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# Patient-reported Outcomes in Sickle Cell Disease and Association with Clinical and Psychosocial Factors: Report from the Sickle Cell Disease Implementation Consortium

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## Abstract

Understanding patient experiences, quality of life, and treatment needs in individuals with sickle cell disease (SCD) is essential in promoting health and well-being. We used measures from the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me), Patient Reported Outcomes Measurement Information System (PROMIS), and Quality of Life in Neurological Disorders (NeuroQol) to evaluate pain impact, sleep impact, social functioning, depressive symptoms, tiredness, and cognitive function [collectively, patient reported outcomes (PROs)] and to identify associated demographic and clinical characteristics. Participants (n=2201), between 18 and 45 years, were recruited through the eight Sickle Cell Disease Implementation Consortium (SCDIC) sites. In multivariate models, PROs were significantly associated with one another. Pain impact was associated with age, education, employment, time since last pain attack, hydroxyurea use, opioid use, sleep impact, social functioning, and cognitive function (F=88.74, $p<.0001$). Sleep impact was associated with household income, opioid use, pain impact, social functioning, depressive symptoms, and tiredness (F=101.40, $p<.0001$). Social functioning was associated with employment, pain attacks in the past year, autoimmune/inflammatory comorbidities, pain impact, sleep impact, depressive symptoms, tiredness, and cognitive function (F=121.73, p<.0001). Depressive symptoms were associated with sex, sleep impact, social functioning, tiredness, and cognitive function (F=239.51, $p<.0001$). Tiredness was associated with sex, education, sleep impact, social functioning, depressive symptoms, and cognitive function (F=129.13, $p<.0001$). These findings reflect the baseline PRO assessments among SCDIC registry participants. Further research is needed to better understand these outcomes and new targets for interventions to improve quality of life and function in people with SCD.

### Keywords

sickle cell disease; patient reported outcomes; quality of life

## Introduction

In the United States sickle cell disease (SCD) is a rare condition that affects approximately 100,000, predominantly African American individuals.[1] The condition is characterized by abnormally shaped red blood cells that can adhere to blood vessel walls, ultimately resulting in vaso-occlusion of the microcirculation with resultant ischemia and reperfusion injury.[2] The pathophysiology of SCD is quite complex, including elements of inflammation and adhesion, all of which contribute to an unpredictable clinical course and significant vascular and organ damage over time.[3] With advances in treatment for SCD, the life expectancy has increased over the past several decades leading to increasing prevalence of mature adults with SCD. This new population not only deals with the common diseases of aging, but SCD related complications that significantly affect their quality of life.[4]

The cumulative effects from disease processes contribute to increased symptom burden, poor quality of life, and impaired function.[5,6] For example, individuals with SCD are at risk for experiencing significant pain,[7] sleep disturbances,[8] depression,[9] deficits in cognitive function,[10,11] and tiredness or fatigue.[5,12] In addition to disease processes, evidence suggests several demographic (age, gender, low socioeconomic status and educational attainment),[5,13,14] disease/clinical (SCD genotype, medical and psychological comorbidities),[6,9,15,16] and treatment (hydroxyurea and opioid use)[17,18] factors influence symptom burden and quality of life in SCD. Furthermore, this disease has deleterious effects on social functioning. In fact, adults with SCD report worse social functioning when compared to individuals with other chronic diseases such as cystic fibrosis and asthma.[6]

Understanding patient experiences, quality of life, and treatment needs is essential in promoting health maintenance, functioning, and well-being in individuals with SCD. Patient-reported outcome (PRO) measures are multi-dimensional and can be used to assess the impact of a particular outcome, such as pain, sleep, emotional distress, cognitive function, or social functioning, to inform health care professionals of the common experiences of those affected by health challenges. In 2002, a need for better mechanisms to evaluate the quality of life and the impact of SCD on individuals' lives was established through several meetings hosted by the National Heart, Lung, and Blood Institute (NHLBI). As a result, the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me®) was developed to provide an improved means to systematically evaluate disease-specific health domains that are impacted by SCD.[19] ASCQ-Me is part of the larger HealthMeasures resource supported by the National Institutes of Health, which also includes the Patient-Reported Outcomes Measurement Information System (PROMIS®) and Quality of Life in Neurological Disorders (Neuro-QoL™).[20] Despite evidence that addressing PROs enhances patient engagement in treatment decision-making and improves overall health,[21,22] comprehensive evaluation of contemporary PRO measures, such as PROMIS, Neuro-QoL and ASCQ-Me measures, and associated demographic and clinical factors in SCD is limited.[23,24] In particular, limitations in studies evaluating these outcomes include small sample sizes and limited studies in adult patients.

