Quality of Life in Latino and Non-Latino Youth aged 8-18 Years with Sickle Cell Disease: A Mixed Methods Study

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ABSTRACT

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While sickle cell disease (SCD) primarily affects those of African heritage, Latinos, the second most commonly affected group, are often not included in studies of youth with SCD. The purpose of this mixed methods study was to complete the linguistic translation validation of the PedsQL SCD Module, a recently validated disease specific quality of life (QOL) instrument, for use in Spanish speaking parents and youth with SCD (Aim 1). Using this instrument, QOL of Latino and African American youth with SCD who participated in an NIH funded study to improve adherence to hydroxyurea therapy (R21 NR013745) were compared (Aim 2) and factors associated with QOL examined (Aim 3). For Aim 1, 10 Latino youth with SCD (n = 5 age, 8-12 years; n = 5 age, 13-18 years) and their parents completed a demographic survey, Spanish version of PedsQL SCD Module and an audio-taped cognitive interview. Across age groups, all reported that the translated PedsQL Sickle Cell Disease Module was easy to understand and had minimal suggestions for further improvement. For Aims 2 and 3, secondary baseline data from 28 youth (mean age 13.6 $\pm$ 2.4 years) with sickle cell disease and their parents who participated in the HABIT feasibility trial were analyzed using descriptive statistics, Wilcoxon Signed Rank and Mann-Whitney test, and linear regression modeling. Latino youth reported higher QOL scores than non-Latino youth for all QOL measures except for the Worry II subscale of the disease-specific QOL measure while Latino parents reported higher QOL scores than non-Latino parents for all subscales except for three: the disease-specific Worry I, Worry II, and Communication I subscales. Poorer disease specific QOL was predicted by greater youth-parent discordance regarding sickle cell disease responsibility for parents (β = -3.07, p = 0.04) but not youth. Poorer disease-specific QOL was predicted by greater number of both emergency room visits during the prior year for both youth (β = -2.89, p = 0.005 [self-report]; β = -5.07, p = 0.002 [electronic medical records]) and parents (β = -3.41, p = 0.002 [self-report]; β = -6.93, p = <0.001 [electronic medical records]) and hospitalizations during the prior year (youth β = -5.72, p = <0.001 [self-report]; β = -7.56, p = 0.03 [electronic medical records]; parents β = -6.48, p = <0.001 [self-report];

$\beta = -9.16$, $p = 0.02$ [electronic medical record]). Based on these findings, greater youth-parent discordance regarding sickle cell family responsibility and greater utilization of emergency rooms and/or hospitals were associated with poorer disease-specific QOL.

Table of Contents

List of Tables

List of Figures

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Dedication

I dedicate this dissertation to Nigel, Rod, Niro, and Nia Osborne.

Chapter I: Introduction

Background

Sickle cell disease is one of the most prevalent genetic disorders in the United States (National Human Genome Research Institute, 2014). It affects approximately 90,000 to 100,000 Americans of African, Spanish, Saudi Arabian, Indian, and Mediterranean descent; worldwide, sickle cell disease affects millions of people (W. Wang et al., 2013), with about 300,000 infants born each year (Strouse, 2016). In the U.S., children of African descent experience the highest prevalence of sickle cell disease (Dale, Cochran, Roy, Jernigan, & Buchanan, 2011; Fisak, Belkin, von Lehe, & Bansal, 2012; Newland, 2008) with a prevalence of 1 in 365 (Hassell, 2010), while children of Latino descent experience the second highest prevalence of sickle cell disease with a prevalence of 1 in 16,000 (Hassell, 2010).

Sickle cell disease occurs as a result of a β-globin gene variation known as hemoglobin S (Hb S) or sickle hemoglobin (Ashley-Koch, Yang, & Olney, 2000). Various forms of sickle cell disease exist. The most common forms of sickle cell disease are hemoglobin SS (a person has 2 copies of hemoglobin S gene) and Hemoglobin SC (a person inherits the hemoglobin C gene from one parent and the hemoglobin S gene from the other).

Regardless of the sickle cell disease type (hemoglobin SS, hemoglobin SC, etc.), a person may be classified as having either mild or severe sickle cell disease (Panepinto, Pajewski, Foerster, Sabnis, & Hoffmann, 2009). In their study of 178 youth and parents: 104 youth with sickle cell disease and 74 youth without sickle cell disease, Panepinto et al. (2009) classified youth with a history of sickle cell-related stroke and/or acute chest syndrome, 3 or more hospitalizations for vaso-occlusive crisis, and/or recurrent priapism in the past 3 years as having severe disease. Youth without any of the above symptoms were considered as having mild sickle cell disease.

Those with sickle cell disease are at risk for acute complications like painful vaso-occlusive crisis and priapism, and chronic complications that affect various organs and systems (Darbari & Panepinto, 2012). While symptom severity differs from person to person, sickle cell disease is characterized by episodic pain as a result of oxygen deprivation in tissues and organs that may cause complications like organ destruction (Bhatia & Sheth, 2015) and acute chest syndrome, described as having pulmonary infiltrate with chest pain, fever, tachypnea, wheezing, or cough, is a leading cause of mortality in adults

(Elmariah et al., 2014). Other symptoms may include anemia, which results in shortness of breath, fatigue, and developmental delays in youth (Cherry et al., 2012).

Sickle cell disease pain symptoms may be acute, chronic, or a combination of both (Okpala & Tawil, 2002), and may range from mild to severe. Mild pain is usually treated at home with oral analgesics (Ballas, Gupta & Adams-Graves, 2012), while severe painful crisis is usually treated in the emergency room or hospital (Amid & Odame, 2014; Ballas, Gupta, & Adams-Graves, 2012) with opioids, non-steroidal anti-inflammatory drugs, and intravenous hydration in addition to other pain relieving therapies (Okpala & Tawil, 2002). Substantial analgesic use as a result of chronic pain often results in damage to tissues and organs (Ballas, Gupta, & Adams-Graves, 2012; Lehrke et al., 2004). Quality of life in individuals with sickle cell disease needs to be measured to inform clinicians who are unfamiliar with sickle cell disease-related pain on how sickle cell disease impacts QOL (McClish et al., 2005).

Sickle Cell Disease Therapy

There is no single best treatment for sickle cell disease. However, depending on symptom, several treatment options are available and can be broadly classified as preventative or therapeutic (Lukens, 1981).

Preventative symptom management. Screenings and vaccinations are used prophylactically to manage symptoms of sickle cell disease. Diagnosis is primarily conducted using a special type of blood test that tests for sickled hemoglobin (Pack-Mabien & Haynes, 2009), and may be used in newborns and adults. Early diagnosis allows for awareness of the diagnosis and the initiation of prophylactic measures like vaccinations against pneumococcal bacteria (Quinn, Rogers, & Buchanan, 2004). As a prophylactic measure, the CDC recommends pneumococcal polysaccharide (Pneumovax) vaccine (given from 2 years of age) and pneumococcal conjugate (Prevnar) vaccine (given from 2 months old to 6 years of age at specific time-points) for youth with sickle cell disease (“Pneumococcal Vaccines: CDC Answers Your Questions” http://www.immunize.org/catg.d/p2015.pdf, n.d.). Twice daily penicillin is also recommended starting in early infancy and continuing throughout age 5 and older, in addition to routine health management with a health care provider who is an expert in sickle cell disease management (Gaston, et al., 1986). In low-income countries, infection is the most common cause of morbidity and mortality (Amid & Odame, 2014). In countries like the U.S. penicillin is used prophylactically to prevent infections like

Streptococcus pneumoniae and Haemophilus influenza type b (Quinn, Rogers, McCavit, & Buchanan, 2010).

Transfusion therapy is used to prevent stroke in children who have abnormal transcranial Doppler ultra-sonographic examinations (Adams & Brambilla, 2005). For over 2 decades red blood cell transfusion has been used to prevent stroke in sickle cell disease (Pegelow et al., 1995) by reducing the concentration of hemoglobin S (Amid & Odame, 2014). Most transfusions for sickle cell disease are simple red blood cell transfusion; red cell exchange transfusion, though effective, is used less frequently (Swerdlow, 2006). Chronic red blood cell transfusion (transfused at least monthly) is considered the main treatment for the prevention of stroke in children with sickle cell disease (Styles & Vichinsky, 1994; Swerdlow, 2006). Red blood cells transfusion can be prescribed as chronic treatment in cases where hemoglobin S levels are elevated or as an acute treatment in emergency situations to decrease hemolysis and prevent further vaso-occlusion and damage to organs (Swerdlow, 2006).

Therapeutic symptom management. Hydrocarbamide (hydroxyurea) and L-glutamine oral powder (Endari) are the 2 disease-modifying agents used in the treatment of sickle cell disease. For the past 2 decades, hydroxyurea was the only medication that was approved by the U.S. Food and Drug Administration (FDA) for therapeutic treatment of sickle cell disease (Rodgers, Dover, Noguchi, Schechter, & Nienhuis, 1990). Hydroxyurea is an antineoplastic drug that is used to treat neoplastic diseases and other diseases, including sickle cell disease. Hydroxyurea has long been considered the pharmacologic agent that is capable of enhancing the quality of life (QOL) of persons with sickle cell disease (Voskaridou et al., 2010). Hydroxyurea primarily works by increasing fetal hemoglobin levels by inducing stress red blood cell production (Green & Barral, 2011), and has been shown to decrease morbidity in persons with sickle cell disease by reducing incidences of chest syndrome and vaso-occlusive crises by almost 50% in adults (Charache et al., 1995; Steinberg et al., 2003).

Although hydroxyurea has not been approved by the FDA as a disease-modifying agent for sickle cell disease in children, it continues to be essential in preventing complications in this population (Estepp et al., 2016). Several clinical trials to examine the safety and effectiveness of hydroxyurea in youth with sickle cell disease have shown that hydroxyurea increased fetal hemoglobin levels in this population (Scott, Hillery, Brown, Misiewicz, & Labotka, 1996; Ware et al., 2002; Ware et al., 2016). Ware et al.

(2002) for example, reported that in their study of 53 youth with sickle cell disease, hydroxyurea decreased symptoms in all participants, with increased percentages of fetal hemoglobin levels ranging from 0.1% to 26.4%.

In July 2017, the FDA approved Endari for patients with sickle cell disease aged 5 years and older ("ENDARI- glutamine powder, for solution," n.d.). Endari works by reducing acute complications of sickle cell disease. To date, 2 placebo-controlled trials (phase 2 study, n = 70 and phase 3 study, n = 230) were conducted in pediatric and adult patients with sickle cell anemia or sickle β^0-thalassemia. Both studies established the safety and effectiveness of Endari in pediatric patients aged 5 or older and in adult patients. Endari holds promise to reduce complications of sickle cell disease and should therefore be explored in additional studies.

Hematopoietic stem cell transplant (HSCT) involving bone marrow donated from a healthy donor is currently the only cure for some patients with sickle cell disease (Bhatia & Sheth, 2015). Even though HSCT has proven to be the only cure, this procedure is mostly limited to patients who live in high-income countries, which excludes the majority of sickle cell disease patients worldwide (Amid & Odame, 2014). Additionally, hematopoietic stem cell transplantation is not used widely because of donor availability, cost, and potentially life-threatening complications (Al-Anazi, 2015).

Quality of Life Measurement

Throughout history and up until the 1950s, mortality rate was used to determine the health of the nation (Linder, 1966). Social indicators and societal resources like the gross national product, infant mortality, and social mobility, were seen as QOL indicators (Power, Bullinger, & Harper, 1999). In the 1960s a new curiosity in a person's perspective of QOL based on their emotional well-being, physical state, and social functioning began to take root (Power et al., 1999). In 1995, the World Health Organization QOL Group defined QOL as a person's perception of the interaction between their physical health, psychological state, independence level, social relationships, environment and their cultural and value systems, in relation to their goals, expectations, concerns, and standards. Traditionally, the parent's perspective of the child's QOL (proxy-report) had been used to assess the child's perception of QOL. Compared to proxy-report, QOL measurements obtained from self-report are more valuable as they provide a subjective report of a person's perspective of disease effect and treatment (McClellan, Schatz,

Sanchez, & Roberts, 2008). Physical, mental, and social development in youth are inherently different from that of an adult's, therefore even though overall QOL definitions apply to youth and adults alike, using a QOL instrument that is not tailored to the youth's experiences, activities, and contexts and are not directly relevant to the youth's age, would be incorrect. Children and adolescents may have different concerns in relation to health and QOL. The daily activities of youth, such as school functioning and play activities, need to be included in questionnaires in order to capture an accurate picture of the youths' perception of his/her QOL (Eiser & Morse, 2001). Additionally, the language of the questionnaire needs to be adapted so that is comprehensible to the appropriate age group being studied (Eiser & Morse, 2001). When the youth is too young or is physically and/or mentally unable to provide self-report, a parent proxy-report may be completed instead (Varni, Limbers, & Burwinkle, 2007). Assessing QOL either by youth self-report or by parent proxy-report or primary caregiver-report has become an integral part of pediatric research and in the trajectory of treatment by assessing disease burden in youth along with their parents/caregivers (Eiser & Morse, 2001).

Quality of life instruments. Quality of life is measured with questionnaires that are either generic or disease-specific. Disease-specific QOL instruments were designed to measure the effect of specific disorders and are valid measures of specific diseases or conditions (Guyatt, Deyo, Charlson, Levine, & Mitchell, 1989; Clark & Eiser, 2004). Several disease-specific instruments have been validated and used as outcome measures of QOL in youth with various diseases/disorders such as cancer (Yeh & Hung, 2003) and diabetes (Ingersoll & Marrero, 1991). Until the development of the Pediatric QOL Sickle Cell Disease Module in 2012, disease-specific QOL appraisal was not possible for children living with sickle cell disease.

Generic QOL questionnaires for the pediatric population usually include domains that measure emotional, physical, social, and school functioning and are not specific to a disease type (Varni, Seid, & Kurtin, 2001). Generic QOL instruments like the Pediatric Quality of Life (PedsQL) Generic Core Scales (Varni, Seid, & Rode, 1999), may not capture a person's concerns regarding a particular disease due to the broad phrasing of questions (Meltzer, 2001; Merikallio, Mustalahti, Remes, Valovirta, & Kaila, 2005).

Need for linguistically validated instruments in the language of the population being studied. Most questionnaires used in clinical trials/settings are developed in English-speaking countries

(Wild et al., 2009). Since QOL instruments are being increasingly used across different cultures in diverse settings, assessment measures have to be validated in the respective languages and cultures of the population being researched (Bullinger & Von Mackensen, 2008; Wild et al., 2005; Wild et al., 2009). To achieve this, original instruments have to be translated and validated to produce a new language version that is conceptually equivalent with the original instrument, is applicable, clear, and easy to understand by the target culture (Wild et al., 2009).

Culture and quality of life. Quality of life perception is in part due to cultural influences. Culture is defined as a system of meanings that influences a particular population's way of living and are transferred from generation to generation (Rohner, 1984). Culture is an important, multi-dimensional concept in QOL that includes: (1) ethnicity, defined as the foundation of a person's culture that determines how a person behaves and how he/she views him/herself and the connection to ancestors (Kagawa-Singer, 2000); (2) interconnectedness, defined as the quality and demands of family life and social relationships, attitudes/beliefs, and spirituality i.e., religious beliefs and practices (Ashing-Giwa, 2005; Bullinger & Von Mackensen, 2008; Maramaldi, Berkman, & Barusch, 2005; Wong, Lee, Ang, Oei, & Ng, 2009); and (3) acculturation, defined as the phenomena that occurs when groups of individuals with differing cultures repeatedly intermingle with resulting variations in the original pattern of either or both groups (Marin & Gamba, 1996; Olmedo, 1979; Redfield, Linton, & Herskovits, 1936). Acculturation can occur over a long period of time (Burnam, Telles, Karno, Hough, & Escobar, 1987; Marin & Gamba, 1996; Olmedo, 1979) with no universally agreed upon length of time when a person has to become acculturated to a specific culture (Burnam et al., 1987; Laroche, Kim, & Hui, 1997). Some Latinos for example, adapt sufficiently to North American culture while others experience difficulty adjusting, which often leads to difficulty managing social, physical, or emotional problems (Cuellar, Arnold, & Maldonado, 1995; Neff & Hoppe, 1993; Perez-Stable, Napoles-Springer, & Miramontes, 1997).

Perception of QOL was shown to be different across cultural groups (Ashing-Giwa, Tejero, Kim, Padilla, & Hellemann, 2007; Fu et al., 2007; Scott et al., 2008). In their cross-cultural study of African-, Asian-, European-, and Latina-American survivors of breast cancer, Ashing-Giwa et al. (2007) reported that perception of QOL was lower in Latino participants compared to non-Latino participants. Scott et al. (2008) likewise reported that in their study of 11 cultures worldwide, participants from Latin America

reported almost the lowest QOL: only participants from South Asia reported QOL that was lower than those from Latin America. Based on this knowledge, this researcher decided to include cultural aspects in the examination of QOL in this dissertation.

Conceptual Model

This dissertation is guided by Ashing-Giwa's Conceptual Model of Health-Related QOL (Ashing-Giwa, 2005; Ashing-Giwa & Lim, 2011; Graves et al., 2012). This conceptual model (Figure 1) was chosen because it most accurately reflects the domains that play important roles in QOL. Ashing-Giwa and Lim's conceptual model comprises 2 contextual levels: systemic-level context, which includes cultural and socio-ecological factors, and individual-level context which contains general health status.

Systemic-level contexts such as demographic information, health care satisfaction, and socio-ecological factors that pertain to social support, life burden, and socio-economic status, comprise variables that are expected to assert a broad yet weaker impact on QOL (Ashing-Giwa & Lim, 2011). Life burden is one of the key aspects of QOL that consist of familial (e.g. having children, disease, etc.) functional (education, housing, etc.) and neighborhood (environment, transportation, etc.) stresses. Life burden for youth with sickle cell disease may include familial stressors like having another family member in the home with sickle cell disease (Ashing-Giwa & Lim, 2011). Traditionally, the effects of life burden of sickle cell disease on QOL were measured by the number of hospitalizations and vaso-occlusive crises or deaths (Charache et al. 1995; Platt et al. 1994). More recently, the focus has been on understanding the impact of life burden of sickle cell disease on the QOL of youth and their families in order to better assist in the decision-making process regarding the most effective ways of preventing or treating sickle cell disease complications (Panepinto, 2008; Panepinto, Hoffmann, & Pajewski, 2009).

Individual-level contexts include variables that are expected to have a stronger influence and directly predict QOL, such as medical factors, general health status, and psychological well-being (Ashing-Giwa, 2005; Ashing-Giwa & Lim, 2011). General health status may be measured using components such as the physical component summary subscale from an established instrument (RAND 12-item Health Survey), and 1 item measuring the number of co-morbidities (Ashing-Giwa & Lim, 2011). For this dissertation research, Ashing-Giwa's Conceptual Model of Health-Related QOL was adapted for use in youth with sickle cell disease to explore the relationship between socio-ecological factors (life

burden) and general health status (poorer health) and disease-specific QOL in Latino and non-Latino youth with sickle cell disease and their parents.

Significance

Prior to the development of the PedsQL Sickle Cell Disease Module, researchers used self-concept instruments like the Piers-Harris self-concept scale to measure QOL in African American children aged 7-18 years with sickle cell disease (Hurtig & White, 1985; Kumar, Powers, & Allen, 1976). Within the last 5 years, a disease-specific QOL measurement for youth with sickle cell disease has been developed (Panepinto et al., 2013). Currently, measurement of disease-specific QOL of youth with sickle cell disease is limited to those who are comfortable completing English language questionnaires. Sickle cell disease QOL research needs to include the Latino population, which is the second highest population diagnosed with sickle cell disease in the U.S. Families of many youth with sickle cell disease living in New York City have emigrated from Caribbean Spanish-speaking countries. From 2000 to 2008, Latino newborns accounted for almost 12% of newborns born with sickle cell disease in New York State (Y. Wang et al., 2013). Some Latinos living in the U.S. have poor English proficiency and as result prefer to read and view information in their native language (De Jesus & Xiao, 2012). In a recent survey of Latino parents and adolescents, 59% of parents and 8% of youth were more comfortable with reading health information in Spanish (Smaldone et al., 2015). Therefore, Spanish language survey instruments that have been linguistically validated using a rigorous methodology are needed.

Racial and/or ethnic disparities in QOL of youth have received minimal interest in research (Nelson, 2002). Ethnicity and culture may be associated with how a person views his/her QOL (Aziz & Rowland, 2002; Ashing-Giwa, 2005). Because Latinos are culturally and ethnically different from African Americans, research conducted in African American samples may not be generalizable to Latinos. Research on QOL in sickle cell disease pediatric population must include Latinos given that Latinos are the fasting growing population in the U.S., the largest ethnic or race minority in the U.S. (Centers for Disease Control and Prevention, 2013), and the second largest population diagnosed with sickle cell disease in the U.S. (Huttle, Maestro, Lantigua, & Green, 2015; Y. Wang et al., 2013). By 2050 it is estimated that Latinos will constitute 30% of the total U.S. population (Centers for Disease Control and Prevention, 2013); therefore, as the number of Latinos in the U.S. increases, the incidence of sickle cell

disease will also increase. This exploratory mixed methods study examined QOL in Latino and non-Latino youth aged 8-18 years with sickle cell disease and their parents.

Contribution to Future Knowledge

Research has shown that health disparities between diverse cultures exist in our society. A linguistically validated QOL instrument in this growing sickle cell disease population would enable better understand QOL in Latino youth with sickle cell disease and the impact of present and future therapies on QOL in this population.

Aims and Hypotheses

Specific Aim 1: To complete the linguistic validation process of the Spanish version of the PedsQL Sickle Cell Disease Module for parents and youth aged 8-12 and 13-18 years.

Specific Aim 2: To compare perception of disease-specific and generic QOL in a sample of Latino and non-Latino youth with sickle cell disease aged 10-18 years and their parents who participated in a NIH funded study to improve adherence to hydroxyurea therapy.

Hypothesis 2.1: Youth perception of disease-specific and generic QOL will be higher compared to parent proxy perception.

Hypothesis 2.2: Perception of disease-specific and generic QOL in Latino youth and parents will be lower compared to non-Latino youth and parents.

Specific Aim 3: To explore the relationship between disease-specific QOL as it relates to sickle cell disease life burden and poorer health in Latino and non-Latino youth with sickle cell disease aged 10-18 years and their parents.

Hypothesis 3.1: Youth with sickle cell disease and their parents with higher sickle cell disease life burden will have lower disease-specific QOL compared to those with lower sickle cell disease life burden.

Hypothesis 3.2: Youth with poorer health and their parents will have lower disease-specific QOL compared to those with better health.

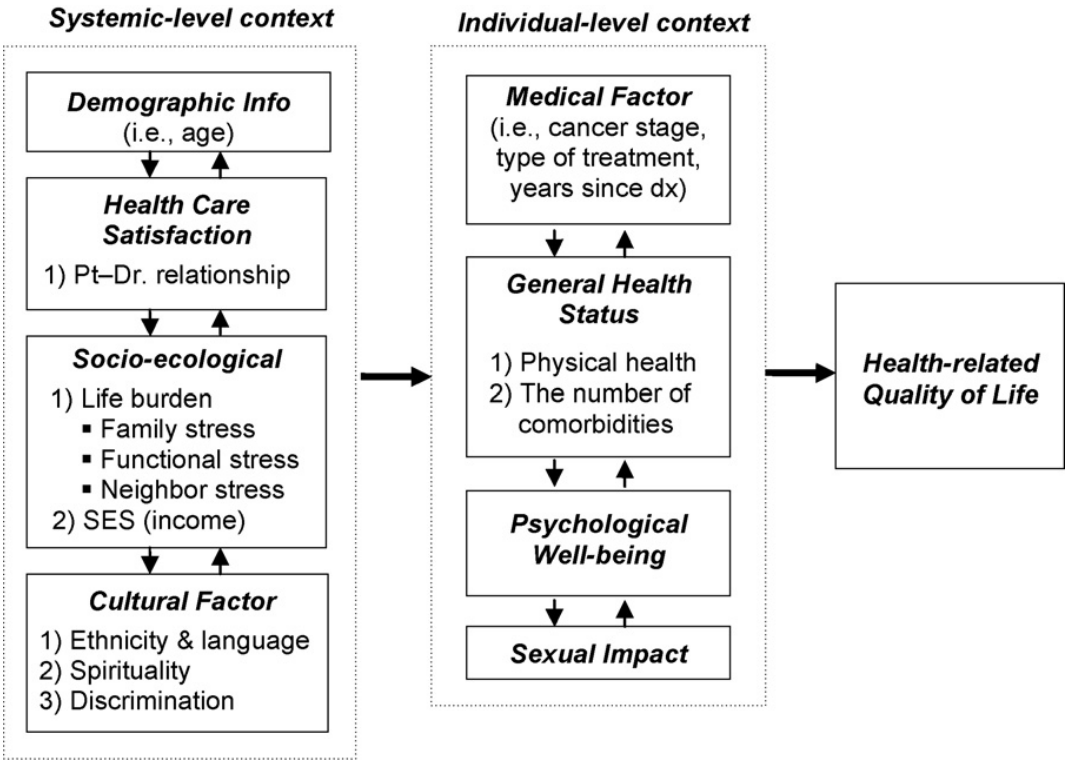

Figure 1. Conceptual model of health-related QOL (Ashing-Giwa & Lim, 2011). Variables within each systemic-level context and individual-level context can be correlated with each other (Ashing-Giwa & Lim [2011], Ashing-Giwa [2005]).

Chapter II: Literature Review

Overview

This chapter presents the methods and findings of 2 integrative literature reviews: (1) disease-specific QOL instruments in youth, the primary area of interest in this dissertation research, and (2) cultural factors associated with QOL to better comprehend the role of culture in perception of QOL. Both integrative literature reviews were guided by Cooper's (1982) and Whittemore and Knafl's (2005) updated integrative review methodology.

Integrative Review Method

The integrative review method is the most inclusive type of research review that facilitates the inclusion of experimental and non-experimental research simultaneously to more fully understand a phenomenon or healthcare problem of concern (Whittemore and Knafl, 2005). The integrative review method has 5 stages: (1) Problem identification and purpose of review, (2) Literature search, (3) Data evaluation and quality appraisal, (4) Data analysis employing data reduction where studies are divided into subgroups according to study design to facilitate analysis; data display using graphs, tables, and flowcharts; data comparison to identify associations between variables, conclusion drawing and verification of results, and (5) Presentation of findings that captures the depth and breadth of the topic including limitations.

Disease-specific Quality of Life Instruments in Youth

Problem Identification and Purpose of Review

Literature related to QOL measurement in youth suggest that QOL may be measured using generic and/or disease-specific QOL instruments by youth self-report and/or parent proxy-report. Additionally, it is important to understand QOL perspectives of normal/healthy youth compared to those with chronic illnesses, as it may improve understanding regarding how the burden of having a chronic illness affects youths' daily activities. For youth with chronic illnesses, measurement and comparison of self-reported symptom-related perceptions of QOL may help to illuminate which chronic illnesses youth perceive as having the most disease burden.

Currently, there are a variety of disease-specific QOL instruments available for youth self-reported and parent proxy-reported QOL that are reliable and valid (Panepinto et al., 2013; Varni et al.,

2014). However, the following areas pertaining to QOL in youth were not readily available and needed to be reviewed to better understand how disease-specific QOL is measured in youth with various diseases: (1) comparison of disease-specific QOL scores in youth, (2) diseases most frequently measured in youth, and (3) comparison of QOL scores by self-report and parent proxy-report. *Therefore, the purpose of this integrative review was to examine literature pertaining to disease-specific QOL instruments in youth as relating to types of diseases measured and QOL scores.*

Literature Search

A literature search using Scopus, Web of Science, PubMed, and PsycINFO databases was carried out. Observational studies of disease-specific QOL instruments in youth were examined for inclusion. Search terms used were: “disease specific quality of life AND children” and “quality of life”. During search, records were excluded if they were: non-English, review, non-pediatric, report or conference papers, non-human, or qualitative, Citations were limited to full text entries between the publication dates 1942 to 2017. Additional records were excluded after screening titles, abstracts and full text articles if necessary. Studies were read and were included if: (1) youth were 0-18 years old, (2) study used established QOL instrument(s) and/or newly developed instrument(s) completed by youth and/or parent/guardian/caregiver, (3) the instrument was disease-specific and outcome measured was QOL, (4) total QOL scores and standard deviation were reported, (5) the article was published in English, and (6) psychometric properties of the instrument were reported. Studies were excluded if: (1) study participants were older than 18 years, (2) studies used only generic QOL instruments, (3) instrument was not pediatric-specific, (4) study was a review of literature, (5) study was qualitative, (6) the article was published in a language other than English, (7) QOL was not the outcome of interest, or (8) total QOL scores and/or standard deviation not reported.

Data Evaluation and Quality Appraisal

The quality of all articles was reviewed by1 reviewer using the Mixed Methods Appraisal Tool (MMAT) – Version 2011 (Pluye et al., 2011). MMAT is a comprehensive instrument for appraising methodological quality of 5 design methods: (1) qualitative, (2) quantitative randomized controlled (trials), (3) quantitative non-randomized, (4) quantitative descriptive and (5) mixed methods. Qualitative and quantitative sections each have 4 questions to appraise study quality. The mixed methods section has 3

additional questions conjunction with the qualitative and appropriate quantitative section. Two screening questions common to all study designs must be answered prior to moving on to completion of the design-specific criteria. If the response to either or both screening questions is “No” or “Can’t Tell” further appraisal of the study was is warranted. Based on the MMAT criteria, a survey response rate of 60% or greater is acceptable for non-randomized controlled trials, cohort, case-controlled, and cross sectional studies; complete outcome data ≥ 80% is acceptable for non-randomized controlled trials, cohort, case-controlled, and cross sectional studies. Following study appraisal, a quality score is calculated by dividing the number of criteria met by the total number of criteria and then multiplying by 100.

A random sample of 20% of the studies was appraised for quality by a second reviewer and inter-rater reliability was assessed. Guided by the MMAT, strengths and weaknesses of studies were evaluated and presented in narrative form. Methodological quality was appraised and a quality score computed for each study; these are presented in narrative and graphical forms.

Data Analysis

Data were extracted from each study including study aim, instrument description, author’s name and year of publication, study design, intended audience, disease/disorder, and Latino participant sample representation for each study. Data were synthesized into tables that present psychometric properties of disease-specific QOL instruments by disease state.

Presentation of Findings

In this section, results of literature search of disease-specific QOL instruments are evaluated and presented. Responses to MMAT were evaluated, appraised, and synthesized into graphs. The reliability and validity of instruments are synthesized into tables. Because perception of QOL may differ between youth and parent, the difference between perception of QOL in youth and parent was examined and presented. The syntheses of subscales across instruments are presented. Additionally, studies were examined in order to address whether Latinos were adequately represented particularly for diseases where Latinos are disproportionately affected.

