SCD (Brown et al, 1993; Sharpe et al., 1994). Positive relationships existed between levels of family functioning and child active coping strategies in three of the study findings (Kell et al., 1998; Kliewer & Lewis, 1995; Lutz et al., 2004). Although greater family cohesion was associated with child active coping, avoidance coping was not significantly related to family cohesion (Kliewer & Lewis, 1995).

Moderator and mediator effects of family functioning. Although the results varied, family functioning was also indirectly associated with outcomes in some of the studies in this review. Parental emotional well-being moderated the adverse effects of children with SCD (Barbarin et al., 1994). Higher levels of family cohesion and adaptation also moderated the potential effects of caring for children who were perceived by caregivers as difficult to manage (Ievers et al., 1998). However, neither disengaged nor engaged coping served as a moderator between disability and stress on child maladjustment (Casey et al., 2000).

Sociodemographic factors. Many sociodemographic factors have been described as risk factors in risk-and-resistance models. These factors are useful in explicating the variations in adaptation among children with SCD. Although variable, some of the sociodemographic factors from study findings in this review were related to gender, age, and socio-economic status. Study findings indicated better family functioning and adjustment outcomes in females with SCD as compared to males (Barbarin et al, 1994 Brown et al., 1993; Brown et al., 1995; Brown & Lambert, 1999; Casey et al., 2000; Lutz et al., 2004; Thompson et al., 2003). Higher family competence levels were associated with fewer internalizing behaviors and emotional problems for girls and younger adolescents (Kell et al, 1998).

Older children and adolescents were reported to be at increased risk for family functioning problems and disability stress (Brown et al., 1993; Lutz et al., 2004). Additionally, adolescents demonstrated more academic failures than younger children (Barbarin et al., 1994). However, Thompson et al. (2003) reported that there was likely not an age effect related to behavioral problems developed over time in the population under study.

Families of higher socioeconomic status (SES) reported better family functioning in a study conducted by Barakat et al. (2005). However, SES did not prove to be a significant predictor of family functioning in a study conducted by Kell et al. (1998). This is consistent with a previous study (Hurtig, 1994). However, psychosocial stress unrelated to SCD has been related to impaired child and family functioning (Barbarin, 1999; Thompson et al., 1993).

Finally, some of the family functioning measures lacked sound psychometric properties. The reliability of the instruments ranged from adequate to high. Test-retest outcomes and validity assessments were not adequate for all family functioning measures. Some measurements have not been tested in demographically matched populations while the majority lacks culturally sensitive constructs relevant for African Americans.

Discussion

Overall, families characterized as having high levels of family functioning (i.e. cohesion) were associated with greater adaptation and adjustment in children and adolescents with SCD. Conversely families with lower levels of family functioning (i.e. conflict) experienced more problematic adaptive behaviors.

Internalizing behaviors of anxiety and depression were identified in many study results and is one of the most common problems related to adaptation and adjustment in children and adolescents with SCD (Thompson et al., 2003). Internalizing behavior patterns occurred more frequently in adolescents as compared to younger children with SCD (Brown et al., 1993; Midence et al, 1993) and in male adolescents as compared to female adolescents with SCD (Barbarin et al., 1994; Brown et al., 1993; Brown et al., 1995; Casey et al., 2000; Lutz et al., 2004). However, adaptive family functioning was unrelated to behavioral competencies, HRQOL, or child adjustment in some of the studies (Barbarin et al., 1994; Brown et al., 1995).The studies that resulted in increased internalizing behaviors for the adolescents could be related to consistencies in study designs. The studies that reflected these findings included informants who served as controls and those within the same age range. The studies were also of the same cross-sectional design.

On the other hand, the inconsistent findings among study results could be related to differences in study designs and techniques. Although the majority of these studies were conducted within close time proximity of each other and had the same cross-sectional designs, the family functioning assessment measures varied as did the sample sizes, informants, and age groups of the affected children. Some of the studies also included controls.

Aspects of family functioning and parental coping styles also influenced child coping processes. Across various studies in this review, these coping outcomes are likely related to how coping is conceptualized, coping strategies used, and specific family functioning assessment measures. Interestingly, only 1 of the studies that was related to coping results included a guiding framework (Lutz et al., 2004) although various measures were used.

Kliewer and Lewis (1995) contended that parents play a key role in coaching children and helping them determine how to appraise stressful events. Parental relationships, coaching styles and assessment strategies have a significant impact on family functioning and child coping outcomes.

Family functioning has served as moderators or mediators of stress, behavioral and psychosocial competencies, and health outcomes on the adaptation of affected children and their caregivers, though there are inconsistencies across the studies. The inconsistencies in these findings could be related to a number of issues. Among them are the lack of sociocultural considerations in working and interacting with African American families, culturally sensitive family functioning measures developed using appropriately matched comparison groups, assessments from multiple informants, and fully understanding the concept of *family* as it relates to African Americans (Kliewer & Lewis, 1995; Lutz et al., 2004; Royal et al., 2000; Sharpe et al., 1994; Thompson et al., 1999).

Recommendations

Question 4: What are the implications for future research?

Because the primary aim of family functioning interventions is to improve the adjustment and general functioning of the child, intervention measures should be developed around child and family factors. Past interventions have targeted the child's self-esteem (Burlew et al., 2000; Thompson, Gustafson, Gil, Godfrey, &Murphy, 1998; Thompson, Gustafson et al., 1999), stress assessment (Gil et al., 2003; Thompson et al., 1998), and mood (Gil et al., 2003). Kaslow et al. (2000) developed a pyschoeducational intervention that proved successful in empowering the child and family members and influencing overall

family functioning by increasing disease knowledge. Family system restructuring may be necessary to decrease parent–child conflict (Robin & Foster, 1989).

Interventions that reduce family conflict and increase general support and cohesion are warranted because family conflict is a risk factor for behavior problems in children with SCD (Burlew et al., 2000; Thompson, Armstrong et al., 1999; Thompson et al., 2003). Families could benefit from interventions involving family groups with a goal of improving family competence (i.e., social assertiveness, problem solving, and communication) and adaptation (Drotar, 1997; Kell et al., 1998). Moreover, theory-driven strategies to improve self-care management could be useful in addressing health-related stigma and including family members as self-care management resources to help mediate the relationship between vulnerability factors and health outcomes (Jenerette & Brewer, 2010).

Future research methods for gathering data should include more qualitative and mixed methods strategies. Additionally, measures other than self-report should be considered (i.e. observational and behavioral). Data gathering methods should be carefully considered. How the information is asked may influence the answers (i.e. terms perceived as negative such as depression and distress compared to terms perceived as positive such as optimistic and hopeful). SCD should be explored through multiple informants when examining family functioning issues in order to understand and discern family issues separate from condition specific and other related issues. These informants may include family members and compositions other than biological parents. Other family members should be incorporated into intervention strategies to increase the acceptance of the intervention being studied. The role of the caregivers must be examined within the context of the family structure and involved family members. Family management styles should be assessed in caregivers of

children with SCD. Measurement of family management styles could be accomplished by using measures such as the Family Management Measure to determine how families manage caring for the child with SCD and the extent to which SCD condition management is incorporated into everyday life (Knafl & Deatrick, 2003).

Health care professionals should also serve as informants when collecting data related to family functioning in children with SCD. Health professionals who work with affected children and their caregivers often interact with this population during stressful periods such as clinic visits, hospitalizations and visits to the emergency department. Therefore, perceptions of and observations made by health professionals related to parent/caregiver and child interactions are during crisis situations are crucial and may not be indicative of true behavior (Radcliffe, Barakat & Boyd, 2006). Research conducted in multiple settings will provide a better understanding of accomplishments and challenges that are general rather than issues unique to specific settings.

Although many of the reviewed studies were guided by a conceptual or theoretical framework (n = 9), 14 lacked them. Future research studies related to family functioning should include a guiding framework. Family researchers have been criticized for failing to include theoretical underpinnings in their work (Lavee & Dollahite, 1991; Schumm, 1982).

Culturally sensitive research designs must be considered for future research. Ideally, a sickle cell disease-specific measure with a family functioning component would be most useful. At minimum, measures of family functioning should include constructs relevant for African Americans. Variables such as religion, spirituality, and sociocultural resources should be examined closely in future studies. Additionally, studies must account for socio-economic status and stressors related to poverty as well as the chronic nature of SCD.

Developmentally appropriate and longitudinal designs are warranted for optimal family functioning assessment and intervention. Developmental assessments will help foster greater adolescent independence, especially during periods before and after transition (Newland, 2008). Longitudinal study designs will be more useful in capturing child developmental concerns and determining the family functioning experiences over time. Study results must reflect the changes in family functioning patterns over time as changes develop that may be related to the child, the family, and/or the disease condition (Hurtig, 1994).

Limitations

The inclusion and exclusion criteria that were established inevitably excluded studies that may have been very useful in this review (i.e., studies not translated into English). Additionally, the search was limited to articles with family-level variables of family functioning. Studies that include family functioning variables more specific to other individual members of the family may provide different results (i.e. mothers, fathers, siblings).

Conclusion

The chronic course of SCD, along with manifestations of the illness, can be particularly burdensome for children and families from the birth of an affected child throughout his or her lifespan. Family functioning issues must be defined, understood, and addressed over the course of the illness for all individuals involved. Sociocultural factors such as race, ethnicity, and culture are key elements in understanding the course of SCD and working with African American families. The results of this integrative literature review highlight the importance of cohesive, well-functioning families for more optimal adaptive

outcomes in children and adolescents with SCD. The findings also indicate that deficits exist in the literature related to family functioning research. These include lack of theoretical or conceptual frameworks to guide the research, and longitudinal research designs with multiple informants from demographically matched populations, and family functioning measures with sound psychometric properties. Family-focused strategies and interventions must be developed within a bio-psychosocial context and implemented accordingly. Finally, many measures used for assessing family functioning in children and adolescents with SCD lacked culturally sensitive variables. Assessments should include constructs and methods that include issues that are unique to African Americans. These interventions are necessary to improve health-related quality of life in children with SCD and their families so that optimal adaptation can be achieved.

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CHAPTER 3

HEALTH-RELATEED QUALITY OF LIFE MEASURES USED IN CHILDREN AND ADOLESCENTS WITH SICKLE CELL DISEASE: AN INTEGRATIVE LITERATURE REVIEW

Health-related quality of life (HRQOL) is a complex and multidimensional construct that can provide a broad assessment of a child's physical, emotional and psychosocial well-being (Bonner, 2010; Eiser & Morse, 2001a; Panepinto, 2008). Additionally HRQOL measurement can be useful in determining the management and treatment effects of health conditions, understanding the burden of the disease, identifying health inequalities, allocating resources, evaluating health policy interventions and understanding the child or parent's perception of the child's state of health (Eiser, Mohay & Morse, 2000; Grange, Bekker, Noyes, & Langley, 2007; Solans et al., 2008). Sickle cell disease (SCD) is one of the most important single gene disorders of humans (Makani, Williams, & Marsh, 2007). Several medical complications, physical symptoms and illness events contribute to reduced HRQOL in children with SCD, and they affect their families as well (McClish et al., 2005; van den Tweel et al., 2008). Individuals with SCD tend to report poor baseline HRQOL (Palermo, Schwartz, Drotar, & McGowan, 2002; Panepinto, O'Mahar, DeBaun, Rennie & Scott, 2004; Panepinto, O'Mahar, DeBaun, Loberiza, & Scott, 2005). Moreover, children and adolescents with SCD, along with their parents, tend to report lower HRQOL than their healthy counterparts (Dale, Cochran, Roy, Jernigan, & Buchanan, 2010; Palermo et al., 2002).

There have been major medical milestones that have benefited individuals with SCD. Among these milestones are penicillin prophylaxis, pneumococcal vaccines, new indications for blood transfusions and the prediction of stroke risk and/or stroke prevention (Arkuszewski, Melhn, & Krejza, 2010; Gaston & Verter, 1990; Hardie, King, Fraser, & Reid, 2009; Lee et al., 2006; Wahl & Quirolo, 2009). Hydroxyurea decreases the frequency of vaso-occlusive pain crises, thereby improving overall HRQOL in affected individuals (Brandow, Brousseau, & Pajewski, 2010; Steinberg et al., 2003). Finally, although the identification of appropriately matched donors can be challenging, hematopoietic stem cell transplantation can provide curative treatment for select individuals with SCD (Hamidieh, Jalili, Khojasteh, & Ghavamzadeh, 2010; Walters et al., 2000).

In light of these revolutionary medical advances, this is an opportune time to measure HRQOL outcomes in children with SCD to provide assessments of condition management and treatment. Pediatric patient-reported outcomes are also essential because children have unique perceptions of health and well-being that require consideration of their physical, emotional, and cognitive development (Eiser & Kopel, 1997; Eiser & Morse, 2001a; Palermo et al, 2002; Stegenga, Ward-Smith, Hinds, Rouhieaux, & Woods, 2004). These child-reported HRQOL outcomes are often different when compared to parental reports of HRQOL outcomes (Eiser & Kopel, 1997).

Ideally, proxy and child self-reports are useful in providing the most complete assessment of child HRQOL (Eiser & Morse, 2001a; Eiser & Morse, 2001b; Palermo et al., 2002; Panepinto, 2008). There is growing recognition that children, even as young as 5 years of age, can describe their quality of health experiences and identify aspects that are important to them (Rebok et al., 2001; Varni, Limbers, & Burwinkle, 2007). However, only a few

HRQOL measures are available for children below the age of 8 years (Eiser & Morse, 2001a). Many measures rely exclusively on parental report even though evidence supports the importance of children and adolescents rating their own HRQOL when possible (Eiser & Morse, 2001a; Eiser & Morse, 2001b). Additionally, few measures provide parallel forms for children, adolescents, and parents to complete.