In 2016, the NHLBI funded eight centers across the United States to participate in the Sickle Cell Disease Implementation Consortium (SCDIC) and to establish a longitudinal registry incorporating objective healthcare data with clinical and PROs.[25] The purpose of this study is to provide a baseline evaluation of the SCDIC registry PROs (pain impact, sleep impact, social functioning, emotional distress – depressive symptoms, tiredness, and cognitive function) and identify associated demographic and clinical (i.e., disease and treatment) characteristics in a large, multi-site cohort of adults with SCD. The findings from this study have the potential to advance our understanding of contemporary PROs and treatment needs that are important to improve quality of life and function of patients with SCD.

## Methods

### Design and Population

We completed a cross-sectional evaluation of PROs among 2201 participants enrolled in the SCDIC registry. Participants were included if they were adults between 18 and 45 years old,

had a confirmed diagnosis of SCD (subtypes SS, SC, Sβ-thalassemia, SO, SC, SG, SE or SF), were literate in English and provided signed informed consent. SCD diagnosis was confirmed by source laboratory documentation from the participant's medical record or confirmatory lab test by the enrolling center. People with sickle cell trait (e.g., Hb AS) or had a successful bone marrow transplant for SCD were excluded. Recruitment occurred in the eight centers participating in the consortium and their affiliated centers. Most participant recruitment occurred in SCD clinics; however, depending on the center, participants were also recruited from inpatient units, emergency departments, pain centers, community events, and via targeted phone calls.

After consent was obtained, eligible participants completed an enrollment survey and had baseline data on their disease characteristics abstracted from their medical records by a member of their treatment center study team. Participants without a self-completed Patient Enrollment Survey (n = 16) or a provider-completed Medical Record Abstraction form (n = 5) were excluded from analysis. Ethical approval was obtained from the institutional review boards at all participating sites. Seven of the eight SCDIC sites provided compensation for participation.

## Measures

**Patient-Reported Outcome Measures.—**Six relevant PROs for patients with SCD were selected to be included in the analyses. These outcomes were chosen from existing, validated patient-reported measurement systems (ASCQ-Me, PROMIS, and NeuroQOL) by the SCDIC investigators and were included in the registry data collection plan.

Select ASCQ-Me items were used to assess pain impact, sleep impact, and social functioning. Pain impact over the past 7 days was assessed using two items: "How often did you have very severe pain?" and "How often did you have pain so bad that it was hard to finish what you were doing?" Sleep impact over the past 7 days was assessed using two items: "How often did you stay up most of the night because you could not fall asleep?" and "How often did you have a lot of trouble falling asleep?" Social functioning over the past 30 days was assessed on the following items: "How much did you rely on others to take care of you because of your health?" and "How much did your health make it hard for you do things with your friends?" All ASCQ-Me items were scored on a 5-point Likert scale (i.e., Never to Always). Item responses were uploaded to the HealthMeasures Scoring Service at assessmentcenter.net, where T-scores and related statistics were generated, using adults with SCD who participated in the ASCQ-Me field test (n = 555) as the reference population, for each PRO.[23] The standardized T-score mean is 50 (SD = 10), with higher scores indicating more desirable (better) outcomes.

Measures used from the PROMIS item bank included Emotional Distress-Depression and Tiredness. The complete 4-item, PROMIS short-form for Emotional Distress-Depression assesses depressive symptoms over the past 7 days. Additionally, a single item ("I felt tired") from the PROMIS Fatigue item bank was used to measure tiredness in the past 7 days. All PROMIS items were scored on a 5-point Likert scale (i.e., Emotional Distress-Depression – Never to Always; Tiredness – Not at All to Very Much). Item responses were uploaded to the HealthMeasures Scoring Service, where T-scores and related statistics were generated

using PROMIS Wave 1 as the reference population, which is representative of the general adult population.[26] Higher T-scores on these PROMIS measures indicate worse outcomes.

Cognitive functioning over the past 7 days was assessed using the complete 4-item NeuroQOL Cognitive Function short form. Item responses were on a 5-item Likert scale (i.e., Never to Very Often [several times a day]). Item responses were uploaded to the HealthMeasures Scoring Service, where T-scores and related statistics were generated using PROsetta Stone W2 as the reference population, which is representative of the general adult population.[27] A higher T-score indicates better cognitive function (i.e., less disease impact).

