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ABSTRACT

Title of Document: HEALTH-RELATED QUALITY OF LIFE IN ADULTS WITH SICKLE CELL DISEASE: THE ROLE OF ILLNESS INTRUSIVENESS AND PERCEIVED CONTROL

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Doctor of Philosophy, 2019

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Adults living with sickle cell disease (SCD) appear to have compromised health-related quality of life (HRQoL) that may be due to the disruptions they experience in their daily lives. While researchers have identified disease and treatment factors that are associated with HRQoL in this population, little is known about mechanisms that may explain the relationship between disease/treatment factors and HRQoL. The Illness Intrusiveness Theoretical Framework (IITF) has been used to explain the associations among disease/treatment factors and HRQoL in chronic health conditions; however, this framework has not been utilized in the context of SCD. The purpose of this study was to examine the relationships among disease/treatment factors, illness intrusiveness, perceived control, and HRQoL among 58 adults living with SCD (69% female, mean age 39.12 years). Participants reported demographic information and completed measures of pain, fatigue, number of emergency department (ED) visits, illness intrusiveness, perceived control, and HRQoL. Mediation analysis showed that illness intrusiveness reduced the association between

fatigue and physical HRQoL. The indirect effect of fatigue on physical HRQoL through illness intrusiveness was significant (b = -0.60), after adjusting for age, pain, and number of ED visits. Additionally, perceived control over life reduced the association between illness intrusiveness and mental HRQoL. The indirect effect of illness intrusiveness on mental HRQoL through perceived control over life was significant (b = -0.09), after adjusting for age. The current findings suggest that illness intrusiveness, or disruptions in activities, may help explain the link between disease/treatment factors and HRQoL. Furthermore, perceived control may explain, at least in part, the association between illness intrusiveness and HRQoL. Future research may benefit from evaluating psychosocial factors (e.g., illness intrusiveness, perceived control, coping) that may impact well-being among adults with SCD.

HEALTH-RELATED QUALITY OF LIFE IN ADULTS WITH SICKLE CELL DISEASE: THE ROLE OF ILLNESS INTRUSIVENESS AND PERCEIVED CONTROL

By

Lakeya S. McGill

Dissertation submitted to the Faculty of the Graduate School of the
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Dedication

To my grandmother, Dorothy Williams, I dedicate this dissertation to you.

Thank you for your support. I love you dearly, Granny.

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Chapter 1: Introduction

Health-related quality of life (HRQoL) is a multidimensional construct that consists of physical, mental, and social domains that are affected by disease and/or treatment factors (Centers for Disease Control and Prevention [CDC], 2000). It is an important construct to evaluate for people living with a chronic health condition, because it goes beyond simply measuring the presence or severity of a disease to assess an individual's happiness and life satisfaction. Assessing HRQoL provides increased awareness of the burden of chronic health conditions, which can help guide interventions and allocation of resources. Sickle cell disease (SCD), the most common genetic blood disorder in the United States, is a condition in which HRQoL appears to be compromised (McClish et al., 2005). Researchers have found that adults with SCD report poorer HRQoL compared to both the general population (Anie, Steptoe, & Bevan, 2002; Ballas et al., 2006) and individuals living with other chronic health conditions such as arthritis, cystic fibrosis, and myocardial infarction (Ballas et al., 2006; McClish et al., 2005). The compromising nature of HRQoL in SCD may be due to the disruptions/intrusions it presents to daily life activities. For instance, adults with SCD experience unpredictable pain and frequent healthcare utilization that contribute to a high rate of unemployment and strained social relationships (Carroll, Haywood, Fagan, & Lanzkron, 2009; Edwards et al., 2005; Smith et al., 2008; Thomas & Taylor, 2002; While & Mullen, 2004).

Illness intrusiveness is defined as the extent to which features of a disease and/or accompanying treatment factors interfere with one's involvement in meaningful activities (Devins, 1983). The illness intrusiveness theoretical framework (IITF) has strong empirical support and proposes that a combination of disease (e.g., pain, fatigue,

disability status) and treatment (e.g., time required for treatment, disruptive treatment schedules, negative side effects) factors disrupt participation in valued activities (Devin, 2010). It also posits that illness intrusiveness compromises HRQoL by: (1) reducing the positive reinforcement that individuals experience when engaging in valued activities; and (2) reducing perceived control (i.e., belief that one can influence outcomes in important life domains) by limiting an individual's ability to obtain positive outcomes or to avoid negative ones. Altogether, it is hypothesized that illness intrusiveness mediates the association between disease/treatment factors and HRQoL and that perceived control mediates the relationship between illness intrusiveness and HRQoL.

The central hypothesis of the IITF is that illness intrusiveness explains the association between disease/treatment factors and HRQoL (Devins et al., 2010). Researchers have found support for this hypothesis in adults with chronic health conditions such as cancer, end stage renal disease (ESRD), and multiple sclerosis (MS; Bloom, Stewart, Johnston, & Banks, 1998; Devins, 2010; Devins et al., 1990; Shawaryn, Schiaffino, LaRocca, & Johnston, 2002). However, the theoretical tenets of the IITF have not been studied in the context of SCD. Thus, the primary aim of the proposed study is to test the central hypothesis of the IITF in a sample of adults with SCD. Specifically, the proposed study will examine whether illness intrusiveness mediates the association between disease/treatment factors (i.e., pain, fatigue, healthcare utilization) and HRQoL. This aim is important in that it will confirm the hypothesized associations among disease/treatment factors, illness intrusiveness, and HRQoL – thereby lending credence to the utility of the IITF for studying HRQoL among adults living with SCD.

In the IITF, psychological (e.g., coping, personality, developmental stage), social (e.g., stigma, culture, social support), and contextual (e.g., age, sex, socioeconomic status, stressful life events) factors provide the context in which an individual experiences their disease (Devins, 2010). This means that individuals who have similar disease and treatment factors may report different levels of illness intrusiveness. Further, people who report the same level of illness intrusiveness may perceive themselves as having a different level of HRQoL. The IITF posits that these psychological, social, and contextual factors are directly and indirectly related to HRQoL. Additionally, SCD researchers have found that contextual factors such as age and sex are associated with HRQoL (Asnani, Reid, Lipps, and Williams-Green, 2008; Dampier et al., 2011; Jackson et al., 2014). Considering this research, it may be important to evaluate the role of age and sex in the context of SCD. Thus, the second aim of the proposed study is to examine the direct effects of age and sex in the IITF. Specifically, the proposed study will examine whether age and sex are directly related to HRQoL.

Perceived control is another factor in the IITF; it may explain the association between illness intrusiveness and HRQoL (Devins et al., 2010). That is, individuals who experience a disruption in valued activities may perceive themselves as having limited control over their life (i.e., perceived control). Lower perceived control has been linked to poorer HRQoL among individuals with chronic health conditions such as epilepsy, multiple sclerosis, and type II diabetes (Bishop, Fraine, & Tschopp, 2008; DeCoster, Killian, & Roessler, 2013; Poochikian-Sarkissian, Sidani, Wennberg, & Devins, 2008a). Additionally, researchers have found that perceived control mediated the relation between illness intrusiveness and HRQoL in multiple sclerosis and type II diabetes

(Bishop et al., 2008; Decoster et al., 2013). In the SCD literature, it has been established that greater perceived control is associated with better HRQoL and the amelioration of disease-factors that most likely contribute to a disruption in daily activities (e.g., pain, depressive symptoms, healthcare utilization) (Clay & Telfair, 2007; Edwards et al., 2001; Gibson et al., 2013). However, no studies have examined whether perceived control mediates the association between illness intrusiveness and HRQoL in a sample of adults with SCD.

Pain is the hallmark symptom of SCD (Platt et al., 1994); therefore, it may be important to consider SCD patients' perceptions of their ability to manage their pain and/or its effect on their lives. Although the IITF does not differentiate between types of perceived control, chronic pain researchers have specifically explored perceived control over pain, which is a multidimensional construct that refers to a person's beliefs about their ability to manage pain and its effect on one's life (Tan, Jensen, Robinson-Whelen, Thornby, & Monga, 2002; Vallerand, Crawley, Pieper, & Templin, 2016). In the chronic pain literature, Tan and colleagues (2002) have identified three dimensions of perceived control over pain: (1) beliefs about one's control over life in general; (2) beliefs about one's control over the impact of pain (and other symptoms) on daily life; and (3) beliefs about one's control over pain itself. Tan et al. (2002) also found that perceived control over life in general and perceived control over the effects of pain on one's life were more strongly associated with functioning than perceived control over pain itself. The results of this study suggest that perceived control over pain is a complex and multidimensional construct and that the relation between perceived control and HRQoL may vary based on the dimension being assessed. The findings also suggest that it may be important for

researchers to clearly define perceived control and to assess multiple dimensions of perceived control in their studies. Thus, the third aim of the proposed study is to explore the role of multiple dimensions of perceived control in the IITF. Perceived control over pain will be assessed in this study, as it captures perceived control in the way it is conceptualized in the IITF while also exploring additional dimensions that may be relevant in SCD. Specifically, the proposed study will examine whether the three dimensions of perceived control over pain mediate the association between illness intrusiveness and HRQoL. Furthermore, the study will compare the relative mediating effects of the different dimensions of perceived control.

If the aims of the study are met, the results may help to bridge the gap between multiple areas of research. First, researchers have found that HRQoL may be compromised in adults with SCD. The SCD experience is characterized by unpredictable pain and high rates of healthcare utilization, which are disease/treatment factors that are associated with poor HRQoL. Results from this study may provide additional support for a significant association between common SCD disease/treatment factors and HRQoL. Second, researchers have demonstrated that the overall SCD experience may be perceived as intrusive, as adults living with SCD experience severe pain and other health-related complications that impact daily activities, including education, employment, and social relationships (Brown, Weisbert, & Sledge, 2016; Edwards et al., 2005; Thomas & Taylor, 2002; While & Mullen, 2004). However, prior research has not examined the IITF in the context of SCD. The results of this study will extend the existing literature on the IITF and be an initial step towards determining whether illness intrusiveness helps explain the association between disease/treatment factors and HRQoL in this population.

Third, perceived control may be conceptualized as a unidimensional construct in the IITF, yet researchers examining perceived control over pain have described it as a multidimensional construct (Haythornthwaite, Menefee, Heinberg, & Clark, 1998; Tan et al., 2002; Vallerand et al., 2016). For the proposed study, perceived control over pain will be used in the model, because it assesses perceived control over life (as it appears to be defined in the IITF); perceived control over the effects of pain (and other symptoms) in one's life; and perceived control over pain itself. Overall, the proposed study has the potential to identify possible mechanisms that may explain poor HRQoL in adults living with SCD.

Chapter 2: Literature Review

Health-Related Quality of Life

The World Health Organization (WHO, 2014) defined health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (p. 1) and recommended that the measurement of health should include an estimation of well-being and not simply assessments of disease severity. Consequently, researchers began to acknowledge the importance of quality of life (QoL). QoL is a complex construct with varying definitions (Meeberg, 1993). According to the WHO (1995), QoL refers to "an individual's perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" (p. 1405). The CDC (2000) defined QoL as "an overall sense of well-being, including aspects of happiness and satisfaction with life as a whole" (p. 5). Although the definition and meaning of QoL varies by individual, community, and academic discipline, the consensus is that QoL is a broad and

conceptually complex construct that is affected by physical, psychological, cognitive, social, and community factors (CDC, 2000). While there are many domains of QoL, such as jobs, housing, school, and neighborhood, health is an area that has received a great deal of attention.

The concept of health-related quality of life (HRQoL) encompasses aspects of overall QoL that affect health. It is defined as a patient's appraisal of his/her well-being and level of functioning compared to their belief about what would be ideal (CDC, 2000; Megari, 2013; Panepinto & Bonner, 2012). HRQoL is a multidimensional construct that consists of three broad domains – physical, mental, and social – that are affected by an individual's disease and/or treatment factors (Megari, 2013). Some measures of HRQoL only include composite scores for physical and mental HRQoL with social functioning being a part of mental HRQoL (Ware & Sherbourne, 1992). For instance, the Short Form Health Survey (SF-36; Ware & Sherbourne, 1992) consists of eight subscales including physical functioning; bodily pain; role limitations due to physical problems; role limitations due to emotional problems; mental health; social functioning; vitality; and general health perceptions. These eight scale scores can be used to calculate physical health and mental health composite scores, which are the two broad domains.

Sickle Cell Disease

Sickle cell disease (SCD) refers to a group of genetic blood disorders that affect approximately 100,000 individuals in the United States (Hassell, 2010; Platt et al., 1994). Although SCD affects people from diverse racial and ethnic backgrounds, the disease primarily impacts people of African descent (Hassell, 2010). SCD is caused by a genetic mutation that produces an abnormal form of hemoglobin, which is a protein in red blood

cells that transports oxygen throughout the body (Ashley-Koch, Yang, & Olney, 2000). This anomalous hemoglobin generates sickle-shaped red blood cells that obstruct blood vessels and inhibit the flow of oxygen and vital nutrients throughout the body. Consequently, the disease affects multiple organ systems and contributes to increased morbidity and early mortality (Ashley-Koch, Yang, & Olney, 2000; Platt et al., 1994).

SCD is a collection of autosomal recessive genetic disorders, meaning those affected by the disease inherited a sickle gene from both parents (Ashley-Koch et al., 2000). Disease expression depends on the type of hemoglobin the individual inherited from his or her parents. The four most common types of SCD (i.e., genotypes) include: hemoglobin SS, hemoglobin SC, hemoglobin $S\beta^+$ (S beta plus) thalassemia, and hemoglobin $S\beta^0$ (S beta zero) thalassemia (Ballas, 2011). Hemoglobin SS (HbSS; sickle cell anemia) is the most common and often most severe form that occurs when an individual inherits two copies of the hemoglobin S variant. Hemoglobin $S\beta^0$ ($HbS\beta^0$) thalassemia is the most indistinguishable type from HbSS, as it is also characterized by severe symptoms. Individuals with $HbS\beta^0$ have one hemoglobin S gene plus one copy of the beta globin gene variant. Hemoglobin SC disease (HbSC) is the second most common type of SCD, and it occurs when a person inherits a hemoglobin S gene from one parent and a hemoglobin C gene from the other. This form of the disease is less severe than hemoglobin SS and $HbS\beta^0$. Another type of SCD is hemoglobin $S\beta^+$ ($HbS\beta^+$) thalassemia. Individuals with $HbS\beta^+$ have reduced levels of the beta globin gene, which leads to smaller red blood cells. Symptoms associated with $HbS\beta^+$ are less severe than the other types.

Individuals with SCD experience a wide range of physical symptoms and complications such as anemia, frequent infections, delayed growth, vision problems, stroke, leg ulcers, and organ damage (Platt et al., 1994). The hallmark symptom of the disease, however, is intermittent and unpredictable episodes of acute pain referred to as "pain crises." These pain episodes along with frequent healthcare utilization negatively affect sickle cell patients' HRQoL (Anie et al., 2002; Ballas et al., 2006; McClish et al., 2005).

Sickle Cell Disease and Health-Related Quality of Life

In the past decade, there has been an increase in the number of studies examining HRQoL in SCD. Researchers have found that SCD patients report lower HRQoL compared to both the general population (Anie et al., 2002; Ballas et al., 2006) and patients with other chronic health conditions such as arthritis, cystic fibrosis, and myocardial infarction (Ballas et al., 2006; McClish et al., 2005). Biological, psychological, and social factors that have been linked to HRQoL include age (Asnani et al., 2008; Dampier et al., 2011), sex (Dampier et al., 2011; Jackson et al., 2014), education (Ahmed et al., 2015; van Tuijn, Beers, Schnog, & Biemond, 2010), employment status (Ahmed et al., 2015; van Tuijn et al., 2010), pain (Anie et al., 2002; Ballas et al., 2006; McClish et al., 2005), fatigue (Ameringer, Elswick, & Smith, 2014), emergency department utilization (Ahmed et al., 2015; Aisiku et al., 2008; dos Santos Pereira et al., 2013), number and duration of hospitalizations (Jackson et al., 2014), number of comorbid conditions (Ahmed et al., 2015), occurrence of hip dysfunction (Malheiros, Lisle, Castelar, Sa, & Matos, 2015), somatization (Sogutlu, Levenson, McClish, Rosef, & Smith, 2011), and internal locus of control (Gibson et al., 2013).

Demographics

In a cross-sectional study, Dampier et al. (2002) evaluated the associations among age, sex, and HRQoL in a cohort of 1,046 patients from the Comprehensive Sickle Cell Centers (CSCC), which consists of 19 clinical sites across the United States. The SF-36 (Ware & Sherbourne, 1992) was used to assess HRQoL. Multiple linear regressions revealed that age was associated with all SF-36 scale scores except the mental health composite and subscale scores. Older participants reported lower scores on the physical composite score (β = -0.22), physical functioning (β = -0.25), role limitations due to physical problems (β = -0.19), bodily pain (β = -0.16), general health (β = -0.13), vitality (β = -0.07), social functioning (β = -0.12), and role limitations due to emotional problems (β = -0.17) scales. The authors also found that sex predicted physical functioning (β = -3.54), vitality (β = -3.33), and the physical composite (β = -1.87). Relative to males, females tended to report poorer physical health including lower physical functioning and vitality.

Ahmed and colleagues (2015) also conducted a cross-sectional study examining the relations between demographic variables and HRQoL (as assessed by the SF-36) among sickle cell patients (N = 652) in Saudi Arabia. In the sample, participants who were unemployed reported lower physical functioning and vitality compared to individuals who were employed. Patients with a university degree had better physical role functioning, vitality, emotional well-being, social functioning, and general health compared to those without a university degree. Multiple linear regressions indicated that employment status was related to vitality (b = 7.3) and pain (b = 6.8) even after adjusting for demographic and clinical characteristics. Individuals who were employed tended to

report better scores of vitality and pain. Additionally, education status predicted vitality (b = 5.3), role limitations due to physical problems (b = 10.9), and role limitations due to emotional problems (b = 13.9) after adjusting for demographic and clinical factors.

Asnani and colleagues (2008) conducted a cross-sectional study examining the association between demographic variables and HRQoL in a sample of 256 adults recruited from SCD clinics affiliated with a university medical center in Jamaica. They found that age was negatively correlated with the physical health composite score of the SF-36 (β = -0.31), such that as individuals increased in age, they were more likely to report poorer physical health. Furthermore, employment status was associated with the physical (β = 0.16) and mental (β = 0.14) health composite scores of the SF-36. Overall, participants who were employed tended to report better physical and mental health.

In another study, Jackson et al. (2014) examined correlates of HRQoL in adolescents and young adults living with SCD. Eighty-seven participants between the ages of 13 and 22 (M = 16.6, SD = 2.1 years) were recruited from a SCD adolescent clinic in the Midwest and asked to complete the pediatric quality of life inventory (PedsQL), which is a 23-item self-report measure of HRQoL that is appropriate for individuals over the age of 5. There are also adolescent and young adult versions, which were completed by participants over the age of 12. Results indicated that sex was associated with physical HRQoL (r = -0.27), but not psychosocial HRQoL. Being a girl or woman was correlated with poorer physical HRQoL.

Pain

The most prominent symptom of SCD is pain. Individuals with SCD experience varying types of pain, including both acute and chronic pain (Darbari, Ballas, & Clauw

2014). Episodes of acute, unpredictable pain, referred to as "pain crises," are the hallmark symptom of the disease (Platt et al., 1994). These painful events vary in frequency, severity, and duration (Darbari et al., 2014). Pain crises occur when sickled red blood cells obstruct blood vessels and block the flow of vital nutrients throughout the body (Ashley-Koch et al., 2000). This leads to secondary complications, such as acute chest syndrome, organ failure, and sudden death. In this population, acute pain is also the leading cause of scheduled and unscheduled visits to a physician's office, emergency department (ED) visits, and hospitalizations (Ballas & Lusardi, 2005).

Among adults with SCD, pain has been found to be correlated with HRQoL (Anie et al., 2002; Ballas et al., 2006; McClish et al., 2005). In a cross-sectional study, Anie and colleagues (2002) examined the association between pain and SF-36 subscales in patients living with SCD. The sample consisted of 96 adults (67% women) who were recruited from sickle cell outpatient clinics and local community-based clinics in London. Participants reported an average of 8.11 pain episodes and a mean pain duration of 155.0 hours during the past 12 months. Additionally, the average pain rating was 7.5 out of a possible 10, with 10 being indicative of pain as bad as it can be. Multiple regression revealed that pain (intensity, duration, frequency) was associated with four of the seven SF-36 domains (the pain scale was excluded from analysis): physical functioning, role limitations due to physical problems, social functioning, and general health perception, after controlling for age, sex, number of complications, and hemoglobin concentration. Pain accounted for between 7.1 and 10.5% of variance in the domains.

