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RESEARCH ARTICLE

Sex-based differences in the manifestations and complications of sickle cell disease: Report from the Sickle Cell Disease Implementation Consortium

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Data Availability Statement: We have ethical restrictions about openly releasing the data set to the public as the nature of the data set would result in loss of participant anonymity. The ethical restrictions were imposed by the Sickle Cell Disease Implementation Consortium (SCDIC). However, data set requests can be made to SCDIC and their data coordinating center at RTI international. Requests will be reviewed by the SCDIC Publications Committee. Data set requests can be sent to SCDIC at scdic-publications-

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Abstract

Introduction

Sex-based clinical outcome differences in sickle cell disease (SCD) remain largely unknown despite evidence that female sex is associated with an increased lifespan. To better characterize sex-based differences in SCD, we assessed pain, treatment characteristics, laboratory measures and complications among males and females currently enrolled in the Sickle Cell Disease Implementation Consortium (SCDIC) registry.

Methods

The SCDIC consists of eight comprehensive SCD centers and one data coordinating center that received funding from the National Heart Lung and Blood Institute to improve outcomes for individuals with SCD. Eligibility criteria included: 15 to 45 years of age and a confirmed diagnosis of SCD. Self-report surveys were completed and data were also abstracted from the participants’ medical records.

Results

A total of 2,124 participants were included (mean age: 27.8 years; 56% female). The majority had hemoglobin SS SCD genotype. Females had worse reports of pain severity (mean

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(SD) T-score 51.6 (9.6) vs 49.3 (10), $p < 0.001$), more vaso-occlusive episodes ($p = 0.01$) and a higher occurrence of 3 or more hospital admissions in the past year (30.9% vs. 25.5, $p = 0.03$). On multivariable analysis, males had higher odds of acute chest syndrome (odds ratio (OR) 1.4, $p = 0.002$), cardiovascular (OR 1.70, $p < 0.001$) and musculoskeletal (OR 1.33, $p = 0.0034$) complications and lower odds of depression (OR 0.77, $p = 0.0381$). Females had higher fetal hemoglobin levels with and without hydroxyurea use (9.6% vs 8.5%, $p = 0.03$ and 3% vs 2.2%, $p = 0.0005$, respectively).

Conclusion

Our data suggests that sex differences in clinical outcomes do occur among individuals with SCD. Future research needs to explore the mechanisms underlying these differences.

Introduction

Sickle cell disease (SCD) is a genetically inherited blood disorder that predominantly affects individuals of African descent [1,2]. One in 365 African Americans is born with SCD and 1 in 14 carry the trait [1,2]. The disease is characterized by polymerization of red blood cells into rigid sickle shapes during periods of low oxygen tension [3–6]. The disease is also associated with endothelial damage and chronic inflammation [3–6]. These factors result in vaso-occlusion and multi-organ dysfunction, leading to numerous complications such as vaso-occlusive pain episodes (VOEs), kidney failure and stroke [6].

Despite these complications, people with SCD are living longer [7]. In the United States, the median age of survival has increased from less than 20 years of age in the 1970s to 48 and 54.7 years of age for individuals with HbSS/HbS β^0 and Hb SC/HbS β^+ respectively, in the 2000s [1,8]. The increased median age of survival with SCD can be attributed to interventions to diagnose individuals with the disease much earlier in the life course (e.g., newborn screening) and interventions to prevent common disease-related complications (e.g., pneumococcal vaccination, use of penicillin prophylaxis, increased availability of hydroxyurea, and use of frequent blood transfusions for patients at increased risk of stroke) [9–13]. Of keen interest is that women live longer than their male counterparts [14].

Few studies have investigated sex-based SCD comparisons such as the frequency of VOEs, occurrence of end-organ dysfunction or complications, quality of life and sociodemographic characteristics [15–19]. The majority of those studies have been limited to urologic and obstetric disciplines [16–19]. A case series by Ballas et al [14] reviewed four women with SCD who lived beyond 80 years of age and linked the participants' increased lifespan and quality of life to milder SCD, long-term family support, a healthy lifestyle and good adherence to medication and clinic appointments [14]. A prospective study by McClish et al [20] on gender differences in pain and healthcare utilization in SCD found an increase in VOEs and healthcare utilization (hospitalizations, doctor visits and ED visits) by men and no gender differences in opioid use and the frequency and intensity of pain [21]. Findings from this study, however, were limited by the small sample size and study scope. These underexplored differences may account for the sex difference in mortality. Therefore, a more comprehensive understanding of the sex differences in pain, treatment characteristics, laboratory measures and complications that exists amongst individuals with SCD is warranted.