We did not use complete short forms for some PRO measures (ASCQ-Me pain impact, sleep impact, social functioning, and PROMIS fatigue) in order to reduce participant burden. However, the PROs that were selected were developed using item response theory allowing for retention of precision in measurement of the construct even when all of the items in a measure are not used.[23,28] In selecting individual items from the ASCQ-Me and PROMIS domains, the SCDIC researchers considered: 1) our research aims, which were exploratory across a number of domains throughout the entire survey instrument; 2) the balance of somewhat less reliability and precision versus respondent burden given that our focus was on screening; 3) feasibility – most sites did not have access to computers for administration of the measures (for example, those in rural outreach clinics or community settings) so use of the computer adaptive tests was not possible; and 4) relevance of the selected items. The SCDIC researchers considered the SCD literature and their experience and selected individual items that best represented the construct. A T-score of 50 on the PRO measures represent the average response of the reference population, with ASCQ-Me being the only measurement system with a reference population of adults with SCD. [23,27]

**Demographic and Clinical Measures.—**Demographic, disease, and treatment related characteristics were captured on the patient-reported enrollment forms or extracted from the medical record. Demographic characteristics included: age, sex, race, ethnicity, marital status, education, employment, and household income. Clinical characteristics included: SCD genotype, number of pain attacks (vaso-occlusive pain episodes or VOC) in preceding year, time since most recent pain attack, current opioid and hydroxyurea use, and the occurrence of comorbidities or SCD related complications. A total of 23 comorbidities and SCD-related complications were collected and clustered according to physiologic systems (i.e., musculoskeletal, genitourinary, nervous system, cardiovascular, respiratory, digestive, and autoimmune/inflammatory). Presence of disease complications were reported as a binary outcome (yes or no/not in record).

## Statistical Analyses

Descriptive summary statistics were generated for all measures. Spearman correlations were generated to examine the relationships between PROs and T-scores were summarized by demographic, disease and treatment measures.

We used univariate models (ANOVA) to examine the relationships between each PRO and demographic and clinical measures. All statistically significant relationships were then included in the initial multivariate models, along with any other PROs that were significantly

correlated with the outcome being modeled. Final multivariate models were generated by PROC GLMSELECT with backward selection. Given the exploratory nature of this study, statistical significance was set at $p < .05$ for the univariate models; however, in the final multivariate models, statistical significance was set at $p \leq 0.01$ to reduce the probability for error. All analyses were conducted in SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

A total of 2201 participants were included in our analysis. Table 1 provides the demographic characteristics of the sample. Participants' mean age was 29.2 years, almost all participants (96.8%) were African-American/Black and 57.6% were female. Table 2 provides an overview of the disease and treatment characteristics of the cohort. Most (73.1%) had one of the more severe genotypes (hemoglobin SS or $S\beta^0$). Nearly half of participants (48.4%) were taking hydroxyurea and 63.2% were currently using opioids. Fifty percent of the participants had four or more pain attacks in the past year, and nearly 30% were concurrently having an acute pain attack at the time the survey was completed or experienced one in the past week. The most commonly reported SCD complications were respiratory (59.4% - acute chest syndrome, asthma) and digestive-related (56.8% - gallstones, splenomegaly) complications.

### Patient-Reported Outcomes

The T-score means (SD) were pain impact 47.1 (9.0), sleep impact 49.2 (9.8) social functioning 51.3 (9.7), depressive symptoms 50.9 (9.6), tiredness 55.5 (9.4), and cognitive function 50.3 (9.1). Figure 1 displays the distribution of scores for the PROs. All PROs were significantly correlated with one another ($p<0.0001$; Supplemental Table 1). The strength of correlation between pain impact and social functioning was moderate (Spearman correlation coefficient of 0.530); however, the strength of all other correlations was weak.

### Associations between Patient-Reported Outcomes and Demographic, Disease, and Treatment Characteristics

Supplemental Tables 2 and 3 provide differences across demographic and disease and treatment characteristics for each of the PROs. In univariate analyses, sex, education, employment, number of pain attacks in the past year, time since most recent pain attack, and presence of an autoimmune/inflammatory co-morbidity were all significantly associated with all six PROs. In addition, age, hydroxyurea use, and current opioid use were significantly associated with all PROs except cognitive function. Lower household income was significantly associated with all PROs except tiredness.