Hydroxyurea (HU) is a medication that increases fetal hemoglobin and decreases the frequency of pain crises in individuals with SCD (Agrawal, Patel, Shah, Nainiwal, &

Trivedi, 2014). In 2006, Ballas et al. conducted a prospective analysis of data from a double-blind randomized controlled trial that aimed to investigate the effects of HU on pain crises. In this particular study, the investigators also examined the association between pain and HRQoL. Participants were 277 adults with sickle cell anemia who were enrolled in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), a large-scale project in which individuals were recruited from 21 sites in the United States and Canada. The researchers randomly assigned participants to the treatment or placebo group and collected data at baseline and every six months for up to two years. The SF-36 was administered at baseline and two weeks later; the mean of these two scores was used as the measure of baseline HRQoL. Participants reported the number of pain crises they had experienced in the past 12 months and completed daily pain diaries that assessed pain severity, use of analgesics, and healthcare utilization. The investigators found no difference in the SF-36 scale scores between the treatment group and the placebo group. However, when the researchers differentiated between participants who had a high (in the upper half in percentage of fetal hemoglobin change) versus low response to HU, they discovered that those who had a high response to HU reported better "general health now" and general health perception compared to the placebo group and participants who had a low response to HU. Results of multivariate generalized estimating equations (GEE) model revealed that having a high response to HU predicted general health now as compared to a year ago, social functioning, pain, and general health perception at two-year follow-up. Baseline daily pain severity was predictive of general health now and for six of the eight SF-36 scales: social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, vitality, and pain at

follow-up. Additionally, number of reported pain crises at baseline predicted general health now, role limitations due to physical functioning, pain, and general health perception. Lastly, based on generalized estimating equations, baseline HRQoL predicted HRQoL at two-year follow-up. The results of this study suggest that both pain severity and frequent pain crises may negatively impact HRQoL. Furthermore, a high response to HU may reduce pain frequency and subsequently have a positive influence on HRQoL.

In Brazil, dos Santos Pereira, Brener, Cardoso, & Proietti (2013) compared HRQoL scores between participants who had and had not experienced a pain crisis in the past month. Four hundred men and women receiving treatment at a SCD clinic completed the World Health Organization Quality of Life - BREF (WHOQOL-BREF), and the researchers obtained healthcare data from their medical records. A series of independent samples *t*-tests were used for the analyses. The authors found that there was a significant difference in HRQoL between patients who had experienced a pain crisis in the past month versus those who had not. For individuals with HbSS, those who had a pain crisis during the past month reported significantly lower scores on the physical (M = 53.6) and general (M = 62.5) quality of life domains compared to individuals who had not had a pain crisis (Ms = 64.3 and 75.0, respectively). As for HbSC patients, individuals who had a pain crisis indicated lower scores on the physical (M = 53.6), social relations (M = 66.7), environmental (M = 46.9), and general (M = 62.5) quality of life domains compared to participants who had not had a pain crisis (Ms = 71.4, 75.0, 54.7, and 75.0, respectively).

Fatigue

Fatigue is defined as “an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's ability to carry out daily activities, including the ability to work effectively and to function at one's usual level in family or social roles” (Ameringer et al., 2014, p. 6-7). Researchers have only recently begun to identify fatigue as a potentially important symptom of SCD. In a review, Ameringer and Smith (2011) indicated that numerous biological and behavioral factors likely contribute to fatigue in SCD, since the disease is characterized by anemia and other factors (e.g., increased levels of stress, depression, and anxiety) that have been found to be associated with fatigue in other chronic health conditions.

Although sickle cell patients may be at risk for fatigue, few studies have examined fatigue in this patient population (Ameringer et al., 2014; Ameringer & Smith, 2011; While & Mullen, 2004). While and Mullen (2004) conducted semi-structured interviews to explore the experience of transitioning from pediatric to adult care for eleven adolescents with SCD who were recruited from a community-based sickle cell clinic in the United Kingdom. Seven of the eleven participants reported that they experienced periods of tiredness and fatigue (While & Mullen, 2004). One participant wrote, “I feel all right but I don’t feel as though I have energy to do any work-related activities. I feel most tired and don’t want to do much” (While & Mullen, 2004, p. 322).

In another study, Ameringer et al. (2014) described fatigue and examined its relationship with HRQoL among 60 adolescents and young adults with SCD who were between the ages of 15 and 30 (M = 22.5, SD = 4.1). The SF-36 was used to assess HRQoL, and fatigue was measured with three instruments including the

Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF), the Brief Fatigue Inventory (BFI), and the PROMIS Fatigue Short Form (PROMIS). In this sample, 69% of the participants reported feeling "unusually tired or fatigued" in the past week. Based on the BFI and the PROMIS, average fatigue scores were moderate to severe, whereas average fatigue as assessed by the MFSI-SF was mild to moderate. The MFSI-SF consists of five subscales (general fatigue, physical fatigue, emotional fatigue, mental fatigue, vigor); the authors provided the mean (standard deviation) of each subscale: general fatigue 9.13 (5.7); physical fatigue 6.83 (5.6); emotional fatigue 4.75 (4.8); mental fatigue 5.52 (4.9); and vigor 11.35 (5.4). With higher scores indicating more fatigue, the authors found that scores were higher for the vigor and general subscales and lowest on the physical fatigue subscale. Additionally, all three fatigue scales were negatively associated with all subscales of the SF-36. The correlations ranged from r = -.34 to -.74. This suggests that as fatigue increases, individuals report worse HRQoL and that there is a moderate to strong relationship between the two constructs.

In adults with SCD, researchers have not systematically measured fatigue, except by use of the vitality subscale of the SF-36. In the studies reporting the SF-36 vitality scale, adult sickle cell patients reported more fatigue than both the general population (McClish et al., 2005) and individuals with other chronic health conditions, such as hemochromatosis, asthma, cystic fibrosis, and those receiving hemodialysis (Anie et al., 2002). While there is limited research in this area, the evidence suggests that it may be important for SCD investigators to further evaluate fatigue and its impact on HRQoL.

Healthcare Utilization

Most sickle cell patients manage their pain at home; however, a subgroup of the population frequently utilizes healthcare services (Carroll et al., 2009; Smith et al., 2008). This group of high utilizers are more like to be younger, male, have SCD-related complications, have parents who completed postsecondary education, and have a family history of psychological disorders compared to low utilizers of healthcare services (Carroll et al., 2009; Carroll et al., 2013; Epstein, Yuen, Samir, Ballas, & Moleski, 2006; McClish et al., 2006). They are also disproportionately African American, homeless, and receive benefits from Medicaid (Mandelberg, Kuhn, & Kohn, 2000). Glassberg and colleagues (2013) found that ED providers harbor negative attitudes towards SCD patients and provide lower quality of care for this population (e.g., lower adherence to national guidelines about use of opioids for sickle cell disease-related acute pain episodes). Furthermore, in a qualitative study, a sample of sickle cell patients with a wide range of healthcare utilization reported that they detest and avoid being admitted to hospitals (Jenerette, Brewer, & Ataga, 2014). In view of the negative experiences associated with ED visits and the disruption these visits may cause in sickle cell patients' daily activities, it is not surprising that frequent healthcare utilization has been linked to lower HRQoL (Aisiku et al., 2008; Jackson et al., 2014).

In a cross-sectional study that consisted of 308 SCD patients receiving treatment at a hematology outpatient clinic in Saudi Arabia, Ahmed and colleagues (2016) examined the association between number of ED visits in the past 12 months and HRQoL (assessed by the SF-36). They found that the number of ED visits was negatively correlated with all domains of the SF-36, except mental health. As number of ED visits

increased, participants indicated worse physical functioning (*b* = -0.007), social functioning (*b* = -0.006), and general health (*b* = -0.018) as well as more pain (*b* = -0.008), role limitations due to physical problems (*b* = -0.006), and role limitations due to emotional problems (*b* = -0.004). After adjusting for several factors such as demographics, disease symptoms, the presence of a chronic disease other than SCD, exercise, BMI, and family support, general health (*b* = -0.014) was the only domain significantly associated with ED visits. This suggests that the relationship between ED visits and HRQoL could be driven, at least in part, by disease severity and other psychosocial factors.

Aisiku and colleagues (2008) conducted a cross-sectional analysis using data from the Pain in Sickle Cell Epidemiology Study (PiSCES), a longitudinal study of pain and its correlates in SCD. Specifically, Aisiku et al. evaluated differences in HRQoL between high utilizers (self-reported three or more visits per year) and low utilizers of ED services. Participants were 308 SCD patients aged 16 or older who were recruited from a variety of networks (e.g., clinics, hospitals, community centers) in Virginia. In the study, number of ED visits ranged from 0 to 125, and 35% of the participants were classified as high utilizers. Wilcoxon rank sum test revealed that individuals who were high ED utilizers, as compared to the low utilizers, reported lower physical functioning (*M*s = 36.0 and 48.1), but not psychological functioning (*M*s = 45.8 and 48.1).

In another cross-sectional study, dos Santos Pereira et al. (2013) evaluated whether there was a difference in HRQoL between SCD patients who had and had not been hospitalized in the past year. Participants were 400 adults who were recruited from a SCD clinic in Brazil. The men and women completed the WHOQOL-BREF, and the

researchers collected information about hospitalizations from the participants' medical records. Results of independent samples *t*-test revealed that there was a significant difference in HRQoL between patients who were hospitalized in the past year compared those who were not. For HbSS patients, those who were hospitalized reported lower scores on the physical (*M* = 57.1), psychological (*M* = 66.7), environmental (*M* = 50.0), and general quality of life domains of the WHOQOL-BREF compared to individuals who were not hospitalized (*M*s = 62.5, 70.8, and 56.3, respectively). As for patients with HbSC, those who were hospitalized indicated lower scores on the physical domain (*M* = 53.6) compared to those who were not hospitalized (*M* = 64.3).

Jackson et al. (2014) examined the association between healthcare utilization (hospitalization, duration of hospitalizations, and ED visits) and HRQoL in a sample of 87 patients aged 13 to 22 (*M* = 16.6, *SD* = 2.1). These patients were recruited from an SCD adolescent clinic in the Midwest and were assessed using the Pediatric Quality of Life Inventory (PEDQL). They found that number of hospitalizations, the duration (in hours) of hospital visits, and the number of ED visits in the past six months were negatively associated with physical HRQoL, but not psychosocial HRQoL. As the number of hospitalizations (*r* = -.25), the length of stay at the hospital (*r* = -.23), and the number of ED visits (*r* = -.24) increased, participants reported lower levels of physical HRQoL. These results suggest that healthcare utilization is negatively associated with HRQoL, but healthcare utilization may be more strongly related to physical aspects of HRQoL compared to psychological components.

Overall Impact of Sickle Cell Disease

Adults with SCD experience severe pain and other health-related complications that interfere with daily activities, including education, employment, and social relationships (Edwards et al., 2005; Thomas & Taylor, 2002; While & Mullen, 2004). The unemployment rate in this population is high, with estimates ranging from 40 to 60% (Abrams, Phillips, & Whitworth, 1994; Bediako, Lavender, & Yasin, 2007; Gil et al., 2004). In fact, sickle cell patients are more likely to be unemployed compared to their same-race counterparts (Farber, Koshy, & Kinney, 1985). Consequently, adults with SCD experience financial hardships that interfere with their ability to meet basic needs and to provide for their families (Barbarin, Whiten, Bond, & Conner-Warren, 1999).

In a prospective study, Gil and colleagues (2004) examined the relation between SCD pain and work activity on the same and subsequent days. Forty-one SCD patients were recruited from a SCD clinic affiliated with a university in the Southeastern United States. Participants rated their daily pain for up to six months and indicated whether they missed work due to pain. Multilevel model analysis indicated that pain was positively associated with a reduction in same-day work attendance ($\beta = 0.06$) among participants who were employed. This suggests that the disease disrupts involvement in work-related activities for adults living with SCD.

SCD also leads to disruptions in social roles and contributes to strained relationships, including marital dysfunction (Brown, Weisberg, & Sledge, 2016; Edwards et al., 2005). In a cross-sectional study, Gil et al. (1992) examined the relation between pain frequency and reductions in social, work, and household activities among 89 patients with SCD who were recruited from a university-affiliated SCD center in the Southeastern

United States. Reduction in social activity was assessed by asking participants to indicate how much they decrease involvement in activities during a pain episode, with options ranging from 0% (do not cut back at all) to 100% (cut back completely). Multilevel linear regressions revealed that pain frequency was predictive of reduction in social activities (β = -0.71). As the number of pain episodes increased, individuals reported a higher percentage of reduced activity in social activities. Interestingly, pain frequency was not significantly associated with work and household activities in this sample.

As a part of a large multi-center randomized control trial, researchers conducted eight one-hour, non-directive focus groups with SCD patients who were aged 15 to 35 years old (M = 25.7) (Thomas & Taylor, 2002). The adolescents and young adults indicated that disease-related factors, such as unpredictable pain and frequent hospitalizations, disrupted participation in activities including school and work. Participants also felt that others did not fully understand their experience. This lack of understanding seemed to exacerbate the negative impact of the disease and contributed to strained social and romantic relationships. They also expressed negative and pessimistic thoughts about their future. This is consistent with other research that shows that individuals with SCD frequently report emotional distress, high rates of mood disorders (e.g., depression and anxiety), and poor psychosocial functioning (Alao, Dewan, Jindal, & Effron, 2003; Dampier et al., 2011; Edwards et al., 2009; Levenson et al., 2008).

Summary

Investigators have found that several SCD-related factors – namely pain, fatigue, and ED utilization – are associated with HRQoL. Additionally, there is some evidence that the disease experience interferes with valued activities, such as employment and

social relationships. I did not find any studies that have examined mechanisms that might explain the association between disease/treatment factors and HRQoL in SCD. Illness intrusiveness (i.e., disruptions in a person's lifestyle and interests as result of disease and/or treatment factors) is a well-studied construct that likely captures disease interference described by sickle cell patients and may also help clarify the link between disease/treatment factors and HRQoL in this patient population (Devins, 2010).

Illness Intrusiveness and the Illness Intrusiveness Theoretical Framework

Illness intrusiveness is defined as the extent to which features of a disease and/or accompanying treatment factors interfere with one's involvement in valued activities (Devins et al., 1983). This construct has been found to be correlated with HRQoL (Devins, 2010). Additionally, illness intrusiveness has helped explain the association between disease/treatment factors and HRQoL in adults with cancer, end stage renal disease (ESRD), and multiple sclerosis (MS; Bloom et al., 1998; Devins, 1990; Shawaryn et al., 2002).

Devins (1983) developed the illness intrusiveness theoretical framework (IITF) to examine disruptions in daily activities among adults with ESRD and later applied the theoretical framework to other chronic illnesses, such as cancer and MS (Devins et al., 2013; Devins, Bezjak, Mah, Loblaw, & Gotowiec, 2006; Edelstein, Coate, Massey, Jewitt, Mason, & Devins, 2016; Devins, Seland, Klein, Edworthy, & Saary, 1993; Devins, Styra, O'Connor, Gray, Seland, Klein, & Shapiro, 1996). According to the IITF (Figure 1), individuals with chronic illnesses experience a cluster of physical symptoms along with invasive, time-consuming treatments that disrupt participation in valued activities, such as living a healthy lifestyle, maintaining a rewarding job, and developing

strong relationships with friends and family. The theoretical framework also posits that illness intrusiveness compromises HRQoL by: (1) reducing the positive reinforcement that individuals experience when engaging in valued activities; and (2) reducing perceived control (belief that one can influence outcomes in important life domains) by limiting an individual's ability to obtain positive outcomes or to avoid negative ones. That is, a combination of disease and treatment factors indirectly compromise subjective well-being and contribute to emotional distress by disrupting participation in lifestyles, interests, and meaningful activities.

Disease Factors

Disease factors contribute to illness intrusiveness (Devins, 2010). Some disease factors that have been found to be associated with illness intrusiveness include: pain, fatigue, disability status, number of symptoms, and disease severity (Bloom et al.,1998; Dancey & Friend, 2008; Devins, 1990; Edelstein et al., 2016; Goudsmit, Stouten, & Howes, 2009; Hundt, Bensadon, Stanley, Petersen, Kunik, Kauth, & Cully, 2015; Snyder, Foley, Farrell, Beier, & Zemon, 2013). Pain and fatigue are two commonly cited correlates of illness intrusiveness.

Devins (1990) evaluated whether there was a difference in illness intrusiveness between ESRD patients who experienced pain compared to those who did not experience pain during a 2-week interval. The sample consisted of 100 ESRD patients receiving dialysis at a center in Canada. Illness intrusiveness was assessed using the Illness Intrusiveness Rating Scale (IIRS; Devins et al., 1983), which measures level of intrusiveness in 13 life domains including health, diet, work, active recreation, passive recreation, financial situation, relationship with partner, sex life, family relations, other

social relations, self-improvement/self-expression, religious expression, and community and civic involvements. The authors found that there was a significant difference in illness intrusiveness between patients who experienced pain and those who did not. Patients who experienced pain reported higher levels of illness intrusiveness.

In another study, Bloom and colleagues (1998) tested the IITF in 307 young women with breast cancer using data from a larger project called Breast Cancer in Young Women. For this project, women who were aged 50 and under were recruited through a registry in the Western United States. The researchers found that pain (higher scores indicate a better health state) was negatively correlated with illness intrusiveness (r = -.40), meaning individuals who reported a better health state (i.e., less pain) experienced less illness intrusiveness.

Fatigue has also been linked to illness intrusiveness. Shawaryn et al. (2002) explored the relation between fatigue and illness intrusiveness among 90 adults with MS. In the study, fatigue was assessed by the Modified Fatigue Impact Scale (MFIS). The authors found that fatigue was positively associated with illness intrusiveness (r = .71). Individuals who experienced higher levels of fatigue felt that the disease interfered with important life domains.

Researchers have also examined the association between fatigue and illness intrusiveness in 24 patients with chronic fatigue syndrome who were recruited from a local patient support group in South London. The Profile of Fatigue-Related Symptoms (PFRS) was used as a measure of fatigue severity. Correlation analysis indicated that fatigue was positively associated with illness intrusiveness (r = .47) in this sample

(Goudsmit et al., 2009). Collectively, these results illustrate that individuals who experience more pain and fatigue report greater illness intrusiveness.

Treatment Factors

Treatment factors are another major contributor to illness intrusiveness, as individuals with chronic health conditions often undergo treatments that require them to miss or reschedule daily activities (Devins, 2010). Researchers have found that treatment factors, such as negative side effects, treatment modality, and the time required for attending treatment are associated with greater perceived interference in activities (Devins et al., 1983; 1990). Conversely, the amelioration of the disease by use of medical and psychological interventions is associated with less illness intrusiveness (Burns et al., 2004; Poochikian-Sarkissian et al., 2008a; Poochikian-Sarkissian, Sikani, Wennberg, & Devins, 2008b; Zhang, Strauss, & Siminoff, 2006).

In Canada, Devins and colleagues (1983) compared illness intrusiveness in ESRD patients receiving different treatment modalities including hemodialysis ($N = 35$), continuous peritoneal dialysis ($N = 10$), or successful renal transplantation ($N = 25$). The authors found that there was a significant difference in self-reported illness intrusiveness depending on treatment modality. Individuals who received renal transplant ($M = 27.7$) indicated that ESRD and its treatment was significantly less intrusive than those receiving hemodialysis and continuous peritoneal dialysis collectively ($M = 33.3$), $t(68) = 1.92$, $p < .05$.

Poochikian- Sarkissian and colleagues (2008a) compared pharmacological and surgical treatment for epilepsy. One hundred forty-five adults were in one of three groups: (1) post-surgical patients who had good seizure control ($N = 52$); (2) patients who

received pharmacological treatment and had moderate seizure control (N = 53); and (3) patients who were recently admitted to an epilepsy unit, had not received continuous pharmacological or surgical treatment, and had poor seizure control (N = 40). Post-surgical patients were more likely to be seizure-free and to experience fewer seizures during the past year compared to the other groups, $F(2, 142) = 11.44$, $p < .001$. This group also reported less illness intrusiveness. After controlling for employment status and seizure frequency, there was no longer a significant difference in illness intrusiveness between the groups, $F(2, 140) = 1.47$, $p = .233$, suggesting that treatment-related differences in illness intrusiveness was attributed to seizure control. Surgery contributed to better seizure control; therefore, patients who received this treatment modality perceived less interference in daily activities. In sum, these results suggest that treatment that is time-consuming and leads to more restrictions is often perceived as more intrusive. Treatment that leads to a major improvement in symptoms is typically viewed as less intrusive.

Psychological, Social, and Contextual Factors

Psychological (e.g., coping, personality, developmental stage), social (e.g., stigma, culture, social support), and contextual (e.g., age, sex, socioeconomic status, stressful life events) factors are also important and provide the context in which an individual experiences the disease (Devins, 2010). This means that individuals may have similar disease and treatment factors but report different levels of illness intrusiveness. Similarly, people who report the same level of illness intrusiveness may perceive themselves as having a different level of HRQoL. According to the IITF, there will be individual differences because a person's background influences their perception. Some

factors, such as sex and age, are present prior to the onset of the disease and moderate the impact of disease/treatment factors on illness intrusiveness. Other factors (e.g., stigma and disfigurement) are consequences of the disease and moderate the impact of illness intrusiveness on HRQoL. Furthermore, the illness intrusiveness theoretical framework acknowledges that psychological, social, and contextual factors are independently related to HRQoL.