In addition to some of the common features of HRQOL measures, it is ideal for the measures to have conceptually strong underpinnings that correspond to the experiences, contexts, age and/or developmental level of the population under study (Davis et al., 2006; Matza, Swensen, Flood, Secnik, & Leidy, 2004). Moreover, given the wide variation of definitions and perspectives of HRQOL, measures should be based on sound theoretical or conceptual frameworks with constant fundamental assumptions. Davis et al. (2006) contend that for a quality of life (QOL) measure to be conceptually strong, it must also have the following attributes:

> 1) It must rest on a clear, operationalized definition of QOL;
> 2) It must be based on a theory of QOL;
> 3) It must include the important domains of life for children; and
> 4) It must have well-constructed items. (p. 312)

The process of determining whether a child is of appropriate age and developmental level to complete a self-report HRQOL tool can be a daunting task. Nevertheless, researchers and health professionals must be able to select appropriate HRQOL measures for child assessments. Appropriate HRQOL and clinical measures can provide a comprehensive assessment of the impact of the disease and treatment related to total health and well-being (Matza et al., 2004).

To date, HRQOL has not been consistently measured in pediatric clinical practices (Baars, Van der Pal, Koopman, & Wit, 2007; Bonner, 2010; Clarke & Eiser, 2004), nor has

HRQOL been consistently measured in children with SCD (Bonner, 2010; Panepinto, 2008), despite the fact that developmental progress and complex, psychosocial coping and adjustment issues can be compromised in this population (Edwards et al., 2005; Kell, Kliewer, Erickson, & Ohene-Frempong, 1998; Pinckney & Stuart, 2004; Varni, Burwinkle, Rapoff, Kamps, & Olson, 2004). Researchers and health-care professionals may also be challenged by the task of selecting the most appropriate HRQOL instrument based on the specific outcomes that must be measured and the overall utility of the instrument (Davis et al., 2006).

Guiding Framework

The guiding framework used in this integrative literature review was Ganong's (1987) framework of Integrative Reviews of Nursing Research. Ganong (1987) contended that reviews included examination of research for suggestions of competing hypotheses, theoretical issues, and identification of needed research. Ganong's process was expanded by Sparbel and Anderson (2000) and included 10 steps: (1) formulation of the purpose and related research questions, (2) delineation of inclusion and exclusion criteria, (3) literature review, (4) development of a data collection tool, (5) identification of rules of inference for data analysis and interpretation, (6) revision of the data collection tool as required, (7) reviewing the studies using the data collection tool for information gathering, (8) systematic analysis of the data, (9) discussion and interpretation of the data, and (10) report the findings.

Formulation of the Purpose and Related Research Questions

The purposes of this systematic review were to (a) identify measures used in studies to assess HRQOL in children and adolescents with SCD, (b) describe the general

characteristics of each measure, and (c) provide recommendations for future measure development. The research questions that were used to guide this integrative review were:

1. What measures were used to assess HRQOL in children and adolescents with SCD?
2. What were the general characteristics and psychometric properties of the measures?
3. What samples has the tool been used with?
4. What are recommendations for future measure development?

Findings from this review will expand the literature by providing an updated, comprehensive and systematic appraisal of the state of the science related to HRQOL measures for children and adolescents with SCD. This will guide health providers in their selection of instruments to fully assess HRQOL in children and adolescents with SCD.

Methods

Delineation of Inclusion and Exclusion Criteria

The inclusion criteria were (a) documents written in English; (b) articles published from 1990 through 2011; (c) HRQOL assessments of children ages newborn through 18 years, (d) instruments that can be completed by children, their caregiver proxies, or both.

Exclusion criteria were (a) documents containing aggregated or grouped HRQOL data received from children and adults, (b) commentary or editorial articles, and (c) unpublished articles (i.e., dissertations, manuscripts).

Literature Search

In light of the medical and treatment advances for SCD that have emerged within the last decade, combined with the increase in patient-reported outcome measurements, this review included research studies that were conducted from 1990 through 2011. Numerous search strategies were employed to identify studies that contained HRQOL measures for children and adolescents with SCD. The following computer databases were used to search

for studies: Cochrane Library, Cumulative Index of Nursing and Allied Health Literature (CINAHL), EMBASE, Health and Psychosocial Instruments, Health Source: Nursing/Academic Edition, PubMed, PSYCHINFO, and Race Relations Abstracts. The Patient-Reported Outcome and Quality of Life Instruments Database was also searched to secure more information pertaining to the various HRQOL measures.

Key search terms that included medical subject headings and text terms were

- anemia, sickle cell; sickle cell disease; sickle cell anemia
- adolescent, child, children, infant, pediatric, paediatric, youth
- quality of life, QOL, health related quality of life, HRQOL
- tool, instrument, measure, measurement, questionnaire, assessment, evaluation, psychometrics

These key search terms were used in many combinations to retrieve studies until no new studies were found. Next, a hand search was conducted using the reference lists from identified articles so that more relevant articles could be located.

Literature Review

The article selection review process is depicted in Figure 3.1. A total of 64 articles were initially retrieved. Of these articles, 25 met the inclusion criteria and 39 articles were excluded. Eighteen articles were excluded because they did not contain HRQOL measures. Two dissertation articles, one editorial and one book review, were eliminated. Ten were excluded because they specifically pertained to adults. Four articles were eliminated because the articles included aggregated and grouped HRQOL data for children and adults. There was no way to separate child data from adult data when the grouped data were reported. The final three articles were excluded because they were reported in languages other than English. Twenty five articles remained. The remaining articles were reviewed in detail and the reference sections were searched for relevant articles that may have been missed during the

original search. Three articles were rejected because they did not meet inclusion criteria. Three articles were retrieved after hand searching each reference section of previous articles. The final sample included 25 articles (Table 3.1).

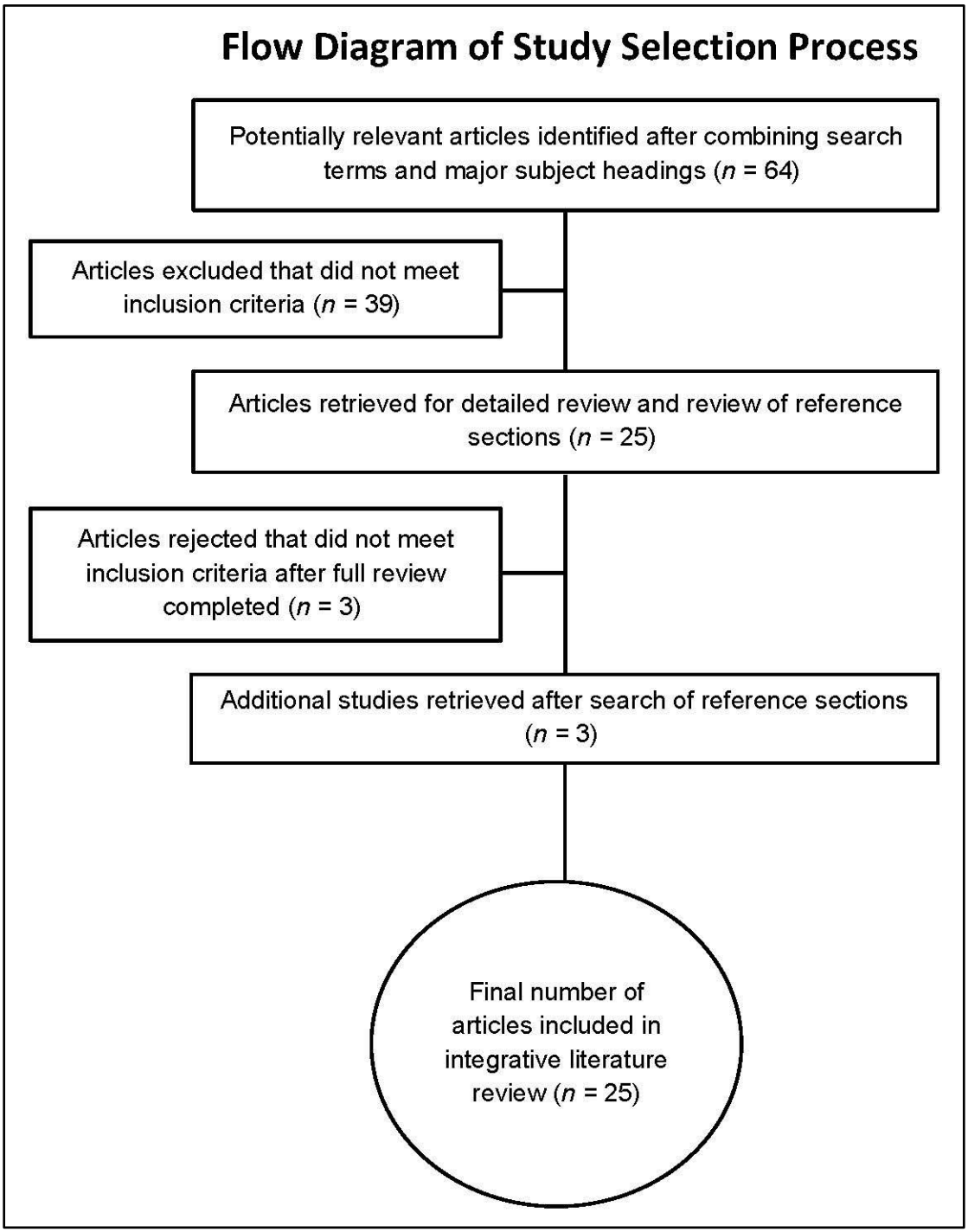

Figure 3.1. Model of the article selection process.

Table 3.1.

Articles Assessing Health-Related Quality of Life (HRQOL) in Children and Adolescents with Sickle Cell Disease

Author and Year	**HRQOL Measure**	**Age Range (Years)**	**Respondents Completing HRQOL Measure**
Barakat et al., 2008	CHQ	12–18	42 Caregivers 42 Children
Drotar et al., 2006	CHQ	5–18	62 Caregivers
Long et al., 2008	CHQ	8–12	26 Caregivers
Palermo & Kiska, 2005	CHQ	13–16	21 Children
Palermo et al., 2002	CHQ	5–18	58 Caregivers
Palermo, Riley & Mitchell, 2008	CHQ	8–17	56 Caregivers
Panepinto et al., 2004	CHQ	5–18	95 Caregivers
Panepinto. et al., 2005	CHQ	5–18	95 Caregivers 53 Children
Patel & Pathan, 2005	EUROQOL, WHO-QOL & Qualitative HRQOL Tool	8–14	25 Children
Hijmans et al., 2010	KIDSCREEN-52	6–18	40 Children
Barakat, Lutz, Smith-Whitley et al., 2005	MPQOL	Birth–18	73 Caregivers 23 Children
Lutz et al., 2004	MPQOL	Birth–18	73 Caregivers 23 Children
Dale et al., 2010	PedsQL	8–18	124 Caregivers 124 Children
Dampier et al., 2010	PedsQL	2–18	1772 Caregivers 1393 Children

Author and Year	HRQOL Measure	Age Range (Years)	Respondents Completing HRQOL Measure
Engelke et al., 2008	PedsQL	5–18	4 Children
Hankins et al., 2007	PedsQL	3–17	30 Caregivers 30 Children
Ingerski et al., 2010	PedsQL	6–15	35 Caregivers 28 Children
McClellan et al., 2008	PedsQL	5–18	68 Caregivers 68 Children
Panepinto et al., 2008	PedsQL	2–18	104 Caregivers 78 Children
Panepinto, Pajewski et al., 2009	PedsQL	2–18	104 Caregivers 69 Children
Panepinto et al., 2010	PedsQL	5–18	66 Caregivers 66 Children
Panepinto, Hoffman et al., 2009	PedsQL	5–18	97 Caregivers
Thornburg et al., 2009	PedsQL	1.5–5	13, 11, & 8 Caregivers by end of study
Brandow et al., 2010	PedsQL-Acute Version	2–18	57 Caregivers 39 Children
Stegenga et al., 2004	Qualitative HRQOL Tool	6–12	10 Children

Note. CHQ = Child Health Questionnaire, MPQOL = Miami Pediatric Quality of Life Questionnaire, PedsQL = Pediatric Quality of Life Inventory Generic Core Scales 4.0, SCD = Sickle Cell Disease, WHO QOL = World Health Organization Quality of Life Scale.

Development of Data Collection Tool

Data were abstracted from each article and categorized according to the author and year of the article, HRQOL measure used, number of children with SCD in the article, the

age range of the children with SCD, and the number of respondents (Table 3.1). Data display matrices were developed so that the data from each article could be displayed and compared.

Studies Reviewed

Seven HRQOL measures were used among the 25 articles included in this review. A brief overview of each measure is given in the following sections.

Systematic Analysis of the Data

Quantitative HRQOL Measures

Child Health Questionnaire (CHQ). The CHQ is a generic HRQOL measure that was developed to assess functional health status and psychosocial well-being for children 5 to 18 years of age (Landgraf, Abetz, & Ware, 1996). The CHQ consists of a form for child self-report (87 items) and two different forms for parent/proxy report (50 or 28 items). The measure contains a wide variety of domains including 14 domains for the parent-completed questionnaire and 12 domains for the child-completed questionnaire. The scales are designed to measure the child's HRQOL and the impact of the child's health condition on the parents/care-givers and family members. An electronic scoring and interpretation manual is available. Two summary scores, the physical health summary score and the psychosocial health summary score, can be generated. There are also numerous translations for the measure. The CHQ has been used with various pediatric illness populations, children in primary care settings, and pediatric research populations.

The CHQ was conceptualized as a generic instrument that measures health in the physical, psychological, and social domains (Rajmil et al., 2004). In addition to SCD, the CHQ scales have been used in pediatric populations such as: liver transplantation, post orthopedic intervention, chronic kidney disease, post injury, rheumatology, hemophilia,

cystic fibrosis, cerebral palsy, asthma, diabetes, Kawasaki disease, obstructive sleep apnea, arthritis, children undergoing chemotherapy, adolescents born small for gestational age, Turners' syndrome, hematopoietic progenitor cell transplantation, fecal incontinence, Duchenne's muscular dystrophy, attention deficit hyperactivity disorder, primary headaches, systemic lupus erythematosus, meningococcal septic shock, HIV-infected children, children with special health-care needs and children in home-based foster care.