Table 3 presents the findings from multivariate analyses. Pain impact was significantly associated with age, educational attainment, employment status, time since most recent pain attack, hydroxyurea use, current opioid use, sleep impact, social functioning, and cognitive function ($F(19, 2035) = 88.74$, $p < .0001$, $r^2 = 0.45$). An increase in age ($p < .0001$), lower levels of education (high school education or less; $p$'s $< .0001$) and being unemployed ($p = .0004$) were associated with greater pain impact. Participants with a recent pain attack (at least one pain attack in the past 6 months; $p$'s $< .001$) had significantly worse pain impact

scores. Participants who never used hydroxyurea ($p < .0001$) had slightly better pain impact scores than those currently taking the medication. Additionally, an increase (better) in sleep impact ($p < .0001$), social functioning ($p < .0001$), and cognitive function ($p = .0001$) scores were associated with less pain impact.

Sleep impact was significantly associated with household income, opioid use, pain impact, social functioning, emotional distress, and tiredness ($F(9, 1880) = 101.40$, $p < .0001$, $r^2 = 0.33$; Table 6). Lower levels of household income ($50,000 or less; $p$'s<0.01) were associated with worse sleep impact scores. Current opioid users had worse sleep impact scores compared to those individuals who were not taking an opioid ($p$=.0004). Additionally, less pain impact and better social functioning were associated with less sleep impact ($p's < .0001$). Worse emotional distress and tiredness were associated with greater sleep impact ($p's < .0001$).

Social functioning was significantly associated with employment status, number of pain attacks in the past year, comorbid autoimmune/inflammatory condition, pain impact, sleep impact, depressive symptoms, tiredness, and cognitive function ($F(12, 2063) = 121.73$, $p < .0001$, $r^2 = 0.41$; Table 6). Participants who were unemployed ($p$<.0001), had an autoimmune/inflammatory condition ($p = .0008$), or had 3 or more pain attacks in the past year (3 pain attacks, $p = .0028$; 4+ pain attacks, $p < .0001$) had worse social functioning scores. Additionally, worse scores for pain impact, sleep impact, depressive symptoms, tiredness, and cognitive function were significantly associated with poorer social functioning ($p$'s < .0001).

Depressive symptoms were significantly associated with sex, sleep impact, social functioning, tiredness, and cognitive function ($F(5, 2126) = 239.51$, $p < .0001$, $r^2 = 0.36$; Table 6). Males had higher (worse) scores ($p = .0075$) for depressive symptoms than females. Higher (better) sleep impact, social functioning, and cognitive function scores were associated with less depressive symptoms ($p$'s < .0001). Additionally, higher (worse) tiredness scores were associated with worse depressive symptoms ($p < .0001$).

Tiredness was significantly associated with sex, educational attainment, sleep impact, social functioning, depressive symptoms, and cognitive function ($F(8, 2100) = 129.13$, $p < .0001$, $r^2 = 0.33$; Table 6). Males had lower (better) tiredness scores than females ($p < .0001$). Compared to college graduates, participants who have less education had better tiredness scores (less than high school, $p = .0009$; some high school, $p$<.0001; high school graduate, $p$<.0001; some college, $p$=.0034). Higher (better) sleep impact, cognitive function, and social functioning scores were associated with decreases (better) in tiredness scores ($p's < .0001$). Higher (worse) depressive symptoms scores were associated with more (worse) tiredness ($p < .0001$).

Cognitive function was significantly associated with sleep impact, depressive symptoms, tiredness, and social functioning ($F(4, 2119) = 215.47$, $p < .0001$, $r^2 = 0.29$; Table 6). Higher (better) sleep impact and social functioning scores were associated with higher (better) cognitive function scores. Additionally, higher (worse) scores for depressive symptoms were associated with worse cognitive function.