Illness Intrusiveness as a Mediator

Research indicates that disease/treatment factors are related to both illness intrusiveness and HRQoL and that illness intrusiveness is negatively associated with HRQoL in chronic health conditions such as asthma, cancer, ESRD, and MS (Bloom et al., 1998; Devins et al., 2006; Hullmann, Eddington, Molzon, & Mullins, 2013; Shawaryn et al., 2002; Sohl, Levin, Case, Danhauer, & Avis, 2014). In a cross-sectional study, Hullmann and colleagues (2013) examined the association between illness intrusiveness and HRQoL in adolescents and young adults with allergies (n = 74) and asthma (n = 74). The IIRS was used to assess illness intrusiveness and the SF-36 was used to measure HRQoL. Results revealed that illness intrusiveness was negatively correlated with the mental component (r = -.28) and physical component (r = -.47) of the SF-36 in individuals with allergies. Additionally, illness intrusiveness was negatively associated with mental (r = -.40) and physical (r = -.71) HRQoL in adolescents and young adults with asthma. In another cross-sectional study, Shawaryn et al. (2002) examined the relationship between illness intrusiveness and HRQoL in a sample of 90 adults with MS. The IIRS and the SF-36 were used to assess illness intrusiveness and HRQOL,

respectively. Illness intrusiveness was inversely associated with the physical (r = -.56) and mental (r = -.47) components of the SF-36.

The central hypothesis of the illness intrusiveness theoretical framework is that illness intrusiveness mediates the association between disease/treatment factors and HRQoL. There is some evidence to support this central hypothesis (Bloom et al., 1998; Devins et al., 1990; Shawaryn et al., 2002). Shawaryn et al. (2002) further examined the role of illness intrusiveness among 90 adults with MS. Hierarchical linear regression revealed that disability status (i.e., a disease factor) was significantly associated with physical aspects of HRQoL (β = -0.62). However, when illness intrusiveness was entered in the model, the association between disability status and HRQoL was significantly reduced (β = -0.19). The results indicated that illness intrusiveness mediated the association between disability status and HRQoL in MS.

Summary

The illness intrusiveness theoretical framework has been used to explain the association between disease/treatment factors and HRQoL. Researchers have found that disease factors, such as higher levels of pain and fatigue, are associated with greater illness intrusiveness. Additionally, greater illness intrusiveness is linked to lower HRQoL. The IITF posits that illness intrusiveness compromises HRQoL by reducing a person's involvement in valued activities and their perceived control. This hypothesis has been partially examined in studies that test whether illness intrusiveness mediates the association between disease/treatment and HRQoL. However, few studies have examined the role of perceived control.

Perceived Control

Perceived control is defined as "the belief that one can determine one's own internal states and behavior, influence one's environment, and/or bring about desired outcomes" (Wallston, Wallston, Smith, & Dobbins, 1987, p. 5). In the IITF, perceived control is hypothesized to be a mediator between illness intrusiveness and HRQoL (Devins et al., 2010). According to the theoretical frameworks, individuals who experience a disruption in meaningful activities may perceive themselves as having minimum control over their life.

Devins and colleagues (1983) conducted a cross-sectional study examining the relations among perceived control, illness intrusiveness, and well-being in 70 patients with ESRD in Canada. Illness intrusiveness was measured by the IIRS, and perceived control was assessed by the Control Rating Scale (CRS), which is a measure that asks participants to rate "how much control" they have over the same 13 life domains included in the IIRS (e.g., health, relationship with partner, social relations, and community and civic involvements). Well-being was derived by a principal component analysis (PCA) using nine measures such as the Beck Depression Inventory (BDI) and the Profile of Mood States (POMS). The authors found that perceived control was significantly correlated with illness intrusiveness (r = -.25) and well-being (r = .23). As perceived control decreased, illness intrusiveness increased, and well-being decreased.

In another cross-sectional study, Devins et al. (1993) evaluated the associations among perceived control, illness intrusiveness, and psychosocial well-being in a sample of 94 MS patients in Canada. The researchers assessed perceived control and illness intrusiveness using the CRS and IIRS, respectively. Five measures (e.g., CES-D, POMS)

were reduced to a single factor of psychosocial well-being using PCA. Results indicated that perceived control was negatively associated with illness intrusiveness (r = -.46) and positively associated with wellbeing (r = .40) in this sample.

Poochikian-Sarkissian et al. (2008a) explored the correlations among perceived control, illness intrusiveness, and HRQoL in 145 patients with epilepsy. Perceived control and illness intrusiveness were assessed by the CRS and IIRS, respectively. The researchers assessed for both general well-being and epilepsy-specific HRQoL. General well-being was assessed by four measures including the CES-D, the Atkinson Life Happiness Rating Scale, the Affect Balance Scale, and the Rosen Self-Esteem Inventory. The Quality of Life in Epilepsy (QOLIE) Scale was used for the measure of disease-specific HRQoL. In the sample, perceived control was negatively associated with illness intrusiveness (r = -.45) and positively associated with HRQoL (r = .56), even after adjusting for employment status and seizure frequency (Poochikian-Sarkissian et al, 2008a). Furthermore, path analysis revealed that personal control over life domains mediated the association between illness intrusiveness and HRQoL in this sample.

While the authors of these three studies utilized the Controls Rating Scale, other researchers have used alternative measures of perceived control. This is likely attributed to limited information about the Control Rating Scale as Devins et al. (1983) did not provide a complete description of the instrument (e.g., the numerical scale is not provided). Subsequently, the few researchers who have examined the role of perceived control in the context of the IITF have used instruments, such as the Multidimensional Health Locus of Control Scale Form C (MHLC) and the Chronic Disease Self-Efficacy (CDSE) questionnaire (Hundt et al., 2015; Paukert, LeMaire, & Cully, 2009). These are

measures that assess locus of control and self-efficacy. The following section includes a description of the relationships among perceived control, locus of control, and self-efficacy. Specifically, this section explains how locus of control and self-efficacy are related, but distinct, constructs that assess different dimensions of perceived control.

Locus of Control

Locus of control refers to the extent to which a person believes outcomes are contingent upon his/her own behaviors (internal control) or outside forces, such as chance or powerful others (external control) (Rotter, 1966). Researchers have examined general locus of control, health-related locus of control, and illness-specific locus of control (e.g., Headache-Specific LOC) (Martin, Holroyd, & Penzien, 1990; Rotter, 1966; Wallston, Stein, & Smith, 1994).

Self-Efficacy

Self-efficacy, a component of social learning theory, refers to one's perceived capacity to perform specific actions that will result in a desired outcome (Bandura, 1977). Self-efficacy focuses on an individual's convictions that they can exercise control over their motivations, behaviors, and social environments. Self-efficacy is not static, but instead, varies by situation and context. Thus, measures of self-efficacy are typically domain-specific (e.g., coping self-efficacy and exercise self-efficacy).

Relation Between Locus of Control and Self-Efficacy

Locus of control and self-efficacy are constructs that are commonly used to assess perceived control in the illness intrusiveness literature and other research areas (Bishop et al., 2008; DeCoster et al., 2008; Paukert et al., 2009; Wallston et al., 1987). While these

concepts are related, they are distinct and differ regarding the object of control (Wallston et al., 1987). The object of control that is being assessed by locus of control is the outcome, whereas the object of control being assessed by self-efficacy is one's behavior. Subsequently, locus of control and self-efficacy assess different dimensions of perceived control.

Locus of Control and Self-Efficacy as Measures of Perceived Control Within the Illness Intrusiveness Theoretical Framework

In a cross-sectional study, Paukert and colleagues (2009) examined the relations among illness intrusiveness, health locus of control, chronic disease self-efficacy, anxious symptoms and depressive symptoms in 104 Veterans with heart failure, half of whom had significant levels of anxiety and/or depression. Participants were recruited from a large VA hospital through the Outpatient Care File and Patient Treatment File databases of the Veterans Health Administration. Perceived control was assessed using the CDSE and the MHLC. Correlation analyses indicated that illness intrusiveness was negatively associated with SE (r = -.36) and anxious symptoms (r = -.20), but positively associated with symptoms of depression (r = .36). Chance locus of control – one of the subscales of the MHLC – was positively associated with depressive symptoms (r = .23). SE was negatively associated with depressive (r = -.37) and anxious symptoms (r = -.27). Hierarchical regressions revealed that chance locus of control continued to be positively associated with depressive symptoms (β = 0.24) after adjusting for physical limitations, intrusiveness, coping, and CDSE. Conversely, there was no longer a significant association between CDSE and depressive symptoms.

In a similar study, Hundt and colleagues (2015) examined the association between illness intrusiveness and perceived control in sample of adults with cardiopulmonary disease. Participants were recruited from two large VA hospitals and asked to complete self-report questionnaires including the MHLC. Correlation analysis indicated that illness intrusiveness was negatively associated with the internal locus of control subscale of the MHLC (r = -.21). That is, individuals who perceived their disease as intrusive tended to feel less confidence in their ability to control outcomes.

Using correlational data, DeCoster and colleagues (2013) tested the IITF in 147 older adults aged 60 years or older who had been diagnosed with type II diabetes. The authors recruited participants from senior activity centers in the Central and Delta regions of Arkansas. The Diabetes Self-Efficacy (DSE) and Diabetes Outcome Expectations (DOE) questionnaires were used to measure perceived control in the model. Greater illness intrusiveness was associated with less perceived control (b = 0.49) and poorer well-being (b = 0.62). Additionally, perceived control was positively correlated with well-being. Results from structural equation modeling indicated that perceived control mediated the association between illness intrusiveness and well-being.

Bishop et al. (2008) conducted a cross-sectional analysis using data from a larger multiphase longitudinal project. Specifically, the authors evaluated the IITF in the context of MS. Participants were 157 adults with MS who were randomly selected from mailing lists of two chapters of the National Multiple Sclerosis Society (NMSS) in the Southeastern United States. In the study, the investigators used the impact and control subscales of the Disability Centrality Scale (DCS) to assess illness-related impact (i.e., illness intrusiveness) and perceived control in MS, respectively. Mediation analysis

revealed that perceived control mediated the association between illness intrusiveness and QoL.

Perceived Control and Sickle Cell Disease

In the SCD literature, perceived control has also been assessed using locus of control and self-efficacy questionnaires. In one cross-sectional study, Gibson et al. (2013) evaluated the association between locus of control, depression, and HRQoL in 143 adults living with SCD. Participants were recruited from a university-affiliated sickle cell unit in Kingston, Jamaica and asked to complete self-report measures including the MHLC, the BDI, and the SF-36. Multiple regressions indicated that the internal locus of control scale was positively associated with HRQoL ($\beta = 0.60$), even after adjusting for demographic and disease-related variables. This finding suggests that individuals who believe that outcomes are contingent upon their own behaviors, as opposed to chance or people of power, are more likely to report better functioning.

In SCD, researchers have explored sickle cell self-efficacy or personal judgements about one's ability to cope with and manage SCD (Edwards et al., 2000; 2001). In the development of the Sickle Cell Self-Efficacy Scale (SCSES), Edwards and colleagues (2000) demonstrated convergent validity by evaluating the relation between the instrument and related constructs including the internal locus of control subscale of the MHLC. They found that the SCSES was positively associated with the internal locus of control scale ($r = 0.41$). The authors concluded that self-efficacy and internal locus of control are conceptually and empirically related. However, the self-efficacy is different from internal locus of control as self-efficacy is a "situation-specific behavioral determination" (Edwards et al., 2000, p. 958) rather than a personality trait. Additionally,

researchers have referred to sickle cell self-efficacy as the belief that one has control over disease symptomatology and may cope more effectively with their condition. These findings are consistent with previous research that suggests that self-efficacy and locus of control are related, yet different dimensions of perceived control. The following section will describe studies that have examined the relation between self-efficacy and HRQoL in adults with SCD.

Clay and Telfair (2007) conducted a cross-sectional analysis of data from the Multi-Site Study of Transition to Adult Care for Adolescents with SCD. The purpose of the study was to examine the relations among self-efficacy, physical symptoms, and psychological symptoms in 131 adolescents living with SCD. They found that sickle cell self-efficacy was significantly associated with physical (β = -0.29), psychological (β = -0.21), and total symptoms (β = -0.27), even after adjusting for demographic variables. As patients' confidence in their ability to management SCD symptoms increased, they reported fewer physical and psychological symptoms such as pain, shortness of breath, and feelings of sadness.

Using a prospective design, Edwards and colleagues (2001) examined the relations among sickle cell self-efficacy and four dependent variables including number of physician visits in the past 12 months, pain severity, physical symptoms, and psychological symptoms. Participants were 147 SCD patients who were recruited from a regional Sickle Cell Association in the Southeastern United States. Results revealed that sickle cell self-efficacy measured at baseline was significantly associated with the number of physician visits in the past 12 months (r = -.30), pain severity (r = -.30), physical symptoms (r = -.40), and psychological symptoms (r = -.38). Greater self-

efficacy was correlated with fewer physical and psychological symptoms, less pain severity, and fewer physician visits. The researchers also found that self-efficacy measured at one-year follow-up was significantly associated with three of the four dependent variables – pain (r = -.42), physical symptoms (r = -.42), and psychological symptoms (r = -.53). As self-efficacy increased, participants reported fewer physical and psychological symptoms and less severe pain. Multiple regression was conducted to examine the association between self-efficacy and changes in the dependent measures from baseline to one-year follow-up. The authors were interested in whether baseline levels of self-efficacy could predict future changes in sickle cell symptomatology and healthcare utilization and whether changes in self-efficacy over a year were independently associated with changes in the adjustment variables. Baseline self-efficacy scores were negatively associated with changes in physical symptoms (β = -0.34), psychological symptoms (β =-0.49), and pain severity (β = -0.39) over the one-year study period. Higher base-line self-efficacy was associated with decreases in physical symptoms, psychological symptoms, and pain severity as assessed one year later. In addition, changes in self-efficacy were independently and inversely associated with changes in physical symptoms (β = -0.30), psychological symptoms (β = -0.40), and pain (β = -0.39). These results suggest that as sickle cell patients experience more disease-related symptoms and require more medical attention that may disrupt participation in meaningful activities, they report lower levels of self-efficacy.

Perceived Control Over Pain

Pain is the hallmark symptom of SCD (Platt et al., 1994). As such, it may be important to consider SCD patients' perceptions of their ability to manage their pain

and/or its effect on their lives. Although the IITF does not differentiate between types of perceived control, chronic pain researchers have specifically explored perceived control over pain, which is a multidimensional construct that refers to beliefs that an individual has about the ability and resources to manage pain and its effect on one's life (Tan et al., 2002; Vallerand et al., 2016).

In the chronic pain literature, investigators use different approaches and instruments to assess perceived control over pain. Using cross-sectional data collected from 252 non-cancerous chronic pain patients receiving treatment at a VA hospital, Tan and colleagues (2002) conducted a study to determine the number of factors or dimensions embedded in multiple measures of control. In the study, Tan and colleagues (2002) measured perceived control in chronic pain using the Control scale of the Survey of Pain Attitudes (SOPA); the Arthritis Self-Efficacy Scale; and the Life Control scale of the West Haven-Yale Multidimensional Pain Inventory (WHYMPI). Results of exploratory factor analysis indicated three primary dimensions of perceived control over pain: (1) beliefs about one's control over life in general; (2) beliefs about one's control over the impact of pain (and other symptoms) on daily life; and (3) beliefs about one's control over pain itself (Tan et al., 2002). The perceived control over life dimension consisted of items from the WHYMPI Life Control scale that assess more general control over life. An example item is "During the past week, how much do you feel that you've been able to deal with your problems?" The perceived control over the effects of pain dimension contained items assessing perceived ability to manage the effects of pain on one's life such as frustration and the ability to enjoy life and engage in daily activities. These items were measured by the Arthritis Self-Efficacy Scale. An example item is

"How certain are you that you can manage your pain symptoms so that you can do the thing you enjoy doing?" Lastly, the perceived control over pain itself dimension included items such as "How much control do you have over your pain?" and "How certain are you that you can decrease your pain?" These items were measured by the SOPA. These findings suggest that no single pain control scale would fully capture the construct.

Tan and colleagues (2002) also found that perceived control over life and perceived control over the effects of pain in one's life were more strongly associated with functioning than perceived control over pain itself. It has also been found that less perceived control over pain is associated with less effective coping strategies and poorer HRQoL (Haythornthwaite et al., 1998; Tan et al., 2002; Vallerand et al., 2016). Conversely, greater perceived control is associated with less distress and better physical and psychological adjustment in adults with chronic conditions (Wells, 1994; Tan et al., 2002).

Altogether, these findings suggest that perceived control over pain is a complex and multidimensional construct and that the relation between perceived control and HRQoL may vary based on the dimension being assessed. Most researchers only assess one dimension and do not clearly define perceived control in the illness intrusiveness and SCD literature. The proposed study will assess multiple dimensions of perceived control over pain. Thus, it has the potential to identify which dimensions of perceived control over pain are associated with illness intrusiveness and HRQoL in the context of SCD and the IITF.

Chapter 3: Present Study

Summary

Adults living with SCD appear to have compromised HRQoL that may be due to the disruptions they experience in their daily lives, as researchers have found that SCD patients experience severe pain and other health-related complications that impact daily activities, including education, employment, and social relationships (Brown, Weisbert, & Sledge, 2016; Edwards et al., 2005; Thomas & Taylor, 2002; While & Mullen, 2004). While researchers have identified disease and treatment factors that are associated with HRQoL in this population, few studies have evaluated mechanisms that may explain these relationships. The IITF has been used to explain the relations among disease/treatment factors and HRQoL in chronic health conditions. However, this framework has not been utilized in the context of SCD. The proposed study will help to fill this gap in the literature. This study has the potential to extend existing literature on the IITF and to identify mechanisms that may explain the link between prominent SCD symptoms/consequences (e.g., pain, fatigue, ED visits) and HRQoL. In the SCD and IITF literature, researchers have explored the association between perceived control and HRQoL. However, few studies have evaluated the multiple dimensions of perceived control and the mediating effect of perceived control on illness intrusiveness and HRQoL. The proposed study aimed to address this gap by examining whether multiple dimensions of perceived control mediate the association between illness intrusiveness and HRQoL. Additionally, this study may provide insight about the relative contributions of the different dimensions of perceived control. Lastly, the IITF proposes that contextual factors are important to evaluate, as an individual's background, perspective, and

worldview may serve as a protective and/or risk factor that increases or decreases their perceived illness intrusiveness and HRQoL. Overall, the purpose of the study was to evaluate the utility of the IITF in studying HRQoL in SCD. In pursuing this purpose, the following aims and hypotheses were tested.

Research Aims and Hypotheses

1. Test the theoretical notion that illness intrusiveness mediates the association between disease/treatment factors and HRQoL (Figure 2).

   H_1: Disease/treatment factors (pain, fatigue, number of ED visits) will be significantly associated with HRQoL.

   H_2: Disease/treatment factors (pain, fatigue, number of ED visits) will be significantly associated with illness intrusiveness.

   H_3: Illness intrusiveness will be negatively associated with HRQoL.

   H_4: Illness intrusiveness will mediate the association between disease/treatment factors (pain, fatigue, number of ED visits) and HRQoL.

2. Test the theoretical notion that perceived control mediates the association between illness intrusiveness and HRQoL (Figure 3).

   H_5: Illness intrusiveness will be negatively associated with (a) perceived control over life in general; (b) perceived control over the effects of SCD symptoms; and (c) perceived control over pain.

   H_6: Perceived control [(a) perceived control over life in general; (b) perceived control over the effects of SCD symptoms; and (c) perceived control of pain] will be positively associated with HRQoL.

H_7: Perceived control [(a) perceived control over life in general; (b) perceived control over the effects of SCD symptoms; (c) perceived control over pain] will mediate the association between illness intrusiveness and HRQoL.

3. Test the theoretical notion that contextual factors are directly associated with HRQoL (Figure 4).

    H_8: Age will be negatively associated with HRQoL.

    H_9: Females will have significantly lower HRQoL compared to males.

Chapter 4: Methods

Design and Procedures

This study utilized a cross-sectional, within-group design. Fifty-eight adults with SCD were recruited from sickle cell clinics and organizations across the United States. Individuals who expressed interest in participating in the study were asked to provide evidence of their sickle cell diagnosis by emailing the following: (1) the name of their sickle cell provider; (2) the name and location of the treatment facility where they receive sickle cell care; and (3) a copy of a medical document with their sickle cell diagnosis listed. After individuals verified their diagnosis, they were sent a link to the survey. Participants who met eligibility criteria – which included (a) being 18 years of age or older; (b) being able to read and write in English; and (c) having access to and ability to use a desktop/laptop computer, tablet, or smartphone – were provided additional information about the study procedures and then asked to provide informed consent. Informed consent was obtained in accordance with procedures approved by the university's institutional review board. Those who consented to participate in the study

were directed to complete the study's primary measures, which are described in the Measures (see below). Eligibility, consent, and study measures took approximately 30 minutes to complete. Participants could complete the survey over several sessions, and those who completed the study were given a $20 Amazon gift card for their participation in the study.