KIDSCREEN Quality of Life Questionnaire (KIDSCREEN). The KIDSCREEN is a generic HRQOL measure that was developed in Europe and designed for use in healthy and chronically ill populations for ages 8 to 18 years. The KIDSCREEN was also validated in a Dutch population and designed to measure subjective health and well-being. There are three forms for use in child self-report as well as parent/proxy report (10, 27, and 52 items). Ten domains make up the KIDSCREEN measure and scores are generated with *t*-values and percentages available for each country. The scores are standardized by age and gender.

Ravens-Sieberer et al. (2005) assert that the KIDSCREEN is based on the definition of HRQOL as a multidimensional construct that encompasses physical, emotional, mental, social, and behavioral components of well-being and functioning as perceived by patients and/or other individuals. The developmental aspect of QOL is derived from the literature according to Bullinger and Ravens-Sieberer (1995); Eiser, Cotter, Oades, Seamark, and Smith (1999); and Eiser and Morse (2001a).

The KIDSCREEN has been used in several populations and has been useful in identifying children at risk regarding their subjective health and suggests use of the instruments in facilitating early intervention services. The instruments have also been useful in epidemiological research and for measuring subjective health in pediatric populations

(Ravens-Sieberer et al., 2005). In addition to SCD, the KIDSCREEN scales have been used in pediatric populations such as obesity, bullied children, cardiovascular disease, cerebral palsy, retinoblastoma, adolescent gender differences, immigrants and native school aged adolescents in Spain, and risk behavior among European adolescents.

Miami Pediatric Quality of Life Questionnaire (MPQOL). The MPQOL was designed to assess objective and subjective perceptions of children's functioning and the importance of each item to children aged 1 to 18 years. Results are compared to healthy children of the same age. The MPQOL is sensitive to late effects of treatment. There are three domains, and the measure is appropriate for child self-report as well as parent/proxy report (39 items for each).

The MPQOL was conceptualized based on objective indices of function and psychological adjustment and according to their subjective importance (Armstrong et al., 1999). Additionally, credence was given to the empirical input from families of children being treated for cancer rather than experts in the field. The MPQOL has been used in populations such as asthma, diabetes, cardiac conditions, and rheumatology as well as oncology conditions and SCD.

Multidimensional Interview-Based Questionnaire (MIBQ). The MIBQ measure was developed based on the conceptualization of QOL by Patrick and Erickson (1992), the European Quality of Life Group (EUROQOL; EUROQOL, 1990), and the World Health Organization Quality of Life BREF (WHO QoL-BREF; World Health Organization Programme on Health, 1996). The MIBQ consists of four domains that were developed encompassing clinico metrics, psychometrics, and the clinical discussion theory (Feinstein, 1987). There are also several sub-domains. Each scale had 37 questions, and it takes

approximately 30–45 minutes on average for each child to complete. Three choices of responses were developed in an effort to make decisions easier for children. Aspects of internal consistency and inter-rater reliability were assessed. Content and construct validity were also assessed.

Patel and Pathan (2005) contend that this scale was conceptualized based on the needs of children with SCD as evidenced by the feedback given during focus group sessions that generated qualitative information. The scale was also useful in helping to distinguish the needs and concerns of children with SCD versus children with sickle cell trait (Patel & Pathan, 2005). This is the only known study and population that this measure was used in.

Pediatric Quality of Life Generic Core Scales 4.0 (PedsQL). The PedsQL generic HRQOL instruments were designed to measure HRQOL in acute, chronic, and healthy pediatric populations. The PedsQL and the associated modules are appropriate for a child self-report module for children ages 2 to 18 years and a parent/caregiver proxy report for children ages 2 to 18 years. The generic core scales consist of 23 items and 4 domains, and it takes approximately 4 minutes to complete. The PedsQL is available in numerous translations and is responsive to change over time. Reliability and validity have been demonstrated in SCD and other populations. A total score may be generated as well as three summary scores. This scale measures HRQOL over a 1-month recall period. The PedsQL 4.0 generic scales have been used in populations such as asthma, diabetes, cardiac conditions, rheumatology, end stage renal disease, cerebral palsy, obesity, gastrointestinal, attention deficit hyperactivity disorder, spinal muscular atrophy and SCD.

Pediatric Quality of Life Generic Core Scales 4.0-acute version. The acute version is a parallel report of the generic core scales. However, the acute version measures HRQOL

over a 7-day recall period. The acute scales can be compared to the same scoring system as the generic core scales.

The PedsQL was conceptually designed to measure the core health dimensions of physical, mental, and social health and also includes role (school) functioning of children and adolescents (World Health Organization Programme on Health, 1996).

Qualitative HRQOL Methods

Qualitative HRQOL Method by Stegenga et al. (2004). The HRQOL method used in the study by Stegenga et al. (2004) was developed using a phenomenological design. A total of six interview questions were developed by health-care professionals from a sickle cell team at the study site. All participants in the study had SCD and answered semi-structured interview questions at the time of receiving chronic transfusion therapy (CTT). Interviews were audio-taped and lasted from 15 to 75 minutes. Participants were instructed to communicate how CTT had affected their QOL. What QOL entails was not defined and thus allowed the participants to fully expound on their perceptions of the concept. Interviews were completed for specific individuals and within groups. This is the only known study and population that this measure was used in.

General Characteristics

Descriptive characteristics for the final seven HRQOL measures are identified in Table 3.2. The CHQ, KIDSCREEN and PedsQL (standard and acute versions) are generic HRQOL measures designed to be used for a wide variety of chronically ill and healthy children and adolescents rather than specific patient populations. The MPQOL was originally designed to assess objective reports of children's functioning and subjective reports of each item's perceived importance in assessing HRQOL issues of children treated for cancer

(Armstrong et al., 1999). However, psychometric testing was published on caregivers only. The MIBQ was developed to identify specific QOL domains and traits affected in individuals with sickle cell anemia and traits with respect to normal children (Patel & Pathan, 2005). The qualitative measure by Stegenga et al. (2004) was developed specifically to explore QOL as affected by CTT from the perspective of the child.

Table 3.2

Health-Related Quality of Life (HRQOL) Measure Information

Measure	Author & Year	Domains	Respondents & Number of Items	Age Range (Years)	Completion Time (Mins.)	Reliability	Type of Validity Assessed	Strengths	Limitations
CHQ	Landgraf et al., 1996	14: -physical functioning -role-social physical -role-social emotional -role-social behavior -bodily pain -self-esteem -mental health -general behavior -caregiver impact: time * -caregiver impact: emotion* -general health --change in health -family activities -family cohesion	Child 87 Parent 50 Parent 28	10–18 5–18 5–18	16–25 10–15 5–10	α = .54–.97 α = .39–.97 α = .07–.88 In SCD: α = .42–.97	Construct Convergent	-self and proxy -separate categories for many dimensions -responsive to change across conditions -multiple language translations -distinguishes between ill & healthy populations -associated with illness severity -useful in comparing children within doctors' offices, schools, clinical trials and large population based research	-too lengthy -lacks distinct dimension for school functioning on short form -lengthy scoring process

Measure	Author & Year	Domains	Respondents & Number of Items	Age Range (Years)	Completion Time (Mins.)	Reliability	Type of Validity Assessed	Strengths	Limitations
KIDSCREEN	Ravens-Sieberer & Bulinger, 1998	10 -physical well-being -psychological well-being -moods and emotions- -self perception -autonomy -parent relation & home life -financial resources -social support & peers -school environment -bullying	Self & Proxy 52 Self & Proxy 27 (5 scales) Self & Proxy 10 (single scale)	8–18	15–20 10–15 5	α = .76–.89 α = .79–.84 α = .82 Not tested in children with SCD	Construct Convergent Discriminant Not tested in children with SCD	-aspect of HRQOL related to mental health -key domains of autonomy exist -simultaneous & collaborative cross-cultural development -financial resources and bullying domains present -positive aspects of health assessed -appropriate for health & chronically ill children -available in several languages	-no indicators defined for very young children -lacks significant testing in clinical settings -lacks cultural, spiritual and general environmental assessments -version 52 only assesses HRQOL over past week
MPQOL	Armstrong, et al., 1999	3 -social competence -self-competence -emotional stability	Child 39 Parent 39	1–18	15–20	α = .76–.89 (parent) -test-retest: .38–.94(1 month parent) -no cross-informant reported Not tested in SCD	-distinguishes between children with brain tumors & children with other cancers -factor analysis conducted with parents only Not tested in SCD	-designed to be sensitive to late effects of treatment -distinguishes between cancer illness types (brain tumors and other cancers)	-physical and functional concerns did not emerge as factors -lacks caregiver and child ratings of total physical symptom severity -lacks cross-informant reliability -not sensitive to change over time -lacks non-English translation. -does not account for different ages or developmental levels.

Measure	Author & Year	Domains	Respondents & Number of Items	Age Range (Years)	Completion Time (Mins.)	Reliability	Type of Validity Assessed	Strengths	Limitations
PedsQL Generic Core Scales	Varni, Burwinkle, Seid, et al., 2003	4- physical functioning -emotional functioning -social functioning -school functioning	Child 23 Parent 23 Short Form 15 Children	2–18 5–7 8–12 13–18	Less than 4 minutes	α = .68–.90 α = .74–.94 In SCD: α = .64–.93	Construct Clinical Convergent In SCD: Internal Construct Criterion	-self and proxy -brief -distinct dimension for school functioning -distinguishes disease severity -responsive to clinical change over time -translated into other languages -can use individually or with other disease-specific measures -parallel forms for caregiver & child reports -allows for potential comparison between different illness groups -acute version available	-lacks re–test reliability for self-report

Measure	Author & Year	Domains	Respondents & Number of Items	Age Range (Years)	Completion Time (Mins.)	Reliability	Type of Validity Assessed	Strengths	Limitations
Multi-dimensional Interview Based Question-naire	Patel & Pathan, 2005	4 Functional Health Perception Opportunity Morbidity	Children 35 each scale	8–14	30–45	-Respondents were a homogenous group -	Content Construct	-distinguished HRQOL in children with SCD vs. SCT -developed specifically for SCD and SCT -pain measured by visual analog	-small sample size -limited ages -no parental assessments

Measure	Author & Year	Domains	Respondents & Number of Items	Age Range (Years)	Completion Time (Mins.)	Reliability	Type of Validity Assessed	Strengths	Limitations
Phenomeno -logical Qualitative Question-naire	Stegenga et al., 2004	6 interview questions	Children 6 questions	6–12 years	15–75 minutes	N/A	N/A	-open ended with no definition for QOL -allows for full perception of concepts	-small sample size -limited age -no parental assessments -ots receiving CTT only

Note. *Not in child questionnaire CF-87. CHQ = Child Health Questionnaire, CTT = chronic transfusion therapy, Mins. = minutes, MPQOL = Miami Pediatric Quality of Life Questionnaire, PedsQL = Pediatric Quality of Life Inventory Generic Core Scales 4.0., QOL = quality of life, SCD = sickle cell disease, SCT = sickle cell trait.

The CHQ, KIDSCREEN and both PedsQL versions were validated separately for child and caregiver-proxy respondents. The MPQOL was validated for caregivers only, and the MIBQ was validated for children only. The MIBQ distinguished aspects of HRQOL in children with SCD versus children with sickle cell trait. The qualitative measure that was developed by Stegenga et al. (2004) provided HRQOL assessments for children with SCD at the actual time of undergoing CTT.

Six of the seven HRQOL measures included different child-age ranges. The MPQOL had the widest age range (1–18 years) even though it was validated for caregiver use only. Caregiver respondents for the PedsQL (standard and acute versions) and CHQ represented children who were 2 to 18 years old, and ages ranged from 5 to18 years for child respondents. The KIDSCREEN was designed to assess HRQOL in children between the ages of 8 and 18 years. The MIBQ included respondents who were between 8 and 14 years. The qualitative measure included respondents between 6 and 12 years.

The number of items on each instrument varied considerably, from 10 to 98 for the quantitative scales. The KIDSCREEN had the fewest number of items on the quantitative scales at 10 for both child and caregiver-proxy reports. Both versions of the PedsQL had the next fewest number of items at 23 for child and caregiver-proxy reports. The CHQ had a significant number of items at 87 for child reports, as did the MIBQ with 37 questions for each scale. The qualitative measure that was developed by Stegenga et al. (2004) had six questions.

The reported completion times ranged from less than 4 minutes (PedsQL) to 20 minutes or greater for the CHQ, KIDSCREEN, and MPQOL. The completion times for the

MIBQ and the Stegenga et al. (2004) measures were 30 to 45 minutes and 15 to 75 minutes respectively.

Domains

The total number of HRQOL domains among the six quantitative measures ranged from 3 for the MPQOL to 14 for the CHQ (see Table 3.2). The CHQ, KIDSCREEN, MIBQ, and the PedsQL versions included domains that assessed physical, psychological, and social functioning. However, physical and functional concerns did not emerge as distinct factors for the MPQOL measure during psychometric testing (Armstrong et al., 1999). Therefore, the domains included in the MPQOL were social competence, self-competence, and emotional stability. Although some of the questions were similar, the content of the domains varied significantly between the measures. For example, all six quantitative instruments contained questions related to pain assessment. However, pain was assessed in the bodily pain domain in the CHQ (physical limitations were assessed in the physical functioning scale), the domain of physical well-being in the KIDSCREEN, and the physical domain for the PedsQL versions. As for the MPQOL, pain and physical discomfort were assessed within the emotional stability domain. Pain was assessed in the domain of morbidity for the MIBQ. Six interview questions were included in the Stegenga et al. (2004) qualitative tool. No specific question addressed pain issues but the interviews were structured such that pain could have been described if it was perceived as an issue that affected the QOL of the participants as they were undergoing CTT.