To address this gap, we compared differences in sociodemographic and SCD disease characteristics and complications between men and women living with SCD currently enrolled in the Sickle Cell Disease Implementation Consortium (SCDIC) registry. Studying these differences may provide insight into the sex difference in mortality.

Methods

Study population

The study population included participants enrolled in the SCDIC patient registry. The SCDIC is a consortium, funded by the National Heart Lung and Blood Institute (NHLBI), including eight comprehensive sickle cell disease centers across the United States and one data coordinating center [22]. The overall goal of the SCDIC is to translate evidence-based SCD treatments to care [22]. One major priority of the consortium was the establishment of a comprehensive research registry that includes patient-reported and clinical data that can serve as a resource for conducting data queries and identifying gaps in research that inform implementation studies [22]. Participants were eligible for recruitment in the registry based on the following inclusion criteria: 15 to 45 years of age, confirmed diagnosis of SCD (subtypes Hb SS, SC, S β -thalassemia, SO, SD, SG, SE or SF), literacy in English and willingness to provide informed consent or assent. Confirmation of SCD diagnosis required laboratory confirmation (such as hemoglobin electrophoresis or newborn screening) of SCD from the participants' medical records. Participants were excluded if they were unwilling or unable to provide informed consent or assent, had sickle cell trait (Hb AS), or had a successful bone marrow transplant. Recruitment occurred in outpatient clinics (e.g., sickle cell and primary care clinics), hospital inpatient settings, SCD support group meetings and conferences [23].

Ethical approval

Ethical approval was received by the institutional review boards at each of the eight SCDIC study sites prior to any data collection efforts. Written informed consent was obtained before participant recruitment and enrollment in the study. For eligible participants younger than 18 years of age, informed consent was obtained from the parent or legal guardian in conjunction with informed assent from the participant. IRB approval was obtained for this analysis of the existing registry data from the Duke University Health System IRB (Protocol ID: Pro00103703). We analyzed partially anonymized data that was collected in the registry from July 2017 to February 2019. We accessed registry data in October 2019.

Data collection

Data were collected using participant self-report surveys, medical records and laboratory abstraction forms (S1 Table) [24]. The data collection instruments were developed by the SCDIC steering committee, which consisted of at least one SCD expert from each of the eight sites [22]. The survey consisted of validated instruments that assessed socio-demographic information hydroxyurea use, opioid use, as well as pain frequency and severity [24]. Pain frequency and severity were assessed using five items from the pain episode frequency and severity domain of the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) [24,25]. ASCQ-Me is a validated measure for assessing the health-related quality of life among people with SCD [24].

The medical records and laboratory forms collected data on the participants' SCD genotype, blood transfusion history, number of VOs in the past year, specialists involved in care,

number of hospital admissions in the past year, SCD complications and standard laboratory measures (S1 Table) [24].

Data for the medical and laboratory forms were abstracted from participants' electronic health records. Laboratory measures were obtained during steady state, which was defined as at least two weeks before or after: 1) hospitalization, 2) a blood transfusion, or 3) a major acute event (e.g., stroke or VOE) [24]. Survey and abstracted health record data were entered into a REDCap database, assessed for completeness and inaccuracies by the data coordinating center, and referred back to each site for correction.

Data analysis

We utilized a cross-sectional study design. Male participants were compared to female participants with regards to sociodemographic characteristics, SCD disease characteristics and complications. Summary statistics were presented as frequencies and percentages for categorical variables, and median and 25th–75th percentiles (Q1-Q2) or mean and standard deviation for continuous variables. Categorical variables were analyzed using Chi-Square or Fisher exact tests when appropriate. Continuous variables were compared using the Mann-Whitney U test or independent sample t-tests depending on the distribution. For each SCD complication, all variables with $p \leq 0.1$ in univariate analysis were included in a multivariable logistic regression with backward elimination. Statistical analysis was performed using SAS version 9.4 (SAS Institute; Cary, NC). A p -value < 0.05 was considered statistically significant. Due to the exploratory and hypothesis generating approach of the study, no adjustment for multiple testing was applied [26].

Results

Demographic characteristics

A total of 2124 participants were included in the study; 1190 were female (Fig 1).