Measures

Demographics

Participants were asked to self-report demographic information regarding their age, sex, race (Asian/Pacific Islander, Black/African American, Native American/Alaska Native, White, More than One Race, Other), ethnicity (Latinx/Hispanic and Non-Hispanic), marital status (never married, married, living with a partner, divorced/separated, or widowed), employment status (unemployed, employed part-time, employed full-time, student, disabled, retired), and level of education (less than high school diploma, high school diploma/GED, some college, associate's degree, bachelor's degree, graduate/professional degree).

Genotype

Participants self-reported their sickle cell genotype. Sickle cell anemia (HbSS) is the most severe variant of SCD, followed by sickle beta thalassemia-plus ($HbS\beta^{+}$), sickle beta thalassemia-zero ($HbS\beta^{0}$), and sickle C disease (HbSC), respectively (Brewster, 2003; Frenette & Atweh, 2007; Stuart & Nagel, 2004).

Emergency Department Visits

Participants were asked how many times they had visited the emergency department in the past 12 months.

Pain

Pain was assessed using the pain severity subscale of the Brief Pain Inventory – Short Form (BPI; Cleeland, 1991). The pain severity subscale of the BPI is a self-administered questionnaire calculated as a mean of responses to four pain rating items (current, worst, least, and average pain), each ranging from 0 (*no pain*) to 10 (*pain as bad as you can imagine*). Higher scores indicate more severe pain.

The BPI has been used to evaluate pain levels in adults with cancer and other chronic health conditions, including SCD (Haines et al., 2012; Oliveros et al., 2013). The pain severity subscale of the BPI has demonstrated good to excellent internal consistency, with Cronbach's alpha coefficients ranging .80 to .95 (Atkinson et al., 2010; Cleeland, 2009; Kapstad, Rokne, and Stavem, 2010; Keller et al., 2004). The BPI severity subscale demonstrates acceptable to excellent test-retest reliability. (Atkinson et al., 2010; Cleeland, 2009). Internal consistency in this sample was excellent ($\alpha = .90$). In general, the instrument also has excellent construct validity and is sensitive to change in pain over time (Atkinson et al., 2010; Atkinson et al., 2011; Kapstad et al., 2010; Keller et al., 2004; Lapane, Quilliam, Benson, Chow, & Kim, 2014; Tan, Jensen, Thornby, & Shanti, 2004).

Fatigue

Fatigue was assessed using the fatigue severity subscale of the Brief Fatigue Inventory (BFI; Mendoza et al., 1999). The fatigue severity subscale of the BFI is a self-administered questionnaire calculated as a mean of responses to three fatigue rating items (current, least, and average fatigue), each ranging from 0 (*no fatigue*) to 10 (*as bad as you can imagine*). Higher scores indicate more severe fatigue.

The fatigue severity subscale has demonstrated excellent internal consistency, with Cronbach's alpha greater than 0.80 (Shuman-Paretsky, Belser-Ehrlich, & Holtzer, 2014; Wang et al., 2004). Internal consistency in this sample was excellent ($\alpha = .94$). Generally, the instrument also has good convergent and predictive validity (Mendoza et al., 1999; Wolfe, 2004. It has found to discriminate between patient groups based on an objective measure of fatigue (e.g., hemoglobin) and detect change in fatigue over time (Mendoza et al., 1999; Wang et al., 2004). The BFI has been used to assess fatigue in a sample of young adults with SCD (Ameringer, Elswick, & Smith, 2014). The BFI was significantly related to all eight subscales of the SF-36 with correlations ranging from 0.38 to 0.60.

Illness Intrusiveness

The Illness Intrusiveness Rating Scale (IIRS; Devins et al., 1983) was used to assess illness intrusiveness. The IIRS is a 13-item, self-report questionnaire that measures illness-induced disruptions in 13 life domains: health, diet, work, active recreation, passive recreation, financial situation, relationship with partner, sex life, family relations, other social relations, self-improvement/self-expression, religious expression, and community/civic involvements. Using a seven-point scale ranging from 1 (*not very much*)

to 7 (*very much*), participants rate the degree to which their illness and/or its treatment interfere with these life domains. This measure yields a composite score, ranging from 13 to 91, based on the sum of the 13 items. Higher scores indicate more illness intrusiveness. During data collection, I omitted two items (both part of the family relations domain) of the IIRS and consequently only have data for 11 of the 13 items. Notably, one of the 11 items assessed for family relations.

The IIRS was originally developed to assess illness intrusiveness in adults with ESRD (Devins et al., 1983) but has now been used in over thirty chronic health conditions (Bloom et al., 1998; Devins, 1994; Devins et al., 2006; Devins, Edworthy, & ARAMIS Lupus State Models Research Group, 2000; Devins, Edworthy, Guthrie, & Martin, 1992; Poochikian-Sarkissian et al., 2008a; Suh et al., 1999). Internal consistency (i.e., alpha coefficients) for the IIRS has ranged from .79 to .85. Based on the 11-item version used in this sample, internal consistency was .88, which is good. The instrument has also demonstrated good concurrent validity (Devins et al., 1983; Devins et al., 1990). IIRS scores differ across disease groups and stages of a disease (Devins et al., 1983, Devins et al., 1990). Devins and colleagues (1983) also found that patient-reported intrusiveness was significantly correlated with intrusiveness reported by physicians and significant others. The IIRS is also sensitive to change over time as researchers have found that IIRS scores significantly decreased following interventions such as group psychotherapy and chronic disease self-management groups (Devins, 2010).

Perceived Control Over Life

The Life Control Scale of the West-Haven-Yale Multidimensional Pain Inventory (WHYMPI; Kerns, Turk, & Rudy, 1985) was used to assess perceived control over life in

general. The scale is calculated as a mean of 2 items. The first item asks, “During the past week, how much control do you feel that you have had over your life?” Response options range from 0 (*not at all in control*) to 6 (*extremely in control*). For the second item, participants are asked, “During the past week, how much do you feel that you’ve been able to deal with your problems?” Response options for this item also range from 0 (*not at all*) to 6 (*extremely well*). Higher scores indicate more perceived control over life.

The WHYMPI has been used to assess pain beliefs in adults with a wide range of pain conditions such as lower back pain, headache, and fibromyalgia (Turk & Rudy, 1988; Turk & Rudy, 1990; Turk et al., 1996). The Life Control Scale of the WHYMPI has demonstrated an internal reliability coefficient (i.e., Cronbach’s alpha) of .79 and two-week test-retest stability (correlation) of .68 (Kerns et al., 1985). In this sample, internal consistency was .89. Researchers have also shown that the Life Control Scale is a valid measure that is sensitive to change following rehabilitation (Kerns & Haythornthwaite, 1988; Kerns, Turk, Holzman & Rudy, 1985).

Perceived Control Over Symptoms of the Disease

In concert with past research, the present study used the Sickle Cell Self-Efficacy Scale (SCSES; Edwards, Telfair, Cecil, & Lenoci, 2000) to assess perceived control over SCD symptoms. The SCSES is a self-report questionnaire that measures perceived ability to engage in daily activities and to manage sickle cell symptomology (e.g., pain, fatigue). Using a scale from 1 (*not at all sure*) to 5 (*very sure*), participants rate how sure they feel about their ability to deal with SCD. Sample items are: “How sure are you that you can do something to cut down on most of the pain you have when having a pain episode?,” “How sure are you that you can keep doing most of the things you do day-to-

day?," and "How sure are you that you can manage your sickle cell disease symptoms so that you can do the things you enjoy doing?". A sum score is calculated using the 9 items of the SCSES, with higher scores indicate more perceived control over SCD symptoms.

The SCSES was developed using a sample of 83 adults with SCD (Edwards et al., 2000). The instrument demonstrated high internal consistency ($\alpha = .89$). Similarly, internal consistency was .86 in this sample. The SCSES has also been found to be related to similar constructs, such as self-esteem ($r = .39$), sense of mastery ($r = 0.45$), and the Internal Health Locus of Control subscale of the Multidimensional Health Locus of Control questionnaire ($r = .41$), which suggests convergent validity. Furthermore, the SCSES was predictive of sickle cell pain severity in the past 30 days ($r = -.30$) and SCD physical symptoms ($r = -.44$). SCSES scores were also associated with number of physician visits ($r = -.42$) and ER visits in the past 12 months ($r = -.25$). Together, these findings support the predictive validity of the instrument. Regarding discriminant validity, the SCSES was not associated with two subscales of the Multidimensional Health Locus of Control – the chance or powerful others subscales. Overall, researchers have found that the SCSES has good reliability and validity in studies of patients with SCD (Clay & Telfair, 2007; Edwards et al., 2000, 2001; Madderom, Heijdra, Utens, Polinder, Rijneveld, & Cnossen, 2016).

Perceived Control Over Pain

The Control scale of the Survey of Pain Attitudes (SOPA-35; Jensen, Turner, & Romano, 2000) was used to measure perceived control over pain. The Control scale is calculated as a mean of 5 items that assess the extent to which a respondent believes he or she can control pain. Participants are provided the following prompt: "Please indicate

how much you agree with each of the following statements about your pain problem." Response options range from 0 (*very untrue*) to 4 (*very true*), with higher scores indicating more perceived control over pain. Example items include: "The amount of pain I feel is out of my control" and "There is little that I can do to ease my pain".

The control items of the SOPA-35 have demonstrated adequate reliability and validity. Internal consistency (Cronbach's alpha) for the SOPA-35 has been estimated to be .78, which is comparable to the original 57 item version of the SOPA (Jensen et al., 2000). In this sample, internal reliability was .77, which is adequate. Furthermore, the 2-week test-retest stability (correlation) coefficients from posttreatment to 2-week follow-up have been found to be .75. Similarly, the 2-week test-retest reliability coefficient from 2-week follow-up to one-month follow-up was 0.80. Regarding construct validity, the Control Subscale of the SOPA-35 was significantly associated with the CES-D (r = -.41) and the Guarding (r = -.25) and Task Persistence (r = .29) subscales of the Chronic Pain Coping Inventory.

Health-Related Quality of Life

The Short Form-12 Health Survey 1.0 (SF-12; Ware, Kosinski, & Keller (1995) was used to assess HRQoL. The SF-12 is a self-report questionnaire that measures eight dimensions of HRQoL including: physical functioning (PF); bodily pain (BP); role limitations due to physical problems (PR); role limitations due to emotional problems (RE); mental health (MH); social functioning (SF); vitality (VT); and general health perceptions (GH). The eight scaled scores can be used to calculate physical health (comprised of the PF, RP, BP, and GH subscales) and mental health (comprised of the VT, SF, RE, MH subscales) composite scores. Scores for the SF-12 physical and mental

composite scores range from 0 to 100, with higher scores indicating better HRQoL.

The SF-12 was developed to a be shorter, yet valid, alternative to the SF-36, which is a generic measure of HRQoL that has been validated and used across a wide variety of disease groups (McHorney, Ware, Lu, & Sherbourne, 1994; McHorney, Ware, & Raczek, 1993). Test-retest for the physical and mental health composite scores of the SF-12 is .89 and .76, respectively (Ware, Kosinski, & Keller, 1995). In this sample, internal reliability was .86, which is good. The SF-12 has also demonstrated good construct and criterion validity, as it is highly correlated with SF-36 physical (r = .96) and mental health scores (r = .97) and is able to reproduce 90% of the variance in the SF-36 (Ware et al., 1995). Furthermore, clinical validity has been established for the measure; researchers have been able to discriminate between the general population and individuals with health conditions. Overall, the SF-12 is a brief measure of HRQoL that has demonstrated adequate reliability and validity in numerous chronic disease populations.

Depression Symptoms

The 9-item Patient Health Questionnaire (PHQ-9; Kroenke & Spitzer, 2002) was used to assess symptoms of depression. The PHQ-9 is a self-report measure that asks individuals to report how often they have been bothered by the following problems over the last two weeks: (1) anhedonia, (2) depressed mood; (3) insomnia or hyperinsomnia; (4) fatigue; (5) poor appetite or overeating; (6) feelings of worthlessness; (7) trouble concentrating; (8) psychomotor changes; and (9) suicidal ideation. Response options ranged from 0 (*not at all*) to 3 (*nearly every day*). A sum score is calculated using the 9 items of the PHQ-9, with higher scores represent more severe symptoms of depression.

Scores of 5, 10, 15, and 20 indicate mild, moderate, moderately severe, and severe depression, respectively.

The PHQ-9 has demonstrated good internal consistency ($\alpha = .89$) and test-retest reliability ($r = .84$) (Kroenke, Spitzer, & Williams, 2001). Internal consistency was .86 in this sample. Criteria validity has been established by conducting 580 structured interviews by mental health professionals. Individuals who scored equal to or greater than 10 on the PHQ-9 were 7 to 13.6 times more likely to be diagnosed with depression. On the contrary, individuals who scored equal to or less than 4 on the measure had a 1 in 25 chance of having depression. A PHQ-9 score of 10 or greater had a sensitivity of 88% and a specificity of 88% for depression. Depression (assessed by the PHQ-9) was negatively associated with functioning (assessed by the SF-20); the PHQ-9 was significantly correlated with all six subscales of the SF-20 including mental health ($r = .73$), general health perceptions ($r = .55$), social functioning ($r = .52$), role functioning ($r = .43$), physical functioning ($r = 37$) , and bodily pain ($r = .33$). Depression was also positively associated with disability days ($r = .39$), healthcare use ($r = .24$), and general amount of difficulty ($r = .55$). The PHQ-9 has been used in various healthcare settings and for diverse conditions, including with people with physical illness (Blackwell & McDermott, 2014). The instrument is free and has been translated into over 30 languages. Overall, the PHQ-9 is a commonly used, reliable, and valid tool for screening, diagnosing, and monitoring symptoms of depression.

Anxiety Symptoms

The Generalized Anxiety Disorder-7 Scale (GAD-7; Spitzer, Kroenke, Williams, & Lowe, 2006) was used to assess symptoms of anxiety. The GAD-7 is a self-report

measure that asks individuals to report how often they have been bothered by the following problems over the last two weeks: (1) feeling nervous, anxious, or on edge (2) difficulty controlling worry; (3) excessive worry; (4) trouble relaxing; (5) restlessness; (6) irritability; and (7) feeling afraid as if something awful might happen. Response options ranged from 0 (*not at all*) to 3 (*nearly every day*). A sum score is calculated using the 7 items of the GAD-7, with higher scores indicate more severe symptoms of anxiety. Cut points of 5, 10, 15 indicate mild, moderate, and severe symptoms of anxiety, respectively.

The GAD-7 has been found to have excellent internal consistency ($\alpha = .92$) (Spitzer et al., 2006), and test-retest is good (intraclass correlation = .83). Internal consistency in this sample was .90, which is excellent. Additionally, it has demonstrated good criterion, construct, convergent, factorial, and procedure validity. As cut point increases, sensitivity decreases and specificity increases. At cut point of 10 or greater, both sensitivity and specificity exceed .80. In terms of construct validity, the GAD-7 is inversely associated with functioning (assessed by SF-20) and positively related to disability days ($r = .27$), healthcare use ($r = .22$), and symptom-related difficulty in activities and relationships ($r = .63$). Regarding convergent, the GAD-7 is strongly correlated with other measures of anxiety, including the Beck Anxiety Inventory ($r = .72$) and the anxiety subscale of the Symptom Checklist-90 ($r = .74$). In sum, the GAD-7 is a widely used reliable and valid measure for screening, diagnosing, and monitoring anxiety symptoms over time.

Data Analysis

Descriptive statistics were used to examine participants' responses to all study measures. Assumptions of independence, normality, homoscedasticity, and linearity were checked for all analyses. Pearson product-moment correlations were conducted to evaluate the relations among continuous variables. Correlations were examined regarding the strengths of the effect sizes, with r = .10, .30, and .50 indicating small, medium, and large effects. All significant effects were evaluated using an alpha level of > .05. The *PROCESS* macro (a custom dialog box used in SPSS and SAS) was used to perform the mediation analyses. Mediation analyses were performed across 2,000 bias-corrected bootstrapped samples.

Chapter 5: Results

Preliminary data screening indicated that most variables met assumptions of the statistical tests; however, there were problems with the assumption of normality for some variables. ED visits and PHQ-9 scores (used to measure depressive symptoms) were positively skewed and positively kurtotic. Additionally, GAD-7 scores (used to measure anxiety symptoms) were positively skewed. There are a few methods that can be used when the assumption of normality (i.e., data are skewed or kurtotic) has not been met including trimming the data (i.e., deleting outliers), winsorizing the data (i.e., replacing outliers with the next highest score that is not an outlier), transforming the data, and using robust tests (Field, 2013). Some researchers have argued that the best option is to use robust tests, which are statistics that do not rely on the assumptions of the statistics and are reliable even when the assumptions are not met. Bootstrapping is a robust test that

estimates properties of the sampling distribution from the sample data, which is treated as a population from which smaller samples are derived. This method, which is robust to the violation of normality, was used for all analyses.

Descriptive and frequency data for continuous and categorical variables are provided in Table 1 and Table 2, respectively. Furthermore, correlations among all study variables are in Table 3. A Pearson's correlation analysis was performed to examine the association between HRQoL (physical and mental) and continuous variables including age, pain severity, fatigue severity, ED visits, illness intrusiveness, perceived control over life (assessed by WHYMPI), perceived control over SCD symptoms (assessed by SCSES), perceived control over pain (assessed by SOPA Control Subscale), depression symptoms (assessed by PHQ-9), and anxiety symptoms (assessed by GAD-7). Additionally, a point-biserial correlation was performed to examine the association between HRQoL (physical and mental) and dichotomous variables including sex, employment status, genotype, and hydroxyurea use.

Using a liberal criterion for statistical significance ($p < .05$), physical HRQoL was significantly associated with age (r = -.36, [-0.540, -0.153], p = .006), pain severity (r = -.59, [-0.727, -0.418], $p < .001$), fatigue severity (r = -.43, [-0.635, -0.181], p = .001), ED visits (r = -.36, [-0.520, -0.163], p = .006), illness intrusiveness (r = -.53, [-0.688, -0.328], $p < .001$), and perceived control over the effects of SCD symptoms (r = .46, [0.217, 0.658], $p < .001$). Physical HRQoL was not significantly associated with sex, employment status, genotype, hydroxyurea use, perceived control over life, perceived control over pain, depression symptoms, and anxiety symptoms. Mental HRQoL was significantly associated with age (r = .30, [0.048, 0.498], p = .023), illness intrusiveness

(r = -.45, [-0.611, -0.271], p < .001), perceived control over life (r = .47, [0.264, 0.639], p < .001), perceived control of SCD symptoms (r = .38, [0.119, 0.602], p = .004), perceived control over pain (r = .30, [0.072, 0.511], p = .022), depression symptoms (r = -.74, [-0.835, -0.627], p < .001), and anxiety symptoms (r = -.71, [-0.794, -0.614], p < .001). Mental HRQoL was not significantly associated with sex, employment status, genotype, hydroxyurea use, pain severity, fatigue severity, and ED visits. Illness intrusiveness was significantly associated with fatigue (r = .38, [0.067, 0.643], p = .003), perceived control over life (r = -.49, [-0.709, -0.207], p < .001), perceived control over SCD symptoms (r = -.64, [-0.772, -0.473], p < .001), and perceived control over pain (r = -.39, [-0.602, -0.147], p = .003). Illness intrusiveness was not significantly associated with pain and ED visits. Intercorrelations among the remaining variables were also examined and are provided in Table 3. Since the probability of making a Type I error increases as the number of tests or comparisons being conducted increases, I applied a Bonferroni correction, which reduces the probability of Type I error. After applying a family-wise Bonferroni correction (.05 / 120 = .0004), several associations were not statistically significant (Field, 2013). Bolded fonts in Table 3 show associations that remained statistically significant after applying the Bonferroni correction.

A one-way ANOVA was conducted to determine whether physical and mental HRQoL were different across levels of education. The assumptions of one-way ANOVA, including normality of residuals and no outliers, were met. Participants were classified into four groups: “high school or GED” (n = 7), “some college” including technical college and associate degree (n = 17), “bachelor’s degree” (n = 21), and “advanced degree,” including Master’s or doctoral degrees (n = 13). Means and standard deviations

are presented in Table 4. There was no significant difference in physical HRQoL, $F(3, 54) = 2.03$, $p = .121$, or mental HRQoL, $F(3, 54) = 0.15$, $p = .928$, among the four groups.

A one-way ANOVA was also conducted to determine whether physical and mental HRQoL were different across groups of marital status. The assumptions of one-way ANOVA were met. Participants were classified into three groups: "single" (n = 36), married or living with a domestic partner, referred to as "partnered" (n = 14), and divorced, separated, or widowed, referred to as "previously partnered" (n = 8). Table 5 provides the means and standard deviations for the three groups. There was no significant difference in physical HRQoL, $F(2, 55) = 1.56$, $p = .219$, or mental HRQoL, $F(2, 55) = 1.61$, $p = .210$, among the groups.