Literature Search. Figure 2 provides details of the literature search. The initial search using search term “disease specific quality of life AND children” and “quality of life” resulted in identification of 1876 records. Additional screening and cross-checking for duplicity resulted in removal of 97 records,

with 1779 records remaining. Additionally, 1,472 additional records were excluded as a result of screening titles, abstracts, and full text articles if necessary. Inclusion/exclusion criteria were applied leaving 307 full-text articles to be assessed for eligibility. An additional 268 articles were excluded after applying inclusion and exclusion criteria. A total of 33 cross-sectional and 6 cohort studies were included for review. Studies ranged in years of publication from 2003 (Otley et al., 2003) to 2017 (Mizuno, Ohya, Nagao, DunnGalvin, & Fujisawa, 2017).

Data evaluation and quality appraisal. All studies received satisfactory responses to both MMAT screening questions. Figure 3 displays results of MMAT appraisal. A major strength is that all studies used appropriate instrument(s) that possessed a clear origin and validity, and clearly defined independent and dependent variables (criterion 3.2). For example, Varni and colleagues (2004) investigated the reliability, validity, and initial responsiveness of the PedsQL 3.0 Asthma Module and compared it to the PedsQL 4.0 Generic Core Scales and the Pediatric Asthma QOL Questionnaire (PAQOL) in a sample of 529 children aged 2-16 years with asthma and their parents and 730 healthy children aged 2–18 years (Varni, Burwinkle, Rapoff, Kamps, & Olsen, 2004) hypothesized that asthma-specific symptoms/problems would correlate with lower Generic Core Total Scale Scores and therefore lower overall QOL perception. They found a statistically significant difference between healthy children (higher QOL) and children with asthma (lower QOL). Another strength noted was that the majority of authors included a representative sample of the population of interest in their study (criterion 3.1).

Another of the strengths noted was that the majority of authors (34/39) reported either complete outcome data (where almost all the participants contributed to almost all measures) or survey response rate (Abdovic et al., 2013; Allan, Flett, & Dean, 2008; Botello-Harbaum, Nansel, Haynie, Iannotti, Simons-Morton, 2008; Bradley et al., 2006; Chang & Yeh, 2005; Chow et al. 2014; Davis et al., 2010; DunnGalvin et al., 2010; Franciosi et al., 2013; Gray, Denson, Baldassano, Hommel, 2011; Hartman et al., 2007; Hopkins et al., 2010; Hu et al., 2013; Iannaccone et al., 2009; Ingerski, Laffel, Drotar, Repaske, & Hood., 2010; Jaser et al., 2011; Kalyva, Malakonaki, Eiser, & Mamoulakis, 2011; Knibb et al., 2013; Kocova, Dvorackova, Vondracek, & Haberlova, 2014; MacKenzie, Roberts, Van Laar, & Dean, 2012; Marino et al., 2011; McCusker et al. 2015; Mizuno et al., 2017; Narayanan et al., 2006; Newcombe, Sheffield, & Chang, 2011;

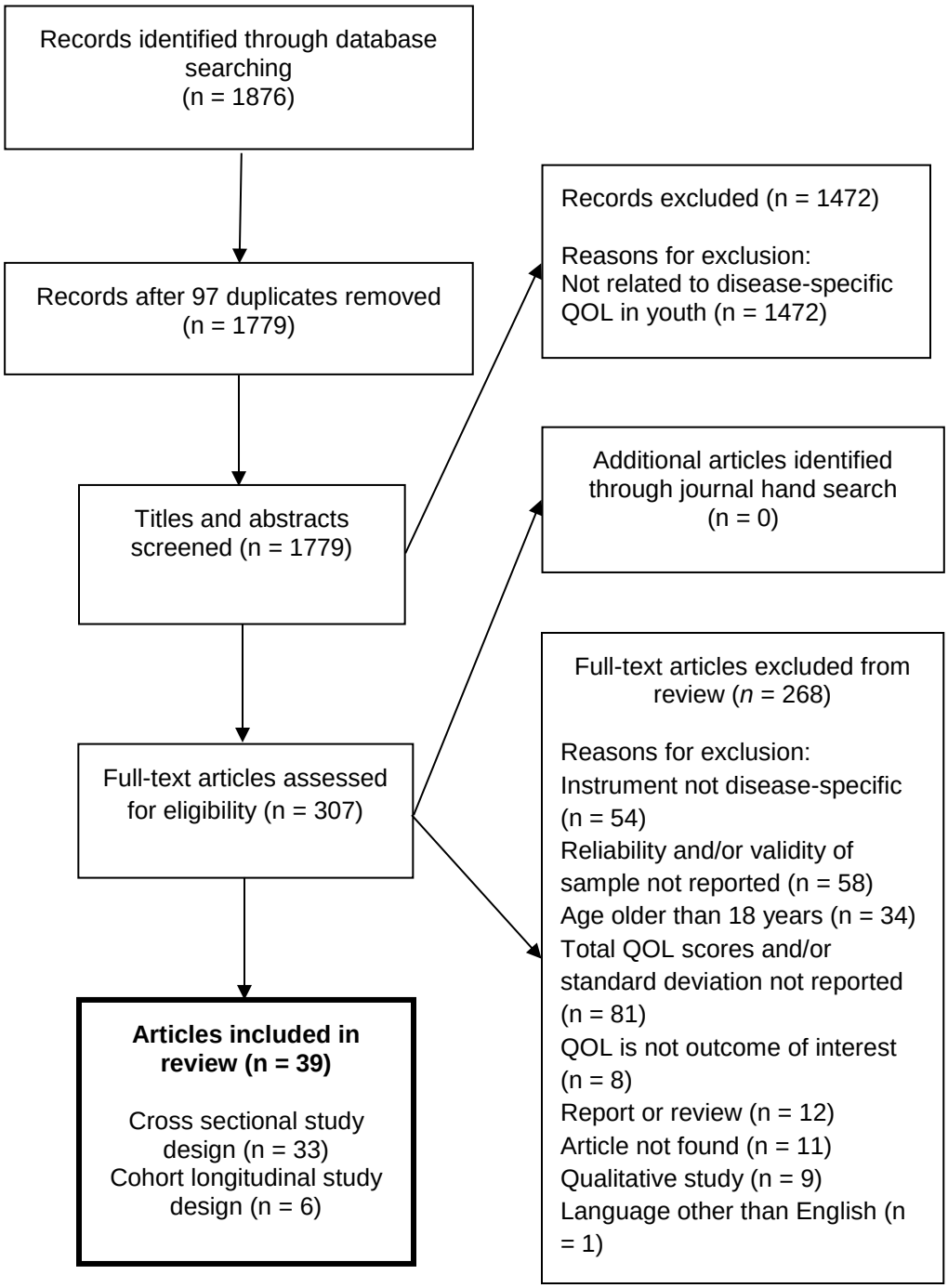

Figure 2. Flow Diagram of Literature Search of Disease-specific QOL Instruments. Results of literature search and selection process for disease-specific instruments. Format for Figure 2 adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Review Analyses: The PRISMA Statement. PLos Med 6(6):

Otley et al., 2003; Panepinto et al., 2013; Petsios et al. 2011; Pollak, Mühlan, Von Mackensen, & Bullinger, 2006; Valenzuela et al., 2006; van Doorn, Winkler, Zwinderman, Mearing, & Koopman, 2008; Varni et al., 2004; Weissberg-Benchell et al., 2010; Varni et al., 2014; Young et al., 2013; Yuksel, Yilmaz, Kirmaz, & Eser,, 2009). Five authors did not report complete outcome data (Klaassen et al., 2013; Moorthy et al., 2007; Zashikhina & Hagglof, 2014).

Seven authors mailed questionnaires to participants (Hartman et al., 2007; Knibb et al., 2013; Mackenzie et al., 2012; van Doorn et al., 2008; Weissberg-Benchell et al., 2010; Young et al., 2013; Zashikhina & Hagglof, 2014); of these, survey response rates were reported in all but1 study (Young et al., 2013). Response rates were greater than 60% for all studies except MacKenzie et al. (2012) and Weissberg-Benchell et al. (2010) (44.5% and 39% respectively).

A weakness noted was less than half of authors reported on the comparability of study groups and/or controlled for differences between groups (criterion 3.3). Bradley et al.'s (2006) study of boys with hemophilia was an exception: the researchers compared but did not control for the characteristics of Canadian and European boys with hemophilia, such as the severity and type of hemophilia, mean age in years, treatment, and QOL, using the CHO-KLAT (Canadian dataset) and the Haemo-QoL (European dataset) QOL instruments. Figure 4 summarizes the quality scores of all studies. The majority of studies met at least 2 of the 4 criteria and scored ≥ 50% in overall quality.

Data Analyses. The majority of researchers used established disease-specific instruments that measure youth and/or parent perception of QOL for a wide range of chronic illnesses affecting children such as asthma (Petsios et al., 2011; Varni et al., 2004; Zashikhina & Hagglof, 2014), Type I diabetes (Botello-Harbaum et al., 2008; Jaser et al., 2011; Ingerski et al., 2010; Kalyva et al., 2011; Valenzuela et al., 2006; Zashikhina & Hagglof, 2014), Type II diabetes (Allan, et al., 2008), epilepsy (Zashikhina & Hagglof, 2014); cancer (Chang & Yeh, 2005), chronic cough as a result of protracted bacterial bronchitis, asthma, or bronchiectasis (Newcombe et al., 2011), Duchenne Muscular Dystrophy (Davis et al., 2010), eosinophilic esophagitis (Franciosi et al., 2013), food allergy (Knibb et al., 2013; Mizuno et al., 2017), gastrointestinal symptoms (Varni et al., 2014), heart disease (Marino et al., 2011), hemophilia (Bradley et al., 2006; McCusker et al., 2015), Hirschsprung Disease or anorectal malformations (Hartman et al.,

2007), inflammatory bowel disease (Abdovic et al., 2013; Gray et al., 2011; Otley et al., 2003), influenza (Chow et al., 2014) and spinal muscular atrophy (Iannaccone et al., 2009; Kocova et al., 2014).

Eight researchers developed new instruments to measure disease-specific QOL for youth with cerebral palsy (Narayanan et al., 2006), food allergy (DunnGalvin et al., 2010; MacKenzie et al., 2012), hemophilia (Pollak et al., 2006), influenza (Chow et al., 2014), organ transplantation (Weissberg-Benchell et al., 2010), systemic lupus erythematosus (Moorthy et al., 2007), and sickle cell disease (Panepinto et al., 2013).

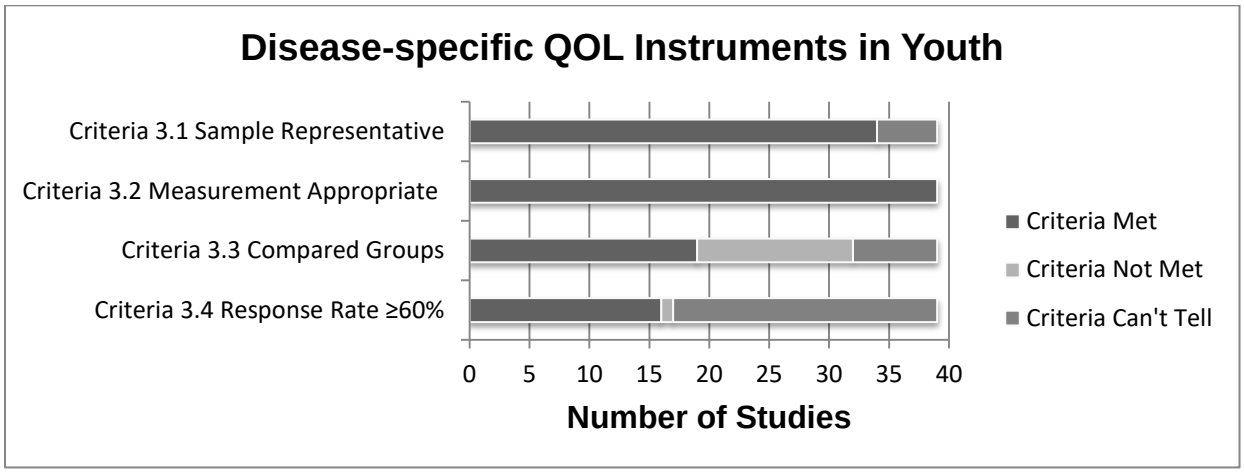

Figure 3 Methodological Quality Appraisal Assessments of All Studies

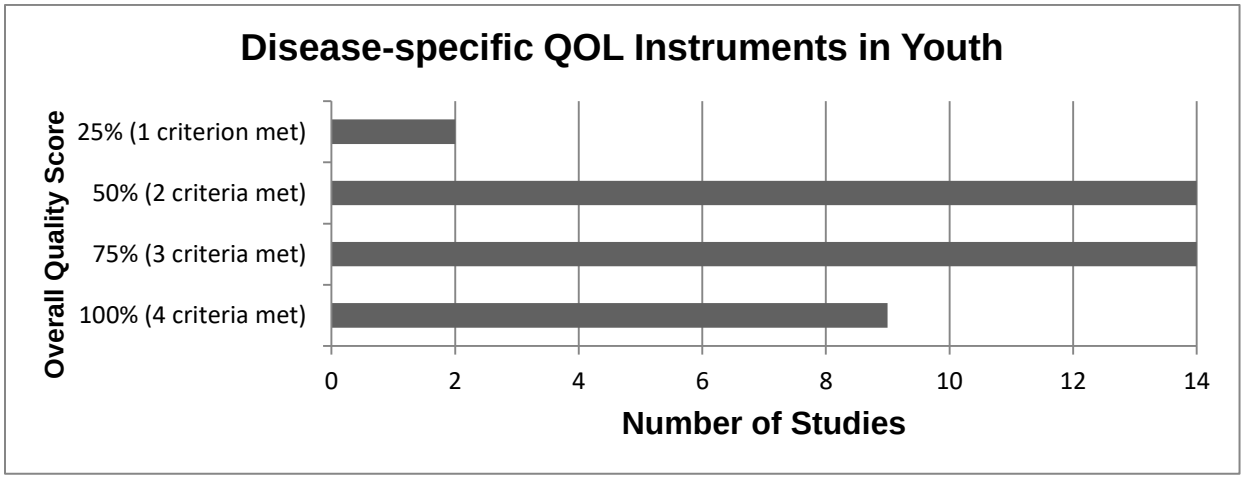

Figure 4 Number of Criteria Met for all Studies

In other studies, researchers adapted an established instrument and then examined its psychometric properties. van Doorn et al. (2008), for example, reduced the 25-item celiac disease instrument (DUX-25) to a shorter 12-item CDDUX questionnaire. Hopkins et al. (2010) modified and abbreviated the 16-item Tonsil and Adenoid Health Status Instrument to the 14-item Paediatric Throat Disorders Outcome Test for youth with tonsil and adenoid disease in the U.K.

Linguistic validation in studies. In 5 studies researchers linguistically and culturally adapted established instruments for use in another culture or population using forward and backward translations and cognitive debriefing/face-to-face interviews, and then examined the psychometric properties of the adapted instruments (Hu et al., 2013; Klaassen et al., 2013; McCusker et al., 2015; Mizuno et al., 2017; Yuksel et al., 2009). Hu et al. (2013) linguistically translated the PedsQL 3.0 Neuromuscular Module from English to Chinese using a process of forward and backward translation, and cognitive debriefing with 6 Chinese youth with Duchenne muscular dystrophy and their parents. Klaassen et al. (2013) linguistically, culturally and clinically translated a North American English parent and youth version of the Kids ITP Tools (KIT) for a sample of 127 families with youth ages 2-18 years with immune thrombocytopenia and their parents across 3 languages (French, German, and Spanish) and adapted to new cultures in France, Germany, UK, and Uruguay. Using a sample of144 boys with hemophilia aged 4-18 years, McCusker et al. (2015) adapted the North American English CHO-KLAT version for use in five countries: France, Germany, the Netherlands, Spain and the United Kingdom (UK). Mizuno et al. (2017) examined the validity and reliability of the Japanese version of food allergy QOL questionnaire – parent form using parents of youth with food allergy (n = 127) and parents of healthy youth (n = 48) aged 0-12 years. Yuksel et al. (2009) adapted the 23-item Pediatric Asthma QOL Questionnaire (PAQLQ) from English into Turkish. The Turkish language version resulted in the same number of items, with Cronbach α scores ranging from 0.80 (Activity) - 0.90 (Symptoms) and significant correlations between PAQLQ and KINDL (Kinderlebensqualita¨tsfragebogen), a short, methodologically suitable, psychometrically sound measure of QOL in youth (subscales were Physical r = 0.33, Psychological r = 0.45, and Well-Being r = 0.31).

Questionnaire language. Authors of 18 studies specified using questionnaires and/or survey language according to participants' preference (Abdovic et al., 2013; Bradley et al., 2006; Chang & Yeh, 2005; Hu et al., 2013; Iannaccone et al., 2009; Kalyva et al., 2011; Klaassen et al., 2013; Kocova et al.,

2014; McCusker et al., 2015; Mizuno et al., 2017; Petsios et al., 2011; Pollak et al. 2006; van Doorn et al., 2008; Varni et al., 2004, Yuksel et al., 2009; Zashikhina & Hagglof, 2014). For example, in their study of American youth (n = 404) with asthma and their parents (n = 526), Varni et al. (2004) reported that the PedsQL 4.0 Generic Core Scales was administered in 5 languages - English, Spanish, Vietnamese, Chinese, and Korean. Varni et al. (2004) investigated the reliability, validity, and initial responsiveness of PedsQL Asthma Module and Generic Core Scales.

In thirteen studies conducted in North America completion of survey instruments was restricted to English language (Botello-Harbaum et al., 2008; Davis et al., 2010; Franciosi et al., 2013; Gray et al., 2011; Ingerski et al., 2010; Jaser et al., 2011; Marino et al., 2011; Moorthy et al., 2007; Otley et al., 2003; Panepinto et al., 2013; Valenzuela et al., 2006; Varni et al., 2014; Weissberg-Benchell et al., 2010). Language option for survey completion was not reported in 6 studies conducted in Canada (Allan et al., 2008; Bradley et al., 2006; Iannaccone et al., 2009; Narayanan et al., 2006; Otley et al., 2003; Young et al., 2013) and 12 studies in Europe (Abdovic et al. 2013; DunnGalvin et al., 2010; Hartman et al., 2007; Hopkins et al., 2010; Kalyva et al. 2011; Knibb et al., 2013; Kocova et al. 2014; Mackenzie et al., 2012; Petsios et al., 2011; van Doorn et al., 2008; Yuksel et al., 2009; Zashikhina & Hagglof, 2014).

All but 4 researchers (Klaassen et al., 2013; McCusker et al., 2015; Narayanan et al. 2013; Young et al., 2013) examined Cronbach's alpha as a measure of instrument reliability. Cronbach's alpha ranged from 0.70 for the Pediatric Cardiac QOL Inventory (Marino et al., 2011) and the Paediatric Asthma QOL Questionnaire (Zashikhina & Hagglof, 2014) to 0.97 for PedsQL Gastro Intestinal Module (Varni et al., 2014) and the PedsQL Sickle Cell Disease Module (Panepinto et al., 2013). In lieu of Cronbach's alpha, test re-test reliability, youth-parent concordance (Klaassen et al., 2013; Young et al., 2013), and intra-class correlation (ICC) with its 95% confidence interval (CI) (Narayanan et al., 2013) were measured as a measure of instrument reliability.

Construct validity was reported for each instrument. According to Pedhazur and Schmelkin (2013), initial information on the construct validity of an instrument is achieved by computing the intercorrelations among instrument scales. Panepinto and colleagues, (2013), for example, computed intercorrelations between the newly developed PedsQL Sickle Cell Disease Module Scales and Total Scale Score with the established PedsQL 4.0 Generic Core Scales and summary scores in order to

determine construct validity of the PedsQL Sickle Cell Disease Module. The majority of intercorrelations for both parents and youth were moderate to large which supported construct validity of the sickle cell disease scales and total scale Score. The instrument is developmentally appropriate and available for youth self-report for ages 5-7, 8-12, and 13-18 years, and parent proxy-report for ages 2-4, 5-7, 8-12, and 13-18 years.

Quality of life measurement over time. Longitudinal data were collected over 2 or more time points for 6 studies. Data of youth with Type I diabetes were collected at baseline and 1 month (Botello-Harbaum et al., 2008). Botello-Harbaum et al. (2008) did not report whether QOL improved over time. DunnGalvin et al. (2010) collected data of youth with food allergy at baseline, months 2 and 6; they reported that QOL improved over time. Hartman et al. (2007), collected data of youth with anorectal malformations or Hirschsprung Disease at baseline and 3 years. Hartman and colleagues reported that there were improvements in disease-specific functioning and mental QOL for adolescents and children, but only adolescents improved over time in physical QOL. Hopkins et al. (2010), collected data of youth with tonsil and adenoid disease at baseline and between 2-6 months, reported improvement in QOL over time. Newcombe et al. (2011), collected data of youth with chronic cough at baseline and between 2-3 weeks reported that scores for 29 of 34 youth showed improvement over time. Young et al. (2013), collected data of boys with hemophilia at baseline and 2 weeks later, but did not report whether QOL improved over time. Table 1 provides the psychometric properties by disease state.

Youth versus parent disease-specific quality of life rating. The majority of studies measured both youth and/or parent/caregiver perception of QOL. Youth reported higher QOL scores compared to ratings of their parent/caregiver in approximately half (10/21) of the studies. For example, youth with Type II diabetes who participated in the Allan et al. (2008) study reported higher scores (indicating better QOL) for the Symptoms and Treatment I subscale compared to their parent suggesting that parents overestimated the impact of diabetes symptoms and treatment on their youth. Youth with Duchenne muscular dystrophy who participated in the Davis et al. (2010) study reported higher total QOL scores 73.8 ± 13.2 compared to parents 59.6 ± 15.5. In 5 studies youth and parents reported similar QOL ratings (Bradley et al., 2006-hemophilia; Chang & Yeh, 2005; Hu et al., 2013; Valenzuela et al., 2006-diabetes; Weissberg-Benchell et al., 2010-organ transplantation).

Table 1 Psychometric Properties of Disease-specific Quality of Life Instruments by Disease State

Author, Year	Instrument, # of items and subscales; Scale range; Age range of youth sample	Psychometric Properties: Reliability	Psychometric Properties: Validity
		Asthma	
Petsios et al. (2011)	DISABKIDS Asthma Module – 11 items, 2 subscales; Score range: 0 (worst) - 100 (best); 4-7, 8-14 years	Impact domain α = 0.83 Worry domain α = 0.84	Construct: Correlation between parent and youth scores showed lower values in children with uncontrolled asthma (actual values not reported)
Varni et al. (2004)	Pediatric QOL Inventory (PedsQL) 3.0 Asthma Module 28 items, 4 subscales; Score range: 0 (worst) – 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth α = 0.85 Parent α = 0.91	Construct: Correlations between PedsQL Asthma Module and PedsQL 4.0 Generic Core Scales were: Asthma Symptoms *r* = 0.55 (youth); *r* = 0.62 (parent) Treatment Problems *r* = 0.50 (youth); *r* = 0.59 (parent) Worry *r* = 0.53 (youth); *r* = 0.49 (parent) Communication *r* = 0.39 (youth); *r* = 0.36 (parent)
Yuksel et al. (2009)	Pediatric Asthma QOL Questionnaire (PAQLQ) – 23 items, 3 subscales; Score range: 1 (worst) – 7 (best) 7-16 years	All subscales α > 0.75	Construct: Correlation between total PAQLQ and KINDL Physical and Psychological Well-Being domains were significant (*r*=0.33, 0.45 & 0.31) PAQLQ overall score and domain scores were higher in youth with mild asthma compared to moderate asthma
Zashikhina and Hagglof (2014)	Paediatric asthma QOL questionnaire (PAQLQ) – 23 items, 3 subscales; Score range: 1 (worst) - 7 (best) 13-16 years	All subscales α ≥ 0.70	Construct: Moderate correlations between symptom, activity, and emotion subscales and medication use and morning peak flow rates (actual values not reported)
		Cancer	
Chang and Yeh (2005)	Quality of Life for Children with Cancer (QOLCC) – 34 items, 5 subscales; Scale range not reported but higher scores reflect lower QOL 7-12, 13-18 years	7-12 years total α = 0.88 Parent of 7-12 year olds total α =0.91 13-18 years total α = 0.89 Parent of 13-18 year olds total α = 0.87	Construct: Inter-correlations between patient report and subscales ranged from *r* = -0.36 to *r* = 0.55

Author, Year	Instrument, # of items and subscales; Scale range; Age range of youth sample	Psychometric Properties: Reliability	Psychometric Properties: Validity
		Celiac Disease	
van Doorn et al. (2008)	Celiac Disease DUX (CDDUX) – 12 items, 3 subscales; Score range: 0 (worst) - 100 (best); 3 versions: 8-11, 12-15, 16-18 years	Youth and parent α = 0.88	Construct: Youth and parent correlation of CDDUX scales ranged from *r* = 0.5 to *r* = 0.6
		Cerebral Palsy	
Narayanan et al. (2006)	Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) – 36 items, 6 subscales; Score range: 0 (*best*) to 100 (*worst*); Caregiver proxy-report for 5-18 year olds	Caregiver total ICC = 0.97 Subscale ICC ranged from 0.88-0.96	Construct: Mean (SD) CPCHILD scores showed youth with poorer function had worse QOL scores (actual values not reported) Face: Valid measure for cerebral palsy (actual values not reported)
		Chronic Cough	
Newcombe et al. (2011)	Parent Cough-Specific Quality-of-Life questionnaire (PC-QOL) – 27 item, 5 subscales; Score range: 1-7 score range; Parent proxy-report for 14-18 years	Parent total scale and subscales α ≥ 0.84	Construct: Significant correlations were found between subscales of the PC-QOL questionnaire and the scales of the Short Form12 version 2 (SF-12v2) and PedsQL4.0 scores (actual values not reported)
		Diabetes Type I	
Botello-Harbaum et al. (2008)	Diabetes QOL scale (DQOL) – 51 items, 3 subscales; Scale range: Higher scores indicate better QOL; 11-16 years	Youth baseline total scale α = 0.75	Construct: No significant association among overall QOL, diabetes-related QOL and DQOL (actual values not reported)
Ingerski et al. (2010)	PedsQL Type 1 diabetes module – 28 items; 5 subscales; Score range: 0 (worst) - 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth total scale α = 0.74	Construct: Treatment Barriers, Treatment Adherence, and Worry subscales positively correlated with PedsQL Generic Total Score (actual values not reported)
Jaser et al. (2011)	PedsQL Diabetes Module – 11 items; 1 subscale; Score range: 0 (worst) – 100 (best) 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth total scale α = 0.75	Construct: Use of primary control coping strategies was associated with better diabetes-related QOL (*r* = 0.40) and better total QOL (*r* = 0.48) in youth
Kalyva et al. (2011)	PedsQL 3.0 Diabetes Module – 28 items, 5 subscales; Score range: 0 (worst) – 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth total scale α = 0.81	Construct: Treatment Barriers, Treatment Adherence, Worry subscales positively correlated with PedsQL Generic Total Score (actual value not reported)

Author, Year	Instrument, # of items and subscales; Scale range; Age range of youth sample	Psychometric Properties: Reliability	Psychometric Properties: Validity
Valenzuela et al. (2006)	PedsQL Type 1 Diabetes Module – 28 items, 5 subscales; Score range: 0 (worst) – 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth and parent total scale was α = 0.84	Construct: Treatment Barriers, Treatment Adherence, and Worry subscales positively correlated with PedsQL Generic Total Score (actual values not reported)
Zashikhina and Hagglof (2014)	Diabetes QOL questionnaire for youths (DQOLY) – 52 items, 4 subscales; Score range: 0 (*best*) - 100 (*worst*) 13-16 years	Youth total scale α = 0.88	Construct: In all subscales except for the Life Satisfaction subscale, lower score indicated higher QOL (actual values not reported)
		Diabetes Type II	
Allan et al. (2008)	PedsQL 3.0 Diabetes Module – 28 items, 5 subscales; Score range: 0 (worst) - 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth total scale α = 0.79 Parent total scale α = 0.89	Construct: Treatment Barriers, Treatment Adherence, and Worry subscales positively correlated with PedsQL Generic Total Score (actual values not reported)
		Duchenne Muscular Dystrophy	
Davis et al. (2010)	PedsQL 3.0 Neuromuscular Module (NMM) – 25 items, 3 scales; Score range: 0 (worst) - 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth total α = 0.85 Parent total α = 0.87 Youth test-retest ICC = 0.59 Parent test-retest ICC = 0.75	Construct: Correlation between total PedsQL Generic Core Scale and total PedsQL 3.0 NMM was *r* = 0.65 (youth) and *r* = 0.71 (parent)
Hu et al. (2013)	PedsQL 3.0 Neuromuscular Module (NNM) - 25 items, 3 scales; Score range: 0 (worst) - 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth total α = 0.81 Parent total α = 0.86 Youth total test-retest ICC = 0.66 Parent total test-retest ICC = 0.88	Construct: Correlation between PedsQL Generic Core Scale and PedsQL 3.0 NMM was *r* = 0.67 (youth) and *r* = 0.60 (parent)
		Eosinophilic esophagitis	
Franciosi et al. (2013)	PedsQL Eosinophilic Esophagitis (EoE) Module - 33 items, 7 subscales; Score range: 0 (worst) - 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	All youth and parent scales α > 0.70 Youth test-retest ICC = 0.88 Parent test-retest ICC = 0.82	Construct: Correlation between PedsQL Generic Core Scale and PedsQL EoE was *r* = 0.56 (youth) and *r* = 0.41 (parents)

Author, Year	Instrument, # of items and subscales; Scale range; Age range of youth sample	Psychometric Properties: Reliability	Psychometric Properties: Validity
		Epilepsy	
Zashikhina and Hagglof (2014)	Quality of life in epilepsy inventory for adolescents (QOLIE-AD-48) – 48 items, 8 subscales; Score range: 0 (worst) - 100 (best); 13-16 years	Youth total scale α = 0.74	Construct: Correlation between youth and parent perception of QOL was *r* = 0.67
		Food Allergy	
DunnGalvin et al. (2010)	Food Allergy QOL Questionnaire – Parent Form (FAQLQ-PF): 14 items (0-3 years), 26 items (4-6 years) 30 items (7-12 years); 3 subscales; Score range: 0 (best) - 6 (worst) Parents of youth 0-12 years	Parent scale α ranged from 0.89 - 0.92	Construct: Correlation between total FAQLQ and Food Allergy Independent Measure *r* = 0.70 (2 months) and *r* = 0.65 (6 months) ICC total scale = 0.90
Knibb et al. (2013)	Paediatric Food Allergy QOL Questionnaire (PFA-QL) -25 items; Score range: 25 (*best*) - 100 (*worst*); 6-16 years	Youth α = 0.77 PFA-QL test-retest ICC = 0.77	Construct: Correlation between PedsQL Generic Core Scales and PFA-QL was *r* = -0.31
Mackenzie et al. (2012)	You and Your Food Allergy – 34 items, 5 subscales; Higher scores indicate better QOL; 13-18 years	Youth total scale α = 0.92 Youth total scale test-retest ICC = 0.87	Construct: Correlation between PedsQL Generic Core Scales and You and Your Food Allergy was *r* = 0.504
Mizuno et al. (2017)	Food Allergy QoL Questionnaire – Parent Form-Japanese (FAQLQ-PF-J) – 30 items, 3 domains; 0 (best) – 6 (worse); 0-12 years	Parents: α = 0.77 ICC > 0.7	Construct: Correlation between FAQLQ-PF-J and the Food Allergy Independent Measure (FAIM) total score was r = 0.56; subscale scales ranged from *r* = 0.39 - 0.64
		Gastrointestinal Disorders	
Varni et al. (2014)	PedsQL Gastrointestinal Symptoms Module (GI Module) -74 items, 14 subscales; Score range: 0 (worst) - 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth and parent total scale α = 0.97	Construct: Correlation between PedsQL GI Module and PedsQL Generic Core Scales ranged from *r* = 0.491 to *r* = 0.684 (youth); *r* = 0.449 to *r* = 0.604 (parents)