## Discussion

This study provides a baseline assessment of the PROs among participants in the SCDIC registry and is one of the first to conduct an evaluation of contemporary PRO measures in a large, multi-site cohort of individuals with SCD. Participants in the SCDIC registry had similar reports of pain impact, sleep impact, social functioning, depressive symptoms, tiredness, and cognitive function compared to the reference populations for the various measures (i.e., ASCQ-Me, PROMIS, NeuroQoL), which included adults with SCD only for ASCQ-Me.[23,27] However, given the reports of variability in this study, as well as associations among the PROs, these findings underscore the complexity of the impact of SCD on symptom experiences and functional outcomes. These findings are consistent with other studies indicating correlated symptoms in SCD.[5,8,14] For the Pain in Sickle Cell Epidemiology Study (PiSCES), the investigators identified 27.8% of adults with high somatic symptom burden (tiredness, pain, trouble sleeping) with co-occurring depression.[5] Additionally, an estimated 70% of adults with SCD experience sleep disturbance, which is correlated with more frequent pain and evidence of clinical depression.[8] Moreover, Adam et al. identified in 142 adults with SCD that depression is significantly associated with worse physical and mental quality of life scores and higher healthcare costs.[9]

Our findings also identified several demographic (age, sex, education status, employment status), disease (recent pain attacks, comorbid conditions), and treatment (hydroxyurea and opioid use) characteristics that were significantly associated with the different PROs. These findings are consistent with previous findings in other studies. For example, among 328 adults with SCD, Wallen and colleagues identified significant associations among sleep quality and increasing age, higher body mass index, more days of pain and frequent acute painful events over the previous 12 months.[8] In a large adult SCD cohort, Dampier and colleagues identified older age, female sex, and opioid usage as associated with worse physical functioning.[29]

One notable finding in this study was that SCD genotype was not associated with any of the six PROs evaluated. SCD genotype is often considered a main determinant of disease severity.[30] For example, HbSS and HbS$\beta^0$ thalassemia genotypes are considered the most severe forms of the disease and have been associated with more disease-related complications when compared to SC or S$\beta^+$ genotypes.[29,31] However, our findings suggest that SCD genotype is not the best indicator of disease impact and quality of life.

Another finding of particular interest in our study was the lower pain impact scores in individuals who have never taken hydroxyurea compared to those currently taking the medication. Previous research has shown that hydroxyurea use significantly improves pain outcomes, reduces the occurrence of disease complications, decreases healthcare costs and improves health related quality of life.[17,32,33] Despite these benefits, uptake and adherence to hydroxyurea is poor. Reasons for poor hydroxyurea uptake and adherence are numerous and include: misconceptions about the drug efficacy, concerns about side effects, difficulty obtaining prescription refills, or forgetfulness. Previous studies showed less pain and better physical functioning in adults with SCD who were taking hydroxyurea compared to those who were not.[17,34,35] Our contrary finding could potentially be a result of individuals whose

disease is stable/milder or is adequately managed through other treatments, or adherence issues in those currently prescribed hydroxyurea.

There are limitations to this study that warrant mention and consideration while interpreting the findings. The cross-sectional nature of the study design does not allow determination of causal relationships between the study variables and the PROs. Additionally, there is recall bias since participants had to remember events that occurred in the past week, month or year. Also, there is potential for selection bias as those participants who did not complete the questionnaires were excluded from the analyses. Furthermore, during the study design we selected certain items from some of the PRO domains, limiting the generalizability of our data to other PRO studies that utilized all the items in each domain of the PRO measures. Nevertheless, the PRO measures allow for using selected items and retains the precision of measurement of the constructs. We also did not capture the effect of factors such as stigma, racial discrimination, self-efficacy, coping and spirituality, which could explain the unaccounted variance in our multivariate models.