Aim 1: Test the Theoretical Notion that Illness Intrusiveness Mediates the Association Between Disease/Treatment Factors and HRQoL

Next, I evaluated models that examined the potential mediating role of illness intrusiveness on the association between disease/treatment factors (pain, fatigue, ED visits) and HRQoL (physical and mental) controlling for age. Analyses were conducted across 2,000 bootstrapped samples with the PROCESS macro for SPSS 25.0 (Hayes, 2013). Model 4 was used for the mediation analyses. In separate analyses for each disease/treatment factor, pain, fatigue, and ED visits were entered as the predictor variables, illness intrusiveness was the mediator, HRQoL (mental or physical) was entered as the outcome variable, and age as the covariate. In analyses with physical HRQoL as the outcome variable, I controlled for the other disease/treatment factors (e.g., adjusted for fatigue and ED visits in the analysis with pain as the predictor variable). Figure 5 and Figure 6 summarize the mediation model and estimates of the indirect and

direct effects of pain on physical and mental HRQoL through illness intrusiveness. As shown in Figure 6, the indirect effect of pain on physical HRQoL through illness intrusiveness (b = 0.13) cannot be interpreted as statistically significant, because the bootstrapped confidence interval includes zero (-0.354 to 0.594). Comparison of the total (c) and direct effects (c') suggests that mediation did not occur in this model. Pain severity was significantly associated with physical HRQoL when illness intrusiveness was excluded from the model (b = -1.50, 95% CI [-2.474, -0.536], p = .003) and when the variable was included in the model (b = -1.64, 95% CI [-2.490, -0.787], p < .001. In Figure 7, the indirect effect of pain on mental HRQoL through illness intrusiveness (b = -0.29) also cannot be interpreted as statistically significant, because the bootstrapped confidence interval includes zero (-0.822 to 0.209). Comparison of the total (c) and direct effects (c') indicates that mediation did not occur in this model. Pain severity was not associated with mental HRQoL when illness intrusiveness was excluded from the model (b = -0.41, 95% CI [-1.522, 0.701], p = .462) or when the variable was included in the model (b = -0.12, 95% CI [-1.120, 0.885], p = .816). In sum, illness intrusiveness did not mediate the association between pain severity and physical or mental HRQoL.

Figures 7 and 8 summarize the mediation model and estimates of the indirect and direct effects of fatigue severity on physical and mental HRQoL through illness intrusiveness. There was a significant indirect effect of fatigue severity on physical HRQoL through illness intrusiveness, b = -0.60, 95% CI [-1.148, -0.118]. The strength of the association between fatigue severity and physical HRQoL was significantly reduced when illness intrusiveness was included in the model (b = -0.85, 95% CI [-1.617, -0.078], p = .032) compared to when the variable was excluded from the model (b = -1.44, 95%

CI [-1.843, -0.459], $p < .001$). Similarly, there appears to be a significant indirect effect of fatigue severity on mental HRQoL through illness intrusiveness, b = -0.65, 95% CI [-1.447, -0.128], as the strength of the association between fatigue severity and mental HRQoL was significantly reduced when illness intrusiveness was included in the model (b = -0.13, 95% CI -1.071, 0.811], $p = .783$) compared to when the variable was excluded from the model (b = -0.78, 95% CI [-1.736, 0.171], $p = .106$). However, fatigue severity was not significantly associated with mental HRQoL when illness intrusiveness was excluded from the model (i.e., no total effect). Thus, illness intrusiveness partially mediated the association between fatigue severity and physical HRQoL. Furthermore, there was a significant indirect effect of fatigue severity on mental HRQoL through illness intrusiveness.

Figures 9 and 10 summarize the mediation model and estimates of the indirect and direct effects of ED visits on physical and mental HRQoL through illness intrusiveness. There appeared to be a significant indirect effect of number of ED visits on physical HRQoL through illness intrusiveness, b = -0.36, 95% CI [-0.982, -0.029], as the strength of the association between ED visits and physical HRQoL was significantly reduced when illness intrusiveness was included in the model (b = -0.96, 95% CI -1.800, -0.129, $p = .025$) compared to when the variable was excluded from the model (b = -1.33, 95% CI -2.260, -0.392, $p = .006$). However, number of ED visits was not significantly associated with illness intrusiveness. In Figure 11, the indirect effect of ED visits on mental HRQoL through illness intrusiveness (b = -0.35) cannot be interpreted as statistically significant, because the bootstrapped confidence interval includes zero (-0.977 to 0.002). Number of ED visits was not associated with mental HRQoL when

illness intrusiveness was excluded from the model (b = 0.34, 95% CI [-0.532, 1.214], p = .437) or when the variable was included in the model (b = 0.69, 95% CI [-0.080, 1.468], p = .078). Overall, there was a significant indirect effect of ED visits on physical HRQoL, but not mental HRQoL, through illness intrusiveness.

Aim 2: Test the Theoretical Notion that Perceived Control Mediates the Association Between Illness Intrusiveness and HRQoL

Next, I evaluated models that examined the potential mediating role of the three dimensions of perceived control (perceived control over life, perceived control over SCD symptoms, and perceived control over pain) on the association between illness intrusiveness and HRQoL (physical and mental) controlling for age. Analyses were conducted across 2,000 bootstrapped samples with the PROCESS macro for SPSS 25.0 (Hayes, 2013). Model 4 was used for the mediation analyses. In separate analyses for each dimension of perceived control, illness intrusiveness was entered as the predictor variable, the three dimensions of perceived control were the mediators, and HRQoL (mental or physical) was entered as the outcome variable. In analyses with physical HRQoL as the outcome variable, I controlled for the disease and treatment factors. Figure 11 and Figure 12 summarize the mediation model and estimates of the indirect and direct effects of illness intrusiveness on physical and mental HRQoL through perceived control over life (assessed by WHYMPI). As shown in Figure 12, the indirect effect of illness intrusiveness on physical HRQoL through perceived control over life (b = 0.04) cannot be interpreted as statistically significant, because the bootstrapped confidence interval includes zero (-0.041 to 0.117). Comparison of the total (c) and direct effects (c') suggests that mediation did not occur in this model. Illness intrusiveness was

significantly associated with physical HRQoL when perceived control over life was excluded from the model (b = -0.26, 95% CI [-0.381, -0.132], $p < .001$) and when the variable was included in the model (b = -0.29, 95% CI [-0.431, -0.159], $p < .001$). The relationship between illness intrusiveness and physical HRQoL does not operate through perceived control over life. In Figure 13, there was a significant indirect effect of illness intrusiveness on mental HRQoL through perceived control over life, b = -0.09, 95% CI [-0.186, -0.017]. The strength of the association between illness intrusiveness and mental HRQoL was significantly reduced when perceived control over life was included in the model (b = -0.21, 95% CI [-0.380, -0.045], $p = .014$) compared to when the variable was excluded from the model (b = -0.30, 95% CI [-0.450, -0.151], $p < .001$). Therefore, perceived control over life partially mediated the association between illness intrusiveness and mental HRQoL but not physical HRQoL.

Figure 13 and Figure 14 summarize the mediation model and estimates of the indirect and direct effects of illness intrusiveness on physical and mental HRQoL through perceived control over SCD symptoms (assessed by SCSES). The indirect effect of illness intrusiveness on physical HRQOL through perceived control over SCD symptoms (b = -0.02) cannot be interpreted as statistically significant, because the bootstrapped confidence interval includes zero (-0.091 to 0.134). Comparison of the total (c) and direct effects (c') suggests that mediation did not occur in this model. Illness intrusiveness was significantly associated with physical HRQoL when perceived control over SCD symptoms was excluded from the model (b = -0.26, 95% CI [-0.381, -0.132], $p < .001$) and when the variable was included in the model (b = -0.28, 95% CI [-0.443, -0.116], $p = .001$). Similarly, the indirect effect of illness intrusiveness on mental HRQoL through

perceived control over SCD symptoms (b = -0.09) cannot be interpreted as statistically significant, because the bootstrapped confidence interval includes zero (-0.205 to 0.034). Comparison of the total (c) and direct effects (c') suggests that mediation did not occur in this model. Illness intrusiveness was significantly associated with mental HRQoL when perceived control over SCD symptoms was excluded from the model (b = -0.30, 95% CI [-0.450, -0.151], $p < .001$) and when the variable was included in the model (b = -0.21, 95% CI [-0.406, -0.019], $p = .032$). The relationship between illness intrusiveness and physical and mental HRQoL does not operate through perceived control over SCD symptoms.

Figure 15 and Figure 16 summarize the mediation model and estimates of the indirect and direct effects of illness intrusiveness on physical and mental HRQoL through perceived control over pain (assess by SOPA Control Scale). The indirect effect of illness intrusiveness on physical HRQoL through perceived control over pain (b = 0.03) cannot be interpreted as statistically significant, because the bootstrapped confidence interval includes zero (-0.027 to 0.112). Comparison of the total (c) and direct effects (c') suggests that mediation did not occur in this model. Illness intrusiveness was significantly associated with physical HRQoL when perceived control over pain was excluded from the model (b = -0.26, 95% CI [-0.381, -0.132], $p < .001$) and when the variable was included in the model (b = 0.29, 95% CI [-0.430, -0.148], $p < .001$). Also, the indirect effect of illness intrusiveness on mental component of HRQoL through perceived control over pain (b = -0.03) cannot be interpreted as statistically significant, because the bootstrapped confidence interval includes zero (-0.102 to 0.046). Illness intrusiveness was significantly associated with mental HRQoL when perceived control

over pain was excluded from the model (b = -0.30, 95% CI [-0.450, -0.151], $p < .001$) and when the variable was included in the model (b = -0.27, 95% CI [-0.430, -0.105], $p = .002$). Thus, the relationship between illness intrusiveness and physical and mental HRQoL does not operate through perceived control over pain.

Post Hoc Power Analysis

To determine whether non-significant results were potentially due to lack of statistical power, I conducted post hoc analyses using G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007) and MedPower (Kenny, 2017). In the analyses, I set $\alpha = .05$ (two tailed) and sample size = 58. The effect size and statistical power ($1-\beta$) for the analyses are provided in Table 6. As Cohen (1992) recommended that researchers should strive for power of .80 (i.e., 80% chance of detecting an effect if one genuinely exists), I provided the approximate sample size needed to obtain recommended statistical power of .80 given the effect sizes obtained in the study. Since statistical power was less than .80 for all but two relationships, it is highly likely that there was inadequate power to detect genuine effects. Limitations regarding statistical power in the sample are further considered in the discussion.

I also considered Cohen's guidelines for effect sizes (Field, 2013). Cohen's guidelines for correlation (r) are: .10 is a small effect; .30 is a moderate effect; .50 is a large effect. To detect small, moderate, and large effect sizes (with $1-\beta = .80$) in correlation, the required sample size was 782, 84, and 29, respectively. Additionally, Cohen's guidelines for f^2 are: .02 is a small effect; .15 is a moderate effect; and .35 is a large effect. To detect small, moderate, and large effect sizes (with $1-\beta = .80$) for individual predictors in multiple regression with four predictors, the necessary sample

size was 395, 55, and 25, respectively. Thus, there was potentially adequate power to detect only large effects for correlation and moderate to large effects for mediation.

Chapter 6: Discussion

Individuals with SCD seem to have compromised HRQoL that may be due to disruptions they experience in their daily lives (Carroll et al., 2009; Edwards et al., 2005; Smith et al., 2008; Thomas & Taylor, 2002; While & Mullen, 2004). While investigators have found disease and treatment factors that are associated with HRQoL in this population (Aisiku et al., 2008; Ahmed et al., 2015; Ameringer et al., 2014; Anie et al., 2002; Asnani et al., 2008; Ballas et al., 2006; Dampier et al., 201; McClish et al., 2005), little is known about mechanisms that may explain the relationship between disease/treatment factors and HRQoL. The IITF has been used to explain the associations among disease/treatment factors and HRQoL in chronic health conditions; however, this framework has not been used in the context of SCD. The purpose of this study was to evaluate the relationships among disease/treatment factors, illness intrusiveness, perceived control, and HRQoL in a sample of 58 adults living with SCD. Based on the central tenet of the IITF, I examined whether illness intrusiveness explained the association between disease/treatment factors (pain, fatigue, ED visits) and HRQoL. Additionally, I examined the relationship between contextual factors and HRQoL – whether age would be associated with HRQoL and whether there would be a difference in HRQoL. Finally, I explored whether three dimensions of perceived control – perceived control over life, perceived control over the effects of SCD symptoms, and perceived control over pain – explained the link between illness intrusiveness and HRQoL.

The first aim of the study was to examine whether illness intrusiveness would mediate the association between disease/treatment factors (pain, fatigue, number of ED visits) and HRQoL (physical and mental). I hypothesized that (1) disease/treatment factors (pain, fatigue, number of ED visits) would be significantly associated with HRQoL; (2) disease/treatment factors (pain, fatigue, number of ED visits) would be significantly associated with illness intrusiveness; (3) illness intrusiveness would be negatively associated with HRQoL; and (4) illness intrusiveness would mediate the association between disease/treatment factors (pain, fatigue, number of ED visits) and HRQoL. Prior to evaluating mediation, bivariate correlations were examined among the primary study variables including pain, fatigue, number of ED visits, illness intrusiveness, and HRQoL. Results indicated that pain, fatigue, and ED visits were negatively associated with physical HRQoL, such that physical HRQoL worsened as individuals reported higher pain severity, higher fatigue severity, and a greater number of ED visits in the past twelve months. This is consistent with previous research (Ahmed et al., 2016; Aisiku et al., 2008; Ameringer et al., 2014; Anie et al., 2002; Ballas et al., 2006; McClish et al., 2005) and suggests that greater disease severity is related to poorer physical HRQoL among adults with SCD. Conversely, pain, fatigue, and ED visits were not significantly associated with mental HRQoL. The nonsignificant association between ED visits and mental HRQoL is consistent with previous studies, as researchers have found that healthcare utilization, including number of ED visits in the past twelve months, is related to physical but not mental HRQoL (Ahmed et al., 2016; Aisiku et al., 2008; Jackson et al., 2014). The finding that pain and fatigue were not associated with mental HRQOL, however, is inconsistent with most of the prior research. There are

several plausible explanations for why the current findings contradict previous studies that have found a significant and positive association between pain/fatigue and mental HRQoL (Ameringer et al., 2014; Ballas et al., 2006; McClish et al., 2005; Pereira et al., 2013).

First, pain and fatigue may simply not be associated with mental HRQoL among adults with SCD. To date, only one empirical study has examined the relationship between fatigue and HRQoL in SCD (Ameringer et al., 2014). In the study, 60 adolescents and young adults between the ages of 15 and 30 (M = 22.50, SD = 4.10) were recruited from pediatric and adult hematology clinics and hospital units. Although Ameringer et al. (2014) did not provide details about the recruitment sites, hospital units are often inpatient compared to clinics, which are typically outpatient. This suggests that some of the participants in Ameringer's study may have been recruited in an inpatient hospital setting. Ameringer and colleagues' (2014) sample differed from the current one in many ways, such as mean age and recruitment location(s). In the present study, participants were between the ages of 18 and 69 (*M* = 39.12, *SD* = 12.75), and they were recruited from adult hematology clinics and SCD organizations across the country. None of the participants were directly recruited from hospital units. Hence, it is possible that the relationship between fatigue and mental HRQoL varies across SCD demographics and on how and where participants are recruited for the study (e.g., in an inpatient versus outpatient setting). It is possible that fatigue may be related to mental HRQoL among adolescents and emerging adults but not the general SCD adult population. Similarly, SCD patients recruited from hospital units may differ from those enlisted from hematology clinics and SCD organizations. For instance, individuals seeking health care

in hospital units could have been experiencing more acute SCD symptoms, which may have impacted self-reported fatigue and its relation to mental HRQoL. In sum, our understanding of fatigue in SCD is limited; therefore, additional research is needed to infer how fatigue functions and how it relates to mental HRQoL in this population.

Second, the use of various instruments to assess pain, fatigue, and mental HRQoL may have contributed to the current findings contradicting previous research. In the study described above, Ameringer and colleagues (2014) assessed HRQoL using the SF-36 rather than the SF-12, which was the measure used in the current study. While the SF-12 was derived from the SF-36, the SF-12 is less reliable than the SF-36 (Ware et al., 1996). Therefore, the relationship between fatigue and mental HRQoL may vary depending on whether the SF-12 or the SF-36 is used to assess HRQoL. Similarly, pain was measured differently in this study compared to previous research. In the current study, pain severity was assessed by the BPI, which asks participants to rate their current pain and worst, least, and average pain during the past 24 hours on a scale from 0 (*no pain*) to 10 (*pain as bad as you can imagine*). Anie et al. (2002) used the Structured Pain Interview (Gil et al., 1989, 1992) and asked participants to rate their pain intensity on a scale from 0 to 10 but also inquired about number and average duration of pain episodes in the past twelve months. Anie and colleagues (2002) did not find a significant association between pain and mental HRQoL, which is consistent with the results of this study. Other researchers, such as McClish et al. (2005) and Ballas et al. (2006), used daily diary methods to collect data about pain. Ballas and colleagues (2006) calculated mean daily pain over 28 days, and McClish et al. (2005) used mean daily pain and the percentage of days in which participants experienced a pain crisis over six months. The researchers found that pain

was significantly correlated with mental HRQoL. These findings suggest that cross-sectional pain data (especially questionnaires that ask about pain in the past 24 hours) may not be representative of usual pain and subsequently not related to mental HRQoL, whereas daily diary data that considers pain over several days may be associated with mental HRQoL. Additionally, pain frequency, duration, and unpredictability may be more strongly related to mental HRQoL compared to pain severity. Thus, investigators should consider examining multiple dimensions of pain in future research, especially when evaluating the correlation between pain and mental HRQoL. Such research may help elucidate which facets of pain are most related to perceived well-being and functioning among adults with SCD.

Another possible explanation for why fatigue was not significantly associated with mental HRQoL, as found in a previous study (Ameringer et al., 2014), is related to statistical power. There was possibly insufficient power to detect significant effects. Specifically, 115 participants were needed to obtain power of .80 and to detect genuine effects that may exist in the population, whereas the current study consisted of 58 participants.

Regarding the relationship between disease/treatment factors (pain, fatigue, ED visits) and illness intrusiveness, fatigue was positively associated with illness intrusiveness, meaning as individuals reported greater fatigue, they also experienced more disease-related interference in their lives. This finding is consistent with the hypothesis and existing literature (Goudsmit et al., 2009; Shawaryn et al., 2002). Contrary to the study hypothesis and previous research (Bloom et al., 1998; Devins, 1990), pain and ED visits were not significantly associated with illness intrusiveness.

There are a number of potential reasons why pain and ED visits were not significantly correlated with illness intrusiveness in this sample.

One possible explanation for the statistically nonsignificant results is that sources of interference in one's life may vary by chronic health condition. This means that some disease and treatment factors that have been found to be related to illness intrusiveness in other conditions may not be most relevant in SCD. While there is support for the IITF, the research has mostly focused on adults with conditions such as breast cancer, type II diabetes, end stage renal disease, and multiple sclerosis (Bloom et al., 1998; Devins, 1990; Devins, 2010; Goudsmit, Stouten, & Howes, 2009; Shawaryn et al., 2002), and less is known about conditions such as SCD that are present at or before birth. For individuals with conditions such as breast cancer, type II diabetes, end stage renal disease, and multiple sclerosis, there is a time frame (i.e., pre-diagnosis of the condition) in which the individual did not experience disease or treatment factors that contribute to lifestyle disruptions. Conversely, those with conditions such as SCD experience disease or treatment factors since birth and may, by extension, have a longer time frame in experiencing the challenges that possibly interfere with activities and interests. Similarly, adults with conditions such as SCD may perceive some disease and treatment factors, such as pain and frequent ED visits, as less intrusive compared to adults with other conditions, because they have been managing the health condition since infancy or early childhood.

Rather than pain and ED visits, other disease and treatment factors (e.g., poor sleep, stiffness, hypertension, obesity, stigma) may be related to illness intrusiveness. As life expectancy has been increasing among adults with SCD (Lanzkron et al., 2013), there

has been more concern about health issues that have historically impacted the broader African American community (Pells et al., 2005; Woods et al., 2001). It may be these newly presenting disease and treatment factors that are perceived as disruptive for adults with SCD. Thus, as the SCD population ages, future studies should assess disease and treatment factors that are potentially newer for SCD patients, or typically more prevalent in older rather than younger communities.

When examining reasons why fatigue but not pain was significantly associated with illness intrusiveness in this sample, it may also be helpful to consider differences between pain and fatigue in this population. Individuals with SCD have likely experienced both pain and fatigue for many years; however, pain is the hallmark symptom of the disease and seemingly the focus in clinical practice, much like research. Therefore, adults with SCD may have a better understanding of pain compared to fatigue. This could lead to individuals with SCD expecting to experience pain and engaging in valued activities despite having pain, whereas they may be less informed about fatigue, have fewer strategies for managing the symptom, and ultimately find it more disruptive. Also, like pain, several biological (e.g., anemia, vaso-occlusive crises) and behavioral (e.g., stress, poor sleep) factors likely contribute to fatigue in SCD (Ameringer & Smith, 2011). Fatigue, however, is also a symptom of major depressive disorder and generalized anxiety disorder, which are psychological disorders characterized by clinically significant distress or impairment in social, occupation, academic, or other important areas of functioning (American Psychiatric Association, 2013). In research and practice, it is difficult to distinguish fatigue related to psychological disorders (e.g., depression, anxiety) from fatigue caused by physical conditions. Nevertheless, SCD patients who

report fatigue may have a psychological disorder, which would lead to disruptions in important life domains and may explain why fatigue, but not pain and ED visits, was associated with illness intrusiveness.