The greatest agreement among all six quantitative scales was within the social domains. All six measures had domains that assessed social well-being. The CHQ had role/social functioning and role/social-emotional behavioral domains as well as unique

domains that assessed parental impact, family limitations and family cohesion. The KIDSCREEN had domains that assessed social support and peers, social acceptance that included bullying, and parent relations and home life. The MPQOL had a social competence domain and the PedsQL versions had social functioning domains. A social functioning subscale was assessed within the domain of function in the MIBQ. Semistructured questions were designed to include social functioning if participants decided to address the specific issue.

Quality Assessment of HRQOL Measures

Quality assessment is determined by evaluating validity and methodological criteria (West et al., 2002). However, there is no universally accepted criteria that specifically determines how all methodological quality should be assessed. Quality assessments of the HRQOL measures were evaluated using a modified version of the CanChild Outcome Measures Rating Form (COMRF). The COMRF is a tool that is used to assess clinical utility, scale construction, and psychometric properties of outcome measures (Law, 2011). The PedsQL was determined to be a well-constructed scale based on scoring criteria. The KIDSCREEN and CHQ scored as moderately constructed scales, and the MIBQ and MPQOL were determined to be poorly constructed scales (Table 3.3).

Table 3.3

Health-Related Quality of Life (HRQOL) Measurement Quality Assessment

HRQOL Measure	Clinical Utility (3)	Scale Construction (3)	Standardization (3)	Reliability (6)	Validity (15)	Overall Utility (3)
CHQ	3	2	2	4	5	2
KIDSCREEN	3	2	2	4	3	2
MIBQ	2	1	1	2	2	1
MPQOL	2	1	1	2	2	1
PEDSQL (both versions)	3	2	2	4	6	3

Note. The total possible score for each domain is in parentheses. Clinical utility relates to clarity of instructions. Reliability includes intra-rater, retest and internal consistency. Validity includes construct, criterion, and responsiveness. Overall utility combines all relevant information available for outcome HRQOL measure. CHQ = Child Health Questionnaire, MIBQ = Multidimensional Interview-Based Questionnaire, MPQOL = Miami Pediatric Quality of Life Questionnaire, PEDSQL = Pediatric Quality of Life Generic Core Scales.

Reliability and Validity

CHQ. The CHQ has been tested and reported to be reliable (Cronbach's α = .42–.88) and valid for use in children with SCD according to a study conducted by Panepinto et al. (2004). Palermo et al. (2008) reported Cronbach's alpha at .63 to .97. The CHQ provided construct validity in assessments of children with SCD by analyzing mean summary scores by disease severity. The CHQ was also able to distinguish between affected children's levels of disease severity.

KIDSCREEN. The KIDSCREEN has not been psychometrically tested specifically in a pediatric SCD population. However, the range for Cronbach's alpha across all three subscales is .70 to .82. Validity has been demonstrated for convergent, discriminant, and construct.

MIPQ. In as much as the MIPQ was developed for use in a single study population, the psychometrics were described accordingly. The scale was prepared in English, translated into Marathi and Hindi, and finally retranslated into English (Patel & Pathan, 2005). Before the final scale was launched, it was pretested in both languages. The number of items on the scales and the inter-rater reliability enhanced the internal consistency. Respondents were homogenous, thus improving reliability. The domains and choice of dimensions were developed based on the needs assessed by the children with SCD in the focus groups. Responses were considered along with the conceptualization of Patrick and Erickson (1992), EUROQOL (1990), and WHO QOL-BREF (1996).

MPQOL. Psychometric testing for the MPQOL has never been completed for HRQOL assessments in children with SCD, only for caregivers of children with cancer. Internal consistencies for all factors ranged from a Cronbach's α of .76 to .88 (Palermo et al., 2008), and the internal consistency of the overall scale was .89 (Armstrong et al., 1999). Overall test–retest reliability was acceptable. Discriminant validity was evident in that the measure discriminated between children with different types of cancer.

PedsQL (standard and acute versions). The internal consistency, construct validity, and criterion validity of the PedsQL were assessed in children with SCD in a study conducted by McClellan, Schatz, Sanchez, Roberts (2008). Satisfactory internal consistency values for clinical purposes were present at the total score level (Cronbach's α = .64–.89), and caregiver proxy reports of specific domains and summary scores were satisfactory for research purposes.

Construct validity was assessed by exploring convergent and discriminant validity between and within the raters and scales. Pearson correlation values were statistically

significant for all scales except for physical health reported by younger children. Intra-class correlation between the caregiver and youth reports revealed statistically significant convergence across participants for the dimensions of physical health (.22 and $p < .05$) and psychosocial health (.29 and $p < .01$). Finally, McClelland et al. (2008) assessed criterion validity in the PedsQL by evaluating the relationship between HRQOL and the morbidity scores of neurological complications and moderate to severe pain.

A study conducted by Panepinto, Pajewski, Foerster, & Hoffman (2008) concluded that the PedsQL was valid, reliable, and feasible for measuring HRQOL in children with SCD. Its feasibility was determined based on the calculation of the number of missing items from caregiver and child reports. The reliability of the PedsQL was satisfactory on all scales (Cronbach's $\alpha = .73–.93$) and its validity supported the conclusion that the HRQOL of children with SCD was worse in the area of physical, social, and school functioning compared to children without the disease. The caregiver-proxy report made a distinction between children with no disease, mild disease, and severe disease. Differences existed in the child's physical functioning between children with mild and severe sickle SCD; severely affected children displayed less physical functioning.

Strengths and Limitations

MPQOL. The MPQOL was the least effective for assessing general HRQOL issues in youth with SCD. Although the MPQOL was designed to be sensitive to late effects of treatment and the tool distinguishes between cancer illness subtypes, the psychometric properties were not strong and unique for individuals with SCD. Moreover, specific physical and functional factors do not exist. This could be detrimental for children with SCD since physical and functional limitations related to pain have been reported as major aspects that

diminish HRQOL in this population (Fuggle, Shand, Gill & Davies, 1996; Palermo et al., 2002; Patel & Pathan, 2005). Furthermore, an evaluation of the functional status of affected individuals would be significant because the chronic course of SCD illness, frequent hospitalizations, visits to health providers, and meticulous care management can lead to abnormal functioning in children with SCD (Edwards et al., 2005). Additionally, there are no known language translations associated with the MPQOL.

CHQ. The CHQ is a valid tool for assessing HRQOL in children with SCD and has many language translations available. It differentiated between youth with mild and severe SCD but not on the bodily pain subscale that assesses pain frequency (Panepinto et al., 2004). It did not have scales that captured 2- to 4-year-olds for caregiver-proxy reports nor 5- to 9-year-olds for self-reports. The short-form version of the CHQ did not include a scale for school functioning. Because a correlation between SCD and academic challenges for affected children has been reported (Schatz, 2004; Schatz, Brown, Pascual, Hsu, & DeBaun, 2001), it is imperative for HRQOL measures to include items to that assess school functioning.

Additionally, the CHQ was lengthy with 28-, 50-, and 98-item scales. The CHQ's 14 domains can complicate matters for respondents as they strive to understand and complete the questionnaire in a timely manner. There is great burden associated with the length and scoring of the CHQ measure. The more time involved with completing instruments, the greater the risk is for nonparticipation and fewer completed surveys (Eiser & Morse, 2001b).

KIDSCREEN. A great strength of the KIDSCREEN measure is the unique ability for cross-cultural comparison in that it was developed simultaneously in 13 European countries. The KIDSCREEN is also appropriate for use in healthy and chronically ill populations. Proxy and self-reports are available as are multiple translations. The KIDSCREEN lacks

significant testing in clinical settings and the KIDSCREEN 52 only assesses HRQOL over the past week.

MIBQ. The MIBQ was developed based on the specific needs and concerns expressed by children with SCD and children with sickle cell trait. This is a unique and humanistic asset for the MIBQ measure. It is also able to be used to distinguish the needs of patients with SCD and sickle cell trait. However, the measure has only been used in one known study and thus lacks generalizability.

Qualitative assessment by Stegenga et al. (2004). This qualitative HRQOL assessment was developed based on a phenomenological design. As such, interview questions were asked in a semistructured manner that allowed the pediatric participants to expound on their responses. Additionally, QOL was not defined and the participants were free to add any and all of their thoughts related to the concept. The assessment was developed specifically for patients with SCD who were actively undergoing chronic transfusion therapy. This could actually be perceived as a strength and a weakness. A unique tool to assess HRQOL in a specific population is an asset for the population under study. However, it is limiting for other populations.

PedsQL. The PedsQL is brief and practical and has specific, corresponding, caregiver-proxy-report forms that allow for direct comparisons between caregivers and children. The PedsQL is also valid, reliable, feasible, and more appropriate for assessing comparisons between different groups of chronically ill patients (Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002; McClellan et al., 2008). Furthermore, the PedsQL was the only measure that had a generic core component that could be used independent of or in conjunction with other disease-specific measures.

According to recent studies (Dampier et al., 2010; Panepinto et al., 2008; Varni, Burwinkle, & Seid, 2006; Varni et al., 2002; Varni et al., 2004; Varni et al., 2007), internal consistency for the PedsQL is sometimes weak with greater ceiling effects for younger children. This could be due to the manner in which items are worded and the difficulty that caregivers' have reporting child activities that are not easily observed (Dampier et al., 2010). The acute version of the PedsQL has a time recall period of the past 7 days rather than the standard generic version of a 1-month recall period. Thus, the acute version is more appropriate for use in children with SCD who are experiencing a painful, vaso-occlusive crisis. Finally, the PedsQL generic core scales are responsive to clinical change over time and many language translations are available for this tool.

Discussion and Interpretation

This integrative literature review identified measurements currently used to assess HRQOL in children and adolescents with SCD. Several issues must be addressed in future measurement development for HRQOL in this population.

HRQOL Definition, Domains, and Conceptual Underpinnings

The number of the domains varied widely, but some of the items were similar. The variation was likely due to different processes used to develop the tools, the definitions used for HRQOL, the theoretical concepts embraced, and whether the tool was developed as a generic measure or for a specific population (Davis et al., 2006; Solans et al., 2008). No universal or generally accepted definition of the HRQOL construct has been established relevant to HRQOL measurement (Levi & Drotar, 1998). For example, in this review, concepts such as health status, functional status, and ability to perform activities of daily living have been used and referenced. Given the complexity of HRQOL measurement and

the lack of evidence for the fundamental assumptions about it, future studies in pediatric SCD involving HRQOL measures should involve children in the developmental process, and the measures should assess the same underlying construct. The HRQOL measures were developed based on distinct definitions of HRQOL. However, constructs should be consistently developed based on sound theoretical foundations (Davis et al., 2006), experiences, and activities that are directly related to the sample under investigation (Matza et al., 2004).

The greatest agreement among the items in the four HRQOL measures was within the social domains and included information such as peer interactions, family life, and school functioning. Questions in the social domains were developed based on expert opinion and direct interviews with children and caregivers. Because children grow and develop at different times, ages, and stages, future measure development should include a developmental framework that encompasses not only the aforementioned aspects of social interactions, but also time ranges for different age groups and developmental levels (Levi & Drotar, 1998; Palermo et al., 2008; Rajmil et al., 2004). This could account for potential variations related to social, emotional, and cognitive functioning.

Cultural, Spiritual, and Environmental Considerations

Domains that specifically addressed cultural, spiritual, and environmental dimensions were missing in all measures. This could be a disadvantage for assessing HRQOL and family functioning in children with SCD. Unique, sociocultural factors may influence overall family functioning and adaptation for children with SCD in African American families because of possible differences in health perceptions and disclosures (Hocking & Lochman, 2005). For this reason, there is a need to understand African Americans within the sociocultural context

that they live and function (Sterling, Petersen, & Weekes, 1997). Additionally, religious involvement and activities such as attending church and praying are important in helping individuals with SCD cope with pain (Harrison et al., 2005). More culturally sensitive and competent research designs will be especially promising for future research. Item generation should include religious and cultural considerations.

Measures should be multidimensional and developed using demographically matched populations of African American children. This includes healthy comparison populations that are of the same race, ethnicity, sex, and age, as well as similar socioeconomic status and neurocognitive functioning (by IQ testing). Constructs that encompass environmental assessments are also important to include when assessing HRQOL in children with SCD. Exacerbated symptoms related to SCD have been reported as a result of chronic exposure to environmental air pollutants such as tobacco smoke (Mittal et al., 2009; West et al., 2003). Moreover, community and neighborhood socioeconomic distress has been associated with decreased HRQOL in children with SCD (Palermo et al., 2008).

Child Versus Parent/Caregiver-Proxy Reports

The usefulness of child and parent/caregiver-proxy reporting has been discussed at length in the literature (Asadi-Lari, Tamburini, & Gray, 2004; Clark & Eiser, 2004; Eiser & Morse, 2001b; Glaser, Davies, Walker, & Brazier, 1997; Schlarmann, Metzing-Blau, & Schnepp, 2008). Ideally, caregiver reports and children's self-reports should be used in complement when assessing HRQOL in children (Clark & Eiser, 2004; Eiser & Morse, 2001a; Varni et al., 1998; Vogels et al., 1998). Caregivers and children's perspectives are important for understanding the full implications and impacts of the SCD experience in children, even though agreement between children's and caregivers' ratings is not always

consistent given the circumstances of age, rater health, and gender (Eiser & Morse, 2001a; Wallander, Schmitt, & Koot, 2001). All four measures were designed for self-report and proxy-report use. The choice as to who the proxy reporter should be must be determined and acknowledged accordingly. The caregiver who is most involved with the child's care, health, and daily activities is most likely the person who can provide the most valuable and accurate assessment related to the child's HRQOL.

Limitations

The search methodology is a limitation of this study in that it may not have identified all of the studies that included HRQOL measurements for children with SCD due to the inclusion and exclusion criteria.