Author, Year	Instrument, # of items and subscales; Scale range; Age range of youth sample	Psychometric Properties: Reliability	Psychometric Properties: Validity
		Heart Disease	
Marino et al. (2011)	Pediatric cardiac QOL inventory (PCQLI) – 23 items (child), 29 items (adolescent) 2 subscales: disease impact and psychosocial impact; Score range: 0 (worst) – 100 (best); 8-18 years	Youth and parent α = 0.70	Construct: Correlations were similar between all items of the PCQLI (actual values not reported)
		Hemophilia	
Bradley et al. (2006)	Canadian Haemophilia Outcomes – Kids' Life Assessment Tool (CHO-KLAT) - 35 items; Score range: 0 (worst) to 100 (best) 4-7, 8-18 years	Total scale α ranged from 0.81–0.91	Construct: Correlation between CHO-KLAT and PedsQL was *r* = 0.59 (youth) and *r* = 0.54 (parents)
	Haemo-QoL – 16 items, 8 subscales (4-7 year olds) and 35 items, 9 domains (8-18 year olds); Score range: 0 (*best*) to 100 (*worst*); 4-7, 8-16 years	Total scale α ranged from 0.81–0.91	Construct: Correlation between the Haemo-QoL and PedsQL was *r* = -0.76 (youth) and *r* = -0.63 (parent)
McCusker et al. (2015)	CHO-KLAT- 35 items; 0 (worse) – 100 (best); 4-18 years	Test–retest: child self-report = 0.67 ICC > 0.7	Construct: Correlations between CHO-KLAT summary scores and PedsQL (r = 0.52); between CHO-KLAT and Haemo-QoL (r = 0.73)
Pollak et al. (2006)	Haemo-QoL Index – 8 items; Score range: 0 (*best*) to 100 (*worst*) 3 versions: 4-7, 8-12, 13-16 years	Youth α = 0.70 Parent α = 0.78 Youth test-retest ICC = 0.76 Parent test–retest ICC = 0.27	Construct: Correlations between Haemo-QOL, KINDL-R, Child Health Questionnaire General Health Index, and a third scale (the Fragebogen zur Lebenszufriedenheit) were moderate to high (actual values not reported)
Young et al. (2013)	CHO-KLAT – 35 items; Score range: 0 (worst) to 100 (best); Parent proxy-report for 4-7 and youth self-report and parent proxy-report for 8-17 years	Youth test-retest ICC = 0.63 Parent test-retest ICC = 0.79 Youth-parent concordance = 0.65	Construct: Correlation between PedsQL and CHO-KLAT was *r* = 0.62

Author, Year	Instrument, # of items and subscales; Scale range; Age range of youth sample	Psychometric Properties: Reliability	Psychometric Properties: Validity
	Hirschsprung Disease (HD)/Anorectal Malformation (ARM)		
Hartman et al. (2007)	Hirschsprung Disease/Anorectal Malformation QOL Questionnaire (HAQL) – 38 items for child questionnaire and 40 for adolescent questionnaire, 9 subscales; Score range: 0 (worst) – 100 (best); 8-11, 12-16 years	Youth α ranged from 0.80 to 0.90	Construct: Discriminant validity: good between age 8-11 and 17+ participants Convergent validity: correlation <40 between HAQL and TNO-AZL Questionnaires for Children's Health-Related QOL (TACQOL) (actual values not reported)
	Inflammatory Bowel Disease		
Abdovic et al. (2013)	IMPACT-III Questionnaire – 35 items, 6 subscales; Score range: 35 (worst) - 175 (best); 9-18 years	Youth total score α = 0.92	Construct: Correlation between total IMPACT-III and PedsQL was *r* = 0.738
Gray et al. (2011)	IMPACT-III questionnaire – 35 items, 6 subscales; Score range: 33 (worst) - 175 (best); 13-17 years	Youth total score α = 0.94	Construct: Intercorrelations for Disease Activity, Behavioral Dysfunction, and QOL ranged between *r* = -0.67 and *r* = 0.54
Otley et al. (2003)	IMPACT – 35 items, 6 subscales; Score range: 0 (worst) to 231 (best) 9-18 years	Youth total score α = 0.96 Youth total score ICC = 0.90	Construct: IMPACT questionnaire was shown to measure QOL in pediatric IBD (actual values not reported)
	Immune Thrombocytopenia		
Klaassen et al. (2013)	Kids' Immune Thrombocytopenia Tools (KIT) – 26 items; 0 Score range: (worst) - 100 (best); 2-18 years	Youth-parent concordance ICC = 0.52 Youth test-retest ICC = 0.71 Parent test-retest ICC = 0.76	Construct: Correlation between KIT and PedsQL *r* = 0.54 Correlation between KIT and KINDL *r* = 0.48
	Influenza		
Chow et al. (2014)	Care-ILI-QoL (Influenza-like illnesses) – 16 items, 4 subscales; 1 (worse) – 7 (best); parent proxy; 6-48 months	Parent subscales: Daily Activities α = 0.90; Perceived Support α = 0.92; Social Life α = 0.78; Emotions α = 0.72	Correlations between Care-ILI-QoL total scores and Mental Component Summary of Short Form-12v2 ranged from r = 0.30–0.52

Author, Year	Instrument, # of items and subscales; Scale range; Age range of youth sample	Psychometric Properties: Reliability	Psychometric Properties: Validity
		Lupus Erythematosus	
Moorthy et al. (2007)	Simple Measure of the Impact of Lupus Erythematosus in Youngsters (SMILEY) – 26 items, 4 subscales; Score range: 0 (worst) - 100 (best); 7-18 years	Youth and parent total α = 0.90 Youth and parent test-retest ICC ranged from 0.70 - 0.90 Youth-parent concordance ranged from 0.6 - 0.7	Construct: Spearman's correlation: rho = 0.3-0.6 (youth) rho = 0.2-0.6 (parent) Spearman's rank correlation of SMILEY and PedsQL was rho = 0.6 (youth and parent)
		Organ transplantation: Liver, Kidney, Heart and Small Bowel Disorders	
Weissberg-Benchell et al. (2010)	PedsQL 3.0 Transplant Module – 46 items, 8 subscales; Score range: 0 (worst) – 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth α = 0.93 Parent α = 0.94	Construct: Youth total effect size = 0.75 Parent total effect size = 0.74 (for differences between healthy youth & youth with solid organ transplants)
		Sickle Cell Disease	
Panepinto et al. (2013)	PedsQL Sickle Cell Disease Module - 43 items, 9 subscales; Score range: 0 (worst) - 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth α = 0.95 Parent α = 0.97	Construct: Inter-correlation between PedsQL Sickle Cell Disease Module and PedsQL Generic Core was *r* = 0.70 (youth) *r* = 0.68 (parent) Total effect size: *r* = 0.28 (youth) and *r* = 0.56 (parent) for difference between mild and severe sickle cell disease
		Spinal Muscular Atrophy	
Iannaccone et al. (2009)	PedsQL 3.0 Neuromuscular Module – 17 items (youth) and 25 items (parent), 3 subscales; Score range: 0 (worst) – 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth α = 0.88 Parent α = 0.89 Youth-parent concordance ICC = 0.45 Youth test-retest ICC = 0.81 Parent test-retest ICC = 0.89	Construct: Correlation between PedsQL 3.0 NMM and PedsQL Generic Core Scales was *r* = 0.79 (youth) and *r* = 0.61 (parent)

Author, Year	Instrument, # of items and subscales; Scale range; Age range of youth sample	Psychometric Properties: Reliability	Psychometric Properties: Validity
Kocova et al. (2014)	PedsQL 3.0 Neuromuscular Module - 25 items, 3 subscales; Score range: 0 (worst) - 100 (best); 4 versions: 2-4, 5-7, 8-12, 13-18 years	Youth α = 0.86 Parent α = 0.90	Construct: Correlation between PedsQL 3.0 NMM and PedsQL Generic Core Scales was *r* = 0.79 (youth) and *r* = 0.61 (parent)
	Tonsil and Adenoid Disease		
Hopkins et al. (2010)	Paediatric Throat Disorders Outcome Test – 14 items; Score range: 0 (best) - 60 (worst); Parents of 1-16 year olds	Parent total α=0.84 Parent test-retest ICC = 0.98	Construct: Good internal consistency (actual values not reported)

Notes. *PedsQL version: Youth self-report and parent proxy-report for 5–7, 8–12, and 13–18 years and parent proxy-report for 2-4 years

Parents reported higher but not significant QOL ratings than youth in several studies (Franciosi et al., 2013; Panepinto et al., 2013; Pollak et al., 2006; Young et al., 2013). Petsios et al. (2011) reported that perception of QOL of youth with asthma was significantly lower compared to that of their parents for all subscales, except for youth with severe asthma in the 8–14 years group, where perception of Impact and Worry were in close agreement. Marino et al. (2011) reported that younger children and adolescents with heart disease perceived their QOL differently: younger youth reported their QOL as higher than parent-proxy report while adolescents reported their QOL as poorer than parent-proxy report.

Four instruments were developed to measure perception of youth's disease-specific QOL from the parent/caregiver's perspective only. The Parent Cough-Specific Quality-of-Life questionnaire (Newcombe et al., 2011) is a 27-item questionnaire that assessed the level of frequency of parent's feelings (15 items) and worry (12 items) related to the youth's cough measured parental perception of QOL for youth aged 17.3 to 38.8 months. The Caregiver Priorities and Child Health Index of Life with Disabilities (Narayanan et al., 2006) consists of 36 items in 6 domains and measured primary caregiver perception of QOL in youth aged 5 to 18 years with cerebral palsy. The 14-item Paediatric Throat Disorders Outcome Test is a 14-item instrument designed to measure parental perception of QOL in youth aged 1-16 years following tonsil and adenoid surgery in the U.K. (Hopkins et al., 2010). The Food Allergy QOL Questionnaire – Parent Form (FAQLQ-PF) is an instrument designed to measure parental perception of QOL in youth 0-12 years with food allergy (DunnGalvin et al., 2010). Sample demographics, disease-specific QOL and subscale scores are provided in Table 2.

Disease impact on youth self-reported quality of life. In the majority of studies researchers examined the relationship between disease and disease-specific QOL using 1 of the PedsQL instruments singularly or in combination with other instruments (Abdovic et al. 2013; Allan et al. 2008; Bradley et al. 2006; Davis et al. 2010; Franciosi et al. 2013; Hu et al. 2013; Iannaccone et al. 2009; Ingerski et al. 2010; Jaser et al. 2011; Kalyva et al. 2011; Knibb et al. 2013; Kocova et al. 2014; Mackenzie et al. 2012; Moorthy et al. 2007; Panepinto et al. 2013; Valenzuela et al. 2006; Varni et al. 2004; Varni et al. 2014; Weissberg-Benchell et al. 2010; Young et al. 2013). The number of items per disease-specific QOL instrument varied considerably, ranging from 8 on the Haemophilia QOL Index, to 74 on the PedsQL Gastrointestinal Symptoms Module.

Table 2 Sample Demographics, Disease-specific Quality of Life and Subscale Scores of the Included Studies

Author, Year	Sample Demographics: Number of participants; Country; Race/Ethnicity/ Nationality	Instrument; All scales are 0 (worst) - 100 (best) unless otherwise noted. Mean Total QOL score (SD)	Subscale: Score Mean (SD).
		Asthma	
Petsios et al. (2011)	504 youth and 504 parents; Greece; 93.05% Greek 6.95% Other	DISABKIDS smiley measure (DSM) for 4-7 years DISABKIDS Asthma Module for 8-14 years; Youth 4-7 years 67.7(18.4) Parent 72.5(11.7)	Independence: 78.2(16.5) Youth; 83.9(11.4) Parent Physical limitation: 53.3(10.2) Youth; 60.9(12.7) Parent Emotion: 74.9(21.5) Youth; 75.1(16.9) Parent Exclusion: 86.4(16.9) Youth; 90.2(11.8) Parent Inclusion: 67.8(12.0) Youth; 69.2(9.1) Parent Medication: 67.1(21.5) Youth; 73.3(20.5) Parent General: 57.9(9.85) Youth; 77.1(11.3) Parent Impact: 72.6(21.4) Youth; 71.6(19.4) Parent Worry: 67.6(19.9) Youth; 68.5(19.1) Parent
Varni et al. (2004)	529 youth and 516 parents; USA: Kansas; 35.2% Latino 25.5% White 8.7% Black 4.9% Asian/Pacific Islander 0.9% American Indian or Alaskan Native 0.9% Other 23.8% Not reported	Pediatric QOL Inventory (PedsQL) 3.0 Asthma Module; Youth 74.7(15.8) Parent 72.4(16.6)	Asthma Symptoms: 64.2(19.2) Youth; 63.3(21.4) Parent Treatment Problems: 80.6(14.2) Youth; 77.3(17.2) Parent Worry: 76.3(21.9) Youth; 77.4(22.4) Parent Communication: 73.7(24.9) Youth; 71.4(26.9) Parent
Yuksel et al. (2009)	122 youth and 122 parents; Turkey; Turkish	Pediatric Asthma QOL Questionnaire (PAQLQ); 1 (worst) – 7 (best); Youth with ≤1 sibling 5.5(1.2) Youth with >1 sibling 5.9(0.9)	Activity: ≤1 sibling 5.2(1.2); >1 sibling 5.7(0.9) Symptoms: ≤1 sibling 5.2(1.2); >1 sibling 5.9(1.0) Emotional: ≤1 sibling 5.5(1.2); >1 sibling 5.9(0.9)
Zashikhina and Hagglof (2014)	49 youth and 49 parents; Russia; Russian	PAQLQ; 1 (worst) – 7 (best); Youth 5.7(0.9)	Youth Activity: 5.2(1.0) Symptom: 5.9(1.0) Emotional: 5.8(0.9)

Author, Year	Sample Demographics: Number of participants; Country; Race/Ethnicity/ Nationality	Instrument; All scales are 0 (worst) - 100 (best) unless otherwise noted. Mean Total QOL score (SD)	Subscale: Score Mean (SD).
		Cancer	
Chang and Yeh (2005)	141 youth and 141 parents; Taiwan; Taiwanese	Quality of Life for Children with Cancer (QOLCC); Scale range not reported but higher scores represent worse QOL; Child 7-12 years 0.8(0.4) Parent of child 0.8(0.4) Adolescent 13-18 years 0.8(0.4) Parent of adolescent 0.6(0.3)	Physical: 0.6(0.6) Child; 0.5(0.7) Parent Psychological: 0.8(0.6) Child; 0.6(0.6) Parent Social: 0.5(0.5) Child; 0.4(0.4) Parent Disease/symptom: 0.8(0.6) Child; 0.9(0.5) Parent Cognitive: 0.8(0.6) Child; 0.7(0.6) Parent Understanding: 1.5(0.8) Child; 1.5(1.0) Parent Communication: 0.8(0.7) Child; 0.8(0.6) Parent Physical: 0.6(0.6) Youth; 0.3(0.4) Parent Psychological: 0.9(0.7) Youth; 0.5(0.4) Parent Social: 0.6(0.5) Youth; 0.4(0.4) Parent Disease/symptom: 0.9(0.6) Youth; 0.8(0.5) Parent Cognitive: 0.9(0.6) Youth; 0.6(0.5) Parent Understanding: 0.7(0.7) Youth; 0.6(0.7) Parent Communication: 0.8(0.8) Youth;0.7(0.6) Parent
		Celiac Disease	
van Doorn et al. (2008)	510 youth and 501 parents; the Netherlands; 98% Dutch	Celiac Disease DUX (CDDUX); Youth 44(15) Parent 39(15)	Communication: 59(21) Youth; 53(20) Parent Having CD: 36(21) Youth; 30(18) Parent Diet: 36(16) Youth; 33(18) Parent
		Cerebral Palsy	
Narayanan et al. (2006)	77 youth and 77 parents; Canada; Canadian	Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD); 0 (best) to 100 (worst); Non-ambulatory youth caregiver 24.3(12.3) Ambulatory youth caregiver 6.2(15.7)	Not reported

Author, Year	Sample Demographics: Number of participants; Country; Race/Ethnicity/ Nationality	Instrument; All scales are 0 (worst) - 100 (best) unless otherwise noted. Mean Total QOL score (SD)	Subscale: Score Mean (SD).
		Chronic Cough	
Newcombe et al. (2011)	34 youth and 34 parents; Australia; Australian	Parent Cough-Specific Quality-of-Life questionnaire (PC-QOL); 1 (worst) – 7 (best); Parents at week 2: 5.6(1.3) Parents at week 3: 6.1(1.1)	Psychologic: 5.7(1.4) Week 2; 6.2(1.1) Week 3 Physical: 5.4(1.4) Week 2; 6.0(1.2) Week 3 Social: 6.0(1.2) Week 2; 6.1(1.3) Week 3
		Diabetes Type I	
Botello-Harbaum et al. (2008)	81 youth; USA: Maryland; 85% White 11% Black 4% Other	Diabetes QOL scale (DQOL); Scale range not reported; Youth baseline: 4.2(0.5) 12-month follow-up: 4.1(0.5)	Not reported
Ingerski et al. (2010)	261 youth and 261 parent; USA: Northeast and Midwest 87.4% White 12.6% Minority race	PedsQL Type 1 diabetes module; Youth 74.0(12.7)	Youth Treatment 1: 74.5(16.8) Treatment 2: 76.7(15.0) Worry: 67.0(19.5)
Jaser et al. (2011)	30 youth and 30 parents; USA: Connecticut; 74% White 13% Black 13% Latino	PedsQL Diabetes Module; Youth 71.4(12.4)	Not reported
Kalyva et al. (2011)	245 youth and 245 parents; Greece; Greek	PedsQL 3.0 Diabetes Module; Youth 61.1(13.4) Parent 54.6(12.1)	Diabetes symptoms: 60.0(13.3)Youth; 53.9(12.0) Parent Treatment barriers: 60.0(19.8) Youth; 50.6(17.0) Parent Treatment adherence: 64.8(15.8) Youth; 59.5(15.0) Parent Worry: 61.2(22.8) Youth; 52.8(21.6) Parent Communication: 58.5(25.8) Youth; 53.0(23.0) Parent

Author, Year	Sample Demographics: Number of participants; Country; Race/Ethnicity/ Nationality	Instrument; All scales are 0 (worst) - 100 (best) unless otherwise noted. Mean Total QOL score (SD)	Subscale: Score Mean (SD).
Valenzuela et al. (2006)	160 youth and 160 parents; USA: Florida; 49% White 39% Latino 12% Black	PedsQL Type 1 Diabetes Module; Youth 69.4(13.4) Parent 70.0(13.6)	Not reported
Zashikhina and Hagglof (2014)	50 youth and 50 parents; Russia; Russian	Diabetes QOL questionnaire for youths (DQOLY); 0 (best) - 100 (worst); Youth 80.3(32.6)	Youth Satisfaction: 36.9(11.4) Impact: 50.4(11.4) Worries: 20.4(7.0) Overall health (not reported)
		Diabetes Type II	
Allan et al. (2008)	28 youth and 28 parents; Canada; 89.3% of Canadian Aboriginal ancestry	PedsQL 3.0 Diabetes Module; Youth 70.8(11.1) Parent 61.5(15.9)	Symptoms: 70.9(13.4) Youth; 59.8(17.2) Parent Treatment I: 74.2(16.2) Youth; 62.5(22.9) Parent Treatment II: 76.4(16.4) Youth; 66.6(23.2) Parent Worry: 63.1(25.2) Youth; 58.0(30.0) Parent Communication: 63.1(30.4) Youth; 60.4(31.2) Parent
		Duchenne muscular dystrophy (DMD)	
Davis et al. (2010)	44 youth and 44 parents; USA: Texas; 84.1% White 4.5% Black 4.5% More than one 6.8% Unknown	PedsQL 3.0 Neuromuscular Module; Youth 73.8(13.2) Parent 59.6(15.5)	About My Neuromuscular Disease: 72.9(13.2) Youth; 60.3(15.3) Parent Communication: 75.6(23.7) Youth; 62.1(27.8) Parent About Our Family Resources: 76.6(19.1) Youth; 55.8(24.9) Parent
Hu et al. (2013)	50 youth and 50 parents; China; Chinese	PedsQL 3.0 Neuromuscular Module; Youth 53.6(10.6) Parent 52.9(9.3)	About My Neuromuscular Disease: 71.2(12.1) Youth; 71.1(11.2) Parent Communication: 39.1(22.5) Youth; 37.5(20.4) Parent About Our Family Resources: 52.5(15.8) Youth; 50.1(15.1) Parent

Author, Year	Sample Demographics: Number of participants; Country; Race/Ethnicity/ Nationality	Instrument; All scales are 0 (worst) - 100 (best) unless otherwise noted. Mean Total QOL score (SD)	Subscale: Score Mean (SD).
		Eosinophilic Esophagitis	
Franciosi et al. (2013)	263 youth and 263 parents; USA: Colorado, Indiana, Ohio, Pennsylvania, Texas; 88.6% White 4.2% Latino 1.9% Black 1.1% Asian/Pacific Islanders 4.1% Others or not reported	PedsQL Eosinophilic Esophagitis; Youth 65.2(19.1) Parent 67.4(17.6)	Symptoms I: 66.7(20.1) Youth; 67.8(20.9) Parent Symptoms II: 70.9(24.3) Youth; 68.2(23.9) Parent Treatment: 55.5(26.8) Youth; 72.5(22.8) Parent Worry: 68.1(26.1) Youth; 72.1(23.5) Parent Communication: 74.0(25.7) Youth; 67.1(27.2) Parent Food and Eating: 60.3(32.4) Youth; 59.8(27.1) Parent Food Feelings: 57.2(32.5) Youth; 55.6(28.0) Parent
		Epilepsy	
Zashikhina and Hagglof (2014)	47 youth and 47 parents; Russia; Russian	Quality of life in epilepsy inventory for adolescents (QOLIE-AD-48); Adolescents 67.1(7.1)	Impact: 74.5(8.7); Memory/concentration: 69.9(17.8) Attitude: 36.9(21.4) Physical functioning: 70.5(14.2) Stigma: 59.8(20.7) Social support: 91.4(8.11) School behavior: 91.2(10.5) Health perception: 60.4(8.8)
		Food Allergy	
DunnGalvin et al. (2010)	82 parents; The Netherlands; Dutch	Food Allergy QOL Questionnaire – Parent Form (FAQLQ-PF); 0 (best) - 6 (worst); Positive for food allergy: Baseline 4.1(1.4) At 2 months 3.6(1.4) At 6 months 2.9(1.5) Negative for food allergy: Baseline 3.9(1.5) At 2 months 3.2(1.5) At 6 months 1.6(1.5)	Allergy positive vs negative Baseline: Emotional impact:4.2(1.3) vs 4.0(1.5) Food anxiety: 4.1(1.4) vs 3.9(1.3) Social and dietary limitations: 4.0(1.6) vs 4.0(1.3) At 2 months: Emotional impact: 3.3(1.3) vs 3.4(1.4) Food anxiety: 3.7(1.6) vs 3.0(1.4) Social and dietary limitations: 3.6(1.2) vs 3.0(1.2) At 6 months: Emotional impact: 2.5(1.2) vs 1.8(1.3) Food anxiety: 3.2(1.6) vs 1.5(1.3) Social and dietary limitations: 3.0(1.3) vs 1.3(1.2)

Author, Year	Sample Demographics: Number of participants; Country; Race/Ethnicity/ Nationality	Instrument; All scales are 0 (worst) - 100 (best) unless otherwise noted. Mean Total QOL score (SD)	Subscale: Score Mean (SD).
Knibb et al. (2013)	103 youth; UK; UK	Paediatric Food Allergy QOL Questionnaire (PFA-QL); Youth: 25 (best) - 100 (worst); Baseline 51.1(7.4) 3 months 50.1(8.8)	Not reported
Mackenzie et al. (2012)	350 youth and 350 parents; UK; 89.7% White British 10.3% Other	You and Your Food Allergy; Youth: Higher scores indicate better QOL; Allergic to ≤ 2 foods 71.7(13.1) Allergic to > 2 foods 67.5(14.1)	Not reported
Mizuno et al. (2017)	Parents of youth with: Food allergy (n = 127) No food allergy (n = 48); Japan	Food Allergy QoL Questionnaire (FAQLQ-PF-J); 0 (best) – 6 (worse) Mean total scores: All ages = 3.1 (1.3)	All ages: Emotional impact: 3(1.4) Food anxiety: 2.8(1.9 Social dietary limitation: 3.6(1.4)
		<u>Gastro-intestinal Symptoms</u>	
Varni et al. (2014)	689 youth and 689 parents; USA: Colorado, Illinois, Massachusetts, New Jersey, Ohio, Texas, and Utah; 75.0% White 9.9% Latino 9.1% Black 1.9 % Asian/Pacific Islander 0.1% Native American 3.9% others	PedsQL Gastrointestinal Symptoms Module; Youth 72.5(16.4) Parent 70.3(16.3)	Stomach pain/hurt: 54.6(26.4) Youth; 51.3(26.5) Parent Stomach discomfort when eating: 74.0(25.7) Youth; 66.0(26.8) Parent Food/drink limits: 68.6(27.0) Youth; 68.2(29.5) Parent Trouble swallowing: 91.1(16.1) Youth; 92.2(15.3) Parent Heartburn & reflux: 78.8(20.0) Youth; 80.8(20.8) Parent Nausea & vomiting: 79.7(22.5) Youth; 78.3(24.9) Parent Gas and bloating: 64.3(24.6) Youth; 62.9(25.3) Parent Constipation: 71.1(23.5) Youth; 66.5(26.0) Parent Blood in poop: 85.9(23.6) Youth; 84.5(24.8) Parent Diarrhea: 78.5(22.7) Youth; 77.4(22.6) Parent Worry about pooping:78.1(25.4) Youth;75.7(26.0) Parent Worry about stomach aches: 60.5(32.8) Youth 60.0(32.0) Parent Medicines: 75.5(21.2) Youth; 78.4(21.6) Parent Communication: 68.9(24.8) Youth; 66.4(28.1) Parent

Author, Year	Sample Demographics: Number of participants; Country; Race/Ethnicity/ Nationality	Instrument; All scales are 0 (worst) - 100 (best) unless otherwise noted. Mean Total QOL score (SD)	Subscale: Score Mean (SD).
		Heart Disease	
Marino et al. (2011)	1545 youth and 1545 parents; USA: Arizona, California, Massachusetts, Ohio, Pennsylvania, Texas, and Wisconsin; 72.5% White 17.9% Black 9.6% Latino	Pediatric cardiac QOL inventory (PCQLI); Higher scores indicate better QOL; Child 73.8(16.3) Parent 76.3(17.6) Adolescent 79.7(15.0) Parent 76.8(17.4)	Disease Impact: 36.9(8.5) Child; 38.2(9.4) Parent Psychosocial Impact: 36.9(8.9) Child; 38.1(9.3) Parent Disease Impact: 38.4(8.3) Adolescent; 37.3(9.5) Parent Psychosocial Impact: 41.3(7.4) Adolescent; 39.5(8.8) Parent
		Hemophilia	
Bradley et al. (2006)	353 youth and 353 parents; Europe and Canada; 85.3% European 14.7% Canadian	Canadian Haemophilia Outcomes – Kids' Life Assessment Tool (CHO-KLAT); Haemo-QoL: 0 (best)-100 (worst); Europe Haemo-QoL: Youth 4-7 years 23.6(17.2); Parent 22.4(14.5) Youth 8-16 years 22.0(11.3); Parent 27.1(14.4) Canada CHO-KLAT Youth 4-18 years 74.6(14.0) Parent 74.5(11.6) Haemo-QOL: 0 (best) – 100 (worst): Youth 4-7 years 16.4(11.7) Parent 17.4(7.7); Youth 8-18 years 17.4(15.4) Parent 23.8(13.4)	Not reported
McCusker et al. (2015)	144 youth (validation phase) France, Germany, the Netherlands, Spain and UK	CHO-KLAT Youth : 77 (11.2) Parent: 76.5 (10.5)	Not reported

Author, Year	Sample Demographics: Number of participants; Country; Race/Ethnicity/ Nationality	Instrument; All scales are 0 (worst) - 100 (best) unless otherwise noted. Mean Total QOL score (SD)	Subscale: Score Mean (SD).
Pollak et al. (2006)	320 youth and 309 parents; France, Germany, Italy, the Netherlands, Spain and UK; French, German, Italian, Dutch, Spanish and UK	Haemo-QOL; 0 (best)-100 (worst); Youth 22.3(17.6) Parent 26.4(17.9)	Not reported
Young et al. (2013)	60 boys and 59 parents; Canada; Canadian	CHO-KLAT; Youth 75.4(12.0) Parent 77(11.6)	Not reported
		Hirschsprung Disease/Anorectal Malformation	
Hartman et al. (2007)	250 youth; the Netherlands; Dutch	Hirschsprung Disease/Anorectal Malformation QOL Questionnaire (HAQL); Youth with anorectal malformation 18.5(1.3) Youth 8-11 years with Hirschsprung disease 18.3(1.3); Youth 12-16 years with Hirschsprung disease 18.3(1.7)	Not reported
		Inflammatory Bowel Disease	
Abdovic et al. (2013)	104 youth; Croatia; Croatian	IMPACT-III Questionnaire; 35 (worst) - 175 (best); Youth 143.1(17.5)	Bowel Symptoms: 29.4(3.9) Systemic Symptoms: 11.9(2.3) Social Functioning:: 51.0(6.8) Body Image: 12.0(2.0) Treatment/Interventions:11.6(2.1) Emotional Functioning: 27.2(4.9)