Participant demographics are highlighted in Table 1. The mean age of our participants was 27.8 years. The majority were Black or African American (95.6%) and never married (78.4%). There were no statistical differences in the age, ethnicity, race, employment, and marital status between sexes. Females had higher levels of education (25.9% vs 16.8% college graduate and 83.6% vs. 79.7% high school education and higher, $p < 0.0001$), but had a household income less than males ($p = 0.04$). Although not statistically significant, more women were on government insurance (i.e. Medicare, Medicaid, or other government sponsored programs).

Disease and treatment characteristics

Most participants (male and female) had the hemoglobin SS genotype and received care from hematologists. The prevalence of hydroxyurea use was higher in males (55.4% vs. 44.6%, $p < 0.0001$) (Table 2). Females had worse ASCQ-Me pain frequency and severity scores ($p = 0.0002$ and < 0.0001 , respectively) and had a higher rate of 3 or more admissions in the past year (30.9% vs 25.5, $p = 0.03$) (Table 2). Females and males had similar rates of taking opioids (80.4% vs. 78.9%). Males had significantly more skin ulcers and respiratory, musculoskeletal, genitourinary and cardiovascular complications. In contrast, females were more likely to have anxiety, depression and autoimmune diseases.

On multivariable analysis, males had higher odds of acute chest syndrome (odds ratio (OR) 1.4, $p = 0.002$; Table 3), cardiovascular (OR 1.70, $p < 0.001$) and musculoskeletal (OR 1.33, $p = 0.0034$) complications and lower odds of depression (OR 0.77, $p = 0.0381$). Unemployed females had higher odds of anxiety (OR = 1.72, $p = 0.0049$).

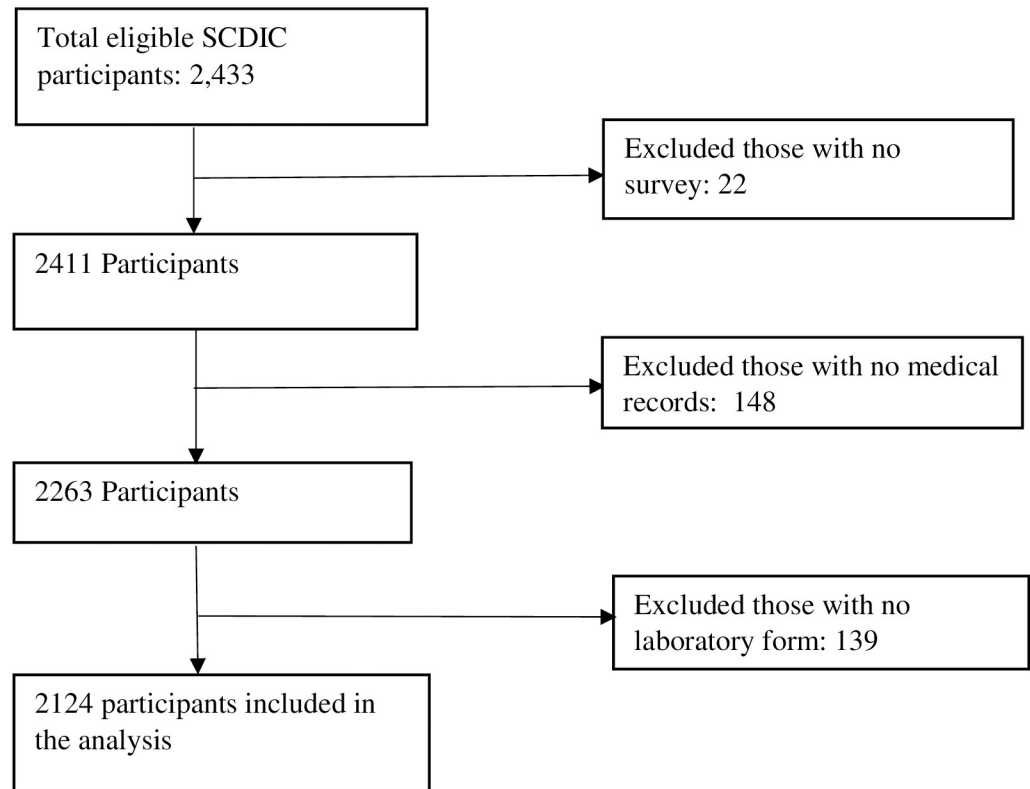


Fig 1. Flow diagram of participant inclusion.