Conclusion

This is the first known review that has evaluated the HRQOL measures that have been used specifically in studies to assess children and adolescents with SCD. A total of 25 studies were selected based on the scientific criteria identified, and seven HRQOL measures were used in the studies. The seven measures were the CHQ, KIDSCREEN, MPQOL, PedsQL (standard and acute versions), MIBQ, and a qualitative questionnaire developed by Stegenga et al. (2004). Characteristics of the measures were identified. All four measures included specific domains that were significant and useful for assessing health, well-being, and QOL in children with SCD. The measures included assessments related to the impact of SCD on various aspects of life and on specific domains of HRQOL.

When assessing HRQOL in children with SCD, the researcher or clinician must consider several factors including the features of the measure, conditions under which the tool will be used, contextual variables, determining specific times to measure, and how to

present results (Eiser & Morse, 2001a, 2001b; Panepinto et al,, 2008). Health-related quality of life measurement in children with SCD remains an evolutionary endeavor that should account for the significance of proxy reporting by caregivers and direct reporting by the children with SCD as well as the significance between disease-specific and generic measures (Sawyer, Drew, Yeo, & Britto, 2007).

The instruments reported in this review have unique strengths and weaknesses for assessing children and adolescents with SCD. Of the seven measures identified, the PedsQL emerged as the most practical and flexible multidimensional measurement for children with SCD in that it had a wide age range (2–18 years), few number of items (23), the shortest estimated time of completion (< 4 and up to 10 minutes), two recall periods, sound psychometric properties, and can be used individually or in conjunction with other disease-specific measures. Moreover, the PedsQL measure has been used in at least 10 studies related to children with SCD.

Plans are underway to develop SCD-specific scales for measuring HRQOL in affected children. In the interim, this review will facilitate HRQOL instrument selection for researchers and clinicians based on the scientific criteria presented. Effective HRQOL measurement in children and adolescents with SCD can help advance the understanding of SCD illness and management, decrease further complications, and improve overall health outcomes for affected children and their family members.

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CHAPTER 4

FACTORS THAT INFLUENCE HEALTH-RELATED QUALITY OF LIFE IN ADOLESCENTS WITH SICKLE CELL DISEASE

Sickle cell disease (SCD) refers to a group of genetic blood disorders characterized by red blood cell abnormalities that lead to sickle-shaped cells and contribute to hemolytic anemia and complications such as infections, acute chest syndrome, leg ulcers, tissue and organ damage, stroke, and death (Bunn, 1997; Mann-Jiles & Morris, 2009; Pack-Mabien & Hayes, 2009; Redding-Lallinger & Knoll, 2006). Vaso-occlusive pain is the most common reason children with SCD seek medical care (Barakat, Lutz, Smith-Whitley, & Ohene-Frempong, 2005; Jacob et al., 2003; Shapiro et al., 1995).

In 2005, there were 31,269 children with SCD in the United States, including 28,426 African American children (Amendah et al., 2010; National Newborn Screening & Genetics Resource Center, 2005). The total pediatric-SCD-attributable expenditures in 2005 were $334,764,427 (Amendah et al., 2010; Raphael et al., 2009). Stressors related to the unpredictable and chronic course of sickle cell disease and related complications can have a negative impact on a child's HRQOL and wellbeing (Edwards et al., 2005, Panepinto, 2008; Panepinto et al., 2005).

Health-related quality of life (HRQOL) is a multidimensional outcome that encompasses the patient's physical, emotional, and social well-being (Panepinto, O'Mahar, DeBaun, Loberiza & Scott., 2005; Varni, Seid, & Rode, 1999). Many biomedical, physical, psychosocial, and emotional factors influence HRQOL in children with SCD, and for their

family members (McClish et al., 2005; van den Tweel et al., 2008). Limitations reflected in HRQOL are even more challenging for adolescents with SCD, ages 13 – 17 years, because adolescents must transition from dependence on others to independence in the care and management of their illness (Baraka, Patterson, Daniel, & Dampier, 2008; Palermo, Schwartz, Drotar, & McGowan, 2002). In their quest to be socially accepted by their peers, adolescents often do not want to be perceived as different or inadequate. The clinical manifestations of SCD can have a significant impact on the HRQOL in adolescents who are already experiencing adjustments related to sexual, mental, and physical maturation. Significant delays in growth and development, restrictions in physical activities such as participating in sports and social activities, and impromptu absences from school or social functions are results of the illness that can significantly impact adolescents and children (Gil et al., 2001; Pinckney & Stuart, 2004; Wethers, 2000). Medical management and care for individuals with SCD are extremely important as they involve a lifelong commitment of intensive treatments and interventions for those who experience more severe and/or frequent complications. Although major milestones related to the prevention and management of SCD have improved lifespans from approximately 14 years in 1973 (Bloom, 1995) to approximately 42 years for males and 48 years for females (Platt et al., 1994), the death rate for adolescents and young adults remains higher than that of their peers without SCD (Shankar et al., 2005). Individuals with SCD who are 15 years of age and older and transition from pediatric care to adult medical care are at high risk for premature death shortly after the transition (Quinn et al., 2010).

Many children and adolescents with SCD are also challenged by complex psychosocial issues. These psychosocial complications can affect all members of the family. Pinckney and Stuart (2004) reported that the psychosocial factors of SCD:

> "are interpersonal (e.g., self-esteem, assertive communication difficulties), stress-producing (e.g., decreased coping strategies, decreased knowledge about sickle cell disease), and family factors (e.g., cohesion, organization and control, family support, parent–child relationship problems)" (Pinckney & Stuart, 2004, p. 5).

Sociodemographic variables such as race, gender, age, socioeconomic status, and education also affect psychosocial adjustment in children and adolescents with SCD (Brown, Kaslow et al., 1993; Edwards et al., 2005; Kell, Kliewer, Erickson, & Ohene-Frempong, 1998; Lutz, Barakat, Smith-Whitley, & Ohene-Frempong, 2004; Thompson et al, 2003). Among the myriad of factors that can have a negative impact on HRQOL and overall well-being, adolescents are at particular risk for poor adaptation and family functioning (Edwards et al., 2005; Gil et al., 2001; Panepinto et al., 2005).

Despite the growing body of research related to HRQOL in children with SCD and the associated acute and chronic stressors, there is a paucity of research regarding the multidimensional assessment of their HRQOL in comparison with children who have other chronic conditions (Bonner, 2010; Palermo et al., 2002). There are even fewer studies that have focused on factors that influence HRQOL as perceived specifically by adolescents with SCD. The purposes of this study were to describe factors that influence HRQOL in adolescents with SCD and to determine if there were relationships between HRQOL, patient-related variables, and caregiver-related variables. The research questions used to guide the study were

1) How is HRQOL described in adolescents with SCD from the perspectives of the adolescents?

2) What are the relationships between adolescent HRQOL and the patient-related variables of gender, race, disease severity, medical comorbidities, chronic transfusion therapy, and hydroxyurea use?
3) What are the relationships between adolescent HRQOL and the caregiver-related variables of family income, size of household, type of health insurance, and parental satisfaction?
4) What are the relationships between adolescent HRQOL and the combined variables from patients and caregivers?

This study will expand the research literature on adolescents with SCD by explicating the relationships of HRQOL with several patient-related and caregiver-related variables. The results will contribute information that can be used by health professionals to target specific interventions that can improve health outcomes and assist adolescents in successfully transitioning from childhood to adulthood.

Conceptual Framework

The conceptual framework used in this study was a modified version of the Conceptual Framework for Health-Related Quality of Life in Adolescents with Sickle Cell Disease derived from the conceptual framework developed by Julie Panepinto (2008; Figure 4.1). The framework by Panepinto (2008) was adapted from Crom et al. (1999) who developed the original framework to assess patient-related variables and cancer-related variables on the health status and quality of life of pediatric solid tumor survivors. Select definitions of the variables are discussed in the following sections

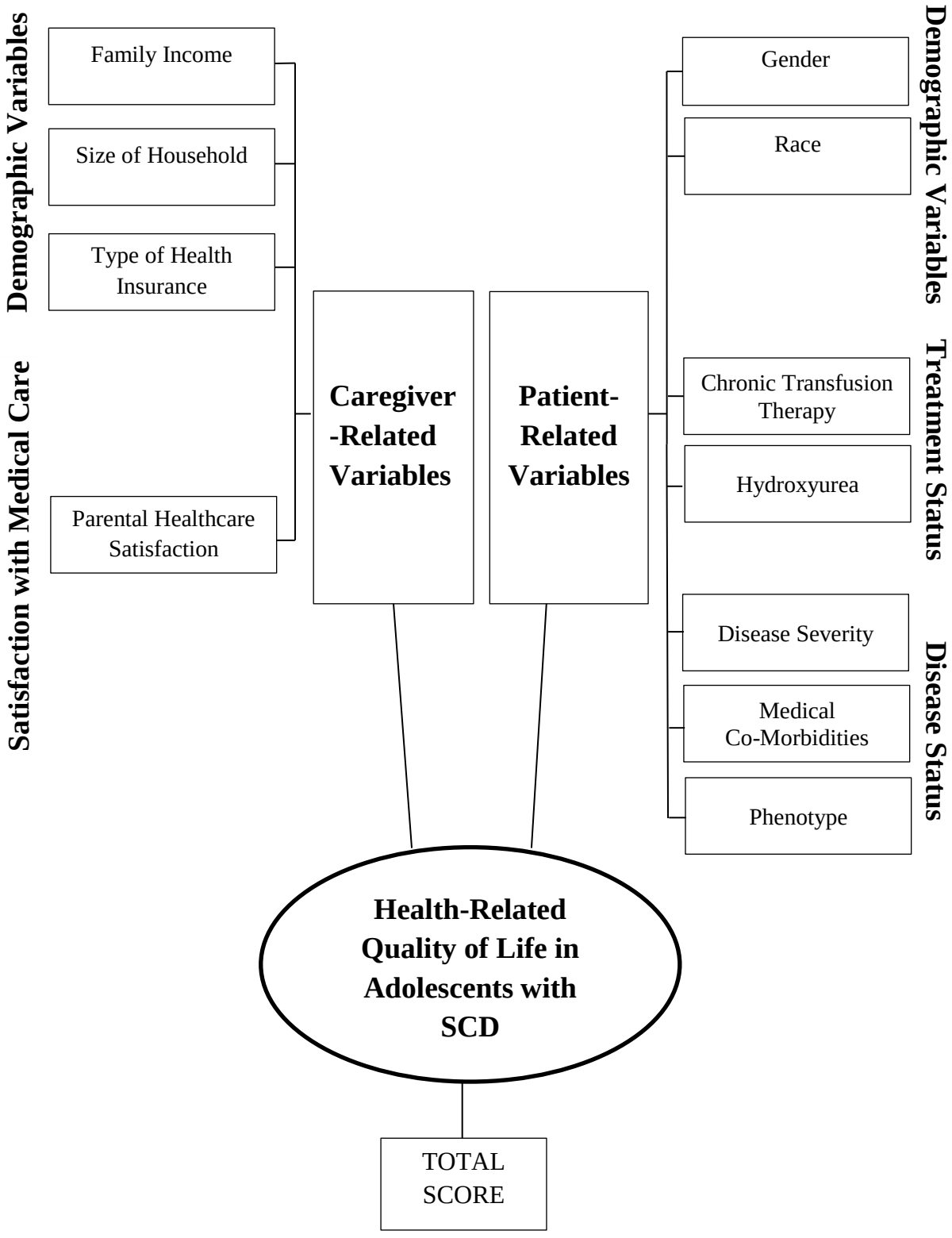

Figure 4.1. Modified conceptual framework for health-related quality of life in children with sickle cell disease. Adapted with permission from Panepinto, 2008.

Predictor Variables With Select Definitions

The patient-related variables of interest were gender, race, ethnicity, transfusion therapy, hydroxyurea use, disease severity, medical comorbidities and phenotype. The caregiver-related variables were family income, size of household, type of health insurance, and parental healthcare satisfaction. Select definitions of variables are listed below.

Transfusion therapy. In the parent study, adolescents were asked whether they received a blood transfusion within the previous year. However, in the original framework, "chronic" transfusion therapy was the specific variable identified. Chronic transfusion therapy (CTT) is the standard of care after the first infarctive stroke and usually involves exchange transfusions via erythrocytapheresis every 4 to 6 weeks (Redding-Lallinger & Knoll, 2006). CTT is also usually indicated when individuals with SCD do not improve after simple transfusion therapy.

Hydroxyurea use. Adolescents were asked if they were presently receiving hydroxyurea.

Disease severity. Categorized as mild or severe, regardless of patient's SCD phenotype. Presently, there is no specific accepted standard to determine clinical severity in SCD. Therefore, severity is often determined by past observations for each patient (Panepinto, et al., 2010). Severe status in this study refers to children with history of stroke, acute chest syndrome, greater than 3 hospitalizations for vasoocclusive pain in the prior 2 years or recurrent priapism. Mild status refers to all others.

Medical comorbidities. Adolescents were asked to identify medical conditions that they have from a list. The top five medical comorbidities identified by the adolescents were identified for analyses.

Phenotype. Phenotypes were identified from medical charts.

The caregiver-related variables of interest were: family income, size of household, type of health insurance, and parental health care satisfaction.

Family income. The parents/primary caregivers were asked to give their total family income. The information was organized based on categories of: (1) $45,0000 and greater, (2) $25,000 - $44,900, (3) less than $25,000, and (4) don't know or prefer not to answer. The categories of don't know and prefer not to answer were combined after applying the Tukey approach for multiple comparisons.

Size of household. The parents/primary caregivers were asked to indicate the total number of members in the household including the person reporting the information. Using the histogram to visualize the distribution of the data, the information was organized based on the following categories: (1) Six or more, (2) four – five, and (3) zero – three.

Type of health insurance. The information was organized based on the following categories: (1) private, (2) Medicaid/Medicare, and (3) other and none. The categories of other and none were combined after applying the Tukey approach for multiple comparisons.