Author, Year	Sample Demographics: Number of participants; Country; Race/Ethnicity/ Nationality	Instrument; All scales are 0 (worst) - 100 (best) unless otherwise noted. Mean Total QOL score (SD)	Subscale: Score Mean (SD).
Gray et al. (2011)	62 youth and 62 parents; USA: Northeast and Midwest; 88.7% White 8.1% Black 1.6% Latino 1.6% Other	IMPACT-III Questionnaire; 35 (worst) - 175 (best) Youth 137.2(18.6)	Bowel Symptoms: 29.4(3.9) Systemic Symptoms: 11.9(2.3) Social Functioning:: 51.0(6.8) Body Image: 12.0(2.0) Treatment/Interventions:11.6(2.1) Emotional Functioning: 27.2(4.9)
Otley et al. (2003)	147 youth and 147 parents; Canada; Canadian	IMPACT-III Questionnaire; 0 (worst) - 231 (best) 180(32) Quiescent disease activity 146(31) Mild disease activity 133(34) Moderate/severe disease activity	Not reported
		<u>Influenza</u>	
Chow et al. (2014)	Parents of 125 youth; Australia; Australian	Care-ILI-QoL (Influenza-like illnesses); 1 (worse) – 7 (best); Mean total = 3.87(0.93)	Social life = 3.24(.84) Daily activity = 3.36(1.41) Emotions = 4.0 (1.30) Perceived support = 4.86 (1.47)
		<u>Immune thrombocytopenia</u>	
Klaassen et al. (2013)	81 youth and 127 parents French, German, UK and Uruguay; 26% French 17% German 33% UK 24% Uruguayan	Kids' Immune Thrombocytopenia Tools (KIT); Youth 74(15) Parent 71(18)	Not reported
		<u>Lupus Erythematosus</u>	
Moorthy et al. (2007)	86 youth and 86 parents; USA: Illinois, New Jersey, New York, and Ohio; 36% African American 28% Mexican/Latino 17% Asian 17% White	Simple Measure of the Impact of Lupus Erythematosus in Youngsters (SMILEY); Youth 65(13) Parent 62(16)	Effect on self: 65(17) Youth; 59(17) Parent Limitations: 63(17) Youth; 60(18) Parent Social: 81(17) Youth; 74(17) Parent Burden: 57(16) Youth; 56(17) Parent

Author, Year	Sample Demographics: Number of participants; Country; Race/Ethnicity/ Nationality	Instrument; All scales are 0 (worst) - 100 (best) unless otherwise noted. Mean Total QOL score (SD)	Subscale: Score Mean (SD).
		Organ Transplantation	
Weissberg-Benchell et al. (2010)	199 youth and 247 parents; USA: Alabama, California, Illinois, Michigan, Nebraska, Texas, and Wisconsin; 72.8% White 9.9% Latino 8.8% Black 3.5% Asian/Pacific Islander 5.0% Other/not reported	PedsQL 3.0 Transplant Module; Youth 79.0(14.4) Parent 79.4(14.9)	Youth vs Parent: About My Medicines I: 83.1(15.0) vs 84.8(16.0) About My Medicines II: 86.6(16.2) vs 83.7(17.7) My Transplant and Others: 74.0(19.8) vs 76.9(19.8) Pain and Hurt: 71.1(23.4) vs 75.6(21.0) Worry: 79.4(21.8) vs 78.1(23.3) Treatment Anxiety: 74.8(27.2) vs 71.6(27.5) How I Look: 76.3(26.8) vs 78.8(24.4) Communication: 76.8(23.5) vs 77.6(26.6)
		Sickle Cell Disease	
Panepinto et al. (2013)	321 youth and 313 parents; USA: Alabama, California, Texas, and Wisconsin; 98.1% Black 0.6% White 0.6% Latino 0.6% Other	PedsQL Sickle Cell Disease Module; Youth 62.4(18.6) Parent 64.2(22.3)	Pain and Hurt: 66.7(20.9) Youth; 67.7(23.6) Parent Pain Impact: 54.0(24.8) Youth; 55.4(29.9) Parent Pain Management: 54.9(29.9) Youth; 61.3(31.7) Parent Worry I: 63.5(26.2) Youth; 60.2(31.7) Parent Worry II: 73.4(29.7) Youth; 69.3(33.1) Parent Emotions: 62.0(33.1) Youth; 64.7(32.7) Parent Treatment: 64.3(21.9) Youth; 69.0(23.2) Parent Communication I: 73.8(24.9) Youth; 76.8(25.0) Parent Communication II: 57.2(30.5) Youth; 65.8(30.2) Parent
		Spinal Muscular Atrophy	
Iannaccone et al. (2009)	125 youth and 174 parents; Canada and USA- DC, Ohio, Massachusetts, Minnesota, Missouri, New York, Oregon, Pennsylvania, Texas, Utah, and Virginia; 81.3% non-Latino 10.8% Latino 8.0% Not reported	PedsQL 3.0 Neuromuscular Module; Youth 67.5(15.6) Parent 59.7(16.8)	Youth vs parent About My Neuromuscular Disease: 66.0(16.5) Youth; 58.8(17.7) Parent Communication: 70.8(23.6) Youth; 67.0(31.1) Parent About Our Family Resources: 74.7(21.7) Youth; 59.6(22.2) Parent

Author, Year	Sample Demographics: Number of participants; Country; Race/Ethnicity/ Nationality	Instrument; All scales are 0 (worst) - 100 (best) unless otherwise noted. Mean Total QOL score (SD)	Subscale: Score Mean (SD).
Kocova et al. (2014)	35 youth and 35 parents; Czechoslovakia; Czech	PedsQL 3.0 Neuromuscular Module; Youth 58.3(14.6) Parent 52.1(16.4)	About My Neuromuscular Disease: 57.2(14.5) Youth; 53.4(17.0) Parent Communication: 72.0(20.3) Youth; 62.4(29.9) Parent About Our Family Resources: 56.8(22.7)Youth; 41.4(21.6) Parent
		Tonsil and Adenoid Disease	
Hopkins et al. (2010)	126 parents; UK; UK	Paediatric Throat Disorders Outcome; 0 (best) - 60 (worst); Parent 30.2(14.8)	Not reported

In our sample of studies, perception of QOL varied among healthy and ill youth and their parents. For example, in a sample of chronically ill (n = 367), acutely ill (n = 148), and healthy youth (n = 401) aged 2-18 years and their parents, Varni et al. (2001) hypothesized that healthy youth and their parents would perceive youth's QOL as better than acutely or chronically ill youth. Varni and colleagues reported mean total scores for chronically ill youth (77.2 ± 15.5), for acutely ill youth (78.7 ± 14.0) and for healthy youth (83.0 ± 14.8). Their hypothesis was confirmed for parent proxy-report also: for chronically ill (74.2 ± 18.4), for acutely ill (80.4 ± 15.3), and for healthy youth (87.6 ± 12.3).

Latino representation in quality of life assessment. Races and/or ethnicities may be disproportionately affected by disease. For example, in 2015, the prevalence of asthma was highest among Black/African America youth (18.7%) compared to Whites (11.7%) and Latinos (12.6%) (Centers for Disease Control and Prevention, 2017). The percent of Latino youth in the U.S. is on the rise and has increased from 15% in 1996 to 24% in 2013 (Murphey, Guzman, & Torres, 2014). As the numbers of Latinos increase, they have unevenly dispersed across the U.S., mainly settling in Arizona, California, Colorado, Florida, Illinois, New Jersey, New York, and Texas (Pew Research Center, 2013).

In order to determine if Latinos were adequately represented in studies that examined disease-specific QOL, study sample composition was extracted for 14 studies that were conducted in the U.S. (Botello-Harbaum et al., 2008; Davis et al., 2010; Franciosi et al., 2013; Gray et al., 2011; Iannaccone et al., 2009; Ingerski et al., 2010; Jaser et al. 2011; Marino et al., 2011; Moorthy et al., 2007; Panepinto et al., 2013; Valenzuela et al., 2006; Varni et al., 2004; Varni et al., 2014; Weissberg-Benchell et al., 2010). Botello-Harbaum et al. (2008), Davis et al. (2010), and Ingerski et al. (2010) did not report the percent of Latinos in their study. For researchers who reported Latino representation, the percentage ranged from 0.6% (Panepinto et al., 2013) to 39% (Valenzuela et al., 2006).

Latino representation was high in 3 studies. In their study of disease-specific QOL in 86 youth with systemic lupus erythematosus, Moorthy et al. (2007) conducted their study in 4 states located in the east coast and mid-west U.S. and included 28% Latinos. Participants were required to understand English to be included in this study. Valenzuela et al. (2006) included 39% Latinos in their study of 160 youth with Type I diabetes and their parent. This study was conducted in Florida and participants were required to be fluent in English in order to be included. Varni et al.'s (2004) study of 404 youth with

asthma and 699 healthy youth was conducted in Kansas. This study included 35% Latinos and was conducted in participants' preferred language choice.

Latinos were under-represented (Latinos were less than 16% in study) in 9 of the studies that were conducted in U.S. states that have a high population of Latinos. Two examples follow: Panepinto and colleagues' study of 321 youth with sickle cell disease and their parents conducted in Alabama, California, Texas, and Wisconsin included only 2 Latino participants. Franciosi et al. (2013) conducted their study of 263 youth with eosinophilic esophagitis and their parents across 6 clinical sites in Colorado, Indiana, Ohio, Philadelphia, and Texas. Even though states like Colorado and Texas have a larger number of Latinos (Pew Research Center, 2013), this study only included 4% Latinos.

Summary of Disease-specific Quality of Life Review

In summary, studies researching QOL in youth with 21 diseases and their parent/caregiver were included in this review. Analysis of studies revealed several main findings. Disease-specific QOL instruments were often used in conjunction with generic instruments to assess QOL of youth with different types of illness. The majority of authors used established or existing disease-specific QOL instruments to measure QOL in youth and/or parent/caregiver. All authors reported reliability and validity of disease-specific QOL instruments. Subscales of disease-specific QOL instruments measured features of the disease of interest. Symptoms, treatment, communication, emotion, impact, and social subscales were most frequently found in disease-specific QOL instruments. Other subscales often found were physical functioning, medicines, psychological impact, food, disease impact, and pain. The PedsQL Sickle Cell Disease Module, for example, include subscales that measured pain and hurt, pain impact, pain management, worry, emotions, treatment, and communication, while the IMPACT III included subscales such as bowel symptoms, body image, and treatment/interventions and measured QOL in youth with inflammatory bowel disease.

Youth-parent perspective of QOL often differed, and QOL scores varied according to disease studied. Perception of QOL was generally lower for youth with chronic illness across disease types. The lowest-rated QOL was 18.5(1.3) by youth with Hirschsprung Disease/Anorectal Malformation. The highest-rated QOL was 79(14.4) by parents of youth who received organ transplantation. Based on these QOL scores, youth viewed themselves as most negatively affected by symptoms of Hirschsprung

Disease/Anorectal Malformation and therefore perceived their QOL poorly, whereas youth who received organ transplantation did not view themselves as being as negatively affected by having received a transplanted organ and perceived their QOL as better.

Cultural Factors Associated with Quality of Life

Problem Identification and Purpose of Review

In the literature review of disease-specific QOL in youth, Latinos were often underrepresented, and QOL was often not reported based on ethnicity. Of the 14 studies conducted in the U.S., while 11 included a representative sample of Latinos (Franciosi et al., 2013; Gray et al., 2011; Iannaccone et al., 2009; Jaser et al., 2011; Marino et al., 2011; Moorthy et al., 2007; Panepinto et al., 2013; Valenzuela et al., 2006; Varni et al., 2004; Varni et al., 2014; Weissberg-Benchell et al., 2010), no study stratified QOL perception by race/ethnicity. Latinos accounted for 24% of the U.S. population in 2013 (Murphey et al., 2014) and are expected to increase to 36.4% by 2050 (Murphey et al., 2014). Considering that the U.S. population is becoming increasingly culturally diverse, it is necessary that researchers consider how culture and ethnicity impact a person's QOL (Kagawa-Singer, 2010). It is therefore important that when measuring QOL, differences in cultural perceptions of illness, health, and other health-related events be included in measurements (Gonzalez-Calvo, Gonzalez, & Lorig, 1997; Herdman, Fox-Rushby, & Badia, 1998). Examining QOL as perceived by different cultures may assist researchers to better understand the construct as perceived by a particular culture (Kagawa-Singer, 2010).

Culture is based on beliefs and values and stipulates how a group of people live (Kagawa-Singer, 2000), and provides a social connection with the world (Lopez-Class et al., 2011). Culture provides identification with and attachment to family, such as the value of familism (the reduction of the personal interests of an individual and an increased interest on the values and demands of the family) among Latinos (Urizar & Sears, 2006). In a study of 598 families of Mexican origin, researchers found that familism values in adolescent and their parents interacted protectively with deviant peer affiliations such as getting drunk/high and/or starting fights (German, Gonzales, & Dumka, 2009).

People connect with each other through language and communication. In several studies, immigrants considered their language barrier an obstacle to good health and reported difficulty communicating with clinicians as contributing to health disparities (Carpenter, Schoster, Shreffler, &

Callahan, 2011; Jacobs, Karavolos, Rathouz, Ferris, & Powell, 2005; Stevens, Vane, & Cousineau, 2011). Jacobs et al. (2005) used secondary data from a longitudinal study of a multiethnic sample of women to examine whether the ability to speak English was associated with their agreement to have breast and cervical cancer screenings. Findings of this study demonstrated that Hispanic, Chinese, and Japanese women who spoke English received more frequent Papanicolaou tests, mammograms, and clinical breast examinations than those who reported either not reading or speaking English at all or reading or speaking their native language more fluently than English. In their study, Carpenter et al. (2011) conducted a cross-sectional study to determine whether racial disparities in health status, QOL, and activity limitations exist for Latino, Black, and White adults living with arthritis who have similar access to a primary care physician. Participants rated having a clinician who spoke the same language as the participant as more important than having access to a clinician. Considering that studies have shown that the meaning and structure of QOL differs greatly depending on the culture being studied, *the purpose of this literature review is to examine existing research related to cultural factors that are associated with QOL.*

Literature Search

A specific focus on culture and QOL facilitated this literature search. Search term “culture AND quality of life” was used in title search. No restriction was placed on year of article’s publication. Searches were conducted in Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, and Web of Science databases. Records were excluded if they: (1) examined organizational culture (how people who are part of an organization behave and the meaning that people attach to that behavior), (2) study was a review of literature, (3) were published in a language other than English, or (4) did not examine culture and QOL/report QOL scores.

Data Evaluation and Quality Appraisal

The Mixed Methods Appraisal Tool (MMAT) (Pluye et al., 2011) was used to evaluate and appraise methodological quality of studies. A description of the MMAT is provided on page 13**.**

Data Analyses

Data analysis was performed using a systematic analytic approach. Data were examined and quality scores and methodological quality of studies were extracted and presented in graph and narrative

form. Data such as the types of disease/disorder researched, country where study was conducted, and religiosity/spirituality, ethnicities, familism, fatalism, disease stigma/shame, patient-provider relationship, and gender were extracted from each study.

Presentation of Findings

This final section presents results of literature search of cultural factors associated with QOL. Here, studies evaluated and appraised with the MMAT are evaluated, appraised, synthesized, and presented in graphs. Data concerning the type of study, author, and year, the percentage of Latinos in each study, the concepts found to be positively, negatively, or not associated with QOL were synthesized and are presented in Table 3.

Literature search. Figure 5 provides details of the literature search. The search resulted in 2376 records. Eighteen records were excluded after cross-checking databases for duplicates, which resulted in 2358 records remaining. Titles and abstracts were screened, resulting in the removal of 2213 records (2197 records were not related to culture and QOL and 16 records were related to organizational culture), leaving 145 articles for full-text review. Ninety seven articles that were literature reviews and 7 articles that did not report QOL scores were further excluded as they did not meet this study's purpose. Forty one articles remained and were included in this integrative review: 34 quantitative, 6 qualitative, and 1 mixed methods design. Studies ranged in years of publication from 1998 (Bernhard et al., 1998; Juarez, Ferrell, & Borneman, 1998) to 2016 (Alaloul, AbuRuz, Moser, Hall & Al-Sadi, 2016; Cruz-Oliver & Sanchez-Reilly, 2016; Kalyva, Abdul-Rasoul, Kehl, Barkai & Lukacs, 2016). Fourteen studies measured QOL in healthy individuals of various races/ethnicities; the majority of participants were female (Aznar & Castañón, 2005; Bhandari, 2012; Cruz-Oliver & Sanchez-Reilly, 2016; Fu, Anderson, Courtney, Hu, 2007; Kim & Sok, 2010; Leung, Wu, Lue, & Tang, 2004; Lieber, Chin, Nihira, & Mink, 2001; Molzahn, Kalfoss, Makaroff, & Skevington, 2011; Olmedo-Alguacil et al., 2016; Power et al., 1999; Skevington, 2010; Utsey et al., 2007; Urzua, Miranda-Castillo, Caqueo-Urizar, & Mascayano, 2013; Verhagen, Ros, Steunenberg & de Wit, 2014). Latinos were a focus of interest in 11 studies (Ashing-Giwa et al., 2007; Aznar & Castañón, 2005; Brice et al., 2011; Brown, McCauley, Levin, Contant, & Boake, 2004; Cruz-Oliver & Sanchez-Reilly, 2016; Graves et al., 2012; Lim, Gonzalez, Wang-Letzkus, & Ashing-Giwa, 2009; Tatis et al., 2005; Urizar & Sears, 2006; Urzua et al., 2013; Wildes, Miller, de Majors, & Ramirez, 2009).

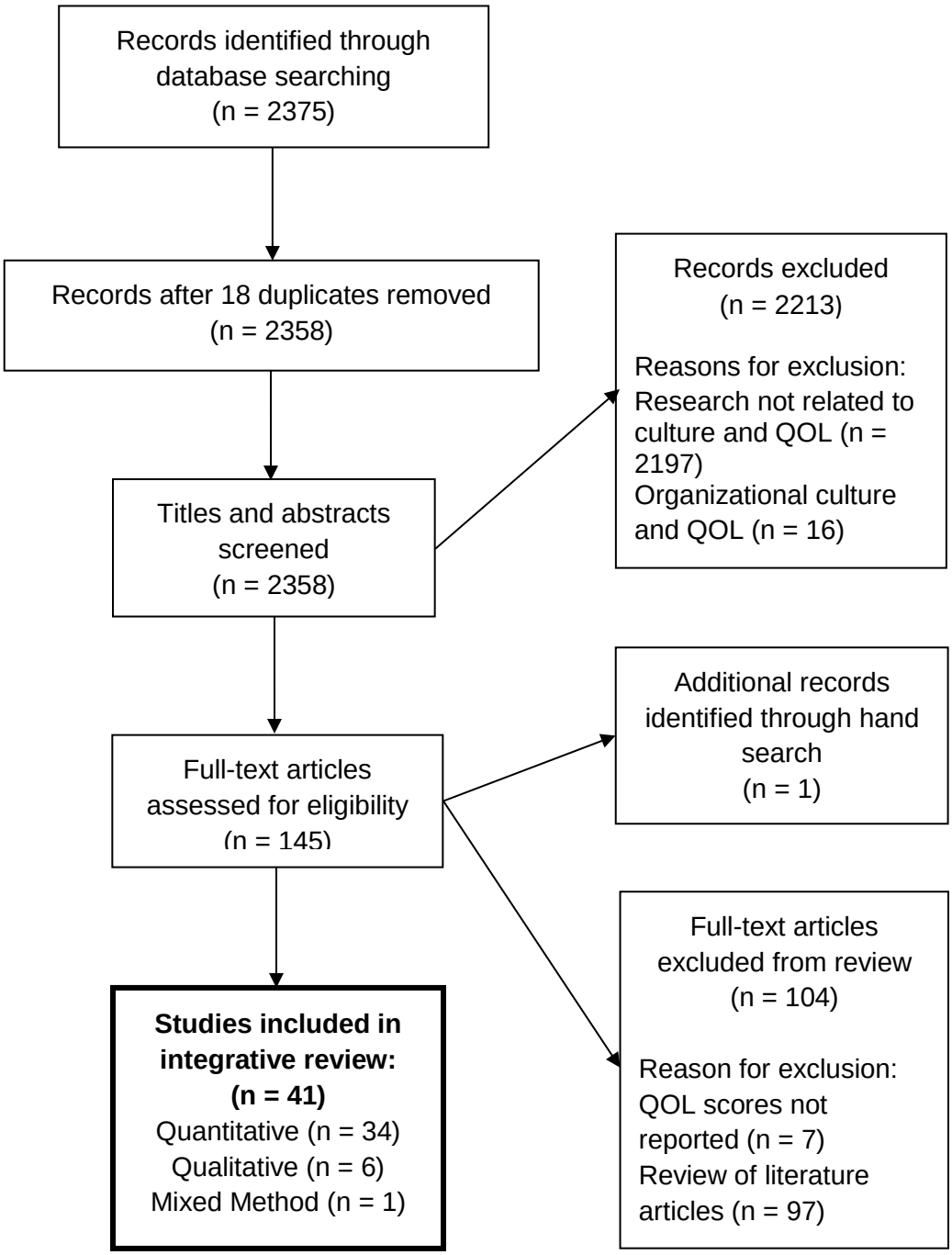

Figure 5. Flow Diagram of Literature Search of Cultural Factors Associated with QOL. Literature search and selection process. Format for Figure 5 adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic *R*eview *A*nalyses: The PRISMA Statement. PLos Med 6(6): e1000097 doi:10.1371/journal.pmed.1000097

To determine inter-rater reliability, 39% of studies (2 cohort and 12 cross sectional studies) were randomly selected for appraisal by a second reviewer. Inter-rater reliability was assessed at 96% for cohort studies and 97% for cross sectional studies. Where appraisal differed, discrepancies were resolved by discussion until consensus was achieved.

Data evaluation and quality appraisal. All studies received satisfactory responses to both MMAT screening questions. Thirty four studies used quantitative non-randomized designs. Of these, 30 were cross sectional (Alaloul et al., 2016; Ashing-Giwa et al., 2007; Aznar & Castañón, 2005; Bhandari, 2012; Brown et al., 2004; Fielding et al., 2013; Forjaz & Guarnaccia, 2001; Fu et al., 2007; Graves et al., 2012; Huang et al., 2010; Jafari et al., 2013; Kalyva, Abdul-Rasoul, Kehl, Barkai and Lukacs, 2016; Kang, 2009; Kim & Sok, 2010; Lim et al., 2009; Molzahn et al., 2011; Myaskovsky et al., 2011; Olmedo-Alguacil et al., 2016; Owolabi, 2011; Pfennings et al., 1999; Pluta-Fuerst et al., 2011; Power et al., 1999; Scott et al., 2008; Skevington, 2010; Soulsby, Masterman, Kelly, & Thomas, 2010; Urizar & Sears, 2006; Urzua et al., 2013; Utsey et al., 2007; Verhagen et al., 2014; Wildes et al., 2009), 1 was quasi-experimental (Tatis, Remache, & DiMango, 2005), 1 was case control (Faresjö et al. 2006), and 2 were cohort studies (Brice et al. 2011; Bernhard et al. 1998). One study used mixed method design (Lieber et al. 2001). Six studies were of qualitative design (Ashing-Giwa et al., 2004; Choe, Padilla, Chae, & Kim, 2001; Cruz-Oliver & Sanchez-Reilly, 2016; Juarez et al., 1998; Leung et al., 2004; Lopez-Class et al., 2011).

A variety of ethnicities were represented in the review. Sample size varied depending on the type of study design. Of the quantitative studies, sample size ranged from 68 (Jafari et al., 2013) to 21,743 (Scott et al., 2008). Qualitative study sample sizes were smaller and ranged from 17 (Juarez et al., 1998) to 122 participants (Ashing-Giwa et al., 2004). Results are reported by study design as follows:

Quantitative studies. Thirty cross sectional studies were appraised. Figure 6 displays results of appraisal by each quality criterion. A major strength noted in the majority of studies was that the sample recruited was representative of the different population sub-groups, such as age, gender, and race/ethnicity (criterion 3.1). The majority of studies met criterion 3.2 for the appropriateness of measurements and definition of dependent and independent variables. Skevington (2010), for example, conducted secondary analysis of data collected about the QOL of 9,404 sick and healthy adults across 24

diverse cultures. Skevington (2010) reported that participants without education reported much poorer QOL than those who completed any educational level; and QOL was better in highly developed countries.

A major weakness of the quantitative studies was poor survey response rate in studies that either mailed questionnaires or conducted interviews via telephone; and poor complete outcome data in studies that administered questionnaires in clinical or community setting (criterion 3.4). Of 7 studies where questionnaires were either distributed via mail or telephone, 5 authors reported response rates of 60% or greater (Bhandari et al. 2012; Faresjo et al. 2006; Pfennings et al. 1999; Soulsby et al., 2010; Wildes et al., 2009).

In 24 studies, questionnaires were administered in clinical or community settings. Of these, 11 authors reported complete outcome data (where almost all the participants contributed to almost all measures) of >80% (Alaloul et al., 2016; Bernhard et al., 1998; Forjaz & Guarnaccia, 2001; Fu et al., 2007; Huang et al., 2010; Jafari et al., 2013; Kang, 2009; Kim & Sok, 2010; Myaskovsky et al., 2011; Owolabi, 2011; Urizar & Sears, 2006; Urzua et al., 2013), while 3 authors reported complete outcome data <80% (Brice et al., 2011; Brown et al., 2004; Tatis et al., 2005) and complete outcome data were unknown for 9 studies (Aznar & Castañón, 2005; Fielding et al., 2013; Lim et al., 2009; Molzahn et al., 2011; Pluta-Fuerst et al., 2011; Power et al., 1999; Scott et al., 2008; Skevington, 2010; Utsey et al., 2007).

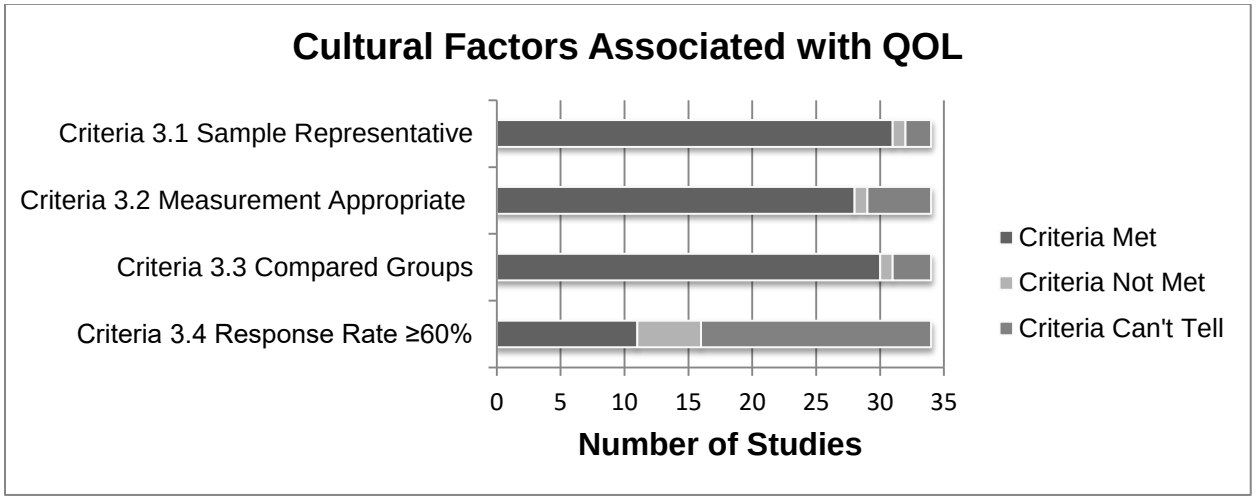

Figure 6 Quality Appraisal Assessments of Quantitative Studies

Figure 7 summarizes the overall quality scores of the quantitative studies. The majority of studies met at least 3 of the 4 criteria and scored ≥75% in overall quality.

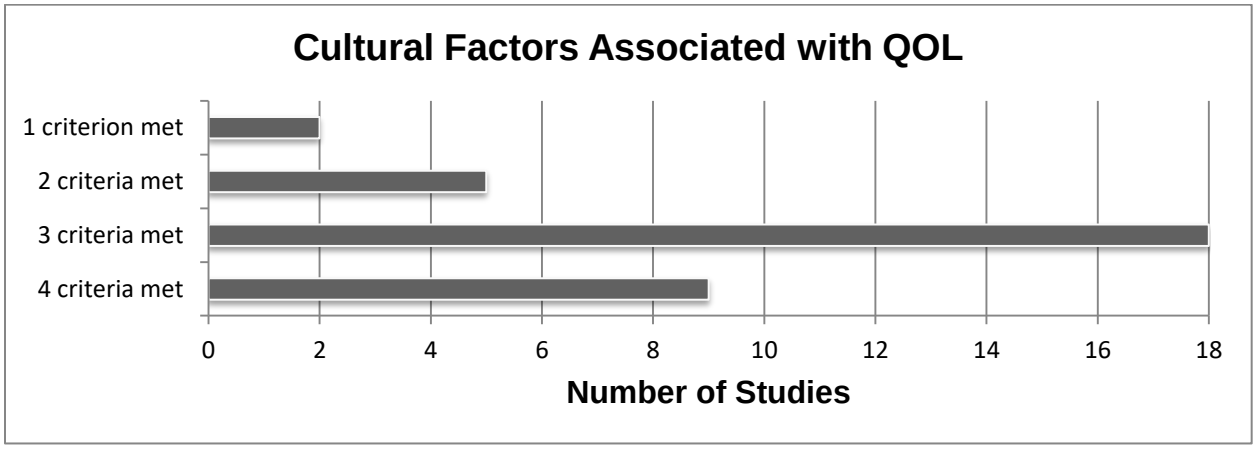

Figure 7 Number of Criteria Met in Quantitative Studies

Qualitative studies. Six qualitative studies were appraised. The majority of authors successfully described the context in which data were collected (criterion 1.3). Ashing-Giwa et al. (2004) for example, stated that focus groups of Latina and Asian cervical cancer survivors were conducted at the recruitment sites where participants attended clinic. Conducting research at this clinical site was meant to provide a familiar, facilitative, non-threatening group environment experience to participants. However, in none of the studies did the authors explain how findings related to their perspective, role, and interactions with participants (criterion 1.4). Figure 8 depicts methodological quality assessment of the qualitative studies by specific criterion.