In the IITF literature, less is known about ED visits specifically, as most research examining treatment factors has focused on treatment modalities, such as radiation compared to chemotherapy in cancer (Bloom et al., 1998), pharmacological versus surgical interventions in epilepsy (Poochikian-Sarkissian et al., 2008a), and a comparison of hemodialysis, continuous peritoneal dialysis, and successful renal transplant in end stage renal disease (Devins, 1983). Notwithstanding the literature, it was hypothesized that ED visits would be positively associated with illness intrusiveness, as individuals who frequently visit the ED may have to miss more work or leisure activities. Notably, there was limited variability for the ED visit scores, which may have reduced the likelihood of detecting significant effects. Scores for number of ED visits ranged from 0 to 14; however, 69% of the sample reported fewer than three visits in the past twelve months. Additionally, the standard deviation was larger than the mean, suggesting that most of the participants visited the ED infrequently.

Next, illness intrusiveness was negatively correlated with physical and mental HRQoL. As disruptions in activities increased, physical and mental HRQoL was worse for individuals. The results are consistent with the study hypothesis and previous research (Devins, 2010). Altogether, pain, fatigue, and ED visits were significantly associated with physical, but not mental, HRQoL. Fatigue, but not pain and ED visits, was significantly correlated with illness intrusiveness. Furthermore, illness intrusiveness was significantly related to physical and mental HRQoL. After evaluating the aforementioned bivariate

correlations, I examined whether illness intrusiveness mediated the association between disease/treatment factors (pain, fatigue, ED visits) and HRQoL (physical and mental). According to Baron and Kenny (1986), the independent variable must be associated with the dependent variable in order to explore mediation (i.e., a third variable mediates or explains the association between the predictor and outcome variables). In this study, some predictor (pain, ED visits) and outcome variables (physical and mental HRQoL) were not related; therefore, many researchers would not examine mediation. However, more recent literature suggests that an indirect effect can be present in the absence of a significant association between the independent and dependent variables (Fairchild & McDaniel, 2017; MacKinnon et al., 2002; Zhao, Lynch, & Chen, 2010). Also, mediation was conducted using the PROCESS macro, which does not require that the predictor and outcome variables be associated (Field, 2013). Thus, I conducted mediation for the proposed hypotheses despite the following associations being statistically nonsignificant: (1) the association between disease/treatment factors (pain, fatigue, ED visits) and mental HRQoL and (2) the association between disease/treatment factors (pain, ED visits) and illness intrusiveness.

Results revealed that illness intrusiveness mediated the association between fatigue and physical HRQoL, which supports the hypothesis and is consistent with previous literature (Ahmed et al., 2016; Anie et al., 2002; Ameringer e al., 2014; Ameringer & Smith, 2011; Ballas et al., 2006; Goudsmit et al., 2009; Jackson et al., 2014; McClish et al., 2005; Shawaryn et al., 2002). As postulated by the IITF, the finding suggests that as fatigue increases among adults with SCD, they are more likely to have compromised physical HRQoL because they have more disruptions in life activities. The

results also indicated a significant indirect effect of (1) fatigue on mental HRQoL through illness intrusiveness and (2) ED visits on physical HRQoL through illness intrusiveness. For the indirect effect of fatigue on mental HRQoL through illness intrusiveness, however, the total effect, or the association between the predictor (fatigue) and outcome variable (mental HRQoL), was nonsignificant. As previously noted, a statistically significant total effect does not have to be established for there to be a significant indirect effect (Fairchild & McDaniel, 2017; MacKinnon et al., 2002; Zhao et al., 2010). According to Zhao and colleagues (2010), such a finding is termed indirect-only mediation. Similarly, for the indirect effect of ED visits on physical HRQoL through illness intrusiveness, the association between the predictor and outcome variable was significant; however, number of ED visits (predictor variable) was not significantly correlated with illness intrusiveness (mediator). My review of the literature yielded less information about how to interpret an indirect effect if the predictor variable is not significantly related to the mediator rather than the outcome variable. Although it may not be necessary to have a significant association between the predictor variable and the mediator or outcome variable, I considered possible reasons for the nonsignificant associations. One plausible explanation is that there was insufficient power to detect significant effects, as statistical power for the regression coefficient for the association between fatigue and mental HRQoL was .39, and 160 participants were needed to obtain power of .80 and possibly detect genuine effects. Furthermore, the regression coefficient for the association between ED visits and illness intrusiveness was .36, and 172 participants were needed to obtain power of .80 and possibly detect real effects that exist in the population. Nevertheless, there was a significant indirect effect of fatigue on

mental HRQoL through illness intrusiveness and of ED visits on physical HRQoL through illness intrusiveness. Regarding the other mediation analyses, the results were inconsistent with hypotheses, as illness intrusiveness did not mediate the association between (1) pain and physical HRQoL; (2) pain and mental HRQoL; and (3) ED visits and mental HRQoL.

In the IITF, contextual factors are hypothesized to be related to HRQoL. Therefore, the second aim of the study was to examine whether age and sex would be associated with HRQoL in this sample. As expected, age was negatively associated with physical HRQoL, meaning older participants reported poorer physical HRQoL. The results also revealed that age was positively associated with mental HRQoL. This finding was inconsistent with previous research that has found a nonsignificant correlation between age and mental HRQoL (Asnani et al., 2008; Dampier et al., 2002). Due to limited research in this area, it is difficult to conclude why age was significantly related to mental HRQoL in this sample but not others. One plausible explanation is that adults with SCD perceive themselves to have poor physical HRQoL over time but have had more time to adapt and develop coping strategies to manage the psychosocial stressors associated with their condition. The present study also showed no sex difference in HRQoL. This means that females and males reported similar levels of HRQoL. This is inconsistent with previous research suggesting that females have poor physical HRQoL compared to males (Dampier et al., 2002; Jackson et al., 2014). Sixty-nine percent of the current sample was female; therefore, there may have been lack of power to detect differences between the groups.

The latter half of the IITF focuses on perceived control. While the framework does not make a distinction between types of perceived control, chronic pain researchers have examined perceived control over pain and identified three primary dimensions: (1) beliefs about one's control over life in general; (2) beliefs about one's control over the impact of pain (and other symptoms) on daily life; and (3) beliefs about one's control over pain itself (Tan et al., 2002). In the third aim of the study, I expanded on previous IITF and chronic pain research by exploring the role of the three dimensions of perceived control in relation to illness intrusiveness and HRQoL. It was hypothesized that (1) illness intrusiveness would be negatively associated with the three dimensions of perceived control – (a) perceived control over life in general; (b) perceived control over the effects of SCD symptoms; and (c) perceived control over pain itself; (2) the three dimensions of perceived control would be positively associated with HRQoL; and (3) the three dimensions of perceived control would mediate the association between illness intrusiveness and HRQoL. In the sample, illness intrusiveness was negatively correlated with all the dimensions of perceived control. These findings are consistent with the study hypothesis, previous research, and the IITF, which proposes that individuals who experience disruptions in meaningful activities may perceive themselves as having little control over aspects of their life (Bishop et al., 2008; DeCoster et al., 2008; Devins et al., 1983; Devins et al., 1993; Devins, 2010; Hundt et al., 2015; Paukert et al., 2009; Poochikian-Sarkissian et al., 2008a).

I also found that the three dimensions of perceived control were positively correlated with mental HRQoL. As perceived control over life, perceived control over the effects of SCD symptoms, and perceived control over pain increased, mental HRQoL

improved. Notably, based on correlations, perceived control over life and perceived control over the effects of SCD symptoms were more strongly related to mental HRQoL compared to perceived control over pain. The results are consistent with the hypothesis and existing literature (Bishop et al., 2008; DeCoster et al., 2013; Devins et al., 1983; Devins et al., 1993; Gibson et al., 2013; Haythornthwaite, Menefee, Heinberg, & Clark, 1998; Poochikian-Sarkissian et al., 2008a; Tan et al., 2002; Vallerand et al., 2016). In a sample of adults with chronic pain, Tan and colleagues (2002) also found that perceived control over life and perceived control over the effect of pain and other symptoms are more strongly associated with functioning (e.g., pain severity, disability, and depression) than perceptions of control over pain. Furthermore, Tan et al. (2002) found that perceived control over the effects of pain and other symptoms was more strongly related to functioning (disability and pain severity) than perceived control over life in general, which suggests that pain/symptom-specific beliefs may be even more important than general control beliefs when the outcome is related to physical health. These findings may help explain why perceived control over the effects of SCD symptoms was positively associated with physical HRQoL, but the other two dimensions of perceived control – perceived control over life and perceived control over pain – were not significantly related to physical HRQoL.

There are a few other possible explanations for why perceived control over the effects of SCD symptoms, but not perceived control over life and pain, was associated with physical HRQoL. First, perceived control over the effects of SCD symptoms may reflect an individual's coping strategy use more than the other two dimensions of perceived control. SCD patients who believe they can manage symptoms of their disease

may utilize more effective coping strategies compared to those who feel that they are able to control their life and pain, which can both be quite unpredictable. Second, the instrument used to assess perceived control over the effects of SCD symptoms considers other aspects of the disease (e.g., sleep, fatigue, and frustration) besides pain. Measures that recognize the impact of multiple disease factors may be more predictive of physical HRQoL compared to ones that solely focus on pain (e.g., SOPA) or control over life in general (e.g., WHYMPI). Finally, few studies have examined the relationship between perceived control and physical HRQoL, as most of the previous literature has evaluated the association between perceived control and psychosocial outcomes such as affect, depression, anxiety, and subjective well-being. Thus, the current study indicates that investigators should carefully identify which dimension(s) of perceived control they are evaluating and consider whether they are interested in physical HRQOL, mental HRQoL, or both, as these components may impact the results of future research.

Next, I examined whether the three dimensions of perceived control mediated the association between illness intrusiveness and HRQoL (physical and mental). Perceived control over life mediated the association between illness intrusiveness and mental HRQoL. This finding supports the study hypothesis and the IITF, which postulates that illness intrusiveness, or disruptions in important life domains, compromises HRQoL by: reducing perceived control (i.e., belief that one can influence outcomes in important life domains) by limiting an individual's ability to obtain positive outcomes or to avoid negative ones. All other mediation analyses were statistically nonsignificant including: (1) perceived control over life mediating the association between illness intrusiveness and physical HRQoL; (2) perceived control over the effects of SCD symptoms mediating the

association between illness intrusiveness and physical HRQoL; (3) perceived control over the effects of SCD symptoms mediating the association between illness intrusiveness and mental HRQoL; (4) perceived control over pain mediating the association between illness intrusiveness and physical HRQoL; (5) perceived control over pain mediating the association between illness intrusiveness and mental HRQoL. Of note, all mediation models were nonsignificant when a multiple mediator model was used or when depression was included as a covariate.

Since there is limited research in this area, it is difficult to draw conclusions about why perceived control over life mediated the association between illness intrusiveness and mental HRQoL, but the other mediation models were nonsignificant. However, there are some plausible explanations. As Tan et al. (2002) found, perceived control over the effects of disease symptoms may be most strongly related to physical HRQoL compared to perceived control over life and pain itself, but perceived control over life is equally, if not more strongly, related to mental HRQoL. This is consistent with the current findings that revealed that perceived control over life was more strongly associated with mental HRQoL compared to perceived control over pain itself and the effects of SCD symptoms. Thus, it is not surprising that perceived control over life served as a mediator between illness intrusiveness and mental HRQoL. Also, most studies that have found support for the IITF have evaluated perceived control over important life domains rather than perceived control over the effects of symptoms or pain. Therefore, it is possible that the IITF is most applicable for examining perceived control over life as a mediator of illness intrusiveness and HRQoL (at least mental HRQoL) compared to perceived control over pain and the effects of disease symptoms. Finally, there was insufficient power to detect

additional significant effects of mediation in the small sample. Based on a priori sensitivity analysis, a sample size of 58 would only detect an indirect effect for joint significance tests with small effects sizes for α and β (Fritz & McKinnon, 2007). To detect an indirect effect of (α)(β) = (0.26) (0.26), a sample size of 148 was needed and to detect an indirect effect of (α)(β) = (0.39) (0.39), a sample size of 71 was needed.

Theoretical Implications

The current findings have important theoretical implications. First, the IITF postulates that disease/treatment factors are associated with HRQoL. The results partially supported the theory, as pain, fatigue, and number of ED visits were negatively associated with physical, but not mental, HRQoL in this sample. This suggests that the IITF should make a distinction between physical and mental HRQoL.

Next, the IITF hypothesizes that disease/treatment factors are associated with illness intrusiveness. In this sample, fatigue, but not pain and number of ED visits, was positively associated with illness intrusiveness, which provides partial support for the theory. This finding indicates that the IITF should be tested in diverse disease populations, as the association between disease/treatment factors and illness intrusiveness may vary across health conditions. Another hypothesis of the IITF is that illness intrusiveness is associated with HRQoL. In the current study, illness intrusiveness was strongly associated with physical and mental HRQoL, which supports the theory. In the IITF, illness intrusiveness, which captures perceived disruptions in life activities, seems to be an important and robust factor, including when studying HRQoL in adults with SCD. Furthermore, the IITF assumes that activities are valuable and reinforcing to individuals (see limitation sections for more discussion of this topic). Rather than making

this assumption, the IITF should incorporate level of importance ascribed to life activities, possibly as a moderator. Finally, the central tenant of the IITF is that illness intrusiveness mediates the association between disease/treatment factors and HRQoL. The results partially supported the theory, as illness intrusiveness served as a mediator between fatigue and both physical and mental HRQoL and between number of ED visits and physical HRQoL. Based on these findings, one can infer that the IITF may be not comprehensive, as illness intrusiveness only partially mediated the association between some disease/treatment factors and HRQoL. The IITF should consider other potential mediators or mechanisms that explain the link between disease/treatment factors and HRQoL and possibly add a direct link between disease/treatment factors and HRQoL.

The present study differed from previous research in the IITF literature, as I examined three dimensions of perceived control including perceived control over life, perceived control over the effects of SCD symptoms, and perceived control over pain. In the IITF, illness intrusiveness is hypothesized to be associated with perceived control. All three dimensions of perceived control were negatively associated with illness intrusiveness in this sample, which supported the theory. Moreover, as hypothesized by the theory, all three dimensions were positively associated with mental HRQoL, whereas perceived control over the effects of SCD was the only dimension significantly correlated with physical HRQoL. Altogether, the results indicate that perceived control over life and perceived control over the effects of SCD may be more robust that perceived control over pain. Perceived control over life was most strongly related to mental HRQoL, and perceived control over the effects of SCD had the strongest correlation with physical HRQoL. This suggests that there are multiple dimensions of perceived control, and the

association between perceived control and HRQoL may vary based on the object of control (i.e., behavior or outcome and life in general or symptoms of disease) being assessed. As such, the IITF should make a distinction between general perceived control (i.e., perceived control over life in general) and disease-specific perceived control (i.e., perceived control over symptoms of disease). Or, the IITF should distinguish between perceived control over outcomes (as assessed by locus of control and perceived control over life in general) from perceived control over behaviors (i.e., self-efficacy or perceived capacity to perform specific actions that will result in a desired outcome).

One of the other main tenants of the IITF is that perceived control mediates the association between illness intrusiveness and HRQoL. In this study, perceived control over life mediated the association between illness intrusiveness and mental HRQoL. The mediation effect was no longer significant after controlling for the other dimensions of perceived control and depression. Moreover, none of the other dimensions of perceived control served as a mediator between illness intrusiveness and physical or mental HRQoL. These findings suggest that perceived control, at least over life, may be an important variable to consider when studying mental HRQoL in the context of the IITF. It also suggests that statistically it may be difficulty to include all three dimensions of perceived control into the same model. Hence, it may be better to include only the two strongest predictors (i.e., perceived control over life and perceived control over symptoms of the disease) or the strongest predictor for the specific outcome (i.e., perceived control over life for mental HRQoL and perceived control over symptoms of the disease for physical HRQoL). As noted above, I also considered the effect of depression. In previous IITF literature, several researchers have evaluated depression as

the outcome variable or proxy for HRQoL. However, it could be considered a psychosocial factor or even disease factor. Thus, the IITF should elaborate on the role of depression, and potentially anxiety.

Regarding contextual factors, the IITF posits that age and sex are related to HRQoL. In this study, age was negatively associated with physical HRQoL and positively associated with mental HRQoL, which supported the theory. There was no sex difference in HRQOL, which did not support the IITF. These findings provide additional support for the need to make a distinction physical and mental HRQoL in the IITF. Furthermore, it suggests that the IITF should continue to include contextual factors in the framework, as they may be related to HRQoL. Additionally, the role of contextual factors may vary by sample and chronic health population. Therefore, the IITF should test how contextual factors relate to HRQoL in various chronic health conditions.

Clinical Implications

A few clinical implications can also be drawn from the results of this study. First, the findings highlight the importance of assessing psychosocial factors in healthcare settings where adults with SCD receive services, as these factors are related to HRQoL in this population. Furthermore, fatigue emerged as an important disease factor in this sample. Since fatigue is likely influenced by several biobehavioral factors, including anemia, pain crises, and poor sleep, and is also a symptom of psychological disorders such as depression and anxiety, healthcare providers should conduct a thorough assessment of fatigue to determine the most probable cause(s) of the symptom. Such an assessment can help with disease management and treatment planning. When fatigue is determined to be mostly related to anemia or other biological processes, providers can

utilize pharmacological interventions according to medical practices and guidelines. For SCD patients who also seem to be experiencing issues with depression and anxiety, healthcare personnel can refer individuals for comprehensive psychological assessment and intervention. Additionally, therapists with expertise in health and rehabilitation psychology likely have training in behavioral interventions for managing pain and fatigue related to physical health conditions. More research is needed to identify how existing behavioral interventions can be adapted for adults with SCD, especially for fatigue management.

The present study also suggests that disruptions caused by disease and treatment factors explain, at least in part, compromised HRQoL in adults with SCD. Furthermore, perceived control serves as a mechanism through which disruptions in life impact HRQoL. These findings illustrate that intervention and prevention efforts that target cognitive appraisals (e.g., beliefs about control over life or the effects of SCD symptoms) and encourage individuals to engage in valued activities despite experiencing disease and treatment factors associated with SCD may lead to improved HRQoL. Cognitive Behavioral Therapy (CBT; Beck, 2011), Behavioral Activation (BA; Jacobson et al., 1996), and Acceptance and Commitment Therapy (ACT; Hayes, Strosahl, & Wilson, 2012) are psychological interventions that address cognitive appraisals and associated behaviors, including avoidance or disengagement from important activities.

CBT is an evidence-based psychotherapy that has been found to be effective for a wide range of problems including depression, anxiety, and marital distress (Beck, 2011). Robust studies suggest that CBT leads to significant improvement in functioning and QoL. The core principles of the treatment are that psychological and some physical

problems are based, in part, on unhelpful or unrealistic ways of thinking and learned patterns of unhelpful behavior. In particular, the cognitive model posits that thoughts, beliefs, and attitudes affect an individual's feelings, emotions, behavior, and physiology. The intervention is rooted in the idea that individuals can learn better ways to cope with their problems by altering their thoughts and related behaviors. Although CBT was originally developed for depression and anxiety, the treatment approach has been applied to the management of chronic pain, and studies have found that it helps improve functioning and QoL for a variety of chronic pain conditions (Murphy et al., 2014). Although there is less research support for behavioral interventions for fatigue compared to pain, CBT has also been used for fatigue management (Deale, Chalder, Marks, & Wesseley, 1997; Malouff, Thorsteinsson, Rooke, Bhullar, & Schutte, 2008; Menting, Tack, Donders, & Hans, 2018; Montgomery et al., 2009). CBT for fatigue involves exercise, pacing (practice of engaging in an appropriate level of physical activity), relaxation training, cognitive restructuring (identify unhelpful thoughts and increase balanced thinking), and behavioral activation (increase engagement in rewarding and meaningful activities). Of note, behavioral activation has been found to be an effective stand-alone intervention for psychological and behavioral issues (Jacobson et al., 1996).

ACT is another empirically supported psychotherapy that focuses on helping individuals identify, and be more willing to experience, their emotions rather than avoid them (Hayes et al., 2012). Instead of changing thoughts, ACT encourages individuals to be more in the present moment and distance the self from negative and unhelpful ways of thinking. Another key element of the intervention is the focus on identifying valued activities and developing a plan to engage in these activities despite psychological and

physical problems. This treatment approach has been found to be efficacious for a wide range of health conditions. Future studies should examine CBT and ACT in adults with SCD.

Limitations

There are several limitations that should be considered. First, the study had fewer participants than originally proposed, which decreased the statistical power to detect small effects for correlation and small to moderate effects for mediation. Since the potential mediating effects of the perceived control variables on the relation between illness intrusiveness and HRQoL were small to moderate, there was a high risk for Type II error, or falsely failing to reject the null hypothesis (Field, 2013). It is recommended that future research explore the potential mediating effects of the perceived control variables in the context of the IITF using a larger sample size. Similarly, underpowered studies with a small sample size also result in larger variance compared to those with adequate power and a larger sample size. In this study, variance was larger than the mean for ED visit and GAD-7 scores, which suggests there were relatively few ED visits and a minority who scored high on the GAD-7. Large variance is concerning, because it can increase the risk of Type I error, or falsely rejecting the null hypothesis. The current study should be replicated using a larger sample size to decrease the risk of Type I error.