Parental health care satisfaction. The Parental Health Care Satisfaction – Parent Survey, is described in the measures section below.

Outcome Variable

The outcome/dependent variable of interest was adolescent health-related quality of life as assessed by the Pediatric Quality of Life Inventory, per the self-reports of the adolescents. The total score was used to determine HRQOL scores, with higher numbers indicating better HRQOL.

Method

This research is a secondary data analysis of a cross-sectional study. The parent study is the Collaborative Data Project (C-Data), a large, multifaceted database effort that was developed to capture information from patients receiving care at comprehensive sickle cell centers (CSCCs). Dampier et al. (2010), the original project's researchers, outlined the C-Data's objectives as the

1) development of a resource for use in planning future multicenter studies in SCD,
2) formulation of standard definitions for the most common clinical complications of SCD,
3) assessment of the social and financial burden of living with SCD, and
4) collection of information relevant to the daily quality of life of individuals with SCD. (p. 2)

Participants and Procedures

A total of nine CSCCs encompassing 19 clinical sites were involved in C-Data. Participants in this sample were enrolled from March 2005 through September 2008 and included 564 adolescents with SCD, ages 13–18 years, and their caregivers. Because this secondary data set was redacted, the ages for the adolescents were categorized as 1 group with a range of 13-17 years rather than individual ages to further protect the identity of the participants. The adolescent participants were considered eligible for the study if they satisfied the age criteria, received care at one of the CSCCs, were seen within the last 24 months, and were expected to return to the same CSCC for follow-up care (Dampier et al., 2010). As long as the adolescent participants met all other study criteria, they were eligible to participate in the study regardless of SCD genotype.

As participants initially enrolled for the study, the baseline data was gathered and included demographic data from the enrollment form, clinical data, psychosocial and health behavior interviews, and data from age-appropriate Pediatric Quality of Life Inventory

Version 4.0 (PedsQL) HRQOL modules. The PedsQL HRQOL forms were self-administered, and only the PedsQL versions completed by the adolescents were used in this study. Participants with documented diagnoses of developmental delay used developmentally appropriate HRQOL forms. Participants with limited literacy were read the questions (Dampier et al., 2010). The Institutional Review Board of the University of North Carolina at Chapel Hill approved the current study under an exempt status based on the secondary data analysis design.

Measures

Demographic and disease characteristics. As part of the original C-Data research, retrospective medical chart abstractions were completed for all participants. This included information on SCD complications, medications, treatments, surgeries, medical tests, and lab tests. As a result of collecting information from the enrollment forms, the medical charts, psychosocial and health behavior interviews, the following patient-related data were retrieved: gender, race, ethnicity, SCD phenotype, disease severity, medical comorbidities, history of chronic transfusion therapy, and hydroxyurea use. Data retrieved on caregivers included family income, size of household, health insurance, and parental healthcare satisfaction.

Parental health care satisfaction. The Health Care Satisfaction Module – Parent Survey (Varni, Burwinkle, & Dickinson et al., 2004; Varni, Quiggins, & Ayala, 2000) was used by parents/primary caregivers to assess adolescent health care satisfaction The Health Care Satisfaction Module – Parent Survey is a 30-item measurement that includes six items measuring *Information,* four items measuring *Inclusion of Family,* three items measuring *Technical Skill*, three items measuring *Services,* seven items measuring *Communication,* four

items measuring *Emotional Needs*, and three items measuring *Overall Satisfaction*. The overall reliability of the scale was α=.96.

HRQOL. The PedsQL Teen Version was used by the participants to assess HRQOL. It is a multidimensional measurement developed to measure the fundamental aspects of health defined by the World Health Organization and the dimension of school functioning (Varni, Burwinkle, Rapoff, Kamps, & Olson, 2004). The PedsQL consists of 23 items and has self-report versions for the following age groups in years: 5 to 7, 8 to 12, and 13 to18. Parallel parent proxy reports exist for each age group. There are four subscales of the measure with scores representing physical, emotional, social, and school functioning. Mean scores are calculated based on the responses given for each item. There are two summary scores, a physical health summary score (the average of items in the functioning scale) and a psychosocial health summary score (the average of items in the emotional, social, and school functioning scales). Together, they represent the total scale score, which is made up of the average of all items and converted to a scale ranging from 0 to 100 with higher scores translating to better quality of life. The estimated time of completion for the PedsQL-Teen Version ranges from less than 4 minutes up to 10 minutes. There are two recall periods, and sound psychometric properties for it have been assessed in children and adolescents with SCD (McClellan, Schatz, Sanchez, & Roberts, 2008). In the parent study, cronbach alpha scores were greater than 0.7 for all of the parent and child report scales except for the child's report for school functioning which was 0.69 (Dampier et al., 2010).

Data Analyses

Statistical analyses were conducted using SAS software, Version 9.2. Descriptive statistics were generated for the dependent and independent variables in order to examine the

distribution of each variable (Table 4.1). Preliminary analyses involved bivariate computations to gain insight in what variables might be important predictors of adolescent health-related quality of life. The variable selection process included a statistical and theoretical approach. Potential multicollinearity among all available predictors was assessed by examining the Variance Inflation Factor (VIF). Multicollinearity occurs when two or more variables are closely related in a way that the model may not be able to assess the independent contribution of each variable (Katz, 2006).

A series of multiple regression analyses was conducted to examine the unique contributions of each individual predictor variable that comprised the conceptual framework. Various model selection methods including hierarchical, backward elimination, forward, and stepwise were used. Since Gil et al. (1989) described the hierarchical selection method as the approach that physicians often use during their assessment of patients with SCD, this selection process was applied first. In addition, hierarchical modeling is generally used to investigate a collection of known relevant factors for their ability to predict the outcome of interest. All predictors were added in forward steps and in the order according to the conceptual framework without eliminating any non-significant predictors. In step 1 of the hierarchical analysis, the patient-related variables of gender and race were entered into the model. In step 2, transfusion history and hydroxyurea history were added together to the model of step 1. Besides the R squared and overall model fit statistics, the partial F-statistic and it's corresponding p-value were calculated as a measure to indicate model improvement of step 2 over step 1(and also subsequent steps). Step 3 added the disease status variables. The caregiver model was developed in 2 steps, per the conceptual framework. Step 1 included the caregiver demographic variables and step 2 added parental healthcare

satisfaction. Finally, a combination of patient-related and caregiver-related variables were entered into a model.

Next, selection methods of backward elimination, forward and stepwise selection were applied using all predictor variables. The significance level at which the variables were entered or eliminated was set to 5% which is different from SAS default level. The final models from each of three selection methods above were compared using their Akaike Information Criteria (AIC) and Predicted Residual Sum of Squares (PRESS) selection criteria.

Results

Sample characteristics can be found in Table 4.1. The total number of adolescents with complete data in the sample was 482 with a known age range of 13-17 years rather than actual ages (and so age is not addressed in Table 4.2). The sample included 274 males (57%) and 208 females (43%). As anticipated, substantially more adolescents were Black/Black Biracial at 456 (95%). More than half (75%) of the adolescents were from households of 3-6 people, Medicaid or Medicare was the insurance for 59%, and family income was reported as less than $25,000 for 35%. Of the top 5 reported medical comorbidities, a history of sickle cell pain was reported by 427 adolescents (89%), followed by acute chest syndrome (66%), dactylitis/hand-foot syndrome (26%), persistent reactive airway disease (26%), and acute splenic sequestration (25%).

Before multiple regression analyses were conducted, the highest VIF value for any of the predictors was 3.9. Because values of VIF exceeding 10 are often regarded as an indication of serious multicollinearity (Katz, 2006), it was concluded that multicollinearity was most likely of no concern.

A simple linear regression analysis was used to examine the association between parental healthcare satisfaction and adolescent health-related quality of life ($p=0.50$). Thus, there was very little correlation between health care satisfaction and adolescent quality of life status.

Analysis of Variance (ANOVA) models were created for each of the categorical predictors along with the regression model for parental healthcare satisfaction and are summarized in Table 4.2.

Table 4.1

Sample Demographics and Disease Characteristics

Variables/Demographics	***n***	**%**
Outcome/Dependent Variable		
Adolescent Health-Related Quality of Life (Mean = 15.76)	482	73.54
Predictor/Independent Variables		
Gender		
Female	208	43.2
Male	274	56.8
Race		
Black/Black Biracial	456	94.6
Not Black/Black Biracial	26	5.4
Patient-Related Treatment Status Variables		
Transfusion Therapy		
No	125	25.9
Yes	357	74.1
Hydroxyurea Use		
No	335	69.5
Yes	147	30.5
Patient-Related Disease Status Variables		
Disease Severity		
Mild	126	26.1
Severe	356	73.9
Sickle Cell Pain		
No	55	11.4
Yes	427	88.6
Acute Chest Syndrome		

No	163	33.8
Yes	319	66.2
Persistent Reactive Airway Disease		
No	358	74.3
Yes	124	25.7
Dactylitis (Hand Foot Syndrome)		
No	356	73.9
Yes	126	26.1
Acute Splenic Sequestratio		
No	361	74.9
Yes	121	25.1
Phenotype		
SC-SB	132	27.4
SS-SB	344	71.4
Other	6	1.2
Caregiver-Related Demographic Variables		
Family Income		
$45,000 or over	86	17.8
$25,000–44,999	107	22.2
Less than $25,000	170	35.3
Don't know/Prefer not to answer	119	24.7
Size of Household		
6 or more	96	19.1
4-5	195	40.5
0-3	195	40.5
Type of Health Insurance		
Private	128	26.6
Medicaid or Medicare	285	59.1
Other or None	69	14.3
Caregiver Satisfaction With Medical Care		
Healthcare Satisfaction Module, Parent Survey	88.52	18.41

Table 4.2

Bivariate Analyses (ANOVA and Regression)

Outcome Variable = Total Functioning HRQOL Score for Adolescents with Sickle Cell Disease

Predictor Variables	**Parameter**	**Estimate**	**Standard Error**	**Probt**	***F* Value**	**ANOVA *P*-value**
Gender		.	.	.	10.81	**0.001***
	Intercept	75.57469842	0.94228398	<.0001	.	.
	Gender: Female	-4.71646359	1.43441117	0.0011	.	.

Predictor Variables	Parameter	Estimate	Standard Error	Probt	*F* Value	ANOVA *P*-value
	Gender: Male	0.00000000	.	.	.	.
Race		.	.	.	0.05	0.827
	Intercept	72.88309517	3.09304068	<.0001	.	.
	Race: Black / Black Biracial	0.69370251	3.17999714	0.8274	.	.
	Race: Not Black / Black Biracial	0.00000000	.	.	.	.
Transfusion Therapy		.	.	.	12.73	**<0.001***
	Intercept	72.04264729	0.82390645	<.0001	.	.
	Transfusion? No	5.77139374	1.61788041	0.0004	.	.
	Transfusion? Yes	0.00000000	.	.	.	.
Hydroxyurea Use		.	.	.	1.53	0.217
	Intercept	72.20164259	1.29881041	<.0001	.	.
	Hydroxyurea Use? No	1.92474174	1.55792618	0.2173	.	.
	Hydroxyurea Use? Yes	0.00000000	.	.	.	.
Disease Severity		.	.	.	19.89	**<0.001***
	Intercept	71.67141989	0.81912606	<.0001	.	.
	Disease Severity 1: Mild	7.14568117	1.60209768	<.0001	.	.
	Disease Severity 2: Severe	0.00000000	.	.	.	.
Sickle Cell Pain		.	.	.	1.19	0.276
	Intercept	73.25832857	0.76232770	<.0001	.	.
	Sickle Cell Pain No	2.46301530	2.25675219	0.2756	.	.
	Sickle Cell Pain Yes	0.00000000	.	.	.	.
Acute Chest Syndrome		.	.	.	12.92	**<0.001***
	Intercept	71.71816195	0.87143059	<.0001	.	.
	Acute Chest Syndrome No	5.38543653	1.49851991	0.0004	.	.
	Acute Chest Syndrome Yes	0.00000000	.	.	.	.

Predictor Variables	**Parameter**	**Estimate**	**Standard Error**	**Probt**	***F* Value**	**ANOVA *P*-value**
Persistent Reactive Airway Disease		.	.	.	8.29	**0.004***
	Intercept	70.05568356	1.40432221	<.0001	.	.
	Persistent Reactive Airway Disease No	4.69033725	1.62947901	0.0042	.	.
	Persistent Reactive Airway Disease Yes	0.00000000	.	.	.	.
Dactylitis (Hand Foot Syndrome)		.	.	.	12.34	**0.001***
	Intercept	69.35152135	1.38738904	<.0001	.	.
	Dactylitis No	5.67007562	1.61434659	0.0005	.	.
	Dactylitis Yes	0.00000000	.	.	.	.
Acute Splenic Sequestra-tion		.	.	.	1.33	0.249
	Intercept	72.10881206	1.43185502	<.0001	.	.
	Acute Splenic Sequestration No	1.91006316	1.65450836	0.2489	.	.
	Acute Splenic Sequestration Yes	0.00000000	.	.	.	.
Phenotype					8.56	**0.004***
	Intercept	72.22275484	0.84539996	<.0001		
	Phenotype 1: SC-SB	4.69633468	1.60538328	0.0036		
	Phenotype 2: SS-SB	0.00000000				
Family Income		.	.	.	3.83	**0.010***
	Intercept	71.38363120	1.19787938	<.0001	.	.
	Family Income: Don’t Know or Prefer not to answer	0.67987799	1.86676019	0.7159	.	.
	Family Income: $45,000 or over	6.19184915	2.06673049	0.0029	.	.