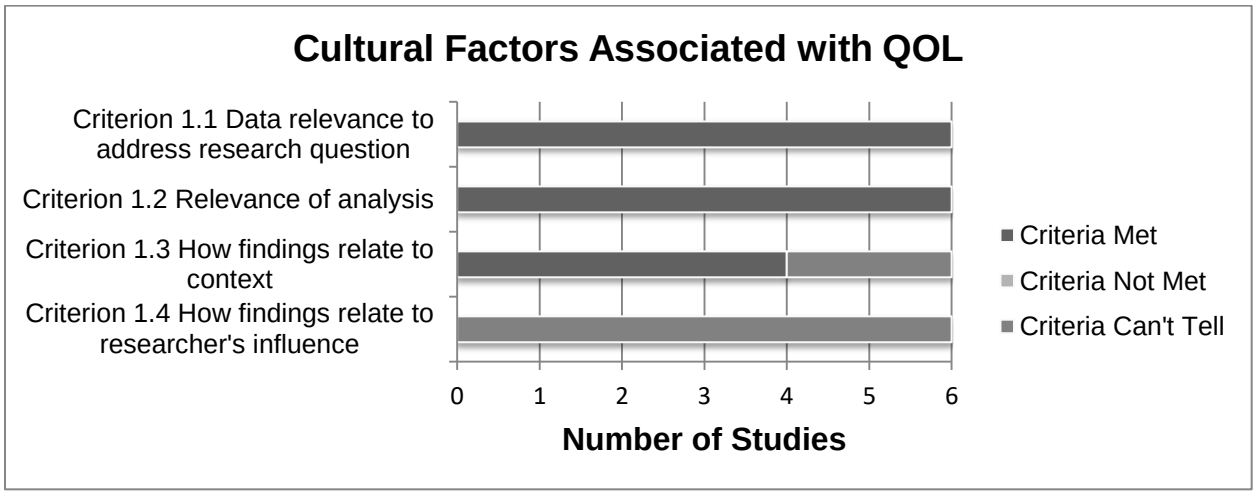

Figure 8 Quality Appraisal Assessments of Qualitative Studies

Characteristics of Studies. Regarding study purpose for quantitative studies, 14 studies examined the relationship between cultural factors and QOL (Bernhard et al., 1998; Graves et al., 2012; Jafari et al., 2013; Kalyva et al., 2016; Olmedo-Alguacil et al. 2016; Myaskovsky et al., 2011; Scott et al., 2008; Skevington, 2010; Soulsby et al., 2010; Urizar & Sears, 2006; Urzua et al., 2013; Utsey et al., 2007; Verhagen et al., 2014; Wildes et al., 2009). Four studies examined predictors of QOL (Alaloul et al., 2016; Ashing-Giwa et al., 2007; Lim et al., 2009; Brice et al., 2011), 3 studies examined perception of QOL (Bhandari, 2012; Brown et al., 2004; Molzahn, et al., 2011), and 1 examined the effect of intervention consisting of training for asthma educators, development of educational materials in English and Spanish, and collaborating with medical staff, on QOL (Tatis et al., 2005). Twelve studies compared perception of QOL across countries (Forjaz & Guarnaccia, 2001; Huang et al., 2011; Kang, 2009; Faresjö et al., 2006; Pluta-Fuerst et al., 2011; Fu et al., 2007; Pfennings et al., 1999; Fielding et al., 2013; Power et al., 1999; Aznar & Castañón, 2005; Kim & Sok, 2010; Owolabi, 2011). Some authors used 1 instrument or a combination of instruments to measure cultural factors associated with QOL. Fu et al. (2007), for example, used 1 contextual measure of culture - the individualism and collectivism scale (INDCOL) in combination with the World Health Organisation QOL BREF (BREF is the abbreviated version of the WHOQOL-100) (WHOQOL-BREF) to measure QOL. In their cross-cultural study, Graves et al. (2012) used a combination of instruments to examine whether contextual and cultural factors influence QOL. Cultural factors were measured using: (1) items from the Body Image after Breast Cancer Questionnaire (shame/stigma); (2) a modified, validated Spanish version of Powe Fatalism Inventory (cancer fatalism); (3) a modified version of the Familism Scale (familism); (4) a modified Spanish version of the Religious Coping Scale (religious and spiritual coping); and (5) the Spanish-language Short Acculturation Survey (acculturation).

Religiosity/Spirituality. Seven studies examined the relationship between religiosity/spirituality and QOL (Ashing-Giwa et al. 2004; Choe et al. 2001; Fu et al. 2007; Graves et al. 2012; Leung et al. 2004; Skevington, 2010; Wildes et al. 2009) All authors reported a positive association between religiosity/spirituality and QOL.

Table 3 Cultural Factors and Their Associations with Quality of Life

Study Design; Author, Year	**% Latinos; Country of Origin**	**Concept/Construct**	**Association with QOL: +, -, or None**
Quantitative			
		Religiosity/spirituality	
Fu et al. (2007)	0%		+
Graves et al. (2012)	100%; USA		+
Skevington (2010)	1%; Argentina		+
Wildes et al. (2009)	100%; Central & South America, Mexico, Puerto Rico, USA		+
		Latino ethnicity	
Ashing-Giwa et al. (2007)	26%; Central & South America, Mexico		-
Brice et al. (2011)	40%; USA		-
Brown et al. (2004)	50%; USA		+
Lim et al. (2009)	47%; USA		-
Scott et al. (2008)	6%+; Argentina		-
		Familism	
Graves et al. (2012)	100%; USA		+
Urizar and Sears (2006)	100%; Central & South America, Cuba, Puerto Rico		+
		Acculturation	
Bhandari (2012)	0%;		-
Graves et al. (2012)	100%; USA		None
Lim et al. (2009)	47%: USA		+
Urizar and Sears (2006)	100%; Central & South America, Cuba, Puerto Rico		+
Wildes et al. (2009)	100%; Central & South America, Mexico, Puerto Rico, USA		+
		Fatalism	
Graves et al. (2012)	100%; USA		-
Urizar and Sears (2006)	100%; Central & South America, Cuba, Puerto Rico		-
		Disease stigma/shame	
Graves et al. (2012)	100%; USA		-
		Patient-provider relationship	
Lim et al. (2009)	47%; USA		+
Wildes et al. (2009)	100%; Central & South America, Mexico, Puerto Rico, USA		+
		Gender (male)	
Bhandari (2012)	0%		+
Kang (2009)	Unknown		None
Urizar and Sears (2006	100%; Central & South America, Mexico, Puerto Rico, USA		+
Qualitative			Relevant Themes that Influenced QOL + or -

Study Design; Author, Year	% Latinos; Country of Origin	Concept/Construct	Association with QOL: +, -, or None
		Religiosity/spirituality	
Ashing-Giwa et al. (2004)	25%; USA		+
Choe et al. (2001)	0%		+
Juarez et al. (1998)	100%; USA		+
Leung et al. (2004)	0%		+
Lopez-Class et al. (2011)	100%; USA		+
		Familism	
Ashing-Giwa et al. (2004)	25%; USA		+
Choe et al. (2001)	0%		+
Juarez et al. (1998)	100%; USA		+
Lopez-Class et al. (2011)	100%; USA		+
			Relevant Themes that Impacted QOL + or -
		Fatalism	
Lopez-Class et al. (2011)	100%; USA		-
		Disease stigma/shame	
Lopez-Class et al. (2011)	100%; USA		-
		Patient-provider relationship	
Lopez-Class et al. (2011)	100%; USA		-
Mixed Method			
		Acculturation	
Lieber et al. (2001)	0%		+

Note: + Positive association; - Negative association; None No association

Disease/disorder. In 13 studies, researchers examined the association of culture and QOL in participants diagnosed with cancer. Of these, the majority focused on breast cancer (Ashing-Giwa et al., 2004; Lopez-Class et al., 2011; Ashing-Giwa et al., 2007; Graves et al., 2012; Lim et al., 2009; Wildes et al., 2009; Bernhard et al., 1998; Jafari et al., 2013). Four studies examined QOL for participants with other forms of cancer: colorectal cancer (Fielding et al., 2013), hematopoietic stem cell transplantation (Brice et al., 2011), hematologic malignancies (Forjaz & Guarnaccia, 2001), and "various cancers" (Scott et al., 2008). One study, Juarez et al. (1998), did not specifically note the type(s) of cancer(s) researched but instead researched perceptions of QOL in participants who were experiencing pain as a result of cancer.

Four studies measured QOL in participants with cardiac disorders. Kang (2009) studied a sample of American and Korean participants with atrial fibrillation using the SF-36 survey (100 point scale). Quality of life scores differed but were not statistically significant between genders: Korean men rated their QOL as better (49.32) than American men (46.12) and American women rated their QOL as slightly better (51.43) than Korean women (45.44). In Taiwanese and American participants with heart failure, Huang et al. (2010) reported that American participants rated their QOL as poorer (52.6) than Taiwanese participants (43.8) on the Minnesota Living with Heart Failure Questionnaire (0 –105 point scale with higher scores indicating poorer QOL). Urizar and Sears' (2006) study of QOL in non-Cuban- and Cuban-American participants with coronary heart disease reported that women had clinically significant lower global and emotional functioning compared to men.

Twelve studies measured QOL in healthy samples using various QOL measures (Azner & Castañón, 2005; Bhandari, 2012; Fu et al., 2007; Kim & Sok, 2010; Lieber et al., 2001; Molzahn et al., 2011; Olmedo-Alguacil et al. 2016; Power et al., 1999; Skevington, 2010; Urzua et al., 2013; Utsey et al., 2007; Verhagen et al., 2014). Four studies (Fu et al., 2007; Skevington, 2010; Urzua et al., 2013; Utsey et al., 2007) used the WHOQOL-BREF, a 26-item Likert scale instrument that assessed 4 domains of QOL: physical health, psychological, social relationships, and environmental well-being. The remaining studies used various QOL measures.

Ethnicity. Of the 18 studies with Latino participants (Ashing-Giwa et al., 2004; Ashing-Giwa et al., 2007; Aznar & Castañón, 2005; Brice et al., 2011; Brown et al., 2004; Cruz-Oliver & Sanchez-Reilly,

2016; Graves et al., 2004; Juarez et al; 1998; Lim et al., 2009; Lopez-Class et al., 2011; Molzahn et al., 2011; Power et al., 1999; Scott et al., 2008; Skevington, 2010; Tatis et al., 2005; Urizar & Sears, 2006; Urzua et al., 2013; Wildes et al., 2009), 5 studies (Ashing-Giwa et al. 2007; Brice et al. 2011; Brown et al. 2004; Lim et al. 2009; Scott et al. 2008) examined the relationship between Latino ethnicity and QOL rating. All studies except Brown et al. (2004) reported lower QOL ratings for Latino participants compared to other ethnic groups after controlling for demographic and individual characteristics such as stage of disease.

Three of the 6 quantitative breast cancer studies (Ashing-Giwa et al., 2007; Bernhard et al., 1998; Lim et al., 2009) found variations in cultural factors affecting QOL. Lim et al. (2009) found Latinas more likely to believe that God, health professionals, and luck have an effect on their health compared to Asian Americans. In their study of 703 breast cancer survivors, Ashing-Giwa et al. (2007) found greater emotional burden and socio-ecologic strain (which are associated with poorer QOL) among Latinas compared to African-, Asian-, and European-Americans. Bernhard et al. (1998) found cultural and language factors had a statistically significant impact on baseline patient-rated QOL.

Latino cultural groups in studies. A wide variety of Latino cultural groups were represented. Several studies included participants from one or more Latin American countries. Six studies included participants with Mexican nativity (Ashing-Giwa et al., 2007; Aznar and Castañón, 2005; Graves et al., 2012; Juarez et al. 1998; Lopez-Class et al., 2011; Wildes et al., 2009), 10 studies included participants with South American nativity (Ashing-Giwa et al., 2007; Aznar and Castañón, 2005; Graves et al., 2012; Lopez-Class et al., 2011; Molzahn et al. 2011; Scott et al., 2008; Skevington et al., 2010; Urizar & Sears, 2006; Urzua et al., 2013; Wildes et al., 2009), 8 studies included participants with Caribbean nativity (Ashing-Giwa et al., 2007; Aznar and Castañón, 2005; Graves et al., 2012; Lopez-Class et al., 2011; Power et al., 1999; Urizar & Sears, 2006; Urzua et al., 2013; Wildes et al., 2009), and 7 studies included participants with Central American nativity (Ashing-Giwa et al., 2007; Aznar and Castañón, 2005; Graves et al., 2012; Lopez-Class et al., 2011; Power et al., 1999; Urizar & Sears, 2006; Wildes et al., 2009).

Familism. Several studies examined the relationship between familism and QOL (Ashing-Giwa et al. 2004; Choe et al. 2001; Graves et al. 2012; Lopez-Class et al. 2001; Urizar & Sears, 2006). Ashing-Giwa et al. (2004), Choe et al. (2001), Graves et al. (2012) and Lopez-Class et al. (2001) reported a

positive association between familism and QOL, and Urizar and Sears (2006) reported a negative association between familism and QOL.

Acculturation. Several studies examined the association between acculturation and QOL. Results varied. Four authors reported acculturation as having a positive association with QOL (Lieber et al. 2001; Lim et al. 2009; Urizar & Sears, 2006; Wildes et al. 2009). In Lim et al.'s (2009) study of Latina and Asian breast cancer survivors, researchers found a positive association between acculturation and QOL. Urizar and Sears (2006) examined the relationship between cultural factors (acculturation, familism, and fatalism) and psychosocial factors such as depression and social support, and QOL in a sample of Latinos diagnosed with coronary heart disease. The researchers reported that higher levels of acculturation were associated with lower levels of familism and a higher socio-economic status but there was no association between cultural factors and QOL. Bhandari et al. (2012) examined the relationship between perceived and acculturative stress and QOL in their cross sectional study of Nepalese students studying in South Korea. They found that acculturative stress was negatively associated with QOL. Lim et al. (2009) and Bhandari (2012) reported that individuals who are better acculturated are more likely to have a better grasp of the language and display greater language fluency. Graves et al. (2012) examined independent associations of culture, social and medical context with QOL in their cross sectional study of Latina breast cancer survivors. They found that acculturation was not independently related to QOL.

Language. All authors reported using questionnaires and/or interviews according to participant's language preference. Several studies examined the relationship between perceived QOL and language choice for questionnaire/interview completion. In their cohort study of 2220 breast cancer survivors, Bernhard et al. (1998) examined how culture, described as language/country groups (example English/Australia, and English/South Africa), biomedical factors (age, treatment assignment, and tumor size), marital status and education are associated with QOL. They found that culture had the strongest impact on baseline QOL. In a sample of 389 Latina- and Asian-American breast cancer survivors Lim et al. (2009) examined: (1) health behaviors and QOL of Latina and Asian-American breast cancer survivors, (2) the association between cultural predictors (acculturation, treatment-related decisions, cultural health beliefs, and doctor–patient relationships) of health behaviors and QOL, and (3) pathways

for predicting health behaviors and QOL in their cross sectional study. The authors did not find a significant relationship between survey language (English, Spanish, Korean, and Chinese) and QOL in Latina (n = 183) and Asian American (n = 206) participants with breast cancer.

Fatalism. All studies that examined the relationship between fatalism and QOL included Latino participants; consistent across studies, a negative association between fatalism and QOL (Graves et al., 2012; Urizar & Sears, 2006) was reported. For example, in their study of QOL among Latino cardiac patients, Urizar and Sears (2006) found fatalism was related to lower social functioning in female participants with coronary heart disease but no differences between non-Latino and Latino participants regarding levels of fatalism were found.

Disease Stigma/Shame. All studies that examined how disease stigma/shame affected QOL in women diagnosed with breast cancer included Latinas (Graves et al., 2012; Lopez-Class et al., 2001). Both studies reported that disease stigma/shame had a negative association with QOL.

Patient-provider relationship. Lim et al. (2009) and Wildes et al. (2009) both examined the relationship between patient-provider relationship and QOL. In their study of cultural health beliefs and health behaviors between Latina and Asian-American breast cancer survivors, Lim et al. (2009) reported a positive relationship between patient-provider relationship and QOL.

Gender. Perception of QOL varied by gender in several studies: Kang (2009) examined gender and cultural QOL differences between Americans and Koreans with atrial fibrillation and found that QOL perception varied according to gender, with men reporting better physical functioning but having worse mental health. Women also reported lower QOL than men in a study of Latino patients with cardiovascular disease (Urizar & Sears, 2006) and in a study of Nepalese students studying in South Korea (Bhandari, 2012). Data regarding disease/disorder, authorship, methodology, demographics, instruments, and QOL rating are presented in the first portion of Table 4 and major themes are presented in the latter portion of Table 4.

Qualitative themes. Researchers in all 6 studies reported that religiosity/spirituality and familism/family centeredness had a positive impact on study participants. Ashing-Giwa et al. (2004) conducted research with 74 breast cancer survivors using focus groups (n = 51) and key informant interviews (n = 23). Ashing-Giwa et al. (2004) reported that less acculturated Asian American breast

cancer survivors believed that religion/spirituality were important in dealing with an illness. In Lopez-Class et al.'s (2011) study of 28 Latina breast cancer survivors using focus group (n = 9) and individual interviews (n = 19), fatalism was reported as being important to participants in the early stages after diagnosis but not as important after learning about breast cancer treatment and outcomes. Disease stigma/shame had a negative impact on participants in 3 studies (Ashing-Giwa et al., 2004; Juarez et al., 1998; Lopez-Class et al., 2011), all of which were conducted with cancer survivors.

Summary of Cultural Factors Associated with Quality of Life Review

In conclusion, this literature review of how cultural factors are associated with QOL found that individual perception of QOL differs among cultures (Utsey et al., 2007; Aznar & Castañón, 2005; Faresjö et al., 2006; Graves et al., 2012; Pluta-Fuerst et al., 2011; Scott et al., 2008; Wildes et al., 2009; Tatis et al., 2005). Eight cultural factors were identified as important to participants' QOL: religiosity/spirituality, Latino ethnicity, familism, acculturation, fatalism, disease stigma/shame, patient-provider relationship, and gender. Of these, religiosity/spirituality, familism, and patient-provider relationship were positively associated with QOL while fatalism and disease stigma/shame were negatively associated with QOL.

Diseases/disorders not only affect patients physically but also psychologically. Some Latinos, for example, may be of the belief that what will happen with illness has already been decided and cannot be changed (Graves et al., 2012; Urizar & Sears, 2006; Lopez-Class et al., 2011). Some cultures believe religion and/or spirituality play a role in their health. Spiritual well-being was found to have some mediating effects between culture-specific coping and QOL in a sample of African Americans (Utsey et al., 2007). Wildes et al. (2009) and Lim et al. (2009) reported that Latinos were found to have more religious/spiritual beliefs than individuals from other cultures. Amongst diseases/disorders researched, cancer was the most frequently studied, followed by cardiac disorders. Almost half of studies included Latinos, the majority of which were female.

A variety of QOL instruments were used. The instrument used most was the Short Form-36, which was used in 9 studies (Alaloul et al., 2016; Brown et al., 2004; Faresjö et al., 2006; Forjaz & Guarnaccia, 2001; Kang, 2009; Kim & Sok., 2010; Olmedo-Alguacil et al., 2016; Pfennings et al., 1999; Verhagen et al., 2014), followed by FACT-G, which was used in 4 studies (Ashing-Giwa et al., 2007; Graves et al., 2012; Lim et al., 2009; Wildes et al., 2009) and WHOQOL-BREF, used in 4 studies (Fu et

al., 2007; Skevington, 2010; Urzua et al., 2013; Utsey et al., 2007). Fourteen studies used disease-specific instruments (Ashing-Giwa et al., 2007; Fielding et al., 2013; Graves et al., 2012; Huang et al., 2010; Jafari et al., 2013; Kalyva et al., 2016; Lim et al., 2009; Owolabi, 2011; Pluta-Fuerst et al., 2011; Scott et al., 2008; Soulsby et al., 2010; Tatis et al., 2005; Urizar & Sears, 2006; Wildes et al., 2009) and 20 studies used generic instruments (Alaloul et al., 2016; Aznar & Castañón, 2005; Bhandari, 2012; Bernhard et al., 1998; Brice et al., 2011; Brown et al., 2004; Faresjö et al., 2006; Forjaz & Guarnaccia, 2001; Fu et al., 2007; Kang, 2009; Kim & Sok, 2010; Molzahn et al., 2011; Myaskovsky et al., 2011; Olmedo-Alguacil et al., 2016; Pfennings et al., 1999; Power et al., 1999; Skevington, 2010; Urzua et al., 2013; Utsey et al., 2007; Verhagen et al., 2014).

Table 4 Quality of Life Rating in Different Cultural Samples Using Various Quality of Life Instruments

Disease/ Disorder	Author, Year	Study Design; Sample Demographics	Instrument Score range; or Type of Qualitative Interview	Type of Instrument	QOL Rating/Major Themes
			Quantitative Studies		
Asthma	Tatis et al. (2005)	Quasi-experimental Total sample (N = 198) Mean age = 38 years 91% Latinos	Mini-Juniper 1 (worst) – 7 (best)	Disease-specific	Mean (SE) Patients who completed all 4 questionnaires 2.68 (1.07)* 3 months posttest 3.35 (.88)* 12 months posttest
Atrial Fibrillation	Kang (2009)	Cross Sectional Total sample (N = 129) Mean age range = 59-67 years 63% Americans 37% Korean	Short Form-36 0 (worst) – 100 (best)	Generic	Mean (SD) Mental health subscale 46.12 (12.59) American men 49.32 (13.84) Korean men 51.43 ((9.66) American women 45.44 (9.84) Korean women
Breast Cancer	Ashing-Giwa et al. (2007)	Cross Sectional Total sample (N = 703) Mean age = 55 years 26% Latinos	FACT-G 0 (worst) -100 (best)	Disease-specific	Mean (SD) 86.1(16.3) Total sample p<.05 80.1 (17.4) Latina p<.0001
Breast Cancer	Graves et al. (2012)	Cross Sectional Total sample (N = 264) Mean age = 51 years 100% Latinos	FACT-G 0 (worst) -100 (best)	Disease-specific	Mean (SD) 83 (15.4)
Breast Cancer	Lim et al. (2009)	Cross Sectional Total sample (N = 389) Mean age range = 53-54 years 47% Latinos 53% Asian Americans	FACT-G 0 (worst) -100 (best)	Disease-specific	Mean (SD) Emotional well-being: 65.96 (17.1) Latina p<.001 72.4 (18.5) Asian American
Breast Cancer	Wildes et al. (2009)	Cross Sectional Total sample (N = 117) Mean age = 55 years 100% Latinos	FACT-G 0 (worst) -100 (best)	Disease-specific	Mean (SD) 85.9 (16.0)

Disease/ Disorder	Author, Year	Study Design; Sample Demographics	Instrument Score range; or Type of Qualitative Interview	Type of Instrument	QOL Rating/Major Themes
Breast Cancer	Bernhard et al. (1998)	Cross Sectional Total sample (N = 1231) Pre- and peri-menopausal women age = <45 or 45+ 11 countries 0% Latinos	LASA 0 (worst) -100 (best)	Generic	Mean (95% CI) 54.6 (48.9 - 60.0)† Slovenian/Slovenia – lowest QOL rating 83.8 (77.4 - 89.1)† Italian/Switzerland – highest QOL rating
		Total sample (N = 989) Postmenopausal women age = < 60 or 60+ 11 countries 0% Latinos			66.5 (62.4 – 70.0)† Swedish/Sweden – lowest QOL rating 84.4 (79.0 - -89.1)† Italian/Switzerland – highest QOL rating
Breast Cancer	Jafari et al. (2013)	Cross Sectional Total sample (N = 68) Mean age = 48 years 100% Iranians	EORTC QLQ-C30 0 (worst) -100 (best)	Disease-specific	Mean (SD) Global QOL 41.42 (18.02) Iranians
Cancer	Fielding et al. (2013)	Cross Sectional Total sample (N = 552) Mean age range = 58-66 years 33% Hong Kong 48% Taiwanese 20% Japanese	Supportive Care Needs Survey 0 (*best*) – 100 (*worst)*	Disease-specific	Mean (SD) Psychological subscale 9.7 (14.50) Hong Kong 17.84 (17.15) Taiwanese 40.73 (27.27) Japanese
Cancer	Scott et al. (2008)	Cross Sectional Total sample (N = 21,743) Mean age range = 51-63 years 11 international cultures <1% Latinos	EORTC QLQ-C30 0 (worst) -100 (best)	Disease-specific	Mean (SD) 55.0 (22.6) South Asia – lowest QOL rating 69.2 (23.6) Australasia – highest QOL rating
Coronary Heart Disease	Urizar and Sears (2006)	Cross Sectional Total sample (N = 120) Mean age = 66 years 100% Latinos	QLMI 1 (worst) – 7 (best)	Disease-specific	Mean (SD) Global functioning 5.7 (0.8)

Disease/ Disorder	Author, Year	Study Design; Sample Demographics	Instrument Score range; or Type of Qualitative Interview	Type of Instrument	QOL Rating/Major Themes
Heart Failure	Huang et al. (2010)	Cross Sectional Total sample (N = 175) Mean age range = 68-73 years 50% Taiwanese 50% American	Minnesota Living with Heart Failure Questionnaire 0 (*best*) – 105 (*worst*)	Disease-specific	Mean (SD) 43.8 (25.1) Taiwanese 52.6 (22.7) American
Hematologic Malignancies	Forjaz and Guarnaccia (2001)	Cross Sectional Total sample (N =105) Mean age range = 49-55 years 23% Portuguese 77% American	Short Form-36 0 (worst) -100 (Best)	Generic	Mean (SD) Mental health subscale 67.04 (23.45) Portuguese 72.48 (20.67) American
Hematopoietic Stem Cell Transplant	Brice et al. (2011)	Cohort Total sample (N = 95) Youths' Mean age=11 years 40% Latinos	PedsQL 4.0 Generic Core Scale 0 (worst) – 100 (Best)	Generic	Mean (SD) 74.07 (13.71) Pre-transplant 79.80 (17.17) 365 days post-transplant
Irritable Bowel Syndrome	Faresjö et al. (2006)	Case Control Total sample (N = 420) Age range = 18-64 years 7% Cretans 21% Swedish 71% Swedish control group	Short Form-36 0 (worst) -100 (best)	Generic	Mean (SD) Mental health subscale 50.0 (26.0) Cretans 72.1 (17.1) Swedish 79.5 (17.3) Swedish control group
Mild-to-Moderate Traumatic Brain Injury	Brown et al. (2004)	Cross Sectional Total sample (N = 218) Mean age=34 years 50% Latinos	Short Form-36 0 (worst) -100 (best)	Generic	Mean (SD) Physical component subscale 46.64 (8.69)
Multiple Sclerosis	Pfennings et al. (1999)	Cross Sectional Total sample (N = 457) Mean age range = 43-46 years 5 countries	Short Form-36 0 (worst) - 100 (best)	Generic	Mean Mental health subscale 54.7 France – lowest rating 69.7 Netherlands – highest rating 74.7 Normative population rating

Disease/ Disorder	Author, Year	Study Design; Sample Demographics	Instrument Score range; or Type of Qualitative Interview	Type of Instrument	QOL Rating/Major Themes
Multiple Sclerosis	Pluta-Fuerst et al. (2011)	Cross Sectional Total sample (N = 484) Mean age = 41 years 30% Austrian 30% German 40% Polish	FAMS 1 (worst) – 5 (best)	Disease-specific	Mean (SD) 3.74 (0.75) Austrian 3.53 (0.68) German 3.32 (0.65) Polish
Spinal Cord Injury	Myaskovsky et al. (2011)	Cross Sectional Total sample (N = 252) Mean age = 26 years 62% Whites 38% African Americans	Satisfaction With Life Scale 1 (worst) – 7(best)	Generic	Mean (SD) 4.20 (1.54) Total sample 4.15 (1.53) African American 4.24 (1.55) Whites
Stomas	Soulsby et al. (2010)	Cross Sectional Total sample (N = 122) Age not reported 39% Asian 61% Non-Asian	Stoma QOL Questionnaire for People with Ostomy 0 (worst) - 100 (best)	Disease-specific	Mean (SD) 46 (13) Asian 60 (12) Non-Asian
Stroke	Owolabi (2011)	Cross Sectional Total sample (N = 353) Age range = 30-99 57% Nigerian 43% German	HRQOLISP 0 (worst) - 100 (best)	Disease-specific	Mean (SD) 73.5 (9.1) Nigerian p<.002 62.8 (8.9) German p<.000001
None	Aznar and Castañón (2005)	Cross Sectional Total sample (N = 180) Age not reported 38% Phase II	Topologic model of QOL (Score range not reported)	Generic	Mean (SD) 4.23 (0.89)
None	Bhandari (2012)	Cross Sectional Total sample (N = 130) Age range = 20-50 years 100% Nepalese	Short Form-12 0 (worst) – 100 (best)	Generic	Mean (SD) Mental health subscale 49.40 (8.93)

Disease/ Disorder	Author, Year	Study Design; Sample Demographics	Instrument Score range; or Type of Qualitative Interview	Type of Instrument	QOL Rating/Major Themes
None	Fu et al. (2007)	Cross Sectional Total sample (N = 676) Age range = 40-59 years 59% Taiwanese 41% Australian	WHOQOL-BREF 4 (worst) – 20 (best)	Generic	Mean (SD) Psychological health subscale 13.38 (2.38) Taiwanese 14.94 (2.98) Australian
None	Kim and Sok (2010)	Cross Sectional Total sample (N = 430) Mean age = 77 years 51% Korean 49% Chinese	Short Form-36 36 (worst) -146 (best)	Generic	Mean 70.66 Korean 57.44 Chinese
None	Molzahn et al. (2011)	Cross Sectional Total sample (N = 7,401) Mean age = 73 years 22 international centers	WHOQOL-OLD 1 (worst) – 5 (best)	Generic	Mean 3.40 Lithuania-lowest QOL rating 4.33 Uruguay-highest QOL rating
None	Power et al. (1999)	Cross Sectional Total sample (N = 4,802) Mean age = 43 years 15 international centers	WHOQOL-100 (Score range not reported)	Generic	Mean Subscales: Physical; Psychological; Social; Environment 13.9; 13.8; 14.2; 3.4 Thailand 13.8; 13.8; 14.2; 3.7 Israel 14.1; 13.9; 14.2; 3.5 Madras, India 14.2; 13.9; 14.3; 3.6 Australia 13.9; 13.8; 14.2; 3.5 New Delhi 13.9; 13.8; 14.2; 3.5 Panama 13.8; 13.8; 14.2; 3.7 U.S. 13.7; 13.8; 14.2; 3.7 Netherlands 13.8; 13.8; 14.2; 3.6 Croatia 13.9; 13.8; 14.2; 3.7 Japan 13.8; 13.8; 14.2; 3.6 Russia 13.8; 13.8; 14.2; 3.6 Zimbabwe 13.8; 13.8; 14.2; 3.6 Spain 14.0; 13.9; 14.3; 3.6 France 13.9; 13.8; 14.2; 3.6 U.K.