Despite these limitations, our study had the largest, most geographically diverse sample in the United States of adults with SCD and had sufficient power to detect statistically significant differences in our data. Additionally, findings from this study underscore the need for a biopsychosocial approach to care that focuses both on the physical manifestations and the psychosocial impact of the disease. Future research should seek to better understand the differences in PROs as they relate to treatments such as hydroxyurea. There is also a need for further research to better understand the complexity of the PROs and the impact of the disease. For example, future studies could identify subgroups who share common experiences of co-occurring physical and psychological symptoms to aid in identification of high-risk patients for adverse outcomes and development of interventions to prevent or manage the humanistic effects of SCD.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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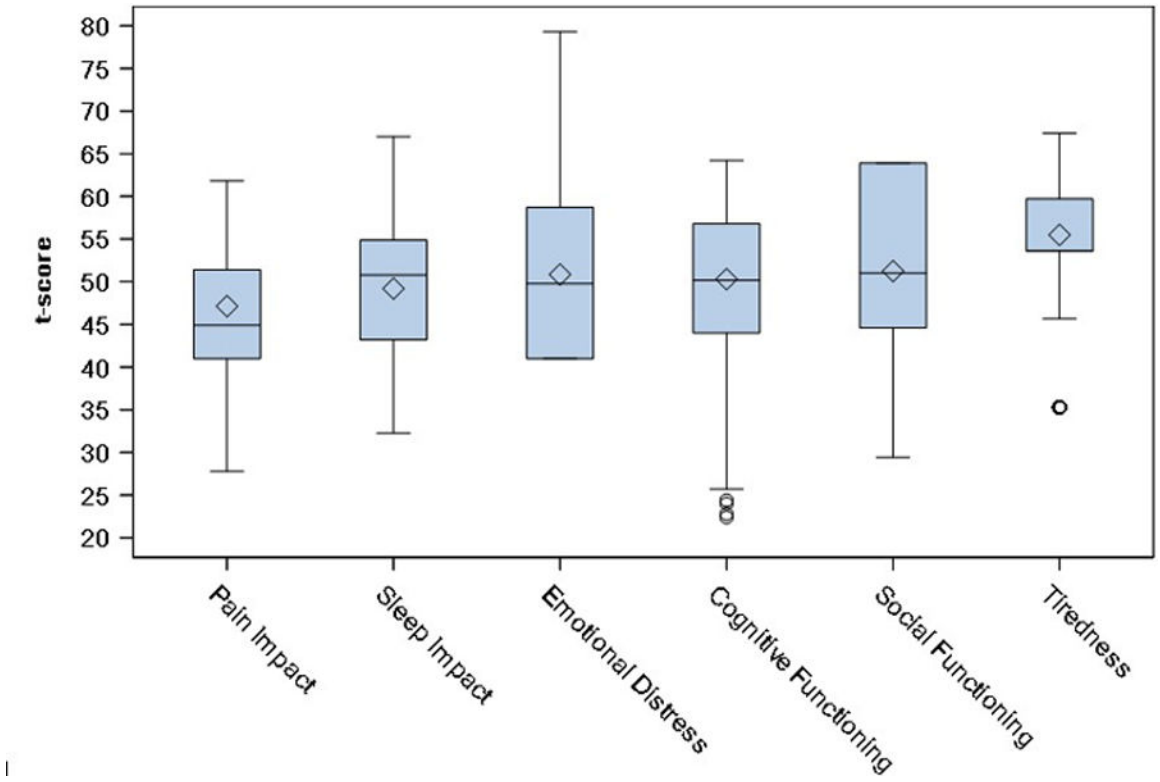


**Figure 1.**
Patient-Reported Outcomes T-score Distributions

**Table 1.**

Sample Demographic Characteristics

| Characteristic | (N = 2201) |
|---|---|
| **Age** | |
| Mean (SD) years | 29.2 (7.2) |
| Range | 18 – 45 |
| | **N (%)** |
| **Female Sex/Gender** | 1,268 (57.6) |
| **Race** | |
| Black or African American | 2,087 (96.8) |
| **Marital Status** | |
| Never married | 1,602 (77.3) |
| Married | 334 (16.1) |
| Divorced/separated/widowed | 136 (6.6) |
| **Education** | |
| Some high school or less | 224 (10.3) |
| High school graduate | 646 (29.8) |
| Some college | 756 (34.9) |
| College graduate | 539 (24.9) |
| **Employment** | |
| Employed | 836 (39.0) |
| Not employed by choice | 364 (17.0) |
| Unemployed | 944 (44.0) |
| **Household income in a year** | |
| $25,000 or less | 1,056 (54.4) |
| $25,001-$50,000 | 429 (22.1) |
| $50,001-$75,000 | 214 (11.0) |
| $75,001-$100,000 | 105 (5.4) |
| ≥$100,001 | 138 (7.1) |