Predictor Variables	Parameter	Estimate	Standard Error	Probt	*F* Value	ANOVA *P*-value
	Family Income: $25,000-$44,999	3.97818191	1.92735221	0.0396	.	.
	Family Income: Less than $25,000	0.00000000	.	.	.	.
Size of Household		.	.	.	1.03	0.359
	Intercept	74.66744322	1.12823151	<.0001	.	.
	Household Size: 6 or more	-2.72858734	1.99271532	0.1716	.	.
	Household Size: 4-5	-1.50101223	1.59556030	0.3473	.	.
	Household Size: 0-3	0.00000000	.	.	.	.
Type of Health Insurance		.	.	.	7.57	**<0.001***
	Intercept	71.24969673	0.92081134	<.0001	.	.
	Insurance 1: Private	5.55452071	1.65401978	0.0008	.	.
	Insurance 2: Other or None	5.69054691	2.08568032	0.0066	.	.
	Insurance 3: Medicaid or Medicare	0.00000000	.	.	.	.
Parental Healthcare Satisfaction		.	.	.	0.46	0.496
	Intercept	71.18561062	3.52994072	<.0001	.	.
	Parental Healthcare Satisfaction	0.02658882	0.03904148	0.4962	.	.

Note. The outcome variable is the total functioning HRQOL score for adolescents with sickle cell disease. The significant predictors of adolescent HRQOL at the bivariate stage of analysis were gender ($p = 0.0011$), transfusion therapy ($p = 0.0004$), disease severity (< .0001), acute chest syndrome (0.0004), persistent reactive airway disease (0.0042), dactylitis (hand foot syndrome) (0.0005), phenotype (0.0036), family income (0.0099), and type of health insurance (0.0006). ANOVA = Analysis of Variance, HRQOL = health-related quality of life. *$p < 0.05$

Table 4.3 summarizes the results of the hierarchical multiple regression analyses described above. As indicated, patient-related variables were entered into the model first. After including patient demographics in step 1, the model was significant (*p=0.005*). Step 2

provided a significant improvement to the model (*p=0.020*) by adding treatment status variables. Step 3 included the addition of patient disease status variables and the change to the model was marginally significant (*p=0.051*). The caregiver-variable-adjusted model was significant (*p=0.004*) upon adding the demographic variables in step 1. However, the addition of parental healthcare satisfaction did not provide a significant improvement (*p=0.998*). The final combined model included the same steps 1-3 above of the patient-variable model, followed by the addition of caregiver demographics in step 4 which generated an insignificant adjustment (*p=0.279*). Finally, in step 5, parental healthcare satisfaction was added and did not contribute to an improved model (*p=1.0*).

Table 4.3

Results of Hierarchical Multiple Regression Analyses

Steps	Model	R2	ANOVA *F*-Value	ANOVA *P*-Value	Partial *F*-Value	Partial *P*-Value
1	Patient -Gender -Race	0.02221	5.44	0.0046	5.44	**0.005***
2	Patient -Transfusion? -Hydroxyurea?	0.05966	5.96	< .0001	9.32528	**0.020***
3	Patient -Disease Severity -Medical Comor-bidities -Phenotype	0.09078	4.21	< .0001	3.17589	**0.051***
1	Caregiver -Family Income - Household Size -Type of Health Insurance	0.04334	3.07	0.0036	3.07	**0.004***

Steps	Model	R2	ANOVA *F*-Value	ANOVA *P*-Value	Partial *F*-Value	Partial *P*-Value
2	Caregiver - Parental Healthcare Satisfaction	0.04444	3.75	0.0056	0.07736	0.998
1	Full Model Patient Gender & Race	0.02221	5.44	0.0046	5.44	**0.005***
2	Full Model Patient -Transfusion? -Hydroxyurea?	0.05966	5.96	< .0001	9.32528	**0.020***
3	Full Model Patient -Disease Severity -Medical Comorbidities	0.09078	4.21	< .0001	3.17589	**0.051***
4	Full Model Caregiver -Family Income -Household Size -Type of Health Insurance	0.11928	3.44	< .0001	1.34446	0.279
5	Full Model Caregiver -Parental Healthcare Satisfaction	0.11928	3.25	< .0001	0.00002	1.000

Note. * $p < 0.05$.

The final model of backward elimination, forward and stepwise methods is summarized in Table 4.4. This model includes the five significant predictors for HRQOL in adolescents with SCD. Reduced adolescent HRQOL was reported for: (1) female gender as an indicator compared to males, and (2) adolescents with a history of receiving transfusions as compared to those with no history of receiving transfusions. Better adolescent HRQOL

was reported for (3) adolescents with mild disease severity compared to those with severe disease severity. As for the two significant predictors related to health insurance, (4) adolescents with private insurance reported better HRQOL compared to those with Medicaid or Medicare, and (5) adolescents with other or no health insurance reported better HRQOL compared to those with Medicaid or Medicare.

Table 4.4

Final Multiple Linear Regression Model

Predictor Variables	**Category**	**Estimate**	**Standard Error**	**P-Value**
Gender	Female	-5.1	1.41	**<0.001***
	Male	0		
Transfusion History	No	3.8	1.74	**0.029***
	Yes	0		
Disease Severity	Mild	5.2	1.72	**0.003***
	Severe	0		
Insurance Type	Private	4.1	1.62	**0.013***
	Other or None	6.2	2.03	**0.003***
	Medicaid or Medicare	0		

Note. The outcome variable is the total functioning HRQOL score for adolescents with sickle cell disease. This final model was generated by all 3 variable selection procedures. HRQOL = health-related quality of life. * $p < 0.05$.

Discussion

This is a secondary data analysis of HRQOL for 482 adolescents with SCD using a well-established multidimensional HRQOL measurement. This secondary analysis is the only

known study using self-report responses from as many as 482 adolescents. After conducting a series of multiple regression analyses to examine the contributions of the predictor variables based on the conceptual framework, the final model of backward elimination, forward and stepwise methods was used. Hierarchical regression analyses indicated a significant improvement in the model at the stage of adding patient treatment status variables and only a marginally significant improvement when patient disease status variables were added. Interestingly, in the hierarchical regression model, the caregiver-variable-adjusted model was significantly related to adolescent HRQOL upon adding the demographic variables alone. However, once parental healthcare satisfaction was added, there was no improvement. This finding suggests that caregiver demographics of family income, size of household, and type of health insurance have a significant impact on the HRQOL of adolescents with SCD. This is consistent with previous studies that examined the independent influence of SES and related variables on child and adolescent adaptation (Barbarin & Christian, 1999, Barbarin et al., 1999, Devine et al., 1998, Garfinkel, 1996, & Lemanek et al., 1986). Psychosocial and adaptational challenges in children and adolescents with SCD may be explained by SES factors notwithstanding illness and disease related factors due to poverty among African American children (Barbarin et al., 1999, Garfinkel, 1996).

Consistent with the extant literature, female gender as compared to male gender (Dampier, Ely, Brodecki, & O'Neal, 2002; Dampier et al., 2010; Palermo et al., 2002; Platt) and a history of transfusion therapy compared to no history of transfusion therapy (Boga, Kozanoglu, Ozdogu, & Ozyurek, 2007; Stengenga et al., 2004; Wayne, Kevy, & Nathan, 1993) were significant predictors of reduced HRQOL. One explanation for lower HRQOL in

females is that caregivers tend to be more protective of girls regarding physical limitations, imposing more physical restrictions. Future studies should be conducted to determine if females have more medical comorbidities, greater disease severity, or other indications of disease-related issues that would warrant more physical limitations than males. Research to examine moderation effects to gender would help address this issue.

CTT is usually indicated for stroke prevention in SCD patients with deteriorating disease who do not improve after receiving simple transfusions (Redding-Lallinger & Knoll, 2006; Stegenga, Ward-Smith, Hinds, Routhieaux, & Woods, 2004). Thus, CTT is most often associated with severe SCD (Boga et al., 2007; Wayne et al., 1993). Moreover, CTT for children has been described as rigorous and time consuming. The chronic and sometimes unpredictable course of receiving blood transfusion therapy for SCD is an indicator for reduced HRQOL in children (Stegenga et al., 2004), particularly in adolescents who may already be overwhelmed with challenges related to the developmental stage of adolescence. Between the side effects of allo-immunization and iron overload, experienced by some children, to the lengthy infusions involved in CTT that sometimes last as long as 8 – 10 hours at least 5 days/weekly, CTT directly influences quality of life in children (Hankins et al., 2005). CTT was also associated with reduced HRQOL in a sample of children, ages 6-12 years, in their ability to participate in school activities as well as the requirement for hospitalization (Stengenga et al., 2004). Strategies targeted at minimizing potential side effects must be implemented for adolescents receiving CTT. Additionally, patients must be prepared for the often long and frequent hours associated with CTT.

The other three variables that were significant predictors for HRQOL in the adolescents were (1) mild disease status compared to severe disease status, (2) private

insurance compared to Medicaid or Medicare, and (3) other or no health insurance status compared to Medicaid or Medicare. As expected, adolescents with mild disease status reported greater HRQOL than adolescents with severe status. Since severe disease status included affected children with a history of stroke, acute chest syndrome, greater than 3 hospitalizations within the last 2 years, or recurrent priapism (mild disease status included all other affected children), this result was anticipated. As for the significant health insurance-related variables, adolescents with private health insurance reported better HRQOL compared to adolescents with Medicaid or Medicare. Reasons for this could be related to lack of primary care providers and medical homes, as well as socioeconomic challenges experienced by adolescents with Medicaid. Children with special health care needs (i.e. sickle cell disease) are more likely to have Medicaid than their peers (Loprest & Wittenburg, 2005). Previous healthcare utilization studies reported significantly more emergency department visits, drug claims, and inpatient hospital admissions for children who had SCD and Medicaid health coverage compared to children with SCD who had private insurance (Amendah, Mvundura, Kavanagh, Sprinz, & Grosse, 2010; Mvundura, Amendah, Kavanagh, Sprin, & Grosse, 2009). Healthcare expenditures for children with SCD who have Medicaid are much lower than expenditures for affected children who have private insurance, even though health care utilization is greater among Medicaid recipients (Amendah et al., 2010; Boulet, Yanni, Creary, & Olney, 2010; Mvundura et al., 2009). This is likely related to lower payments and reimbursement to providers for Medicaid claims. Therefore, disparities such as denied appointments and longer wait times for physician appointments, particularly specialists, exist among children who have Medicaid and Childrens's Health Insurance Program (CHIP) compared to privately insured children (Baisgaier, & Rhodes, 2011).

Finally, children who have Medicaid health insurance coverage tend to have fewer resources, lower health literacy, lower income and education and sometimes a language barrier (Skinner, & Mayer, 2007). This combination of factors can lead to reduced HRQOL in children with SCD who have Medicaid compared to children with private insurance.

Interestingly, adolescents with other or no health insurance reported better HRQOL compared to adolescents with Medicaid or Medicare. Access to the data set was not available to determine what specific information comprised the "other" health insurance category. A small segment of the population still includes children who do not qualify for Medicaid because of family income, yet do not have private insurance because the family is unable to afford it (Holahan, Uccello, Feder, & Kim, 2000). State children's health insurance programs (CHIP) are often designed to capture these uninsured children. However, for the children who are not eligible to be covered under the CHIP, an uninsured status can be risky. Given the chronic and often unpredictable nature and complications related to SCD, the lack of health-care coverage could be a major risk factor for receiving compromised quality of care (McCavit, Hua, Zhang, Ahn et al, 2011). Moreover, an uninsured status has been associated with decreased length of hospital stays for patients with SCD (McCavit et al., 2011). One explanation for better HRQOL in adolescents who have other or no health insurance compared to Medicaid or Medicare is that children who have Medicaid often have more health problems and comorbidities than children with no insurance or private insurance. Children with greater comorbidities and health problems tend to have reduced HRQOL compared to children with fewer comorbidities. The finding of better HRQOL among adolescents with other or no health insurance could also be related to strengths that African Americans often possess, including values that support resilience (Boyd-Franklin, Morris, &

Bry, 2003; Boyd-Franklin, Aleman, Steiner, Drelich, & Norford, 1995; Radcliff et al., 2006; Murry, Bynum, Brody, & Willert, et al., 1995). Moreover, adolescents with SCD tend to show resilience related to personal adjustment, based on their appraisal and stress-producing capacities (Ziadni, Patterson, Pulgaron, Robinson, & Barakat, 2011).

There are strengths and limitations associated with this study. The greatest strength is the large sample of adolescents from multiple sites reported during the original study. This large sample size is helpful in making stronger generalizations related to the overall findings. Another strength is that the PedsQL was used to assess HRQOL. The PedsQL is a well-established multidimensional measurement with sound psychometric properties and has been used and validated in several studies involving children and adolescents with SCD. HRQOL was uniquely reported by the adolescent participants. Although it is ideal to have both child and proxy reports when assessing children's HRQOL (Eiser & Morse, 2001a; Rebok et al., 2001; Varni, Limbers, & Burwinkle, 2007), the child-reported outcomes are crucial because children have unique perceptions of their overall health and well-being (Eiser & Kopel, 1997; Eiser & Morse, 2001; Palermo et al., 2000; Stegenga et al., 2004).

As for limitations, the redacted data only included the range of ages for the participants instead of their specific ages. This limited the ability to analyze the data in a manner that would discern patterns related to specific ages of the participants and age-specific correlations with other outcomes. For example, in a previous study, child demographics and disease-related complications were significant predictors associated with poor HRQOL with increasing age and female gender in children and adolescents with SCD (Palermo et al., 2000). Secondly, only the total score was generated for HRQOL using the PedsQL. Score results that are itemized based on specific scales and summary scores

(physical functioning and psychosocial functioning summary scores) generate data specific to high and low functioning (i.e. patients may have significant scores related to poor HRQOL on physical functioning scales). Distinct scale and summary score results can help determine more specific and targeted interventions for health professionals and educators. Next, a potential concern with the effect of chronic transfusion therapy on HRQOL is that the participants were asked to respond yes or no to whether they received a transfusion within the year prior to the enrollment period. A period up to one year prior to enrollment in the study does not necessarily indicate that the adolescents were on chronic transfusion therapy. Finally, resistance factors such as family functioning, coping and appraisal were not assessed in this study. Resistance factors play a significant role in psychosocial adaptation for children and adolescents with SCD (Barakat et al., 2006; Burlew et al., 2000). Overall psychosocial adaptation influences HRQOL. Future studies should include methods to assess variables such as cognitive appraisal, family functioning, family management styles, social support, self-esteem, coping, and appraisal.