Disease/ Disorder	Author, Year	Study Design; Sample Demographics	Instrument Score range; or Type of Qualitative Interview	Type of Instrument	QOL Rating/Major Themes
None	Skevington (2010)	Cross Sectional Total sample (N = 9,404) Age range = 32-61 years 24 cultures in 23 countries	WHOQOL-BREF 0 (worst) - 100 (best)	Generic	Mean (SD) Countries with high Human Development Index: Australia; USA; Netherlands; Norway; Japan; UK; Germany; Italy; Spain; Israel; Greece; Argentina; Hungary; Croatia. Subscales: Physical; Psychological; Social; Environment 66.4 (20.4); 66.8 (17.9); 66.8 (20.3); 64.9 (16.4) Countries with medium Human Development Index: Russia; Malaysia; Romania; Bulgaria; Brazil; Turkey; China; India, Delhi; India, Madras. Subscales: Physical; Psychological; Social; Environment 60.4 (17.0); 59.7 (16.6); 63.2 (19.6); 55.2 (16.3)
None	Urzua et al. (2013)	Cross Sectional Total sample (N = 821) Mean age range = 52-62 years 39% Chilean 24% Spaniard 37% Cuban	WHOQOL-BREF 4 (worst) – 20 (best)	Generic	Mean (SD) Psychological health subscale 13.09 (2.11) Chilean 13.99 (1.74) Spaniard 12.11 (2.27) Cuba
None	Utsey et al. (2007)	Cross Sectional; Total sample (N = 281) Mean age = 25 years 100% African Americans	WHOQOL-BREF 0 (worst) – 100 (best)	Generic	Mean (SD) Psychological subscale 94.09 (15.15)

Disease/ Disorder	Author, Year	Study Design; Sample Demographics	Instrument Score range; or Type of Qualitative Interview	Type of Instrument	QOL Rating/Major Themes
			Mixed Method Study		
None	Lieber et al. (2001)	Total sample (N = 83) Mean age = 46 years 100% Chinese	QOL Scales 1 (worst) – 5 (best)	Generic	Mean (SD) Total Life Satisfaction subscales 3.05 (0.49) Qualitative Results/Major Theme Groups were distinguished by how well the participants seemed to understand or appreciate cultural differences and the strategies they took to manage the challenges
			Qualitative Studies		
Breast Cancer	Ashing-Giwa et al. (2004)	Qualitative Descriptive: Focus Groups (N = 51): Age range = 25-70 years 6 Chinese 4 Mixed Asian 5 Caucasian 10 African American 26 Latina Age range = 22-73 years; Key Informant Interviews (N = 23) 7 African American, 6 Asian American, 6 Latina, 4 Caucasian;	Focus Group Discussions; Key Informant Interviews	Not applicable	Major Themes 1. Spirituality is significant to QOL for breast cancer survivors
Breast Cancer	Lopez-Class et al. (2011)	Qualitative Descriptive Individual Interviews (N = 19) Focus Group (N = 9); Mean age = 47 years 100% Latinos	Individual Interview; Focus Group	Not applicable	Major Themes 1. Relationship with God 2. Fatalism 3. Familism

Disease/ Disorder	Author, Year	Study Design; Sample Demographics	Instrument Score range; or Type of Qualitative Interview	Type of Instrument	QOL Rating/Major Themes
Cancer	Juarez et al. (1998)	Qualitative Descriptive Total sample (N = 17) Mean age = 56 years 100% Hispanic	Individual Interview	Not applicable	Major Themes 1. Spiritual beliefs 2. Family support
Diabetes, Type II	Choe et al. (2001)	Qualitative Descriptive Total sample (N = 22) Age range = <30 - > 60 years 100% Korean	Individual Interview	Not applicable	Major Themes 1. Satisfactory family relationships 2. Spiritual life, relationship with God
None	Leung et al. (2004)	Qualitative Descriptive Total sample (N = 44) Mean age = 75 years 100% Taiwanese	Focus group interview	Not applicable	Major Themes 1. Religion and death 2. Economic status
None	Cruz-Oliver and Sanchez-Reilly (2016)	Qualitative Descriptive Total sample (N = 45) > 50 years = 73% 27% Latino 73% White	Focus group interview	Not applicable	Major Themes 1. Language 2. Religion 3. Familism 4. Education 5. Community leaders 6. Use of leaders

FACT-G: Functional Assessment of Cancer Therapy; LASA: Linear Analogue Self-Assessment; EORTC QLQ-C30: The European Organisation for Research and Treatment of Cancer QOL; QLMI: MacNew QOL after Myocardial Infarction; FAMS: Functional Assessment of Multiple Sclerosis; SF-12: Medical Outcomes Study Short Forms; WHOQOL-BREF: World Health Organisation QOL BREF; HRQOLISP: Health Related QOL in Stroke Patients

* Mean (SE)

† Mean (95% CI)

Chapter III: Methodology

The aims of this dissertation were three-fold. In Aim 1, we completed the final phase of linguistic validation of the Spanish version of PedsQL Sickle Cell Disease Module. Aim 2 compared perceptions of disease-specific and generic QOL in a sample of Latino and non-Latino youth with sickle cell disease aged 10-17 years and their parents who participated in an NIH funded feasibility study (Hydroxyurea Adherence for Personal Best in Sickle Cell Treatment [HABIT]; R21 NR013745) (Green et al., 2017; Smaldone et al., 2016; Smaldone et al., in press). Also using data from the HABIT study, Aim 3 explored the relationship between disease-specific QOL as it relates to sickle cell disease life burden and poorer health. This chapter presents a description of the research design for this dissertation. The methods for Aim 1 are presented first and those for Aims 2 and 3 follow. Study procedures, survey instruments, description of concepts and variables, data management, data analysis plan, and protection of human subjects are described.

Research Design

The dissertation employed a mixed methods study approach. Mixed methods research involves the collection and analysis of data, the integration of findings, and the making of inferences using both qualitative and quantitative methods in a single study (Creswell, 2009). The mixed-methods design was chosen because it uniquely addressed our data collection process: Aim 1 used an approach that combined the collection of data using a Spanish language translation of the PedsQL Sickle Cell Disease Module in conjunction with an open-ended cognitive interview for Latino youths with sickle cell disease age 8-18 years and their parents. Aims 2 and 3 quantitatively examined the perception of QOL of youth with sickle cell disease using baseline data collected as part of the HABIT study. Hypotheses for Aims 2 and 3 were driven by the literature review that is presented in Chapter II. Aims 2 and 3 were guided by a conceptual model that was adapted from Ashing-Giwa's (2005) Contextual Model of Health-Related QOL.

Aim 1

Sample and setting

Participants were sampled from 2 clinics at New York Presbyterian/Columbia University Medical Center: Columbia's Pediatric sickle cell disease clinic, and the Transplant Center. Columbia Pediatric sickle cell disease clinic delivers service tailored to the pediatric hematology communities of Harlem,

Northern Manhattan, and the tristate area. Services provided include newborn screening, stroke prevention, chronic transfusion and iron-chelating therapy, stem cell transplantation, pain management, community outreach and patient education programs. Columbia Pediatric sickle cell disease clinic provides comprehensive services to approximately 200 youth aged 0-19 years with sickle cell disease, almost half of whom are of Latino descent.

The New York-Presbyterian Hospital/Columbia University Medical Center (NYP/CUMC) provides services for heart, liver, lung, and kidney, pancreatic, intestinal and multi-visceral transplantation. Patients from across the U.S. and the globe, who have complex and challenging problems, including multi-organ transplant recipients, are treated at NYP/CUMC's organ transplantation program.

Subject recruitment

A list of participants who fit the inclusion/exclusion criteria were obtained from both clinics. Using a telephone script that was approved by Columbia's IRB, participants were recruited by telephone by our bilingual research assistant. Participants were informed regarding study purpose and procedures (i.e. the completion of PedsQL Sickle Cell Disease Module and demographic questionnaires using pen and paper, and audio-taping during cognitive interviews). Participants were informed that they may choose to complete questionnaires and participate in cognitive interviews either at their home or at the clinic based on their preference and convenience.

Inclusion/exclusion criteria

Because this aim related to the linguistic validation of the Spanish version of PedsQL Sickle Cell Disease Module, dyads were included based on the following criteria: (1) both youth and parent identify as Latino and speak Spanish as their primary language, (2) youth is between 8-18 years, and (3) youth has diagnosis of sickle cell disease.

Study Procedures

Following informed parental consent and youth assent, parents completed a 5-item demographic survey and the translated 43-item Spanish PedsQL Sickle Cell Disease Module. After questionnaires were completed, participants partook in a one-on-one cognitive interview to determine whether the Spanish survey directions, questions, and choices were clear and easy to understand. While all participants completed Spanish language surveys, cognitive interviews were conducted in Spanish or

English depending on participant's preference. Cognitive interviews were audiotaped. The time taken to complete surveys and interviews was timed.

Data Collection

Participants completed the PedsQL Sickle Cell Disease Module, which had been previously linguistically translated for the HABIT study using forward and backward translation methodology. Parents completed the Demographic Survey. The PedsQL Sickle Cell Disease Module was completed by parent and youth independently. Following completion of the questionnaire audiotaped face-to-face cognitive interviews regarding the usability of the questionnaire items were conducted separately with parent and child.

Survey Questionnaires

PedsQL Sickle Cell Disease Module

The 43-item PedsQL Sickle Cell Disease Module is used to measure disease-specific QOL in youth aged 2-18 years with sickle cell disease by Panepinto et al. (2013). The PedsQL Sickle Cell Disease Module has 9 subscales that measure concepts that are specific to sickle cell disease. A complete description of the PedsQL Sickle Cell Disease Module can be found on page 75 and 76.

Demographic Questionnaire

The 5-item demographic questionnaire was completed by the parent to capture data pertaining to parent and youth age, gender, ethnicity, sickle cell disease status, the number of years living in the U.S. This questionnaire was available in Spanish and English (Appendix A).

Cognitive Interview Guide

Six cognitive open-ended questions with probes were designed to prompt information regarding clarity, relevance, appropriateness, and understandability of questionnaire directions, questions, and response choices as they were intended. The cognitive interview guide was made available in Spanish and English and was administered by the bilingual Spanish research assistant. Participants were asked for their opinion regarding what each item on the questionnaire meant (Mapi Research Trust, 2002). Parent and youth interviews were conducted separately.

Data Management

Participants' confidentiality was maintained throughout the research process. All study-related materials and data were maintained in a locked file cabinet. Each research participant was assigned a non-identifiable numeric code and data were entered into a password protected database.

Data Analysis Plan

Audio files of each cognitive interview were transcribed and translated to English by a native Spanish speaker. Item-by-item analysis was conducted using the interview transcript and review notes to examine participant responses and understanding of the PedsQL Sickle Cell Disease Module's directions, questions, and choices, and the questionnaire as a whole. A table was constructed in order to perform a side by side comparison of each section of the Spanish version with the English version and the PedsQL Sickle Cell Disease Module was revised as necessary based on the results of the cognitive interviews.

A report of the cognitive interviews was revised and sent to Mapi Research Trust for approval per their guidelines (Mapi Research Trust, 2002). This report summarized the number and age of parents and youth interviewed for each version of the instrument by age group (8-12 year old; 13-18 year old), the time it took to complete the questionnaire, any difficulties encountered, suggestion of changes to be made and retained, and the final suggested Spanish language version of the questionnaire was produced. The final version of the questionnaire was proof-read prior to being considered as final.

Aims 2 and 3

Aims 2 and 3 were guided by a conceptual model that was adapted from Ashing-Giwa's (2005) Contextual Model of Health-Related QOL. Figure 9 illustrates the adapted Conceptual Model of Health-related QOL for Youth with sickle cell disease. Ashing-Giwa's (2005) Contextual Model of Health-Related QOL was developed to investigate health disparities and risk factors for poor outcomes in health-related QOL research with cancer survivors. This model was adapted for this dissertation by tailoring components of life burden (in Socio-ecological Context) by adding 3 variables to form "Sickle Cell Disease Life Burden". Additionally, cancer-specific components from General Health Status such as cancer characteristics and age at diagnosis were changed to the sickle cell disease-specific component of Poorer Health (a higher number of emergency room treatments or hospitalizations within the past year that indicate severe sickle cell disease).

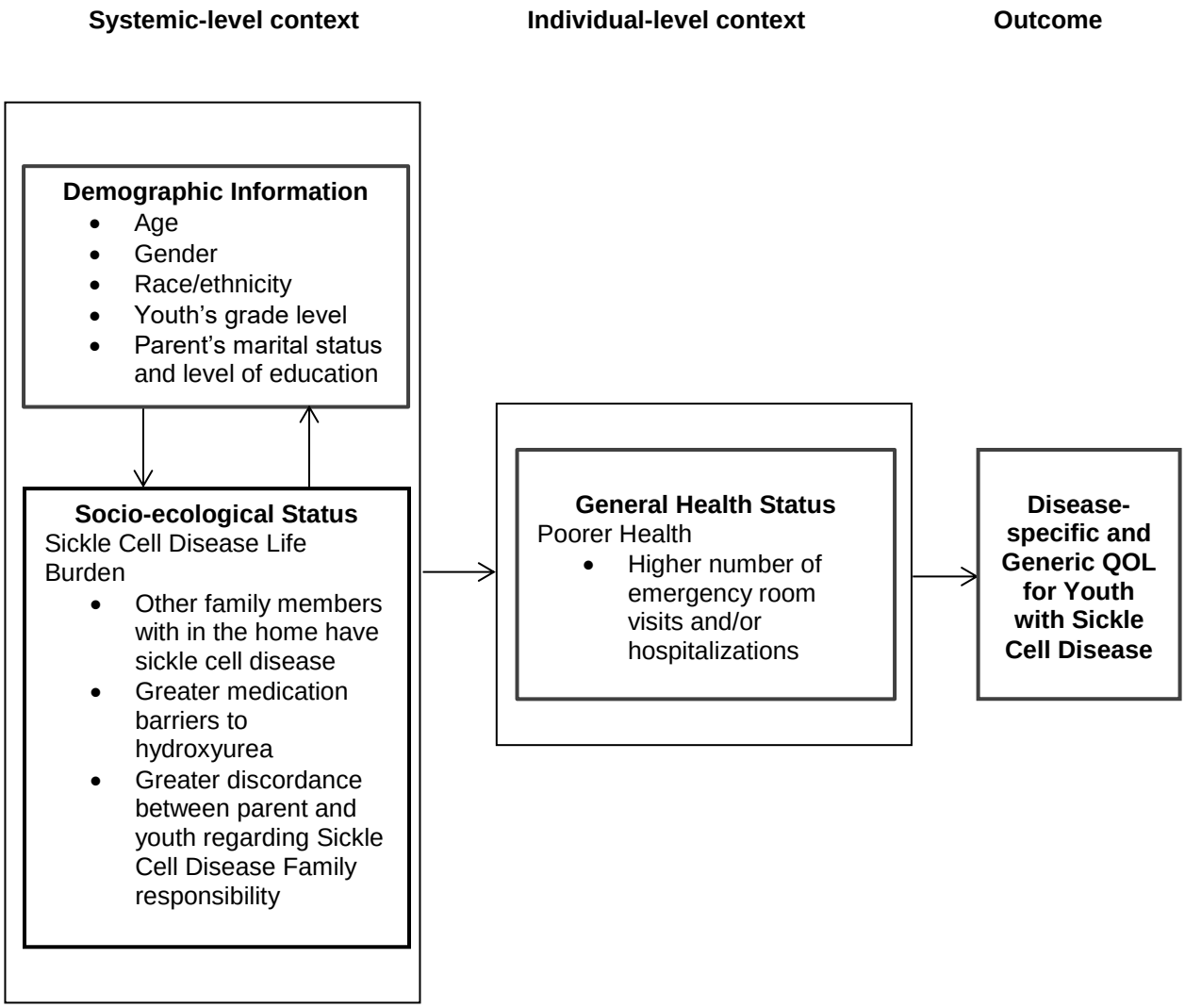

Figure 9 The adapted Conceptual Model of Quality of Life for Youth with Sickle Cell Disease. This model was adapted from Ashing-Giwa and Lim's (2011) Conceptual Model of Health-related QOL.

Concepts and Variables in Adapted Conceptual Model

The concepts and variables included in the adapted conceptual model are described below. Table 5 lists each variable, its operational definition and its questionnaire source within the HABIT dataset.

Systemic-level Context

Demographic Information. Demographic information was collected from the parents using the 28-item questionnaire (Appendix B), which contained information on youth-parent demographic, sickle cell disease history, prescribed medications, and emergency room and hospital resource use (emergency room and hospital resource use in the prior 12 months). For this dissertation, demographic information was restricted to survey language, age, gender, ethnicity, race, number of years lived in the United States, level of education, employment/grade level in school, and marital status as listed in Table 5.

Socio-ecological Status. Socio-ecological status contains socio-economic (e.g. income, education, employment) status, life burden (e.g. living situation, neighborhood character, day-to-day strain), and social support (e.g. emotional, social networks) components (Ashing-Giwa, 2005). For this dissertation socio-ecological status was defined by sickle cell disease life burden. Life burden increases when a disease is present and results in poorer perception of QOL (Moorthy et al. 2007; Panepinto et al. 2013). Two studies of adults that examined medication adherence and QOL found that greater barriers to medication adherence were related to worse QOL (Holt, Muntner, Joyce, Webber, & Krousel-Wood, 2010; Williams et al., 2009). In a study of youth aged 10-18 years with diabetes and their parents, greater concordance of treatment responsibility was associated with better QOL (Cousino, Hazen, MacLeish, Gubitosi-Klug, & Cutter, 2013). Conversely, 1 study of youth aged 5-19 years with sickle cell disease found that treatment adherence was associated with poorer QOL (Barakat, Lutz, Smith-Whitley, & Ohene-Frempong, 2005).

For this dissertation, three variables were used to examine sickle cell disease life burden: (1) other family members in the home have sickle cell disease, (2) greater medication barriers to hydroxyurea, and (3) greater discordance between parent and youth regarding sickle cell disease responsibility. Two items were culled from the Parent Demographic Questionnaire to form the first variable “sickle cell disease in family members”: “Do you (parent) have sickle cell disease” and “Do other

people in the home (excluding participating youth) have sickle cell disease." The second variable greater medication barriers to hydroxyurea, was measured using the Medication Barriers Scale. The third variable greater discordance between parent and youth regarding sickle cell disease family responsibility was measured using the Sickle Cell Family Responsibility Scale.

Medication Barriers Scale. Socio-ecological status was measured with the 26-item Medication Barriers Scale (youth) and the 25-item Medication Barriers Scale (parent). The Medication Barriers Scale for youth and parent were adapted from Simons and Blount's (2007) 16-item Parent Medication Barriers Scale which had a maximum score of 80, and the 17-item Adolescent Medication Barriers Scale which had a maximum score of 85, by adding 9 hydroxyurea-specific items. Simons and Blount's scales were created to assess perceived barriers to medication adherence in adolescent transplant recipients using a sample of 78 pediatric patients aged 11-21 who had received solid organ transplants and their parents. Response choices were scored on a 5-point Likert scale as follows: 1 = Strongly disagree, 2 = Disagree, 3 = Not sure, 4 = Agree, and 5 = Strongly agree. Construct and criterion validity were supported by significant associations between barriers scale scores and relevant disease, medical regimen, child, and family factors. Internal consistency for parent and adolescent scales were reported as Cronbach alphas of 0.87 for the parent and 0.86 for the adolescent versions (Simons & Blount, 2007).

Response choices for the adapted scale used in this dissertation were similar to the original scale by Simons and Blount (2007). This scale has a maximum of 25 items for parents and 26 items for youth. Items 1-23 (with a raw score range of a minimum of 23 to a maximum of 115) pertain to parents of male youth while items 1-25 (with a raw score range of a minimum of 25 to a maximum of 125) pertain to parents of female youth. Items 1-24 (with a raw score range of a minimum of 24 to a maximum of 120) pertain to male youth while items 1-26 (with a raw score range of a minimum of 26 to a maximum of 130) pertain to female youth. Scores were calculated and transformed from a raw score to a 100-point score by dividing the raw score by the maximum obtainable score and multiplying it by 100. Higher scores are associated with higher barriers to medication adherence (Simons & Blount, 2007).

Sickle Cell Family Responsibility Questionnaire. The 11-item Sickle Cell Family Responsibility Questionnaire was used to measure greater discordance between parent and youth regarding sickle cell disease family responsibility. The Sickle Cell Family Responsibility questionnaire was adapted from the

17-item Diabetes Family Responsibility Questionnaire that was developed by Anderson, Auslander, Jung, Miller and Santiago (1990). The Diabetes Family Responsibility Questionnaire has also been adapted for, and applied to, other diseases like asthma (McQuaid et al., 2001), cystic fibrosis (Drotar & Ievers, 1994), and inflammatory bowel disease (Greenley, Doughty, Stephens, & Kugathasan, 2010). McQuaid et al. (2001) used the 10-item Asthma Responsibility Questionnaire to rate mother-child dyads (N = 351). Response choices were on a 5-point Likert scale that ranged from 1 (parent is completely responsible) to 5 (child is completely responsible). Cronbach's alpha was 0.88 for items 1-10 which suggests very good internal consistency.

Based on the scoring method used by Anderson et al. (2009) which captured extreme reports (as recommended for the Diabetes Family Responsibility Questionnaire), dyad responses were grouped into 3 dyadic variables: parent takes charge (Parent(s) take responsibility all of the time or Parent(s) take responsibility most of the time), perfect agreement (Parent(s) and child share responsibility about equally), and child takes responsibility (Child takes responsibility most of the time or Child takes responsibility all of the time).

Each item was examined to determine the extent to which parent and child disagreed regarding who was responsible for that aspect of sickle cell management. Discordance between parent and youth was identified when, for example, the parent reported that the youth was primarily responsible for sickle cell related tasks and the youth reported that the parent was primarily responsible for sickle cell related tasks. The number of items where there was dyadic discordance was summed to obtain a total discordance score. Dyadic scores were composed by summing the number of items of self-care where parents and youth disagreed regarding who was responsible for the self-management task. Scores could range from 0 (no discordance regarding who was responsible) to 10 (discordance for all self-management items).

Individual-level Context

General Health Status. Poorer health was measured 2 ways: (1) by using self-reported emergency room visits and/or hospitalizations within the past year (obtained from the Parent Demographic Questionnaire) and, (2) by electronic medical record review of the number of emergency room visits and/or hospitalizations within the past year. Currently there is no universal scale for classifying

sickle cell disease severity (Cameron, Christian, Lobel, & Gaston, 1983; Panepinto et al., 2013). In this study, higher resource use was a proxy for poorer health and greater disease severity.

Quality of Life Outcome

Sickle Cell Disease Quality of Life. The 43-item PedsQL Sickle Cell Disease Module is a modular instrument used to measure disease-specific QOL in youth aged 2-18 years with sickle cell disease by Panepinto et al. (2013). Items were developed using a multiphase methodology of sickle cell disease literature review to create interview guides, and the development of a conceptual model with the aid of 10 healthcare experts. Interviews were conducted with youth with sickle cell disease aged 5-18 years and their parents using focus groups (n = 13) and cognitive interviews (n = 33). This initial development process resulted in 48 items and 6 scales (Panepinto, Torres, & Varni, 2012). Nationwide multisite field testing for the psychometric validation phase of instrument development resulted in 43 items and 9 subscales that measure concepts that are specific to sickle cell disease: (1) Pain and Hurt, (2) Pain Impact, (3) Pain Management and Control, (4) Worry I, (5) Worry II, (6) Emotions, (7) Treatment, (8) Communication I, and (9) Communication II (Panepinto et al., 2013). Participants respond to each item/statement using a 5-point Likert scale rated from never (0) to always (4). Items are reverse-scored and linearly transformed to a 100 point scale with higher scores indicating better QOL. Cronbach's alpha exceeded 0.90 for both youth self-report and parent proxy-report. Confirmatory factor analysis demonstrated an acceptable to excellent model fit and intra-class correlation coefficient (ICC) ranged between poor to fair agreement for youth self-report and moderate agreement for parent proxy-report. The majority of inter-correlations were in the medium to large effect size range which supported construct validity. Participants in the psychometric validation phase of this instrument were 98.1% self-reported Black non-Hispanic (Panepinto et al., 2013).

The PedsQL Sickle Cell Disease Module has 9 subscales: Pain and Hurt (9 items); Pain Impact (10 items); Pain Management and Control (2 items); Worry I (5 items that pertain to situations surrounding sickle cell disease); Worry II (2 items that pertain to having a stroke and having a chest crisis); Emotions (2 items); Treatment (7 items); Communication I (3 items that pertain to telling others about sickle cell disease); and Communication II (3 items that pertain to having difficulty regarding others not understanding about sickle cell disease and/or pain; difficulty telling others that he/she has sickle cell

disease). For Aim 1, the Spanish version of this questionnaire was used to determine whether the questionnaire directions, questions, and response choices were clear, relevant, appropriate, and easily understood.

Generic Quality of Life. Generic QOL was measured with the 23-item PedsQL Generic Core Scale (Varni et al. 1999). Scoring is the same as with the PedsQL Sickle Cell Disease Module where items are reverse-scored and linearly transformed to a 100 point scale with higher scores indicating better QOL. The PedsQL Generic Core Scale was developed by Varni et al. (1999), using a sample of 291 youth aged 8-18 years with cancer and their parents, using multiple cycles of two iterative phases: Phase I, item generation (assembling of multiple choice and open-ended questions) and Phase 2, item revision with administration to patients, families, and healthcare professionals who were not included in phase 1 (Varni et al. 1999). Cronbach's alpha was 0.83 for youth self-report and 0.86 for parent proxy-report. The PedsQL Generic instrument has been used to assess QOL in youth with various diseases, including cancer (Varni et al., 1999), Duchenne muscular dystrophy (HU et al., 2013), and sickle cell disease (Panepinto et al., 2008).

The PedsQL Generic Core Scale is a modular questionnaire that measures generic QOL in 2-18 year old youth. This questionnaire has multidimensional youth self-report and parent proxy-report scales that were developed as the generic core measure, and may be combined with other PedsQL disease-specific modules, such as the PedsQL Sickle Cell Disease Module. This questionnaire includes 4 subscales: (1) Physical Functioning (8 items), (2) Emotional Functioning (5 items), (3) Social Functioning (5 items), and (4) School Functioning (5 items) (Varni et al., 1999).

Sample and Setting

Data for aims 2 and 3 of this dissertation were obtained from baseline data collected as part of the Hydroxyurea Adherence for Personal Best in Sickle Cell Treatment (HABIT) study, NINR # R21 NR013745 (Green et al., 2017; Smaldone et al., 2016; Smaldone et al., in press). The sample included Latino and non-Latino youth 10-18 years with sickle cell disease who received care either at Columbia University Medical Center or Albert Einstein/Montefiore Medical Center, were treated with hydroxyurea, and had a history of suboptimal adherence to hydroxyurea.

The purpose of the HABIT's feasibility study was to test the feasibility and acceptability of a community health worker intervention augmented by text messaging designed to improve adherence to hydroxyurea therapy. Participants were recruited from Columbia and from Albert Einstein/Montefiore Medical Center. Inclusion criteria for youth were: (1) 10-18 years of age, (2) had a diagnosis of sickle type HbSS or HbS-B0 thalassemia, (3) had been treated with hydroxyurea for a minimum of 15 months, (4) youth's average fetal hemoglobin assessments over the past year were greater than10% below the youth's personal best value; (5) both youth and parents had to be able to read/speak English or Spanish, (6) had no cognitive disabilities, and (7) have a cell phone with text messaging capability. Female youth were excluded if they were pregnant or sexually active and not using a reliable method of contraception. Fetal hemoglobin samples were collected and self-reported adherence and resource use questionnaires were completed during 6 clinic appointments.

Participants were randomized prior to study initiation to intervention group (community health workers augmented by customized text messages) or to control group (usual clinic-based care). Youth and parents completed questionnaires, the youth's hemoglobin F was measured monthly, and prescription refill information was obtained from the youth's pharmacy over the six month study period. Hospitalizations and emergency room visits for the year prior to study entry were obtained by both self-report and review of the electronic medical record.

For this dissertation baseline parent and youth questionnaire data and electronic medical record review of hospitalization and emergency room use for the year preceding study entry were used. Baseline questionnaire data included Parent demographic questionnaire, PedsQL Sickle Cell Disease Module, PedsQL Generic Core scale, Medication Barriers scale, and the Sickle Cell Family Responsibility scale.

Data management

Baseline data were downloaded from a RedCap database and maintained on a password-protected computer throughout the dissertation process.

Data Analysis Plan

Aim 2. Aim 2 compared the perception of disease-specific and generic QOL in a sample of Latino and non-Latino youth with sickle cell disease aged 10-17 years and their parents. Two hypotheses were tested.

Table 5 Operational Definition of Variables for Aims 2 and 3

Variable	Operational Definition	Variable Type	Source/Questionnaire, item(s) number
Demographics			
Survey language	Spanish or English	Categorical	(Obtained from database)
Gender	Male or Female	Categorical	(Obtained from database)
Age	Age in years	Continuous	Demographic, #4; #19
Ethnicity	Hispanic or Latino? Yes/No	Categorical	Demographic, #5; #20
Race	Black, White/Caucasian, Asian, Other	Categorical	Demographic, #6; #21
Number of years living in U.S.	Number of years	Continuous	Demographic, #7; #22
Youth's grade level	1 through 12	Continuous	Demographic, #23
Parent's education level	Elementary school through graduate school	Categorical	Demographic, #8
Parent's employment status	Full time, part time, laid off, unemployed, disabled, or attending school	Categorical	Demographic, #10
Parent's marital status	Married, single, separated, or divorced	Categorical	Demographic, #11
Socio-ecologic Status			
Sickle cell disease life burden	(1) Do other people in the home have sickle cell disease?	Dichotomous	Demographic, #14; #15
	(2) Greater medication barrier to hydroxyurea. The number of items is different for boys versus girls (24 vs 26) and for parents of boys versus parents of girls (23 vs 25). Total scores were transformed to a 100 point scale.	Continuous	Medication Barriers Scale
	(3) Greater discordance between parent and youth regarding sickle cell disease family responsibility. Self-care task where parents and youth do not completely agree about who is responsible for task. Discordant scores range from 0-10	Continuous	Sickle Cell Family Responsibility Scale
General Health Status			
Poorer health	(1) Self-reported emergency room visits and/or hospitalizations within the past year	Continuous	Demographic, #27; #28
	(2) Electronic medical record data of the number of emergency room visits and/or hospitalizations within the past year	Continuous	Electronic Medical Records
Outcome			
Sickle Cell Disease QOL	Higher scores indicate better disease-specific QOL	Continuous	PedsQL Sickle Cell Disease Module
Generic QOL	Higher scores indicate better disease-specific QOL	Continuous	PedsQL Generic Core Scale

Notes: PedsQL = Pediatric Quality of Life; QOL = quality of life

Hypothesis 2.1: Youth perception of disease-specific and generic QOL will be higher compared to parent proxy perception.

Hypothesis 2.2: Perception of disease-specific and generic QOL in Latino youth and parents will be lower compared to non-Latino youth and parents.

Data were exported from the HABIT REDCap database to SPSS. First, data were cleaned to verify that there were no data entry errors. New variables were transformed where necessary. Total and subscale scores for parent and youth were created for PedsQL Sickle Cell Disease Module and the PedsQL Generic Core Scales.

Descriptive statistics were computed to describe the sample (Shi & McLarty, 2009), and included frequencies, percentages, means, and standard deviations. The distribution of disease-specific and generic QOL scores was visually inspected for assumption of normality using a Q-Q plot. Scores were assessed as not normally distributed; therefore to test these hypotheses, Wilcoxon Signed Ranks Test and Mann-Whitney test were conducted where total scale and subscale scores for disease-specific and generic QOL questionnaires were calculated. Because our sample size was small in this exploratory study, we did not consider using multivariate analysis to compare QOL means.

To interpret the differences in disease-specific and generic QOL questionnaire scores between Latino and non-Latino youth and parents, minimal clinically important difference (MCID) values were calculated. Jaeschke, Singer, and Guyatt (1989) defined MCID as the minimum difference in a score in an area of interest which patients perceive as beneficial and which may require a change in the patient's management. As used by Varni, Burwinkle, Seid and Skarr (2003), the MCID for PedsQL Generic Core Scale was calculated using Standard Error of Measurement (SEM). Standard Error of Measurement was estimated using the standard deviation (SD) of the total score and subscale score multiplied by the square root of 1 minus the Cronbach alpha reliability coefficient (Hilliard et al., 2013; Junger, Morita, & Modi, 2015; Varni et al., 2003). MCIDs were calculated for disease-specific QOL total and subscale scores, and generic QOL total and subscale scores.