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Concerning laboratory measures, males had significantly higher blood urea nitrogen (BUN), serum creatinine and liver enzymes (aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) and albumin (Table 4). Reticulocyte count, white blood cell count and differentials (neutrophils and monocytes) were similar in both sexes. Males had significantly higher mean steady state hemoglobin (10 g/dl vs 9.3 g/dl, $p < 0.0001$). Female participants had significantly higher fetal hemoglobin levels with and without hydroxyurea use (9.6% vs 8.5%, $p = 0.03$ and 3% vs 2.2%, $p = 0.0005$, respectively).

Discussion

This study identified important sex differences in disease characteristics and complications. In this cohort of 2124 people, females had higher fetal hemoglobin levels despite reporting less hydroxyurea use than males. Females also had more opioid use, significantly worse ASCQ-Me pain frequency and severity scores, and more VOs and hospitalizations. Despite more hydroxyurea use and less hospitalizations, males had more life-threatening complications; while females had higher rates of anxiety, depression and autoimmune diseases.

Recurrent occurrences of VOs are the hallmark presentation of SCD and are the leading cause of hospitalization [27]. Almost half of our participants reported having four or more VOs in the past year, majority of whom were female. A prospective cohort study on life expectancy and risk factors for early death in SCD by Platt et al [1] revealed that patients with SCD have an average of two or more VOs per year in the absence of treatment [1]. In our study, females reported worse ASCQ-Me pain frequency and severity scores and were taking more opioids. The higher pain and opioid usage in females may be explained by previous

Table 1. Participant socio-demographic characteristics.

Characteristic	Females (n = 1190)	Males (n = 934)	P-value	Total (n = 2124)
Age				
Mean (SD) years	27.9 (7.8)	27.6 (8.0)	0.3	27.8 (7.9)
Median (Q1-Q2)	27 (22–34)	27 (21–33)		27 (21–34)
Race, N (%)				
Black or African American	1,128 (96.6)	856 (94.3)	0.1	1,984 (95.6)
Multiracial	28 (2.4)	41 (4.5)		69 (3.3)
American Indian/Alaskan	6 (0.5)	4 (0.4)		10 (0.5)
Asian	3 (0.3)	3 (0.3)		6 (0.3)
White	3 (0.3)	4 (0.4)		7 (0.3)
Ethnicity, N (%)				
Hispanic/ Latino	44 (3.8)	45 (4.9)	0.2	89 (4.3)
Marital Status, N (%) - adults only				
Never married	827 (79.1)	614 (77.3)	0.1	1,441 (78.4)
Married/Living as married	162 (15.5)	129 (16.2)		291 (15.8)
Divorced/separated/widowed	56 (5.4)	51 (6.4)		107 (5.8)
Education, N (%)				
Less than high school	31 (2.6)	33 (3.6)	<0.0001	64 (3.1)
Some high school	161 (13.7)	152 (16.6)		313 (15.0)
High school graduate or GED equivalent	285 (24.3)	305 (33.4)		590 (28.3)
Some college	391 (33.4)	270 (29.5)		661 (31.7)
College graduate	303 (25.9)	154 (16.8)		457 (21.9)
Employment, N (%)				
Employed	413 (35.5)	339 (37.4)	0.3	752 (36.3)
Not employed by choice	286 (24.6)	198 (21.9)		484 (23.4)
Not employed, other	464 (39.9)	369 (40.7)		833 (40.3)
Household income in a year, N (%)				
\$25,000 or less	610 (56.5)	412 (50.6)	0.04	1,022 (54.0)
\$25,001-\$50,000	234 (21.7)	194 (23.8)		428 (22.6)
\$50,001-\$75,000	98 (9.1)	103 (12.6)		201 (10.6)
\$75,001-\$100,000	55 (5.1)	48 (5.9)		103 (5.4)
>\$100,001	82 (7.6)	58 (7.1)		140 (7.4)
Medical Insurance, N (%)				
None	48 (4.0)	47 (5.0)	0.2	95 (4.5)
Medicare, Medicaid or government-sponsored	826 (69.4)	618 (66.2)		1,444 (68.0)
Private	316 (26.6)	268 (28.7)		584 (27.5)

Missing values were not included in the comparison. The p-values reported represent strength of associations between variables.

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literature which identified an increase in VOs at different stages of the menstrual cycle [28–30]. In addition to the increase of VOs with menstruation, a study by Brandow et al [31] revealed that females with SCD expressed more neuropathic pain than males [31]. Further investigations on the assessment of pain and the influence of hormonal and physiological changes related to menstruation and the impact they may have on the frequency of VOs in females with SCD are warranted.