**Table 2.**

Sample Clinical Characteristics

| Characteristic | N (%) |
|---|---|
| **Sickle cell genotype** | |
| Hb SS or $S\beta^0$ | 1,609 (73.1) |
| Hb SC | 452 (20.5) |
| Hb $S\beta^+$ | 112 (5.1) |
| Other (Hb S/HPFH, SE, SO, SD) | 23 (1.0) |
| **Hydroxyurea use** | |
| Currently using | 1,044 (48.4) |
| Past use only | 555 (25.7) |
| Never used | 560 (25.9) |
| **Currently using opioids** | 1,391 (63.2) |
| **Number of pain attacks (crises) in past year** | |
| 0 | 243 (11.1) |
| 1 | 218 (10.0) |
| 2 | 283 (12.9) |
| 3 | 351 (16.0) |
| 4 or more | 1,095 (50.0) |
| **Time since most recent pain attack (crisis)** | |
| Currently having one | 283 (12.9) |
| <1 week ago | 361 (16.5) |
| 1–3 weeks ago | 472 (21.5) |
| 1–6 months ago | 610 (27.8) |
| 7–11 months ago | 129 (5.9) |
| 1–5 years ago | 230 (10.5) |
| 5+ years ago | 79 (3.6) |
| Never had a pain attack (crisis) | 28 (1.3) |
| **Sickle cell disease complications** | |
| Respiratory[1] | 1,308 (59.4) |
| Digestive[2] | 1,250 (56.8) |
| Musculoskeletal[3] | 690 (31.3) |
| Autoimmune/Inflammatory[4] | 455 (20.7) |
| Genitourinary[5] | 391 (17.8) |
| Nervous system[6] | 366 (16.6) |
| Cardiovascular[7] | 311 (14.1) |

[1] Respiratory complications included: acute chest syndrome, asthma

[2] Digestive complications included: gallstones, cholecystitis, splenomegaly, splenic sequestration, splenic infarcts, hypersplenism, autosplenectomy

[3] Musculoskeletal complications included: avascular necrosis, dactylitis, osteomyelitis

[4] Autoimmune/Inflammatory complications included: deep venous thrombosis, lupus, rheumatoid arthritis, gout, sarcoidosis

[5] Genitourinary complications included: chronic kidney disease, end stage renal failure, priapism

[6] Nervous system complications included: stroke, intracranial bleeding

[7] Cardiovascular complications included: Left ventricular dysfunction

**Table 3.**

Significant Multivariate Relationships Between Patient-Reported Outcomes and Demographic and Clinical Characteristics

| Model | Predictor | Estimate | SE | 95% CI | P-value* |
|---|---|---|---|---|---|
| **Pain Impact** | Intercept | 36.08 | 2.06 | 32.05, 40.12 | <.0001 |
| | Age | −0.11 | 0.02 | −0.16, −0.07 | <.0001 |
| | Education[5] | | | | |
| | *Some high school or less* | −2.40 | 0.58 | −3.54, −1.25 | <.0001 |
| | *High school* | −1.87 | 0.43 | −2.70, −1.03 | <.0001 |
| | *Some college* | −0.91 | 0.40 | −1.69, −0.12 | .0237 |
| | Employment[1] | | | | |
| | *Unemployed* | −1.29 | 0.36 | −2.00, −0.57 | .0004 |
| | *Not employed by choice* | 0.44 | 0.45 | −0.44, 1.32 | .3279 |
| | Time since most recent pain attack[2] | | | | |
| | *Currently having one* | −10.17 | 1.46 | −13.03, −7.31 | <.0001 |
| | *<1 week ago* | −9.69 | 1.44 | −12.51, −6.87 | <.0001 |
| | *1 – 3 weeks ago* | −6.19 | 1.42 | −8.98, −3.40 | <.0001 |
| | *1 – 6 months ago* | −4.17 | 1.41 | −6.93, −1.42 | .0030 |
| | *7 – 11 months ago* | −3.15 | 1.50 | −6.09, −0.21 | .0359 |
| | *1 – 5 years ago* | −2.89 | 1.44 | −5.71, −0.07 | .0449 |
| | *5+ years ago* | −2.39 | 1.55 | −5.44, 0.65 | .1234 |
| | Hydroxyurea use[3] | | | | |
| | *Never used* | 1.63 | 0.37 | 0.91, 2.36 | <.0001 |
| | *Past use only* | 0.26 | 0.37 | −0.46, 0.98 | .4813 |
| | Current opioid use | −1.62 | 0.34 | −2.27, −0.96 | <.0001 |
| | Sleep impact score | 0.14 | 0.02 | 0.10, 0.17 | <.0001 |
| | Social functioning score | 0.24 | 0.02 | 0.21, 0.28 | <.0001 |
| | Cognitive function score | 0.07 | 0.02 | 0.03, 0.10 | .0001 |
| **Sleep Impact** | Intercept | 55.79 | 2.57 | 50.75, 60.83 | <.0001 |
| | Household income[6] | | | | |
| | *$25,000 or less* | −2.48 | 0.75 | −3.95, −1.01 | .0009 |
| | *$25,001-$50,000* | −2.06 | 0.79 | −3.61, −0.50 | .0095 |
| | *$50,001-$75,000* | −0.59 | 0.88 | −2.32, 1.14 | .5024 |
| | *$75,001-$100,000* | 1.13 | 1.05 | −0.92, 3.18 | .2807 |
| | Current opioid use | −1.43 | 0.41 | −2.23, −0.64 | .0004 |
| | Pain impact score | 0.21 | 0.03 | 0.16, 0.26 | <.0001 |
| | Social functioning score | 0.13 | 0.02 | 0.09, 0.18 | <.0001 |
| | Emotional distress – depressive symptoms score | −0.18 | 0.02 | −0.22, −0.14 | <.0001 |
| | Tiredness score | −0.21 | 0.02 | −0.25, −0.16 | <.0001 |