Absolute differences and 95% confidence intervals (CI) were calculated between Latinos and non-Latinos for disease-specific and generic QOL scores. Absolute difference was calculated as follows: the mean QOL scores for Latinos minus the mean QOL scores for non-Latinos. Ninety five percent

confidence intervals were calculated using independent samples confidence interval calculator ("Independent samples confidence interval calculator," n.d.) that uses a *t* statistic and 2 sample means to produce an estimate of the difference between the 2 means (which for our study meant QOL scores of Latino and non-Latino youth and parents). We calculated a MCID score for each total score and its respective subscales. Where the absolute difference exceeded the MCID, the difference in score between Latino and non-Latino subjects was considered clinically relevant.

Aim 3. Aim 3 explored the relationship between disease-specific QOL and sickle cell disease life burden and poorer health in Latino and non-Latino youth with sickle cell disease aged 10-17 years and their parents. We considered Latino ethnicity the most important predictor because of its theoretical relevance to our study.

Hypothesis 3.1: Youth with sickle cell disease and their parents with higher sickle cell disease life burden will have lower disease-specific QOL compared to those with lower sickle cell disease life burden.

Sickle cell disease life burden was operationalized with 3 variables: (1) other family members in the home have sickle cell disease, (2) greater medication barriers to hydroxyurea, and (3) greater discordance between parent and youth regarding sickle cell disease responsibility. We looked at 3 simple linear regression models for hypothesis 3.1. If the model was statistically significant ($p<0.05$), we added ethnicity as a second step. Multivariate models were tested for collinearity once the model was significant. Tolerance and variance inflation factor (VIF) determined whether multicollinearity was a factor in any of the models. Multicollinearity was considered an issue if the value of tolerance was <0.2 and the VIF was ≥ 5 or the tolerance was <0.1 and the VIF was ≥10.

Adjusted R-square (R^2) was obtained from the multivariate regression model. The adjusted R^2 is a modified version of R^2 that has been adjusted for the number of predictors in the model (Miles, 2014). For Aim 3.1, the adjusted R^2 represents the proportion of variance in disease-specific QOL which was explained by the following predictor variables: others in the home have sickle cell disease; greater barriers to hydroxyurea; and youth-parent discordance.

Two items from the Parent Demographic Questionnaire (Do you [parent] have sickle cell disease; Do other people in the home [excluding participating youth] have sickle cell disease) were combined to

form the variable “Other family members in the home have sickle cell disease”. To examine the relationship between other family members in the home have sickle cell disease and disease-specific QOL, simple linear regression modeling for youth and parents was used. Greater medication barriers to hydroxyurea were measured with the Medication Barriers Scale, while greater discordance between parent and youth regarding sickle cell family responsibility was measured using the Sickle Cell Family Responsibility Questionnaire.

Hypothesis 3.2: Youth with poorer health and their parents will have lower perception of disease-specific QOL compared to those with better health.

Poorer health was measured 2 ways: by self-reported number of emergency room visits and hospitalizations within the prior year obtained from the Parent Demographic Questionnaire, and by electronic medical records from Columbia University Medical Center and Montefiore Medical Center regarding the number of emergency room visits and hospitalizations within the prior year.

Four simple linear regression models were executed for hypothesis 3.2. If the model was statistically significant ($p<0.05$), we added ethnicity as a second step. Multivariate models were tested for collinearity once significance was established. Variance inflation factor and tolerance determined whether multicollinearity was a factor in any of the models. Collinearity was considered an issue if the value of tolerance was <0.2 and the VIF was ≥ 5 or the tolerance was <0.1 and the VIF was ≥10. Table 6 provides a summary of the data analysis plan. For Aim 3.2, the adjusted R^2 represents the proportion of variance in disease-specific QOL which was explained by emergency room visits and/or hospitalizations during the past year.

Protection of Human Subjects

The HABIT study was approved by the IRBs at CUMC and Montefiore Medical Center. For this dissertation’s Aim 1, the study received approval by CUMC IRB.

Table 6 Summary of Data Analysis Plan for Aims 2 and 3

Aims & Hypotheses	Analysis Plan
Aim 2: To compare perception of disease-specific and generic QOL in a sample of Latino and non-Latino youth with sickle cell disease aged 10-17 years and their parents who participated in a NIH funded study to improve adherence to hydroxyurea therapy. *Hypothesis 2.1:* Perception of disease-specific and generic QOL will be higher in youth compared to parent proxy perception. *Hypothesis 2.2:* Perception of disease-specific and generic QOL in Latino youth and parents will be lower compared to non-Latino youth and parents	**Aim 2:** Wilcoxon Signed Ranks Test was used for hypothesis 2.1 and Mann-Whitney U test was used for hypothesis 2.2. Total scale scores and subscale scores for youth and parents were analyzed for disease-specific and generic QOL questionnaires.
Aim 3: To explore the relationship between disease-specific QOL as it relates to systemic- (sickle cell disease life burden) and individual-level context factors (poorer health) in Latino and non-Latino youth with sickle cell disease aged 10-17 years and their parents.	**Aim 3:** Simple linear regression model. If model was statistically significant, then ethnicity was added to the model.
Hypothesis 3.1: Youth with sickle cell disease and their parents with higher sickle cell disease life burden (other family members have sickle cell disease; greater medication barriers to hydroxyurea; greater discordance between parent and youth regarding sickle cell disease family responsibility) will have lower disease-specific QOL compared to those with lower sickle cell disease life burden.	One regression model for parents and 1 model for youth was explored for: • Other family members in the home have sickle cell disease • Sickle cell disease family responsibility • Medication barriers If a model achieved statistical significance, ethnicity was added
Hypothesis 3.2: Youth with poorer health and their parents will have lower disease-specific QOL compared to those with better health.	One regression model for parents and 1 model for youth were explored. If model was statistically significant, then ethnicity was added.

Chapter IV: Results

Chapter IV presents the results of the study by Aim. Findings for Aim 1 are based on a sample of Spanish speaking youth-parent dyads who participated in the linguistic validation of the Spanish language version of the sickle cell disease-specific QOL instrument. Findings for Aims 2 and 3 are based on baseline data of youth-parent dyads who participated in the HABIT randomized controlled pilot study, hydroxyurea Adherence for Personal Best in Sickle Cell Treatment: HABIT (R21 NR013745).

Specific Aim 1

Specific Aim 1: To complete the final phase of linguistic validation of the Spanish version of PedsQL Sickle Cell Disease Module.

Characteristics of the Linguistic Validation Sample

A sample of 10 Spanish speaking youth-parent dyads was recruited from 2 sources: those who participated in the HABIT study (5 dyads), and the Division of Pediatric Hematology, Oncology, and Stem Cell Transplantation at the New York Presbyterian Morgan Stanley Children's Hospital at Columbia University Medical Center (5 dyads). All participating youth had sickle cell disease. One youth who had been recruited from the Division of Pediatric Hematology, Oncology, and Stem Cell Transplantation had received hematopoietic stem cell transplantation, while the remaining youth were awaiting transplantation at the time of the study.

Recruitment occurred between February and April of 2016. Five dyads participated in linguistic validation of the PedsQL Sickle Cell Disease Module designed for youth 8-12 years of age with the remaining dyads participating in validation of the instrument designed for youth 13-18 years of age.

Table 7 provides characteristics of the linguistic validation sample. The mean age of youth in the 8-12 year age group was 10.8 ± 1.1 years, while in the 13-18 year age group it was 16 ± 1.0 years. The majority of youth (80%) was male, and was born in the U.S. The mean age of parents was 36.9 ± 7.3 years and the majority (90%) was female. All parents reported the Dominican Republic as their country of birth. One parent reported having sickle cell disease. All interviews were conducted in Spanish and the majority of interviews were conducted in participants' homes.

Table 7 Characteristics of the Linguistic Validation Sample

	8-12 Group (n = 5)				13-18 Group (n = 5)			
	Youth		Parent		Youth		Parent	
	n	(%)	n	(%)	n	(%)	n	(%)
Age in Years (Mean ± SD)	10.8 ± 1.1		35.2 ± 7.0		16.0 ± 1.0		38.6 ± 8.1	
Gender (Male)	4	(80.0)	0	(0.0)	4	(0.0)	1	(20.0)
Country of birth (Dominican Republic)	0	(0.0)	5	(100)	2	(40.0)	5	(100)
Recruitment Site								
NIH HABIT Study	3	(60.0)		--	3	(60.0)		--
Pediatric Hematology, Oncology, & Stem Cell Transplant Clinic	2	(40.0)		--	2	(40.0)		--
Location of Interviews								
Home		--	5	(100)		--	2	(40.0)
Pediatric Hematology, Oncology, & Stem Cell Transplant Clinic		--	0	(0.0)		--	2	(40.0)
St. Giles Comprehensive Sickle Cell and Thalassemia Center		--	0	(0.0)		--	1	(20.0)
Survey completion time (Minutes) (Mean ± SD)	10.4 ± 3.1		9.4 ± 2.4		9.0 ± 2.0		8.6 ± 1.9	

Notes. SD = Standard deviation; HABIT = Hydroxyurea Adherence for Personal Best in Sickle Cell Treatment; Sickle Cell Transplant Program = New York-Presbyterian/Morgan Stanley Children's Hospital Sickle Cell Transplant Program

Linguistic Validation

On average, survey completion time was 10 minutes or less. During cognitive interviews parents and youth reported that the PedsQL Sickle Cell Disease Module items were clear, appropriate, and easy to understand. Only 1 youth (female, age 16 years) had a suggestion to improve the wording of an item (#18) of the questionnaire. She suggested that the item “I wake up at night when I have pain” should “ask if it is hard to sleep during the night when you have pain, or if you wake up many times?” Results of the linguistic validation were summarized and sent to Mapi Research Trust. Questionnaires validated by independent parties must first be sent to Mapi Research Trust for approval prior to being used. The Spanish language versions of the PedsQL Sickle Cell Disease Module are now available to researchers upon request to the Mapi Research Trust. The report of the validation process is included as Appendix C.

Specific Aim 2

Specific Aim 2: To compare perception of disease-specific and generic QOL in a sample of Latino and non-Latino youth with sickle cell disease aged 10-18 years and their parents who participated in the HABIT study.

Characteristics of the HABIT Sample

Demographics

Table 8 provides baseline characteristics of youth and parents who participated in the HABIT study. The sample was equally divided between Latinos and non-Latinos. The mean age of youth was 13.6 ± 2.4 years and the majority (57%) was male. Most youth were born in the U.S. and completed surveys in English. The mean age of parents was 42.9 ± 9.3 years. The majority of parents (79%) had immigrated to the U.S. and had lived in the U.S. for 6 or more years; 43% completed surveys in Spanish. The majority of parents (57%) reported having a high school education or less. Almost half of the parent sample was employed 35 hours or more per week.

Resource Use

Parents reported higher hospitalization and emergency room use compared to that obtained by electronic medical record review. Parents reported that youth had visited the emergency room for sickle cell disease in the prior year 2.0 ± 3.5 times versus 0.8 ± 2.1 times identified by medical record review.

Table 8 Characteristics of the Sample for Aims 2 and 3

	Youth n = 28		Parents n = 28	
Demographics				
Ethnicity (Latino) n, (%)	14	(50)	14	(50)
Age (years) (Mean ± SD)	13.6	2.4	42.9	9.3
	n	(%)	n	(%)
Gender (Male)	16	(59)	--	--
Survey completion in Spanish	7	(25)	12	(43)
Time lived in the United States				
1 to 5 years	3	(11)	1	(4)
6 or more years	3	(11)	22	(79)
Born in the U.S.	22	(79)	5	(18)
School grade				
4^{th}-6^{th}	7	(26)	--	--
7^{th}-8^{th}	6	(22)	--	--
9^{th}-12^{th}	14	(52)	--	--
Marital status				
Married	--	--	13	(46)
Single	--	--	13	(46)
Divorced or Separated	--	--	2	(7)
Education				
≤ High school graduate	--	--	16	(57)
Some college or more	--	--	12	(43)
Employment				
Full time	--	--	13	(46)
Part time	--	--	6	(21)
Not currently employed	--	--	9	(32)
Other family members in the home have sickle cell disease	--	--	6	(22)
Number of children in the home (Mean ± SD)	--	--	2.7	1.7
Resource Use				
	n	(%)		
Self-report - ≥1 Emergency room visit for Sickle Cell Disease in past year	15	(58)	--	--
Self-report - ≥1 Hospitalization for Sickle Cell Disease in past	11	(48)	--	--

	Youth n = 28		Parents n = 28		
year					
EMR - ≥1 Emergency room visit	8	(29)	--	--	
EMR - ≥1 Hospitalization	7	(25)	--	--	
Psychosocial Measures					
	Mean ± SD		**Mean ± SD**		**P-value**[§]
Medication Barriers total scores [a]	47.3 ± 12.5		42.8 ± 10.3		**0.02**
SCFR total scale scores [b]	27.4 ± 7.9		19.9 ± 8.2		**0.001**
SCFR dyadic discordant scores [c]	--		5.3 ± 2.7		--

Notes. EMR = Electronic medical records review; [a]Scores range 0-100 where higher scores indicate higher barriers to medication adherence; [b]Total Scale scores range from 10 (more parent responsibility) – 30 (more youth responsibility); [c]Dyadic discordant scores range from 0 (no discordance) – 10 (most discordant); SCFR = Sickle Cell Family Responsibility.

While parents reported that more than half (58%) of youth had visited the emergency room during the last year for treatment of sickle cell disease, electronic medical records review identified 29% of youth having received similar care over the same time period. Similarly, parents reported that their youth had been admitted to the hospital 1.4 ± 2.7 times during the prior year versus 0.5 ± 1.0 times during the past year identified through electronic medical records review.

Psychosocial Measurements

Internal consistency for all parent and youth surveys was high with all alpha results ≥ 0.78. Medication barriers mean total scores were higher (higher barriers to medication adherence) for youth compared to parents were (47 ± 12.5 versus 42.8 ± 10.3, p = 0.02). Youth reported greater responsibility for sickle cell disease self-management compared to parent responsibility (27.4 ± 7.9 versus 19.9 ± 8.2, p = 0.001), with high discordance between youth and parents regarding who was responsible for self-care (5.3 ± 2.7). Of the 10 self-management items, more than half of dyads reported discordance for 4 self-management tasks: “Making decisions about adjusting activity when pain starts” (68%), “Telling teachers about sickle cell anemia” (64%), “Telling friends about sickle cell” (61%), and “Noticing signs and symptoms of a sickle cell pain crisis” (61%). Least discordance was present for 2 self-management tasks: “Remembering day of clinic appointment” (36%) and “Remembering to take daily medications” (36%).

Hypothesis 2.1: Perception of disease-specific and generic QOL will be higher in youth compared to parent-proxy perception.

Hypothesis 2.1 was partially supported for perception of total disease-specific but not perception of total generic QOL. Table 9 provides disease-specific and generic QOL scores as reported by youth and parents. On average, youth reported significantly higher total disease-specific QOL scores compared to parents (68.7 ± 16.8 versus 61.4 ± 21.1, p = 0.02). Additionally, compared to parents, youth reported significantly higher scores for 3 of 9 subscales: Worry I (youth worried less about having pain, being treated in the emergency room, and/or being hospitalized; 67.1 ± 26 versus 43.5 ± 31.4, p = 0.007), Worry II (youth worried less about having a stroke and/or chest crisis; 75.4 ± 25.1 versus 57.9 ± 39.4, p = 0.03), and Treatment (youth had less problems with medication, e.g. administration, taste, side effects, and efficacy; 79.1 ± 17.4 versus 71.3 ± 23.1, p = 0.045).

There were no significant differences in total generic QOL scores between youth and parents. However, youth reported higher scores than parents for School subscale (youth reported having less problems relating to paying attention in class, forgetting things, schoolwork, and missing school because of illness/appointments) than parents; 68.4 ± 22.8 versus 57.8 ± 28, p = 0.04).

Table 9 also presents the MCID for both youth self-report and parent proxy-report. The MCID for the youth PedsQL Sickle Cell Disease Module total scale was 4.2 and for parent proxy-report 4.2. For PedsQL Generic Core total scale, the MCID for youth self-report was 4.8 and for parents 5.1.

Hypothesis 2.2: Perception of disease-specific and generic quality of life in Latino youth and parents will be lower compared to non-Latino youth and parents.

Youth

Hypothesis 2.2 was partially supported. Overall, Latino youth reported higher QOL scores than non-Latino youth for all QOL measures except for the Worry II subscale of the disease-specific QOL measure (see Table 9). There were no significant differences in total generic QOL or its subscales or disease-specific QOL total score between Latino and non-Latino youth. However, compared to non-Latino youth, Latino youth reported significantly higher QOL scores for 3 of the 9 subscales: Emotions (Latino youth had less anger about having sickle cell disease and/or pain; 84.8 ± 26.9 versus 46.4 ± 34.8, p = 0.002), Treatment (Latino youth had less problems with medication, e.g. administration, taste, side effects, and efficacy; 85.7 ± 15.7 versus 72.4 ± 17, p = 0.04), and Communication II (Latino youth had less difficulty regarding others not understanding about sickle cell disease and/or pain; less difficulty telling others that he/she has sickle cell disease; 86.9 ± 17.8 versus 46.4 ± 34.1, p = 0.004).

The absolute differences between Latino versus non-Latino youth QOL scores are shown in Table 10. All exceeded its respective MCID except Worry I subscale and Physical subscale.

Parents

Hypothesis 2.2 was partially supported in parents. While there were no significant differences in perception of disease-specific QOL total score between Latino and non-Latino parents (66.4 ± 16.7 versus 56.7 ± 24.1, p = 0.28), Latino parents reported lower subscale scores for Worry II (Latinos worried more about their child having a stroke and/or chest crisis; 41.3 ± 42.2 versus 73.2 ± 30.6, p = 0.04).

Table 9 Comparison of Disease-specific and Generic Quality of Life Scales between Youth and Parents

	Youth			Parents		
	Mean ± SD	**Alpha[a]**	**MCID[b]**	**Mean ± SD**	**Alpha[a]**	**MCID[b]**
Disease-specific QOL total scores*****	68.7 ±18.8	0.95	4.2	61.4 ± 21.1	0.96	4.2
Subscales (Number of items)						
Pain and Hurt (9)	73.7 ± 24.4	0.93	6.5	69.0 ± 26.0	0.94	6.4
Pain Impact (10)	57.6 ± 26.2	0.92	7.4	50.2 ± 28.2	0.94	6.9
Pain Management and Control (2)	56.7 ± 33.6	0.92	9.5	58.3 ± 34.8	0.97	6.0
Worry I (5)******	67.1 ± 26.0	0.80	11.6	43.5 ± 31.4	0.84	12.6
Worry II (2)*****	75.4 ± 25.1	0.66	14.6	57.9 ± 39.4	0.95	8.8
Emotions (2)	65.6 ± 36.3	0.90	11.5	61.1 ± 39.4	0.91	11.8
Treatment (7)*****	79.1 ± 17.4	0.75	8.7	71.3 ± 23.1	0.79	10.6
Communication I (3)	77.1 ± 24.4	0.77	11.7	81.2 ± 29.3	0.88	10.2
Communication II (3)	66.7 ± 33.7	0.85	13.1	66.4 ± 31.8	0.92	9.0
Generic QOL total scores	76.8 ± 17.0	0.92	4.8	70.5 ± 20.8	0.94	5.1
Subscales (Number of items)						
Physical (8)	77.0 ± 20.1	0.87	7.2	69.2 ± 25.1	0.90	7.9
Emotional (5)	78.0 ± 20.7	0.78	9.7	75.9 ± 22.7	0.83	9.4
Social (5)	83.8 ± 20.0	0.84	8.0	79.6 ± 23.0	0.80	10.3
School (5)*****	68.4 ± 22.8	0.80	10.2	57.8 ± 28.0	0.84	11.2

Notes: Mean scores and standard deviation (SD) were calculated using Wilcoxon Signed Ranks Test. [a]Cronbach's alpha; [b]MCID- Minimal Clinically Important Difference represents SEM which indicates Standard Error of Measurement and was derived by multiplying the standard deviation of the sample mean by the square root of 1-alpha. MCID scores represent the transformed value of 1 SEM (for instance, a change in PedsQL Sickle Cell Disease Module Total Scale Score for youth of 4.2 represents a minimal clinically important difference).

Table 10 Quality of Life Scores Stratified by Ethnicity

Scale	Youth				Parents			
	Latino Mean±SD (n = 14)	**Non-Latino** Mean±SD (n = 14)	P-Value[b]	Absolute Difference[a] (95% CI)	**Latino** Mean±SD (n = 13)	**Non-Latino** Mean ±SD (n = 14)	P-Value[b]	Absolute Difference[a] (95% CI)
Disease-specific quality of life								
Total scale	75.9±16.5	61.6±18.9	0.06	**14.3**(10.5-18.1)	66.4±16.7	56.7±24.1	0.28	**9.7** (5.0-14.4)
Subscale (Number of items)								
Pain and Hurt (9)	80.2±20.9	67.3±26.6	0.21	**12.9** (7.7-18.1)	73.1±25.3	65.3±26.9	0.41	**7.8** (1.9-13.7)
Pain Impact (10)	64.1±27.6	51.1±24.0	0.20	**13.0** (7.4-18.6)	57.1±26.1	43.8±29.6	0.22	**13.3** (7.0-19.6)
Pain Management & Control (2)	61.6±30.8	51.8±36.6	0.46	**9.8** (2.5-17.1)	65.4±31.9	51.8±37.3	0.36	**13.6** (5.8-21.4)
Worry I (Pain, ER, Hosp.) (5)	71.8±26.3	62.5±25.9	0.31	9.3 (3.7-14.9)	41.9±36.3	45.0±27.5	0.59	3.1 (-4.1-10.3)
Worry II (Stroke, chest crisis) (2)	67.0±28.8	83.9±18.0	0.09	**16.9**(11.7-22.1)	41.3±42.2	73.2±30.6	**0.04**	**31.9**(23.6-40.2)
Emotions (2)	84.8±26.9	46.4±34.8	**0.002**	**38.4**(31.7-45.1)	76.9±36.0	46.4±37.8	**0.04**	**30.5**(22.2-38.8)
Treatment (7)	85.7±15.7	72.4±17.0	**0.04**	**13.3** (9.8-16.8)	80.2±15.4	63.0±26.4	0.06	**17.2**(12.4-22.0)
Communication I (about pain) (3)	84.5±19.0	69.6±27.5	0.09	**14.9** (9.8-20.0)	80.1±29.4	82.1±30.3	0.88	2.0 (-4.7 - 8.7)
Communication II (about sickle cell disease) (3)	86.9±17.8	46.4±34.1	**0.004**	**40.5**(34.6-46.4)	82.1±15.9	51.8±36.3	**0.02**	**30.3**(24.0-36.6)
Generic quality of life								
Total scale	81.5±13.0	72.1±19.5	0.20	**9.4** (9.4-16.6)	75.9±15.3	65.4±24.3	0.22	**10.5** (5.9-15.1)
Subscale (Number of items)								
Physical (8)	79.0±17.4	74.9±23.0	0.66	4.1 (-0.3 - 8.5)	70.4±20.9	68.1±29.3	0.92	2.3 (-3.4 - 8.0)
Emotional (5)	83.9±16.7	72.1±23.3	0.20	**11.8** (7.4-16.2)	80.8±14.8	71.4±28.0	0.51	**9.4** (4.4-14.4)
Social (5)	89.3±15.9	78.2±22.7	0.12	**11.1** (6.9-15.3)	87.3±14.7	72.5±27.2	0.16	**14.8** (9.9-19.7)
School (5)	75.4±20.5	61.4±23.6	0.10	**14.0** (9.2-18.8)	68.5±24.4	47.9±28.3	0.06	**20.6**(14.7-26.5)

Notes. [a]The absolute difference is the mean QOL score in Latinos minus the mean QOL score in Non-Latinos; [b]Mann-Whitney *U* tests; Scores are on 0-100 scale where higher scores indicate better QOL; ER = Emergency room visits; Hosp = Hospitalizations
Bold absolute difference values are greater than the minimum clinically important difference.

Similar to Latino youth, Latino parents reported higher subscale scores for Emotions (Latino parents had less anger about their child having sickle cell disease and/or pain; 76.9 ± 36 versus 46.4 ± 37.8, p = 0.04), and Communication II (Latino parents had less difficulty regarding others not understanding about sickle cell disease and/or pain; less difficulty telling others that their child has sickle cell disease; 82.1 ± 15.9 versus 51.8 ± 36.3, p = 0.02) compared to non-Latino parents. Similar to youth, there were no significant differences in either total generic QOL or its subscales between Latino and non-Latino parents.

The absolute differences between Latino versus non-Latino parents QOL scores are shown in Table 10. All exceeded or was equal to (Emotional subscale) its respective MCID except Worry I subscale, Communication I subscale, and Physical subscale.

Specific Aim 3

Specific Aim 3: To explore the relationship between disease-specific quality of life as it relates to systemic- (sickle cell disease life burden) and individual-level contextual factors (poorer health) in youth with sickle cell disease aged 10-18 years and their parents who participated in the HABIT study.

Hypothesis 3.1: Youth and parents having greater sickle cell disease life burden (other family members in the home have sickle cell disease, greater medication barriers to hydroxyurea, greater discordance between youth and parents regarding sickle cell disease responsibility) will have lower disease-specific quality of life.

Life Burden and Disease-specific Quality of Life

Hypothesis 3.1 was partially supported. Table 11 provides details regarding the results of regression analyses for youth and parents. Having additional family members with sickle cell disease and medication barriers did not predict youth or parent perception of disease-specific QOL as hypothesized. Therefore, further testing by adding Latino ethnicity to the model was not conducted.

While greater discordance between youth and parents regarding sickle cell family responsibility did not predict youth disease-specific QOL, in the parent model there was an inverse association between youth-parent discordance and parent perception of disease-specific QOL. For each unit increase in youth-parent discordance, parent perception of disease-specific QOL decreased by approximately 3 points (β = -3.07; p = 0.04). In this model, 12.5% of the variation in parent perception of disease-specific QOL can be explained by discordance between parent-youth perception of sickle cell responsibility and management.

Table 11 Prediction Model of Life Burden and Disease-specific Quality of Life in Youth and Parents

		Youth						Parents					
			Unstandardized Coefficient			Collinearity Statistics			Unstandardized Coefficient			Collinearity Statistics	
	Variable	R^{2a}	Beta	SE[b]	P-value	Tol.[c]	VIF	R^2	Beta	SE	P-value	Tol.	VIF
Others in Home have Sickle Cell Disease													
Step 1	(Constant)		67.00	4.19					58.51	4.75			
	Others with sickle cell disease		8.78	8.88		--	--		12.03	9.90		--	--
	Model	-.001			0.33			.019			0.24		
Step 2	Not conducted							Not conducted					
Greater Barriers to Hydroxyurea													
Step 1	(Constant)		88.18	13.88					92.52	16.82			
	Greater barriers		-0.41	0.28		--	--		-0.72	0.38		--	--
	Model	.039			0.16			.092			0.07		
Step 2	Not conducted							Not conducted					
Youth-Parent Discordance													
Step 1	(Constant)		77.75	7.87					77.76	8.44			
	Discordance		-1.71	1.33		--	--		-3.07	1.41	**0.04**	--	--
	Model	.023			0.21			.125			**0.04**		
Step 2	(Constant)	Not conducted							73.57	10.50			
	Discordance								-2.78	1.49	0.07	0.92	1.09
	Latino								5.47	8.00	0.50	0.92	1.09
	Model							.106			0.10		

Notes: [a]R^2 is Adjusted R^2; [b]SE = Standard error; [c]Tol. = Tolerance; Tolerance was considered to be an issue if tolerance was <0.2 and the variance inflation factor (VIF) was ≥ 5 or the tolerance was <0.1 and the value of the VIF was ≥10

Variation in parent perception of disease-specific QOL decreased from 12.5% to 10.9% once ethnicity was added to the model. When ethnicity was added to the model, the model did not retain significance (p = 0.10). Collinearity was not an issue for Aim 3.1.

Hypothesis 3.2: Youth with poorer health and their parents will have lower perception of disease-specific QOL compared to those with better health.

Poorer Health and Disease-specific Quality of Life

Two variables representing poorer health (number of emergency room visits within the past year and number of hospitalizations within the past year due to sickle cell disease) were tested as predictors of youth and parent perception of disease-specific QOL. Hypothesis 3.2 was supported. Table 12 provides details regarding the results of multivariate regression analyses for youth and parents. Collinearity was not an issue for Aim 3.2.

Emergency Room Visits

Youth

Using self-reported emergency room visits for sickle cell disease during the past year, there was an inverse association between number of emergency room visits and youth perception of disease-specific QOL. For each unit increase in the number of emergency room visits due to sickle cell disease, youth perception of disease-specific QOL decreased by 2.9 points (β = -2.89; p = 0.005). After controlling for ethnicity, the multivariate linear model retained significance (p = 0.008). In the multivariate model,, for every unit increase in the number of emergency room visits, youth perception of disease-specific QOL decreased by 2.5 points. Twenty eight percent of the variance in youth perception of disease-specific QOL can be explained by this model.

Using electronic medical record documentation of emergency room visits, for each unit increase in emergency room visits for sickle cell disease, youth perception of disease-specific QOL decreased by 5.1 points (β = -5.07; p = 0.002). After controlling for ethnicity, the multivariate linear model retained significance (p = 0.001). Controlling for ethnicity, for every increase in the number of emergency room visits for sickle cell disease youth perception of disease-specific QOL decreased by 4.7 points. Thirty six percent of the variance in disease-specific QOL in youth can be explained by this model.