Conclusion

Several factors emerged as significant predictors of HRQOL as perceived by adolescents with SCD. Factors associated with better HRQOL included having mild disease severity compared to severe, and having other or no health insurance compared to Medicaid or Medicare. Factors associated with worse HRQOL included female gender as an indicator compared to male gender, having a history of transfusion therapy compared to no history, and having private insurance compared to Medicaid or Medicare.

Although HRQOL has been influenced by psychosocial and demographic factors in adolescents with SCD, these findings support the notion that biomedical factors such as

disease severity also play a significant role in HRQOL for this population. Having a severe disease status requires rigorous, often unpredictable, and long-term care for affected patients. Additionally, access to comprehensive medical care for children with SCD who have public coverage (i.e. Medicaid) or no insurance, is often compromised due to barriers such as difficulty getting appointments, and long waiting times as compared to affected children with private insurance. Because children with Medicaid tend to have more health care needs and comorbidities than children with private insurance, these children may be at risk for suboptimal care. Health professionals are in pivotal positions to develop family-focused interventions that target care during various stages of the disease process. Adolescents and young adults need consistent and quality care, established medical homes, and routine follow-up. Moreover, family-focused interventions aimed at improving management and disease-related complications are crucial. These strategies are imperative for improving overall adjustment and optimal HRQOL for adolescents with SCD and their families.

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CHAPTER 5

FINDINGS AND IMPLICATIONS

The significant progress in the prevention and management of complications related to SCD has improved the average lifespan for individuals with SCD such that survivorship has been extended to a median age of 42 years for males and 48 years for females (Bloom, 1995; Platt et al., 1994). Biomedical, psychosocial, developmental, physical, and environmental factors contribute to optimal family functioning and HRQOL in affected individuals and their families (Gustafson, Bonner, Hardy, & Thompson, 2006). Adolescence is a key developmental stage as children transition from childhood to adulthood. The burden of having SCD can be even more devastating for adolescents as they are often concerned with challenges related to physical, sexual, and emotional maturation (Edwards et al., 2005). Adolescents have varied responses for how they adapt to and cope with the complications related to SCD. In light of these factors, this is an opportune time to assess family functioning as it relates to overall HRQOL in adolescents with SCD. The findings from these studies help explicate strategies to accomplish this.

Study Results

Aim 1

To synthesize and appraise existing research related to family functioning and child and adolescent outcomes in families of children and adolescents with SCD.

A total of 23 studies were identified in the integrative literature review found in Chapter 2. One mixed method, one qualitative measure, and twelve quantitative measures were used to assess family functioning. The studies identified were useful in elucidating the variability and complexity associated with family functioning in children and adolescents with SCD from the perspectives of various family members. The key findings were organized according to the following categories: (a) behavioral problems, (b) social competencies, (c) coping processes, (d) moderator and mediator effects of family functioning, and (e) sociodemographic factors. Overall, the findings suggested that families with high levels of family functioning were associated with children who had better adaptation and adjustment. Low levels of family functioning were associated with affected children who had poorer adaptive outcomes. Family functioning assessments were influenced by issues such as number and relationships of informants, settings, study designs, family functioning measures, scales, parenting styles, and coping mechanisms.

General family functioning and parental influences on child coping and appraisal of stressful situations had a significant impact on how children ultimately responded to challenges related to SCD. Although somewhat inconsistent, the role of family functioning as a moderator and mediator was explicated along with likely reasons for the variation in findings. Internalizing behaviors of anxiety and depression emerged as key symptoms that were negatively associated with adaptation and adjustment in children and adolescents with SCD (Brown et al., 1993; Brown & Lambert, 1999; Burlew et al., 2000; Thompson, 2003). Many existing studies rely primarily on the mother as the sole informant in rating adjustment issues in SCD (Brown et al, 1995; Casey et al., 2000; Thompson et al., 2003). Key issues

were raised relevant to including multiple informants in future studies. Techniques other than self-report assessments were also encouraged (i.e., behavioral and observational).

One of the most compelling deficits related to the findings in most of these studies was the lack of culturally sensitive measurement designs and processes for assessment. Many family functioning measures included standardized constructs that were not culturally sensitive for the population under study. Culturally appropriate measurements and research techniques that account for accomplishments and challenges over time must be included in future research (Brown & Lambert, 1999; Drotar 1997).

Aim 2

To identify measures used to assess HRQOL in children and adolescents with SCD.

A total of seven HRQOL measures were identified in this review found in Chapter 3. These measures were unique for evaluating HRQOL in children. As of the date of the submission of this research, no SCD-specific measures for HRQOL had been developed. Accordingly, health-care providers must identify and determine the most useful tool for measuring HRQOL in children with SCD. Of the seven measures, the PedsQL emerged as the most valuable HRQOL tool for measuring HRQOL in children and adolescents with SCD.

Several factors were considered in making comparisons and ultimately selecting the PedsQL as the most beneficial HRQOL measure. The general characteristics of the various tools varied greatly, though some of the items on the measures were similar. Because there is no one routine or generally accepted definition of HRQOL, one of the main concerns that arose from the findings was a lack of consistency in measuring the same underlying constructs related to HRQOL. These findings suggested a need to develop future measures

based on sound theoretical foundations. The findings also indicated that the measures generally lacked developmental structure. Because children are unique in that they grow and develop at different ages with different considerations for progress, it is imperative to provide for developmental aspects related to HRQOL over time.

As with measures related to family functioning, the HRQOL measures lacked domains and constructs related to cultural dimensions. Spiritual and environmental dimensions were also missing from the measures. Cultural considerations continue to be a growing concern for children and adolescents with SCD. Sociocultural factors that include race, ethnicity, and culture influence and shape perceptions of health and disclosures (Hocking & Lockman, 2005; Radcliffe et al., 2006). Additionally, these sociocultural considerations may be determinants for whether patients are at risk or resilient to disease-related conditions. Religion was also key for providing a more culturally sensitive component to research designs related to HRQOL in the population under study. Primary characteristics for all measures were compared and contrasted and depicted in a matrix. Issues related to child versus parent/caregiver proxy reports were also discussed as well as the identification of the actual primary caregiver.

These findings validated the selection of the PedsQL as the most practical HRQOL tool for use in children and adolescents with SCD that presently exists. The PedsQL has been used in and validated by many studies on children with SCD. It is also brief, practical, diverse, and can be used independent of or in conjunction with other disease-specific measures. The PedsQL is also responsive to change over time.

Aim 3

To describe factors that influence HRQOL in adolescents with SCD.

A series of multiple linear regression models were conducted based on specific patient-related and caregiver-related variables from the Modified Conceptual Framework for Health-Related Quality of Life in Children With Sickle Cell Disease (Panepinto, 2008). The total sample, after statistical analyses, included 484 adolescents of the original sample of 564. According to authors from the parent study, the adolescent participants were from multiple sites over diverse geographical regions (Dampier et al., 2010). The secondary data set was redacted and protected such that only data related to the age range of 13 to 17 years was included. Therefore, specific ages were unfortunately eliminated from the model. However, findings related to adolescents as a group were reported

Findings resulted in five significant predictors for HRQOL in adolescents with SCD: (1) female gender compared to male, (2) a history of transfusion therapy compared to no history of transfusions, (3) mild disease severity compared to severe disease, (4) private insurance compared to Medicaid or Medicare, and (5) other or no health insurance compared to Medicaid or Medicare.

Consistent with existing literature, the following factors were related to reduced HRQOL in the adolescents: (1) female gender compared to male gender, and (2) a history of transfusion therapy compared to no history of transfusion therapy. In previous studies, these factors were associated with reduced HRQOL on physical dimensions for patients with SCD (Dampier et al., 2010; Palermo et al., 2000 Platt et al., 1991, Redding-Lallinger & Knoll, 2006, Stegenga et al., 2004). One explanation for lower HRQOL in females is that caregivers tend to be more protective of girls regarding physical limitations, imposing more physical restrictions. Future studies should be conducted to determine if females have more medical comorbidities, greater disease severity, or other indications of disease-related issues

that would warrant more physical limitations than males. Chronic transfusion therapy is a rigorous and time-consuming process that is most often associated with severe SCD (Boga et al., 2007). Thus, it was expected that adolescents with history of transfusions would have poorer HRQOL compared to those with no history of transfusions.

Better HRQOL was reported for adolescents with mild disease status compared to severe disease status and is reflected in the literature as such (Panepinto, Hoffmann, Pajewski, 2009; Panepinto, Pajewski, Foerster, & Hoffman, 2008). The chronic, often frequent, and sometimes unpredictable course of SCD complications along with the financial and psychosocial challenges can be very burdensome to individuals with severe disease status and less challenging for patients with mild disease status. Adolescents who had private health insurance reported better HRQOL compared to those with Medicaid or Medicare. Children with Medicaid tend to have fewer resources, lower health literacy, lower income and education and sometimes a language barrier (Skinner & Mayer, 2007). Additionally denied appointments and longer wait times for physician appointments exist among children who have Medicaid and coverage by the Children's Health Insurance Program (CHIP) compared to privately insurance children (Baisgaier, & Rhodes, 2011). These factors can lead to reduced HRQOL in children with SCD.

Interestingly, adolescents who had other or no health insurance reported greater HRQOL scores compared to those with private insurance. One explanation for this could be that children who have Medicaid often have more health problems and comorbidities than children with no insurance or private insurance.

Additionally, better HRQOL in this population, despite lack of health-care coverage, Medicaid, or Medicare, may be attributed to the overall resilience portrayed by African

Americas, particularly in times of great distress (Boyd-Franklin, 2003; Boyd-Franklin et al, 1995; Radcliff et al., 2006). Additionally, adolescents have been known to have better family functioning outcomes, even when their families have great conflict and less cohesion (Barakat et al., 2007).

Implications for Research

The findings from this program of research indicate that intervention measures should be developed around child and family variables. Interventions that reduce family conflict and increase family cohesion must be implemented since family conflict is a risk factor for behavior problems in children with SCD (Burlew et al., 2000; Thompson, Armstrong et al., 1999, Thompson et al., 2003). Culturally sensitive and developmentally appropriate designs are also warranted for optimal HRQOL and family functioning assessment. Factors such as religion, prayer, spirituality, and sociocultural resources must be included. Studies must also account for socioeconomic status and stressors related to poverty. Longitudinal studies are more useful for capturing developmental concerns and determining family functioning experiences over time (Hurtig, 1994).

Future research methods for data collection should include more qualitative and mixed methods strategies. Measures other than self-report should be considered (i.e. observational, behavioral). Health professionals should serve as informants and data collection and interviews should be conducted in settings other than health care settings. Research conducted in multiple settings is useful in determining issues that may be unique to specific settings. Research studies should include guiding frameworks.

Finally, health professionals and other professionals who work with children (educators, social workers, specialists) must collaborate to develop family-focused

interventions that will improve overall HRQOL and optimal adaptation for children and adolescents, as well as their family members.

Implications for Practice

These studies highlight key issues related to improved practice management and clinical priorities for health care providers who care for children and adolescents with SCD. As the life expectancy continues to improve, along with more treatment options, health care providers must be able to effectively assess family functioning and HRQOL in the population under study. Health professionals must also be able to identify and respond to factors that may influence HRQOL in adolescents.

Adolescents continue to be considered at risk for optimal adaptive behavior, particularly relating to social competence (Barakat et al, 2006). A multidisciplinary approach is necessary for the complex management of the disease and the comprehensive care required for this population. Family-focused interventions are crucial, and steps must be taken to maintain as much cohesion and as little conflict as possible since family cohesion and conflict are associated with adaptive functioning in children with SCD. Additionally, given that adolescents and young adults are at greater risk for problems and early death during the period shortly after transitioning from pediatric to adult health care (Quinn, Rogers, McCavit, & Buchanan, 2010), effective HRQOL assessment techniques and appropriate interventions should be targeted for adolescents with SCD, during these risky periods. Finally, in as much as SCD occurs primarily in African Americans, care and services should be rendered in a culturally and developmentally sensitive manner based on some of the study recommendations.

The medical management of and health-care delivery for adolescents with SCD are often complicated by physical and psychosocial stressors (Pinckney & Stuart, 2004), limited resources, cultural differences, socioeconomics, and educational background. Findings from these studies will also assist health professionals and educators who must work collaboratively so that affected children and family members can receive optimal care, support, services, and programs in order to improve HRQOL, psychological adaptation, and health outcomes. Strategic and family-focused interventions must be employed by health professionals to improve HRQOL outcomes for children and adolescents with SCD as well as their families. Additionally, factors that influence HRQOL must be identified and HRQOL must be effectively assessed and evaluated in affected adolescents. This will aid in determining how the chronic course of SCD illness, complications, and treatments are experienced by affected children and adolescents (Panepinto, 2008).

Conclusion

A growing body of research supports several deficits related to HRQOL and family functioning in children, and particularly adolescents, with SCD. The findings in this program of research indicated that effective and strategic assessments of family functioning and HRQOL are imperative for affected children, adolescents, and their families. Family functioning issues must be identified, defined, and assessed over the course of the SCD illness. Family-focused interventions should be developed to achieve optimal adaptation and HRQOL. Psychometrically sound and theoretically based measurements should also be used to assess HRQOL. Health professionals and researchers must be knowledgeable regarding appropriate measurements that will improve practice efficiency and assessment. Additionally, factors that influence HRQOL must be identified and acknowledged so that

strategies can be developed to improve the overall well-being and health outcomes for affected individuals and families throughout their lifespan.

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