Second, there were some issues during the data collection phase. Initially, participants were recruited from a single adult sickle cell clinic in the mid-Atlantic. Due to limited interest in the study, I expanded the scope of recruitment to other sickle cell clinics and sickle cell organizations across the United States. Interested persons were required to provide evidence of their sickle cell diagnosis by emailing the following: 1)

the name of their sickle cell provider; 2) the name and location of the treatment facility where they receive sickle cell care; and 3) a copy of a medical document with their sickle cell diagnosis listed. Only individuals who provided proof of their diagnosis were sent a link to the survey. The inclusion criteria was designed to strengthen the quality and integrity of the study; however, it possibly limited who gained access to and completed the study, as individuals needed a desktop/laptop computer, tablet, or smartphone, to be able to obtain documentation with their sickle cell diagnosis listed, and to feel comfortable sharing this information via email. Nevertheless, it is recommended that future researchers obtain evidence of participants' sickle cell status, or ideally, for individuals to be directly recruited and enrolled in the study from multiple sickle cell clinics across the country where investigators have access to patients' medical records. If possible, it would also strengthen the results if individuals interested in the study were given the option to complete a hardcopy or online version of the survey.

Although participants were recruited from multiple sites across the country, the findings of this study have limited generalizability, because the sample mostly consisted of females (i.e., 69% identified as female) and was highly educated (i.e., 88% completed at least some college and 59% earned a bachelor's or advanced degree). For this reason, I caution against generalizing the findings to males and individuals with lower levels of education. Future research should include a broader sample that includes more males and individuals with a wider range of educational backgrounds. Furthermore, I do not know how representative this sample is of the SCD population, which means that the results of this study may not generalize to individuals with SCD of any sex, education, or other demographic characteristic.

Another limitation of this study is that all variables were assessed using self-report questionnaires, which are prone to social desirability and recall bias. Participants may have had difficulty remembering how many times they visited the ED in the past year. While there is research that self-reported number of ED visits is strongly related to estimates found in medical records, it is recommended that future research obtain demographic and clinical information, such as age, sex, genotype, and number of ED visits in the past twelve months, from chart review, which is likely more reliable and valid than self-report.

In the current study, I used the IIRS to assess disruptions in 13 life domains including health, diet, work, active recreation, passive recreation, financial situation, relationship with partner, sex life, family relations, other social relations, self-improvement/self-expression, religious expression, and community and civic involvements. I unintentionally omitted two items (both from family relations subscale) from the measure assessing illness intrusiveness; therefore, I cannot be sure that I fully captured the illness intrusiveness construct. On the contrary, one item of the family relations subscale was included; therefore, all 13 life domains were assessed, which means that the construct was likely captured to some extent. Additionally, participants reported substantial interference in their lives with two items omitted from the family relations subscale. The inclusion of the two items could have potentially resulted in higher levels of reported illness intrusiveness and a stronger association between illness intrusiveness with disease/treatment factors, perceived control, and HRQoL.

There are assumptions of the framework and mediation analysis that should also be considered. First, the IITF proposes that illness intrusiveness mediates the association

between disease/treatment factors and HRQoL and that perceived control mediates the association between illness intrusiveness and HRQoL. According to Fairchild and McDaniel (2017), mediation "implies a causal process that connects at least two variables." Moreover, the authors note the following:

> Mediation in cross-sectional data undermines an assumption of the statistical mediation model: the presumption that temporal ordering of variables in the causal chain of mediation is correct. Cross-sectional data preempt the evaluation of alternative temporal ordering of the variables to test the correct causal ordering assumption, and the nature of cross-sectional data lies in contradiction to examining a process that unfolds over time (p. 1265).

This point highlights that a causal relationship or the temporal ordering could not be established among variables in this cross-sectional data. Furthermore, future research using the IITF should conduct experimental studies, so we can evaluate the temporal ordering of the variables in the framework and make inferences about causality. Future studies should also utilize path analysis to examine the goodness of fit for the full model proposed within the IITF, as most previous research has only evaluated parts of the theoretical framework. If path analysis is used, 10-20 observations will be needed for every parameter (Streiner, 2005); therefore, researchers should consider conducting a priori power analysis and recruit an adequate sample size to conduct path analysis and subsequently test the framework.

Another assumption inherent in the IITF is that the 13 life domains assessed by the IIRS are valuable or meaningful for individuals. While the 13 life domains are often important for individuals, this is not necessarily true for all individuals or people with a

specific chronic health condition. In this study, participants were able to indicate if a domain was "not applicable" for them, which is possibly a way for them to express that a domain is not important for them. However, this would be another assumption. In one study, Bishop et al. (2008) administered the Disability Centrality Scale, which assesses the following for all 13 life domains: 1) How important is this part of your life to your overall quality of life; 2) How satisfied are you with how this part of your life is going? 3) How much control do you have over changing this part of your life? 4) How much does your illness or disability and/or its treatment impact your ability to function. Instead of assuming life domains were important, the authors simply asked participants. Additionally, there was good internal consistency for the importance subscale (Cronbach α= .74). To my knowledge, this is the only study that has included a measure of perceived importance for each domain. To explicitly test the assumption that each domain is valuable to participants, it recommended that future research examining the IITF consider including the importance subscale of the Disability Centrality Scale.

Strengths

Despite these limitations, the present study had some strengths. First, I considered several demographic and disease-related variables, including age, sex, education, employment status, marital status, genotype, and hydroxyurea use, as potential covariates. Age was the only variable significantly associated with HRQoL in this sample; therefore, it was the only demographic and disease-related factor, besides pain and fatigue, included as a covariate. Nevertheless, consideration of these variables reduced the likelihood that significant findings were due to a confounder or spurious effects. Another strength of the study is that I utilized well-developed, reliable, and

validated self-report measures with sufficient internal consistency. Regarding data analysis, I carefully chose appropriate statistical tests to answer research questions and test specific hypotheses. For example, to examine whether HRQoL was associated with dichotomous variables such as sex and genotype, I conducted a point-biserial correlation, and to explore whether HRQoL was associated with pain and fatigue (continuous variables), I conducted a Pearson correlation. Similarly, I used biased-corrected bootstrapping, which is the most powerful test of mediation (Fritz & MacKinnon, 2007). I also conducted preliminary data screening to check for problems with the assumptions of each statistical test. The assumption of normality was not met for the analyses. ED visits and PHQ-9 scores were positively skewed and positively kurtotic. Furthermore, GAD-7 scores were positively skewed. To address issues with normality, robust tests (e.g., bootstrapping) were used for all analyses.

Recommendations for Future Research

Since there were several limitations in this study, the following are recommendations for future research. First, I strongly recommend that researchers conduct a priori power analysis to determine the sample size necessary to detect genuine effects and then collect data from an adequate sample. When evaluating mediation, it is recommended that researchers consult Fritz and MacKinnon's (2007) article that provides the necessary sample size for six of the most common and strongly recommended tests for mediation for various combinations of parameters (i.e., combinations of α and β with small, moderate, and large effects). Second, it is recommended that future research include additional psychosocial variables that may be associated with HRQoL, such as health insurance status, sleep, stiffness, perceived stress, catastrophizing, acceptance,

coping, social support, patient-physician communication, (mis)trust of healthcare providers, and perceived stigma; this will increase the internal validity of the study. Furthermore, these psychosocial factors may function as disease/treatment factors or mediators within the IITF. Third, future studies should use a prospective or longitudinal design to evaluate mediation in the context of the IITF. Additionally, using daily diary methods and assessing various aspects of pain, such as pain frequency, duration, and unpredictability, may strengthen future research. Finally, researchers should consider using a disease-specific measure of HRQOL (e.g., ASCQ-Me) rather than general instruments such as SF-12, SF-36, and WHOQOL-BREF.

Conclusion

The present study is the first to examine illness intrusiveness and perceived control as mechanisms that may explain the association between prominent disease/treatment factors and HRQoL in a sample of adults living with SCD. The results of this study indicated that pain, fatigue, and ED visits were related to compromised HRQoL; however, fatigue was the only disease or treatment factor associated with disruptions in activities in this sample. This highlights that fatigue is an important symptom of the disease. Additional research is needed to better understand the nature and mechanisms of fatigue among adults with SCD. The current findings also revealed that disruptions in activities, coined illness intrusiveness, served as a mediator between fatigue and HRQoL. Finally, perceived control over life explained the association between illness intrusiveness and mental HRQoL. Future studies may benefit from evaluating psychosocial factors (e.g., illness intrusiveness, perceived control, coping) that may impact well-being among adults with SCD. An enhanced understanding of such

factors may contribute to the development of high-quality assessments and interventions that can aid in improving HRQoL in this population.

Table 1.

Descriptive Statistics for Continuous Study Variables (N = 58)

	Minimum	Maximum	Mean	SD	Skewness	Kurtosis
Age	18	69	39.12	12.73	.57	-.86
BPI	0	9	3.25	2.34	.20	-.71
BFI	0	9.67	5.20	2.71	-.48	-.68
ED	0	14	2.17	3.01	2.07	4.81
II	11	72	41.38	15.52	.20	-.70
WHY	0	6	3.61	1.64	-.48	-.68
SCSES	10	44	27.67	7.17	.02	-.16
SOPA	0.40	3.60	2.25	0.90	-.22	-.97
SFp	18.17	59.38	38.39	11.23	.19	-1.17
SFm	17.90	60.90	43.86	10.06	-.25	-.49
PHQ	0	25	7.41	5.43	1.26	1.63
GAD	0	20	5.62	5.34	1.14	.41

Note. BPI = Brief Pain Inventory; BFI = Brief Fatigue Inventory; ED = Emergency Department Visits; II = Illness Intrusiveness; WHYMPI = West-Haven-Yale Multidimensional Pain Inventory Life Control Scale; SCSES = Sickle Cell Self-Efficacy Scale; SOPA = Survey of Pain Attitudes Control Scale; SFp = Physical HRQoL; SFm = Mental HRQoL; PHQ = Patient Health Questionnaire; GAD = Generalized Anxiety Disorder 7-Item Scale.

Table 2.

Frequencies for Categorical Study Variables (N = 58)

	Groups	n	Percentage
Sex			
	Male	18	31.00
	Female	40	69.00
Race			
	Black	55	94.80
	Biracial	3	5.20
Education			
	High School / GED	7	12.10
	Some college	17	29.30
	Bachelor's degree	21	36.20
	Advanced degree	13	22.40
Employment			
	Employed	33	56.90
	Not employed	25	43.10
Marital status			
	Single	36	62.10
	Partnered	14	24.10
	Previously Partnered	8	13.80
Genotype			
	SS / $S\beta^0$	38	65.50
	SC / $S\beta^+$ / Other	20	34.50
HU			
	Yes	26	44.80
	No	32	55.20

Note. HU = Hydroxyurea.

Table 3.

Correlations Among Study Variables (N = 58)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1 Sex	-														
2 Employ	-.09	-													
3 Geno	-.22	.10	-												
4 HU	-.01	.08	.36^	-											
5 Age	.20	.05	.10	.11	-										
6 BPI	-.01	.37^	.14	.08	.12	-									
7 BFI	.17	.11	-.07	-.18	-.19	.40^	-								
8 ED	-.21	.16	.23	.15	-.19	.27*	.13	-							
9 II	.04	.05	.06	.06	.003	.15	.38^	.20	-						
10 WHYMPI	-.05	.15	-.12	.06	.17	-.13	-.43^	-.01	**-.49#**	-					
11 SCSES	.07	-.11	-.27*	-.11	-.12	**-**.38^	-.24	-.14	**-.64#**	**.52#**	-				
12 SOPA	.22	-.23	-.33*	-.14	.05	-.29*	.05	-.24	-.39^	.26*	**.69#**	-			
13 SFp	-.25	-.24	-.12	.02	-.36^	**-.59#**	-.43^	-.36^	**-.53#**	.16	**.46#**	.20	-		
14 SFm	.10	-.05	.12	-.08	.30*	-.06	-.26	.04	**-.45#**	**.47#**	.38^	.30*	-.07	-	
15 PHQ	-.19	.03	-.14	-.03	-.21	.12	.34^	-.01	**.45#**	-.42^	**-**.38^	-.27*	-.01	**-.74#**	-
16 GAD	-.26*	-.02	-.11	-.01	-.32*	.05	.24	-.02	.43^	-.41^	**-.45#**	-.34*	.05	**-.71#**	**.86#**

Note. Employ = Employment status; Geno = Genotype; HU = Hydroxyurea; BPI = Brief Pain Inventory; BFI = Brief Fatigue Inventory; ED = Emergency Department Visits; II = Illness Intrusiveness; WHYMPI = West-Haven-Yale Multidimensional Pain Inventory Life Control Scale; SCSES = Sickle Cell Self-Efficacy Scale; SOPA = Survey of Pain Attitudes Control Scale; SFp = Physical HRQoL; SFm = Mental HRQoL; PHQ = Patient Health Questionnaire; GAD = Generalized Anxiety Disorder 7-Item Scale.

Employment status: Employed = 0, Not Employed = 1; Genotype: SS / $S\beta^0$ = 0, SC / $S\beta^+$ / Other = 1; HU: Yes = 0, No = 1

*p < .05
^p < .01
#p<.001

Table 4.

Physical and Mental HRQoL for Four Education Groups (N = 58)

	Physical HRQoL		Mental HRQoL	
Education	*M*	*SD*	*M*	*SD*
HS/GED	39.62	12.28	45.78	10.63
Some college	37.89	11.65	44.45	9.71
Bachelor's	34.78	10.54	43.15	10.55
Advanced	44.21	9.86	43.18	10.45

Note. HS = High School; Bachelor's = Bachelor's degree; Advanced = Advanced degree.

Table 5.

Physical and Mental HRQoL for Three Marital Status Groups (N = 58)

	Physical HRQoL		Mental HRQoL	
Marital status	*M*	*SD*	*M*	*SD*
Single	40.40	11.76	44.16	10.81
Partnered	34.80	10.00	46.19	8.96
Previously	35.64	9.77	38.39	38.39

Note. Previously = Previously partnered.

Table 6.

Post Hoc Power Analyses

Relationship	**Effect size(s)**	**Statistical power (1-β)**	***N* need for 1-β = .80**
1. Pain and mental HRQoL	r = .06	.07	2200
2. Fatigue and mental HRQoL	r = .26	.51	115
3. ED visits and mental HRQoL	r = .04	.06	5000
2. Pain and II	r = .15	.20	350
3. ED visits and II	r = .20	.33	195
4. WHYMPI and physical HRQoL	r = .16, f^2 = .03	.23, .25	300, 265
5. SCSES and physical HRQoL	r = .46, f^2 = .004	.96, .08	--, 2000
6. SCSES and mental HRQoL	r = .38, f^2 = .04	.84, .32	--, 200
7. SOPA and physical HRQoL	r = .20, f^2 = .02	.33, .18	195, 395
8. SOPA and mental HRQoL	r = .30, f^2 = .02	.63, .18	85, 395
9. Indirect effect of pain on physical HRQoL through II	ab = .03	.07	1100
10. Indirect effect of pain on mental HRQoL through II	ab = -.07	.19	300
11. Indirect effect of ED visit on mental HRQoL through II	ab = -.11	.36	170
12. Indirect effect of II on physical HRQoL through WHYMPI	ab = .05	.13	530
13. Indirect effect of II on physical HRQoL through SCSES	ab = .03	.06	4800

Note. HRQoL = Health-Related Quality of Life; II = Illness Intrusiveness; WHY = West-Haven-Yale Multidimensional Pain Inventory Life Control Scale; SCSES = Sickle Cell Self-Efficacy Scale; SOPA = Survey of Pain Attitudes Control Scale; ab = beta for indirect effect.

Post Hoc Power Analyses (continued)

Relationship	**Effect size**	**Statistical power (1-β)**	***N* need for 1-β = .80**
14. Indirect effect of II on mental HRQoL through SCSES	ab = -.13	.27	235
15. Indirect effect of II on physical HRQoL through SOPA	ab = .05	.10	1010
16. Indirect effect of II on mental HRQoL through SOPA	ab = -.05	.14	440

Note. HRQoL = Health-Related Quality of Life; II = Illness Intrusiveness; WHY = West-Haven-Yale Multidimensional Pain Inventory Life Control Scale; SCSES = Sickle Cell Self-Efficacy Scale; SOPA = Survey of Pain Attitudes Control Scale; ab = beta for indirect effect.

Figure 1.

Devins' Illness Intrusiveness Theoretical Framework

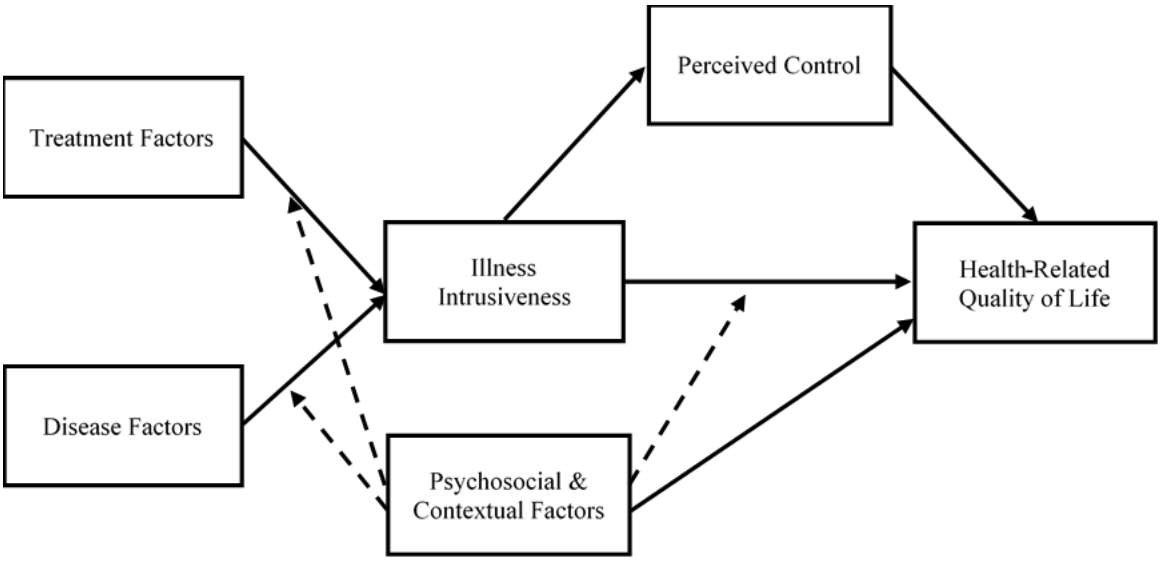


Figure 2.

Test the Theoretical Notion that Illness Intrusiveness Mediates the Association Between Disease/Treatment Factors and HRQoL

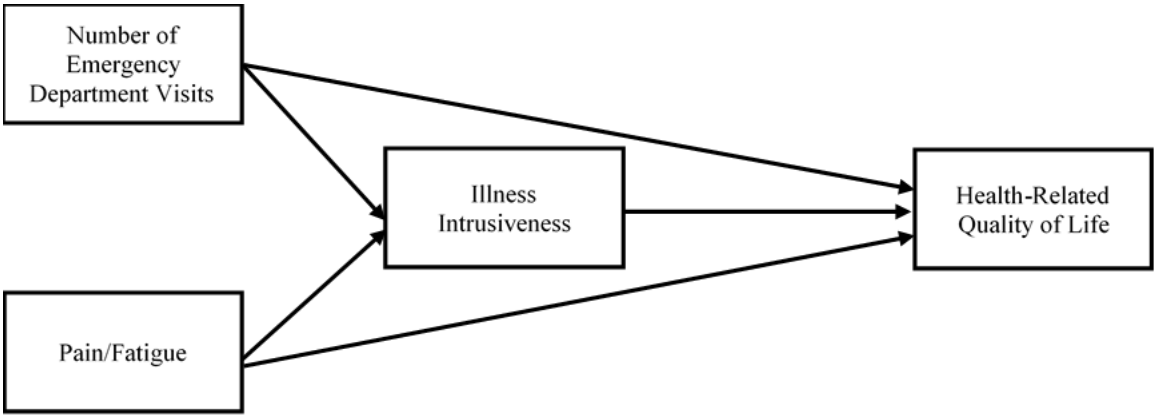


Figure 3.