Table 12 Prediction Models of Poorer Health and Disease-specific Quality of Life in Youth and Parents

		Youth						Parents					
		Unstandardized Coefficient				Collinearity Statistics		Unstandardized Coefficient				Collinearity Statistics	
	Variable	R^{2a}	Beta	SE[b]	P-value	Tol.[c]	VIF	R^2	Beta	SE	P-value	Tol.	VIF
Emergency Room (ER) visits during past year Self-reported													
Step 1	(Constant)		74.03	3.69					67.08	4.04			
	ER visits		-2.89	0.93	**0.005**	--	--		-3.41	0.99	**0.002**	--	--
	Model	.258			**0.005**			.309			**0.002**		
Step 2	(Constant)		69.02	5.16					66.84	5.71			
	ER visits		-2.48	0.96	**0.02**	0.90	1.11		-3.39	1.07	**0.004**	0.91	1.10
	Latino		9.06	6.63	0.19	0.90	1.11		0.46	7.48	0.95	0.91	1.10
	Model	.284			**0.008**			.278			**0.01**		
Electronic Medical Record													
Step 1	(Constant)	.	72.89	3.27					67.27	3.25			
	ER visits		-5.07	1.50	**0.002**				-6.93	1.46	**<0.001**	--	--
	Model	.279			**0.002**			.451			**<0.001**		
Step 2	(Constant)		66.63	4.31					63.91	4.44			
	ER visits		-4.70	1.42	**0.003**	0.99	1.02		-6.75	1.47	**<0.001**	0.99	1.01
	Latino		11.93	5.74	**0.048**	0.99	1.02		6.66	6.02	0.28	0.99	1.01
	Model	.361			**0.001**			.456			**<0.001**		
Hospitalizations during Past Year Self-reported													
Step 1	(Constant)		78.53	3.29					70.02	3.72			
	Hospitalizations		-5.72	1.10	**<0.001**	--	--		-6.48	1.22	**<0.001**	--	--
	Model	.541			**<0.001**			.565			**<0.001**		
Step 2	(Constant)		72.51	4.72					67.10	5.48			
	Hospitalizations		-5.14	1.11	**<0.001**	0.91	1.10		-6.21	1.29	**<0.001**	0.92	1.09
	Latino		9.94	5.81	0.10	0.91	1.10		5.01	6.85	0.47	0.92	1.09
	Model	.580			**<0.001**			.555			**<0.001**		
Electronic Medical Record													
Step 1	(Constant)		72.24	3.68					65.77	4.12			
	Hospitalizations		-7.56	3.39	**0.03**	--	--		-9.16	3.73	**0.02**	--	--
	Model	.129			**0.03**			.162			**0.02**		

		Youth						Parents					
		Unstandardized Coefficient				Collinearity Statistics		Unstandardized Coefficient				Collinearity Statistics	
	Variable	**R^{2a}**	**Beta**	**SE[b]**	**P-value**	**Tol.[c]**	**VIF**	**R^2**	**Beta**	**SE**	**P-value**	**Tol.**	**VIF**
Step 2	(Constant)		65.95	5.15					62.72	5.89			
	Hospitalizations		-6.11	3.39	0.08	0.94	1.07		-8.47	3.88	**0.04**	0.94	1.06
	Latino		11.23	6.64	0.10	0.94	1.07		5.64	7.72	0.47	0.94	1.06
	Model	.187			**0.03**			.146			0.057		

Notes: [a]R^2 is Adjusted R^2; [b]SE = Standard error; [c]Tol. = Tolerance; Tolerance was considered to be an issue if tolerance was <0.2 and the variance inflation factor (VIF) was ≥ 5 or the tolerance was <0.1 and the value of the VIF was ≥10.

Parents

Using self-reported emergency room visits, there was an inverse association between number of emergency room visits and parent perception of their youth's disease-specific QOL. For each unit increase in the number of emergency room visits due to sickle cell disease, parent perception of their youth's disease-specific QOL decreased by 3.4 points ($\beta = -3.41$; $p = 0.002$). When ethnicity was added to the model, the model retained statistical significance ($p = 0.01$). Twenty eight percent of the variance in parent perception of disease-specific QOL can be explained by this model. Using electronic medical record documentation of emergency room visits, there was an inverse association between number of emergency room visits and parent perception of their youth's disease-specific QOL. For each unit increase in the number of emergency room visits due to sickle cell disease, parent perception of disease-specific QOL decreased by 6.9 points ($\beta = -6.93$; $p < 0.001$). After controlling for ethnicity, the multivariate linear model retained significance ($p < 0.001$). Forty six percent of the variance in parent perception of their youth's disease-specific QOL can be explained by this model.

Hospitalizations

Youth

Using self-reported hospitalizations, there was an inverse association between number of hospitalizations in the past year and perception of disease-specific QOL. For each unit increase in the number of hospitalizations in the past year for sickle cell disease, disease-specific QOL in youth decreased by 5.7 points ($\beta = -5.72$; $p < 0.001$). After controlling for ethnicity, the multivariate linear model retained significance ($p < 0.001$). Controlling for ethnicity, for every increase in the number of hospitalizations during the past year due to sickle cell disease youth perception of disease-specific QOL decreased by 5.1 points. Fifty eight percent of the variance in youths' perception of disease-specific QOL can be explained by this model.

Using electronic medical records documentation, for each unit increase in hospitalizations for sickle cell disease, disease-specific QOL decreased by 7.6 points ($\beta = -7.56$; $p = 0.03$). After controlling for ethnicity, the multivariate linear model retained significance ($p = 0.029$). Nineteen percent of the variance in disease-specific QOL in youth can be explained by this model.

Parents

Using self-reported hospitalizations, there was an inverse association between self-reported number of hospitalizations in the past year and parent perception of youth's disease-specific QOL. For each unit increase in the number of hospitalizations due to sickle cell disease, parent perception of their youth's disease-specific QOL decreased by 6.5 points ($\beta = -6.48$; $p < 0.001$). When ethnicity was added to the model, the model retained statistical significance ($p < 0.001$). Fifty six percent of the variance in parent perception of disease-specific QOL in youth can be explained by this model.

Using electronic medical record documentation, there was an inverse association between number of hospitalizations and parent perception of their youth's disease-specific QOL. For each unit increase in the number of hospitalizations due to sickle cell disease, parent perception of disease-specific QOL decreased by 9.2 points ($\beta = -9.16$; $p = 0.02$). After controlling for ethnicity, the multivariate linear model no longer retained significance ($p = 0.057$).

Chapter V: Discussion

In this exploratory mixed methods study, we adapted the Conceptual Model of Health-related QOL (Ashing-Giwa, 2005) for use in youth with sickle cell disease to guide our study. In the adapted model, the construct sickle cell disease life burden was operationalized in 3 ways: other family members in the home have sickle cell disease, greater medication barriers to hydroxyurea, and greater discordance regarding sickle cell family responsibility. The construct poorer health was operationalized as greater number of emergency room visits and/or hospitalizations within the past year.

Summary of Study

Generic QOL in youth with sickle cell disease has been studied over the past several years but a disease-specific instrument was lacking. In 2013 a valid and reliable disease-specific measure, the PedsQL Sickle Cell Disease Module, was developed by Panepinto et al. (2013) but was only available for use with subjects with English language fluency. For use with Spanish speaking subjects enrolled in the hydroxyurea Adherence for Personal Best in Sickle Cell Disease (HABIT) feasibility trial (R21 NR013745), the PedsQL Sickle Cell Disease Module had undergone a forward and backward Spanish language translation to produce a Spanish language version. As a first step of this dissertation research, the final phase of the process of linguistic validation was conducted using a sample of Spanish speaking youth age 9-17 years with sickle cell disease and their parent (10 youth, 10 parents). Completion of this process produced a validated equivalent Spanish language version of the PedsQL Sickle Cell Disease Module for age 8-12 and 13-18. The Spanish language version is now available by request from the MAPI Institute (Mapi Research Trust, 2015).

This is one of the first studies to examine disease-specific and generic QOL in Latino youth with sickle cell disease. Youth and parent proxy-report of baseline disease-specific and generic QOL of subjects who participated in the HABIT feasibility trial was used to compare perception of disease-specific and generic QOL by ethnicity; half of the sample was Latino. All youth were treated with hydroxyurea but did not adhere to the medication regimen. We explored the relationship between conceptually relevant factors such as Latino ethnicity, life burden, and poorer health to examine their contribution to perception of QOL.

Interpretation of Quality of Life Scores in the Sample

Disease-specific Quality of Life. Disease-specific QOL scores on the PedsQL Sickle Cell Disease Module provide researchers and healthcare providers a guide in assessment of QOL in the sickle cell disease population. In prior research (Beverung, Varni, & Panepinto, 2015), Pain and Hurt and Pain Impact subscale scores of ≤ 60 were associated with poor QOL, while scores of ≥ 81 were associated with good QOL in youth with sickle cell disease. In the sample of youth who participated in the HABIT study, Pain and Hurt subscale scores reflected QOL that was between poor and good (73.7 ± 24.4), while Pain Impact scores (57.6 ± 26.2) on average, reflected poor QOL. Our results are similar to those reported in Panepinto et al. (2013) where youth with sickle cell disease also reported Pain and Hurt subscale scores that can be associated with poor to good QOL (66.7 ± 20.9) and Pain Impact subscale score that can be associated with poor QOL (54.0 ± 24.8). In this study, the mean disease-specific QOL scores for each subscale were similar to those reported by Panepinto et al. (2013) with the exception of the Treatment and Communication II subscales. Specifically, youth in our study reported higher Treatment subscale scores compared to youth who participated in the Panepinto study (79.1 ± 17.4 versus 64.3 ± 21.9), which means that youth in the current study perceived sickle cell disease-related treatment impact such as remembering to take sickle cell disease medication, not liking the taste, and worrying about the therapeutic effect of sickle cell disease medication, as having less of a negative effect on their QOL compared to the sample in Panepinto et al. (2013).

Youth versus Parent Quality of Life. Hypothesis 2.1, that youth would report higher disease-specific and generic QOL than parents was partially supported for total disease-specific but not for total generic QOL. Youth scores were significantly higher ($p = 0.02$) than parent proxy scores for disease-specific QOL total score and 6 points higher, though not statistically significantly higher, than parent proxy for generic QOL total score. As others have reported, there is imperfect agreement between youth self-report and parent proxy-report of QOL in youth with chronic illnesses (Garetz et al., 2015; Hilliard et al., 2013; Lins, Tassitano, Brandt, de Castro Antunes, & da Silva, 2015). Parents may overestimate the impact of chronic illness on youth's QOL. Eiser and Morse (2001) conducted a review of 14 studies that examined QOL in youth with a range of chronic conditions to examine the extent of concordance between youth self-report and parent/caregiver proxy-report. The researchers reported that concordance was

commonly found between youth and parent for Physical, Functioning, and Symptoms subscales but not Social or Emotional subscales. Eiser and Morse (2001) concluded that additional research is needed to provide conclusive evidence to determine if youth self-report of QOL is more reliable than parent proxy-report.

Latino versus Non-Latino Quality of Life. Based on the literature review reported in Chapter 2, I hypothesized that the perception of disease-specific and generic QOL in Latino youth and parents would be lower compared to non-Latino youth and parents. This was not the case. Compared to non-Latino, Latino youth reported higher QOL scores for all subscales except for one, the disease-specific Worry II subscale. Latino parents reported higher QOL scores than non-Latino parents for all disease-specific subscales except for three: Worry I, Worry II, and Communication I subscales. The hypothesis was based on results of 4 studies (Ashing-Giwa et al., 2007; Brice et al. 2011; Lim et al., 2009; Scott et al., 2008) in the integrative literature review of cultural factors that compared perception of QOL of Latino participants with non-Latino participants. One possible reason for this hypothesis not being fully supported is that in this study non-Latino parents reported a higher number of hospitalizations during the past year compared to Latino parents (on average, 11 versus 5). As this study and others (Gonzalez-Gil, Jenaro, Gómez-Vela, & Flores, 2008; Hegarty, Macdonald, J., Watter, P., & Wilson, 2008; Kullowatz, Kanniess, Dahme, Magnussen, & Ritz, 2007) have reported, increased hospitalizations are associated with poorer QOL.

While there were no significant differences in mean total disease-specific QOL and for the majority of subscale scores between ethnicities in our study, Latino youth reported significantly higher scores for Emotions (Latino youth reported feeling less mad about having sickle cell disease or when he/she has pain), Treatment (Latino youth reported less problems with treatment), and Communication II (Latino youth had less difficulty regarding others not understanding about sickle cell disease and/or pain; less difficulty telling others that he/she has sickle cell disease) subscales.

Latino parents reported significantly lower disease-specific QOL scores for Worry II (Latino parents worried more than non-Latino parents that their child might have a stroke or a chest crisis). Latino parents reported significantly higher disease-specific QOL scores for Emotions (Latino parents reported feeling less mad about their child having sickle cell disease or when he/she has pain), and

Communication II (Latino parents had less difficulty regarding others not understanding about sickle cell disease and/or pain; less difficulty telling others that their child has sickle cell disease).

The differences in Emotions subscale scores may possibly be explained by the concept of familism. Sabogal, Marin, Otero-Sabogal, VanOss Marin, & Perez-Stable (1987) described familism (or familismo) as having a high regard for family relationships with close family ties, interconnectedness, and prioritizing of family before self, and is a central feature of Latino culture. Familism has been found to promote health and appears to be generally beneficial to those who view familism as ideal (Corona, Campos, & Chen, 2017).

Considering that pain is a hallmark of sickle cell disease, it is possible that non-Latino youth and parents reported significantly lower QOL for the aforementioned subscales because of a difference in treatment regimen prescribed by their physician. In a study of disagreement in pain perception between adult patients and their physicians in primary care, Staton et al. (2007) reported that almost 50% of the time, physicians underestimated pain levels in African American patients with chronic pain by 2 or more points on an 11-point numeric pain rating, compared to 33.5% of the time for non-African Americans with chronic pain. Moreover, when pain level was overestimated, physicians were more likely to overestimate pain levels in non-African Americans 18.9% compared to 9.5% in African Americans (Staton et al., 2007).

Our study findings showed that Latino youth and parents reported significantly higher scores on Communication II subscale (Latinos had less difficulty regarding others not understanding about sickle cell disease and/or pain; less difficulty telling others that he/she has sickle cell disease) compared to non-Latino youth and parents. To better understand results obtained in our study, additional studies with Latino and non-Latino youth with sickle cell disease need to be conducted.

Not all studies examining QOL in youth with sickle cell disease report the ethnicity of participants (Graves, Hodge, & Jacob, 2016; McClellan et al., 2009). Some researchers in studies of sickle cell disease have described the ethnicity of participants in their samples but did not examine QOL scores by ethnicity because the number of Latino participants was small (Newland, 2008; Panepinto et al., 2010; Panepinto et al., 2013). The incidence of sickle cell disease is greatest in African Americans, with incidence in Latinos coming in a distant second (Wang et al., 2013). In earlier research, sickle cell disease study samples consisted mainly of African Americans and of those who are proficient in English

and few if any Latinos were included. While sickle cell disease is less prevalent among Latinos, every state in the U.S. has varying percentages of people living with sickle cell disease, ranging from <1 case per 1,000 births in Montana to 34.1 cases per 1,000 births in Mississippi (Ojodu, Hulihan, Pope, & Grant, 2014); therefore, when possible, race/ethnicity should be considered when examining the influence of QOL in youth with sickle cell disease.

While limited, research comparing the perception of QOL by race/ethnicity is accumulating. Using the PedsQL Generic Core Scale, McManus and colleagues compared parent proxy perception of health-related QOL by race/ethnicity in a longitudinal sample of 660 very-low-birth-weight infants age 2 and 3 years with and without asthma (McManus, Robert, Albanese, Sadek-Badawi, & Palta, 2012). Quality of life was similar, on average, for non-Hispanic White and Hispanic children but significantly lower for non-Hispanic Black infants. Using the 36-item Short Form Health Survey, McLaughlin et al. (2016) examined the relationship between race, adherence, chronic pain, and generic QOL in a sample of 80 adolescents and young adults with hemophilia. In this sample, 61 participants were White (12% Hispanic and 88% non-Hispanic) and 19 participants were non-White (14% Hispanic and 86% non-Hispanic). Quality of life scores of non-White subjects were significantly lower compared to Whites for Physical health (63.4 vs 78.0; $p = 0.02$) and 3 of its subscales: Bodily Pain (60.6 vs 74.8; $p = 0.02$), Physical Function (63.7 vs 79.8; $p = 0.03$), and Role Limitations (61.8 vs 79.5; $p = 0.01$). McLaughlin et al. (2016) reported that racial differences in perception of chronic pain accounted for statistically different QOL scores.

Minimal Clinically Important Difference. Minimal clinically important difference (MCID) values enable interpretation of changes in QOL scores over time or differences between QOL scores in different subject groups. A change in score that exceeds its MCID may be interpreted as a clinically meaningful change. In this sample the absolute differences between Latino and non-Latino subjects for disease-specific and generic QOL total and subscale scores exceeded their respective MCID values. This occurred for all disease-specific subscales except Worry I (both youth and parent proxy report), and Communication I (parent proxy report). For the generic QOL measure, scores exceeded MCIDs for all but the physical subscale. In some cases, the differences in QOL scores were not statistically significant and may have lacked statistical power due to our modest sample size. Nonetheless, these absolute

differences across both QOL measures provide preliminary insight into differences in perception of QOL by Latino and non-Latino youth with sickle cell disease and require validation in future studies.

Minimal clinically important difference has been previously reported for other pediatric diseases or conditions such as asthma (Wyrwich, Tierney, & Wolinsky, 2002), dermatologic disorders (Basra, Salek, Camileri, Sturkey, & Finlay, 2015), diabetes (Hilliard et al., 2013), and epilepsy (Junger et al., 2015). Minimal clinically important differences were more recently applied to sickle cell disease by Panepinto et al. (2017). Minimal clinically important differences calculated using disease-specific scores from our study sample were comparable to those reported by Panepinto et al. (2017) in their study 1 week post hospital discharge. A 6.5 point change in the Pain and Hurt subscale in our study for example, was considered clinically meaningful compared to a 7.4 point change at 1 week post discharge in the Panepinto et al. study; while changes had to exceed 14.6 points for Worrying II (worrying about a stroke or chest crisis) in our study compared to 14.6 at 1 week post discharge in the Panepinto (2017) sample to be perceived as clinically important.

Poorer Health

In this study emergency room and hospitalizations were measured in 2 ways: by parent self-report and by electronic medical records. While data provided by self- or proxy-report may be inaccurate due to self-report bias (De Vriendt, Huybrechts, Ottevaere, Van Trimpont, & De Henauw, 2009; Kee et al., 2017), data retrieved from electronic medical records are not without challenges such as information not accurately entered electronically (Cowie et al., 2017). However, when used together as in our study, they provide a strong support for accuracy of study results.

Painful vaso-occlusive sickle cell crisis is the most common cause of emergency room and/or hospitalization of patients with sickle cell disease. In our sample, multivariate analyses showed that there was an inverse association between number of emergency room visits and/or hospitalization and perception of disease-specific QOL. Our findings are consistent with the findings of Panepinto et al. (2017), who reported that youth with sickle cell disease who had acute painful vaso-occlusive crises reported significantly lower QOL scores while hospitalized compared to higher QOL scores 1 week post discharge. Jackson, Lemanek, Clough-Paabo, and Rhodes (2014) reported that a greater number of emergency room visits or hospitalizations were significantly associated with poorer physical QOL in their

study of 87 adolescents and young adults with sickle cell disease. Jackson et al. (2014) also stated that greater emergency room visits or greater hospitalizations indicated greater physical impact of the disease.

Strengths and Limitations

Strengths

This study was 1 of only a few to examine QOL in Latino and non-Latino youth using disease-specific and generic QOL instruments. Furthermore, few studies examining QOL in youth are stratified based on youths' ethnicity. While the study sample was modest, Latinos in our study represent a subset of individuals largely overlooked in research of QOL in those with sickle cell disease. Our study used report of emergency room visits and hospitalizations from 2 perspectives: self-report and objective electronic medical record review. Results from both perspectives pointed in the same direction: greater number of emergency room visits and/or hospitalizations resulted in poorer QOL.

Limitations

This study has several limitations. The sample size was small and did not allow for statistical control of demographic variables like age and gender. This study used secondary data that was not designed to study cultural factors and was therefore confined to the type of data that were captured in the primary study. We were unable to measure factors such as acculturation, familism, patient-provider relationship, and religiosity/spirituality, which were identified as important factors of QOL in participants in previous studies. Measuring the relationship between disease-specific and generic QOL in youth with sickle cell disease and cultural factors would have provided a broader understanding of QOL in this sample. Furthermore, this study was unable to examine some of the variables that might be associated with variations in QOL, such as mental health (depression), cognitive issues, immigration status, and family instability.

The sample for Aims 2 and 3 was derived from the HABIT study and included Latino and non-Latino youth with sickle cell disease from Columbia University Medical Center and from Albert Einstein/Montefiore Medical Center who had not successfully integrated a daily hydroxyurea adherence routine and self-management into a standard health habit. This study design limits generalizability to other Latinos and non-Latinos with sickle cell disease who have successfully integrated their daily

hydroxyurea adherence routine and self-management into a standard health habit, because our findings would only represent those who had a history of not successfully incorporating their daily hydroxyurea adherence routine and self-management into a healthy practice. Additionally, because our sample of Latinos were either born in the Dominican Republic or their parents were born in the Dominican Republic, study findings may not pertain to other Latinos from other Spanish-speaking countries.

This study found significant associations between emergency room visits in the past year and disease-specific QOL, and hospitalizations within the past year and disease-specific QOL. These results however, are correlational in nature and as a result, a causal relationship cannot be established. It is possible that visiting the emergency room and/or being hospitalized leads to poor disease-specific QOL in youth with sickle cell disease and parents, but it is also possible that disease-specific QOL may have an influence on the number of emergency room visits and/or hospitalizations. Experiencing chronic pain and hurt, for example, may result in increased emergency room visits and/or hospitalizations. Moreover, the self-reported nature of some of this data collection relied on participants' recollection of past events such as barriers to medication adherence and sickle cell family responsibility and may have presented an element of recall bias over that period.

Implications for Practice

This exploratory study emphasizes the relevance of understanding the relationship between poorer health and QOL in youth with sickle cell disease. Greater number of hospitalizations was related to poorer QOL in youth with sickle cell disease. Routine QOL screening with a disease-specific QOL instrument like the PedsQL Sickle Cell Disease Module during regular office visits for youth with sickle cell disease may lead to better management of sickle cell disease and to less emergency utilization of healthcare resources. Routine screening has the potential of identifying youth with poor QOL. Routine screenings can potentially supplement clinical findings by using MCIDs to identify meaningful changes in QOL scores.

Recommendations for Policy

A goal of Health People 2020 is to "Improve health-related QOL and well-being for all individuals" (Office of Disease Prevention and Health Promotion [ODPHP], 2017). The importance of this goal was underscored by its inclusion as one of Healthy People's (HP) 2020 overarching goal of "promoting quality

of life, healthy development, and health behaviors across all life stages" (ODPHP, 2017). To improve QOL and well-being for Latinos on how sickle cell disease impacts their life, we recommend that health care staff be educated regarding the importance of having valid and reliable questionnaires that are culturally and linguistically sound in the language that the patient is most comfortable with.

Conclusion

In conclusion, this exploratory study of Latino and non-Latino examined disease-specific and generic QOL in youth aged 8-18 years with sickle cell disease. Moreover, we completed the translation and linguistic validation of a sickle cell disease-specific QOL instrument for use among Spanish-speaking sickle cell disease population. This study highlighted the importance of having QOL questionnaires available in the preferred language of participants, so that the influence of sickle cell disease on their sense of well-being can be assessed, and to offer a useful addition to more objective clinical measures. The findings of this study emphasized the relationship between QOL and greater number of emergency room visits and/or hospitalizations among youth with sickle cell disease and could serve as a call to action for clinicians and researchers to find ways of improving the lives of those affected with this disease by preventing painful vaso-occlusive crises. Furthermore, the results of this study may help to increase understanding and utility of measurement of QOL in clinical settings in patients with sickle cell and other chronic illnesses.

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Appendix A

Demographic Survey

Name: _____ Date: _____

INSTRUCTIONS: *Please complete the following questions by indicating an X next to your answer. Your information will be kept strictly confidential.*

1. How old are you? _____ years

2. What is your gender? Male ____ Female ____

3. Are you Latino or Hispanic? Yes ____ No ____

4. Do you have sickle cell disease? Yes____ No ____

5. Were you born in the United States? Yes ____ No ____

If you answered no to question 5, what is your country of birth? _____

Appendix B

Subject ID _____ Parent Demographic Questionnaire Date _____

Name: _____

Address: _____

Home Phone number: _____

Personal cell phone number: _____

Date of birth: _____

Do you consider yourself Latino/Hispanic?

- Yes
- No
- Prefer not to respond

What is your race?

- White
- Black/African American
- Asian
- Native Hawaiian/Pacific Islander
  (Please specify: _____)
- American Indian/Alaskan Native
- Multiracial
- Other: _____
- Prefer not to respond**.**

How long have you lived in the United States?

- Less than one year
- 1 to 3 years
- 4 to 5 years
- 6 to 10 years
- More than 10 years
- Born in the United States

Subject ID _____ Parent Demographic Questionnaire Date _____

What is your highest level of education?

- Elementary school
- Some high school
- High school graduate
- Some college
- College graduate
- Graduate school

Are you the person who takes care of your child most of the time? YES NO

Employment:

- Full time (35 hours per week or more)
- Part time (less than 35 hours per week)
- Laid off
- Unemployed or currently looking for work
- Disabled/retired
- Attending school

Marital status:

- Married, living with spouse
- Married, living separately
- Single
- Separated from spouse
- Divorced

Number of children in household: _____

Number of people living in the home of child with sickle cell: _____

Do you have sickle cell disease? Yes No

Do other people in the home have sickle cell disease?

Yes (if yes, who)_____ No

Subject ID _____ Parent Demographic Questionnaire Date _____

Information about your child

Child's name: _____

Address: _____

Home Phone number: _____**Child's** personal cell phone number: _____

Child's date of birth: _____

Is your child Latino/Hispanic?

- □ Yes
- □ No
- □ Prefer not to respond.

What is your child's race?

- □ White
- □ Black/African American
- □ Asian
- □ Native Hawaiian/Pacific Islander
  (Please specify: _____)
- □ American Indian/Alaskan Native
- □ Multiracial
- □ Other: _____
- □ Prefer not to respond.

Does your child live in the same house as you? Yes □ No □

How long has your child lived in the United States?

- □ Less than one year
- □ 1 to 3 years
- □ 4 to 5 years
- □ 6 to 10 years
- □ More than 10 years
- □ Born in the United States

What is your child's grade level in school? _____

Subject ID _____ Parent Demographic Questionnaire Date _____

Who is the person who takes care of the child most of the time?

- Mother
- Father
- Grandmother or Grandparent
- Foster parent
- Someone else _____

List information about your child's medications:

Name	Dose (mg)	Times per day	Date started (more than 6 months ago; less than 6 months ago)
Hydroxyurea			
Penicillin			
Folic acid			
Exjade			
Tylenol			
Ibuprofen			

What is the name and address of the pharmacy that you use to fill your child's hydroxyurea prescriptions?

_____

_____

In the past year, has your child been treated in the emergency room? Yes □ No □

If yes, how many times? _____
Did you go to the emergency room for treatment of sickle cell disease? Yes □ No □

Are you the one who usually takes your child to his or her appointments/takes your child to the ER when needed? Yes □ No □

In the past year, has your child been hospitalized? Yes □ No □

If yes, how many times? _____

Was the problem related to sickle cell disease? Yes □ No □

Appendix C

Report of Translation Process for PedsQL Sickle Cell Disease Module

A total of 10 Latino parent-child dyads participated in the cognitive interview component of the translation process of the PedsQL Sickle Cell Disease Module Child Report (ages 8-12), the PedsQL Sickle Cell Disease Module Parent Report for Children (ages 8-12), the PedsQL Sickle Cell Disease Module Teen Report (ages 13-18), and the PedsQL Sickle Cell Disease Module Parent Report for Teens (ages 13-18). All subjects currently receive care at New York Presbyterian/Columbia University Medical Center. All interviews were conducted at the location requested by the parent. The majority of interviews were conducted in participants' homes except for two which were conducted either at New York Presbyterian/Columbia University Medical Center Transplant Center or at Columbia's Pediatric sickle cell disease Clinic.

Child Demographics

Overall, youth ranged in age from 9-17 years (average 13.4 years).

8-12 years. Children ranged in age from 9-12 years (average 10.8 years). Four out of five children were male. Children in this age group all reported being born in the United States. PedsQL Sickle Cell Disease Module completion time ranged from 8-15 minutes (average 10.4 minutes). One parent reported having sickle cell disease.

Table A provides a summary of the demographic characteristics of the children who participated in the linguistic validation process for the PedsQL Sickle Cell Disease Module Child Report (ages 8-12). While all youth were born in the United States, all were fluent in Spanish.

Table A Children in 8-12 Age Group

Age (years)	Gender	Ethnicity	Born in U.S.	Module Completion (minutes)
9	Male	Latino	Yes	15
11	Male	Latino	Yes	9
11	Male	Latino	Yes	8
11	Female	Latino	Yes	8
12	Male	Latino	Yes	12

13-18 years. Children ranged in age from 15-17 years (average 16 years). Four out of five children were male. Only 2 children (age 15 and 17 years) reported Dominican Republic as their country of birth while the remaining majority reported being born in the United States. PedsQL Sickle Cell Disease Module completion time ranged from 7-12 minutes (average 9 minutes). Table B provides a summary of children demographics for the 13-18 age group.

Table B Youth in 13-18 Age Group

Age in years	Gender	Ethnicity	Born in the U.S.	If not U.S. born, what country	Completion time in minutes
15	Male	Latino	Yes		9
15	Male	Latino	No	Dominican Rep.	8
16	Male	Latino	Yes		12
17	Male	Latino	Yes		7
17	Female	Latino	No	Dominican Rep.	8

Parent Demographics

Overall, parents ranged in age from 29-48 years (average 36.9 years). The entire sample of parents reported Dominican Republic as their country of birth.

Parents of 8-12 year olds. Parents ranged in age from 30-47 years (average 35.2 years). PedsQL Sickle Cell Disease Module completion time ranged from 6-12 minutes (average 9.4 minutes). All parents were female. Table C summarizes demographics of parents of children in the 8-12 year olds.

Table C Parents of Children in 8-12 Age Group

Age in years	Gender	Ethnicity	Parent has sickle cell disease	Born in U.S.	If no, country	Completion time in minutes
30	Female	Latino	No	No	Dominican Republic	8
30	Female	Latino	Yes	No	Dominican Republic	11
34	Female	Latino	No	No	Dominican Republic	6
35	Female	Latino	No	No	Dominican Republic	10
47	Female	Latino	No	No	Dominican Republic	12

Parents of 13-18 year olds. Parents ranged in age from 29-48 years (average 38.6 years). Completion time ranged from 7-12 years (average 8.6 minutes). All parents were female except for one parent. Table D summarizes demographics of parents of children in the 13-18 year olds.

Table D Parents of Children in 13-18 Age Group

Age in years	Gender	Ethnicity	Parent has sickle cell disease	Born in U.S.	If no, country	Completion time in minutes
29	Female	Latino	No	No	Dominican Republic	7
35	Female	Latino	No	No	Dominican Republic	8
35	Female	Latino	No	No	Dominican Republic	8
46	Male	Latino	No	No	Dominican Republic	12
48	Female	Latino	No	No	Dominican Republic	8

Cognitive Interview

After the completion of the PedsQL Sickle Cell Disease Module, individual face to face interviews were conducted in Spanish by a bilingual research assistant with children for the age appropriate child self-report questionnaires and with parents for the corresponding parent proxy-report questionnaires. Youth and parent interviews were conducted separately. Item-by-item analyses were conducted where participants were asked whether the PedsQL Sickle Cell Disease Module directions and questions were clear, response choices were appropriate, they understood each item, questions were relevant for youths with sickle cell disease, and were questions too difficult to answer. Participants reported that there was no difficulty understanding and completing questionnaires. Participants stated that directions and questions were clear and easy to understand, response choices were appropriate, and questions were relevant to youths with sickle cell disease.

Only one participant had a suggestion regarding solutions for enhancing wording of a questionnaire item. The participant, aged 16 years, stated that the questions were “clear except for one: when they asked me if I was able to sleep in the night and did not ask if I normally have pain” (About MY Pain Impact, #9: I wake up at night when I have pain). In order to make the question clearer, she suggested that the questionnaire should “ask if it is hard to sleep during the night when you have pain, or if you wake up many times.”