| Model | Predictor | Estimate | SE | 95% CI | P-value* |
|---|---|---|---|---|---|
| **Social Functioning** | Intercept | 47.21 | 2.78 | 41.75, 52.66 | <.0001 |
| | Employment[1] | | | | |
| | *Unemployed* | −2.49 | 0.38 | −3.24, −1.74 | <.0001 |
| | *Not employed by choice* | −1.11 | 0.47 | −2.04, −0.18 | .0195 |
| | # of pain attacks in past year[4] | | | | |
| | *1* | −1.06 | 0.71 | −2.46, 0.34 | .1377 |
| | *2* | −1.26 | 0.68 | −2.60, 0.07 | .0632 |
| | *3* | −1.98 | 0.66 | −3.28, −0.68 | .0028 |
| | *4+* | −3.89 | 0.60 | −5.06, −2.72 | <.0001 |
| | Autoimmune/inflammatory condition | −1.39 | 0.42 | −2.21, −0.58 | .0008 |
| | Pain impact score | 0.27 | 0.02 | 0.22, 0.31 | <.0001 |
| | Sleep impact score | 0.11 | 0.02 | 0.07, 0.15 | <.0001 |
| | Emotional distress – depressive symptoms score | −0.17 | 0.02 | −0.21, −0.13 | <.0001 |
| | Tiredness score | −0.10 | 0.02 | −0.14, −0.06 | <.0001 |
| | Cognitive function score | 0.09 | 0.02 | 0.05, 0.13 | <.0001 |
| **Emotional distress – depressive symptoms** | Intercept | 77.00 | 2.19 | 72.70, 81.30 | <.0001 |
| | Male | 0.93 | 0.35 | 0.25, 1.62 | .0075 |
| | Sleep impact score | −0.17 | 0.02 | −0.21, −0.13 | <.0001 |
| | Social functioning score | −0.21 | 0.02 | −0.25, −0.17 | <.0001 |
| | Tiredness score | 0.15 | 0.02 | 0.11, 0.19 | <.0001 |
| | Cognitive function score | −0.31 | 0.02 | −0.35, −0.27 | <.0001 |
| **Tiredness** | Intercept | 77.15 | 2.32 | 72.60, 81.69 | <.0001 |
| | Male | −3.34 | 0.35 | −4.02, −2.66 | <.0001 |
| | Education[5] | | | | |
| | *Some high school or less* | −4.39 | 0.63 | −5.62, −3.15 | <.0001 |
| | *High school* | −2.87 | 0.46 | −3.77, −1.97 | <.0001 |
| | *Some college* | −1.28 | 0.44 | −2.15, −0.42 | .0038 |
| | Sleep impact score | −0.19 | 0.02 | −0.23, −0.15 | <.0001 |
| | Social functioning score | −0.13 | 0.02 | −0.17, −0.09 | <.0001 |
| | Emotional distress – depressive symptoms score | 0.15 | 0.02 | 0.11, 0.20 | <.0001 |
| | Cognitive function score | −0.21 | 0.02 | −0.25, −0.16 | <.0001 |
| **Cognitive Function** | Intercept | 68.79 | 2.32 | 64.25, 73.34 | <.0001 |
| | Sleep impact score | 0.07 | 0.02 | 0.03, 0.11 | .0006 |
| | Social functioning score | 0.09 | 0.02 | 0.05, 0.13 | <.0001 |
| | Emotional distress – depressive symptoms score | −0.31 | 0.02 | −0.35, −0.27 | <.0001 |
| | Tiredness score | −0.19 | 0.02 | −0.23, −0.15 | <.0001 |

[1] Compared to the employed group

[2] Compared to never had a pain attack

[3] Compared to current use

[4] Compared to none

[5] Compared to college graduates

[6] Compared to $100,000+