Test the Theoretical Notion that Perceived Control Mediates the Association Between Illness Intrusiveness and HRQoL

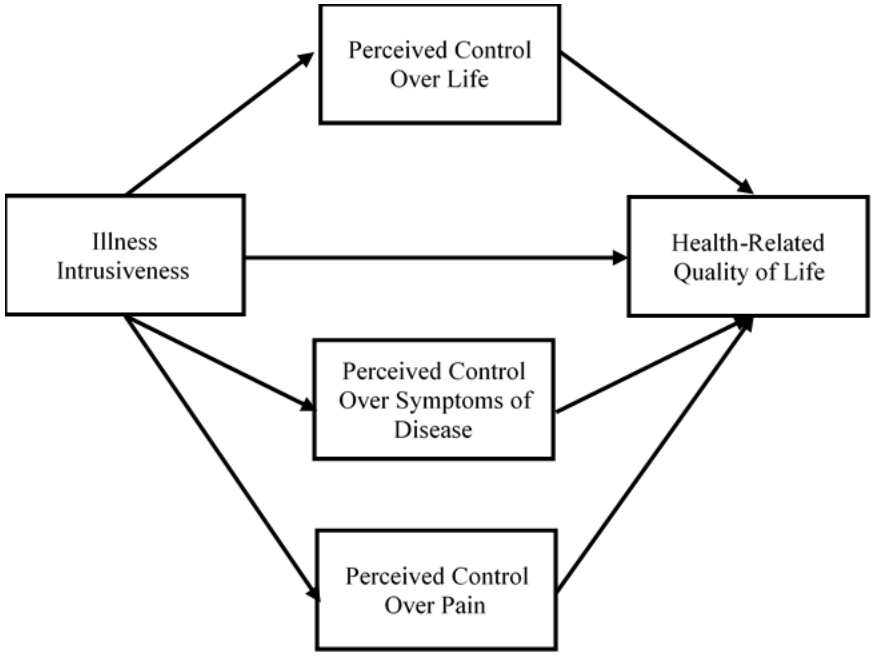


Figure 4.

Test the Theoretical Notion that Contextual Factors are Directly Associated with HRQoL

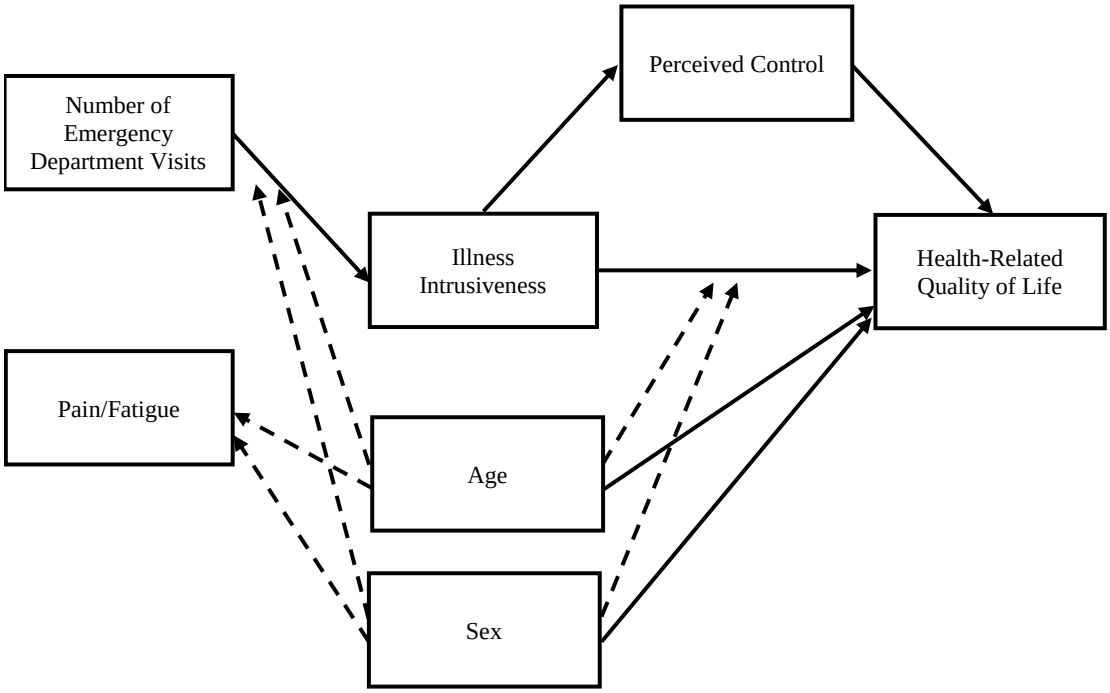
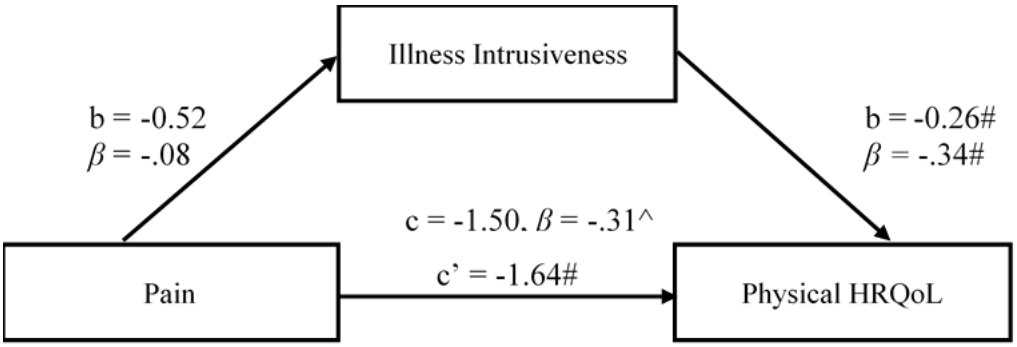


Figure 5.

Illness Intrusiveness as Mediator Between Pain and Physical HRQoL (N = 58)



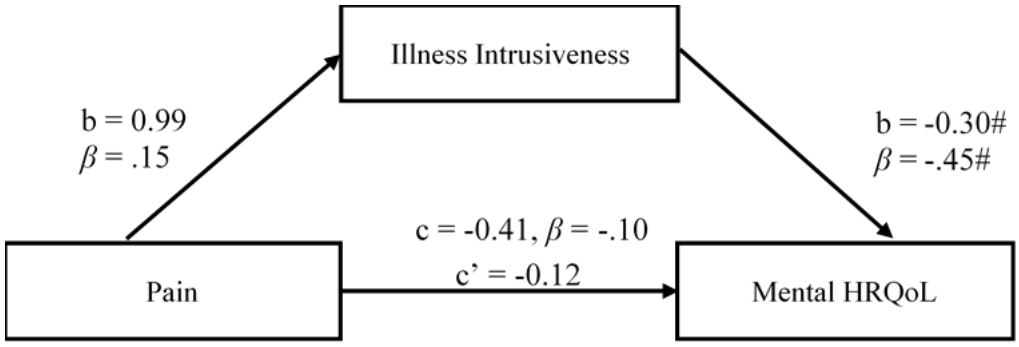
Direct effect, b = -1.64, < .001

Indirect effect, b = 0.13, 95% CI [-0.354, 0.594]

#p < .001

Figure 6.

Illness Intrusiveness as Mediator Between Pain and Mental HRQoL (N = 58)



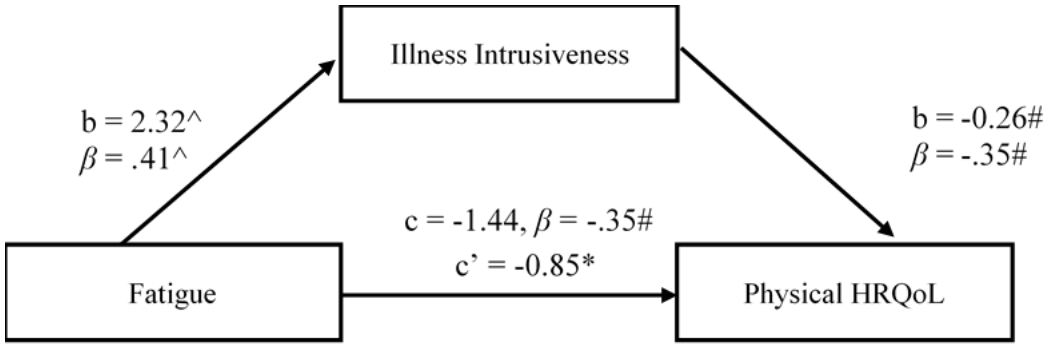
Direct effect, b = -0.12, p = .816

Indirect effect, b = -0.29, 95% CI [-0.822, .209]

#p < .001

Figure 7.

Illness Intrusiveness as Mediator Between Fatigue and Physical HRQoL (N = 58)



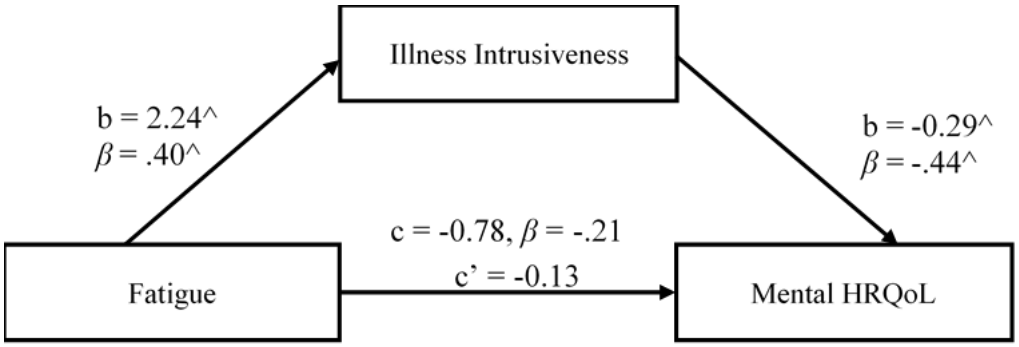
Direct effect, b = -0.85, p = .032

Indirect effect, b = -0.60, 95% CI [-1.148, -0.118]

*p < .05
^p < .01
#p < .001

Figure 8.

Illness Intrusiveness as Mediator Between Fatigue and Mental HRQoL (N = 58)



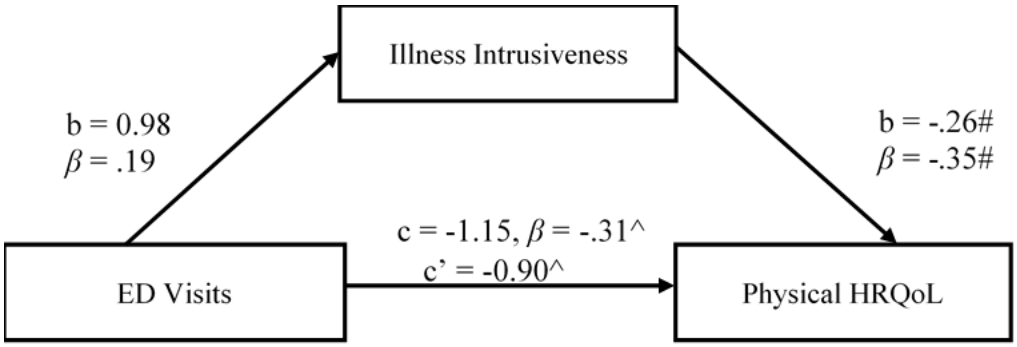
Direct effect, b = -0.13, p = .783

Indirect effect, b = -0.65, 95% CI [-1.447, -0.128]

^p < .01

Figure 9.

Illness Intrusiveness as Mediator Between ED Visits and Physical HRQoL (N = 58)



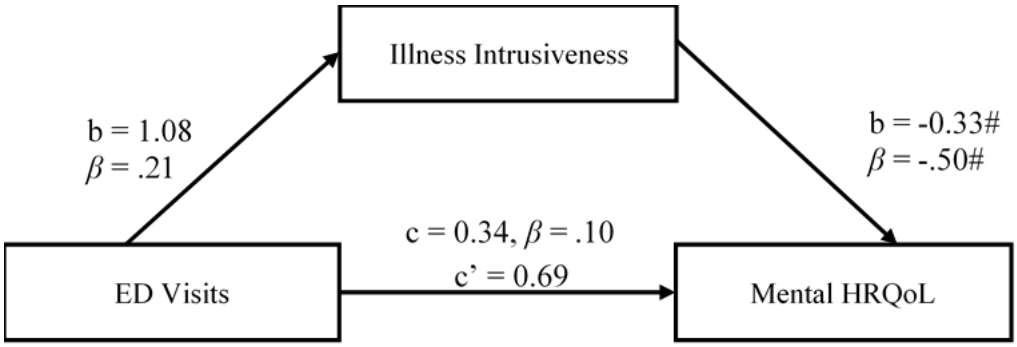
Direct effect, b = -0.90, p = .005

Indirect effect, b = -0.25, 95% CI [-0.624,-0.023]

*p < .05
^p < .01
#p < .001

Figure 10.

Illness Intrusiveness as Mediator Between ED Visits and Mental HRQoL (N = 58)



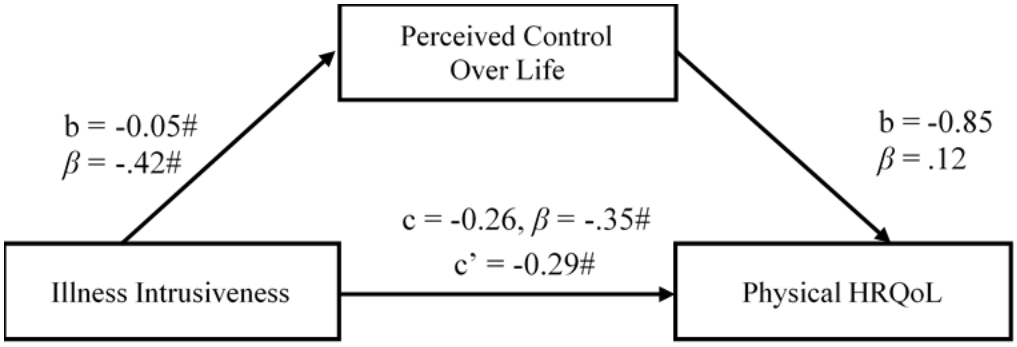
Direct effect, b = 0.69, p = .078

Indirect effect, b = -0.35, 95% CI [-0.974, -0.019]

#p < .001

Figure 11.

Perceived Control Over Life as Mediator Between Illness Intrusiveness and Physical HRQoL (N = 58)



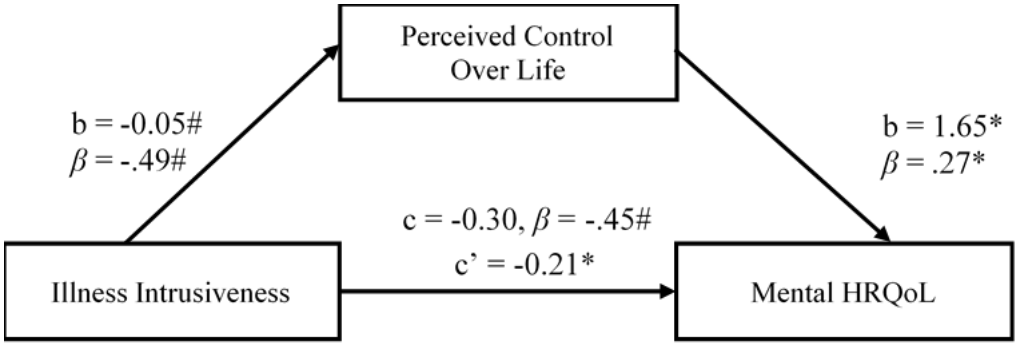
Direct effect, b = -0.29, $p < .001$

Indirect effect, b = 0.04, 95% CI [-0.041, 0.117]

#p < .001

Figure 12.

Perceived Control Over Life as Mediator Between Illness Intrusiveness and Mental HRQoL (N = 58)



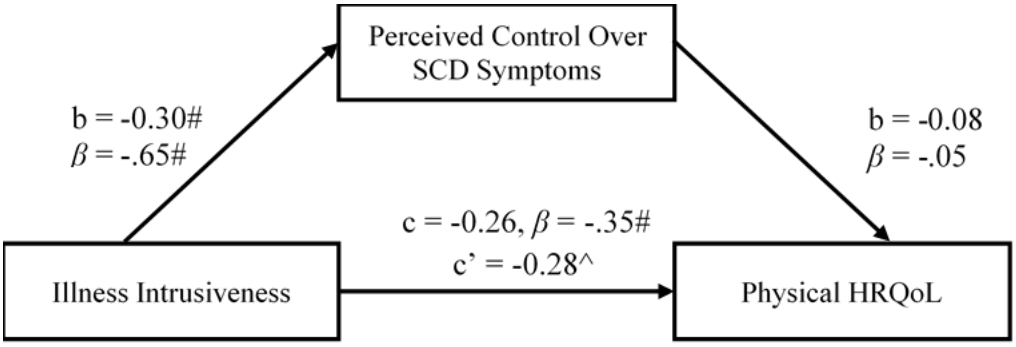
Direct effect, b = -0.21, p = .014

Indirect effect, b = -0.09, 95% CI [-0.186, -0.017]

*p < .05
#p < .001

Figure 13.

Perceived Control Over SCD Symptoms as Mediator Between Illness Intrusiveness and Physical HRQoL (N = 58)



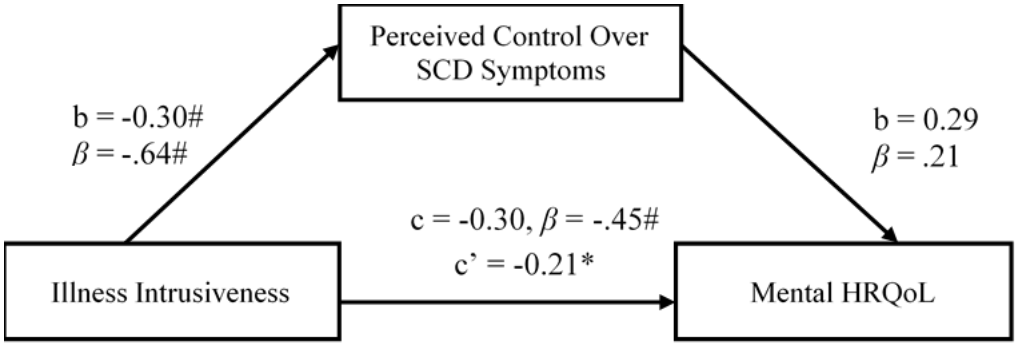
Direct effect, b = -0.28, p = .001

Indirect effect, b = -0.02, 95% CI [-0.091, 0.134]

#p < .001

Figure 14.

Perceived Control Over SCD Symptoms as Mediator Between Illness Intrusiveness and Mental HRQoL (N = 58)



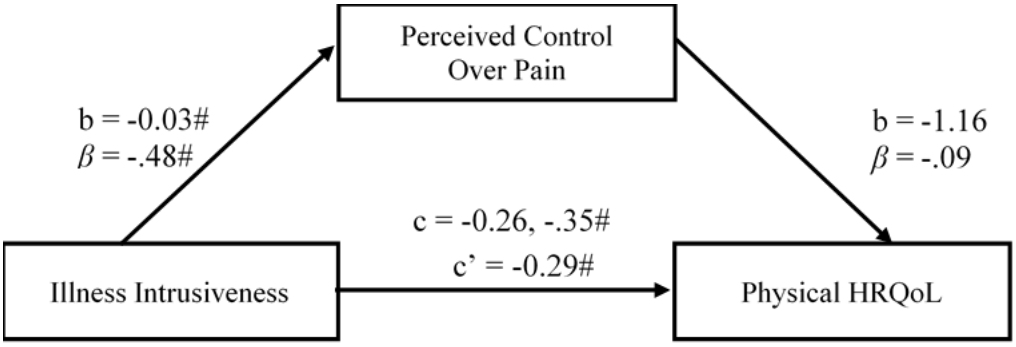
Direct effect, b = -0.21, p = .032

Indirect effect, b = -0.09, 95% CI [-0.205, 0.034]

#p < .001

Figure 15.

Perceived Control Over Pain as Mediator Between Illness Intrusiveness and Physical HRQoL (N = 58)



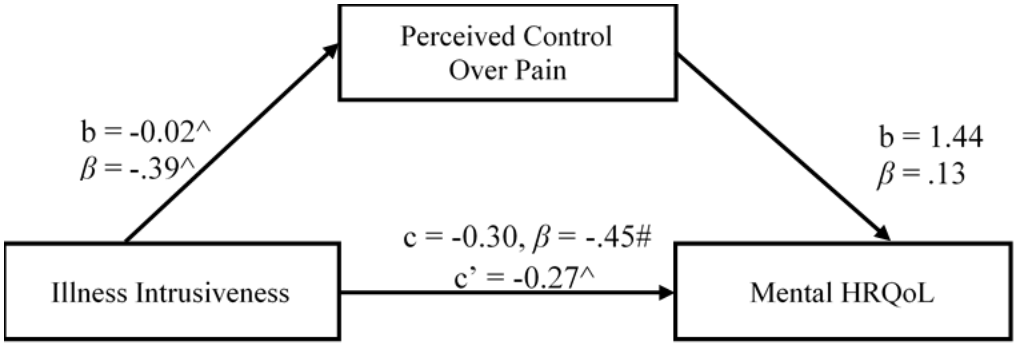
Direct effect, b = -0.29, $p < .001$

Indirect effect, b = 0.02, 95% CI [-0.027, 0.112]

^p < .01
#p<.001

Figure 16.

Perceived Control Over Pain as Mediator Between Illness Intrusiveness and Mental HRQoL (N = 58)



Direct effect, b = -0.27, p = .002

Indirect effect, b = -0.03, 95% CI [-0.102, 0.046]

^p < .01
#p<.001

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