In our registry, more males self-reported taking hydroxyurea than females; however, females had higher levels of fetal hemoglobin. Hydroxyurea use increases levels of fetal hemoglobin and has been associated with a reduction in blood transfusion dependency and

Table 2. Disease characteristics.

Characteristic	Females (N = 1190)	Males (N = 934)	P-value
Sickle cell genotype, N (%)			
Hb SS	805 (67.7)	642 (68.7)	0.4
Hb SC	255 (21.4)	194 (20.8)	
Hb S beta+ thalassemia	75 (6.3)	45 (4.8)	
Hb S beta0 thalassemia	40 (3.4)	43 (4.6)	
Other variants	14 (1.2)	10 (1.1)	
Hydroxyurea use, N (%)			
Currently using	519 (44.6)	511 (55.4)	<0.0001
Opioid Use, N (%)			
Currently using opioids	957 (80.4)	737 (78.9)	0.4
Number of vaso-occlusive episodes in the past year, N (%)			
0	140 (11.8)	139 (15.0)	0.01
1	109 (9.2)	109 (11.7)	
2	151 (12.7)	134 (14.4)	
3	196 (16.5)	147 (15.8)	
4 or more	590 (49.7)	400 (43.1)	
Time since most recent vaso-occlusive episode, N (%)			
Currently having one	150 (12.6)	108 (11.6)	0.1
<1 week ago	204 (17.2)	127 (13.6)	
1–3 weeks ago	255 (21.5)	189 (20.3)	
1–6 months ago	319 (26.9)	257 (27.6)	
7–11 months ago	73 (6.2)	63 (6.8)	
1–5 years ago	119 (10.0)	120 (12.9)	
5+ years ago	47 (4.0)	46 (4.9)	
Never had a pain attack	19 (1.6)	21 (2.3)	
ASCQ-Me Pain Episode frequency T-score, mean (SD)	49.2 (11.1)	47.4 (11.7)	0.0002
ASCQ-Me Pain Episode severity T-score, mean (SD)	51.6 (9.6)	49.3 (10)	<0.001
Prior History of Blood Transfusion, N (%)	1195 (64.0)	672 (65.4)	0.2
Number of hospital admissions in the past year, N (%)			
0	344 (35.0)	318 (41.6)	0.03
1	215 (21.9)	172 (22.5)	
2	120 (12.2)	80 (10.5)	
3	84 (8.6)	50 (6.5)	
4+	219 (22.3)	145 (19.0)	
Specialists involved in care, N (%)			
PCP only	26 (2.2)	8 (0.9)	0.049
Hematologist only	700 (59.4)	579 (62.9)	
Co-management (PCP & Hematologist)	442 (37.5)	329 (35.7)	
Other	10 (0.8)	5 (0.5)	
Sickle cell disease related complications, N (%)			
Acute chest syndrome	658 (55.4)	581 (62.3)	0.001
Asthma	319 (26.9)	253 (27.1)	0.9
Digestive ^a	729 (61.3)	544 (58.4)	0.1
Musculoskeletal ^b	351 (29.5)	332 (35.6)	0.003
Autoimmune/Inflammatory ^c	228 (19.6)	141 (15.5)	0.01
Central nervous system ^d	200 (16.8)	162 (17.3)	0.7
Genitourinary ^e	84 (7.1)	304 (32.6)	<0.001

(Continued)

Table 2. (Continued)

Characteristic	Females (N = 1190)	Males (N = 934)	P-value
Cardiovascular ^f	138 (11.6)	160 (17.1)	0.0003
Multi-organ failure	62 (5.2)	49 (5.2)	0.9
Pneumococcal sepsis	40 (3.4)	47 (5.0)	0.06
Skin ulcers	33 (2.8)	54 (5.8)	0.0005
Retinopathy	165 (13.9)	145 (15.5)	0.3
Diabetes mellitus	28 (2.4)	20 (2.1)	0.7
Iron overload	308 (25.9)	226 (24.2)	0.4
Chronic refractory pain	263 (22.1)	184 (19.7)	0.2
Anxiety	174 (14.6)	104 (11.1)	0.02
Depression	259 (21.8)	154 (16.5)	0.002
Cancer	4 (0.3)	4 (0.4)	0.7

Missing values were not included in the comparison. The p-values reported represent strength of associations between variables.

^aDigestive complications: splenomegaly, splenic sequestration, splenic infarcts, hypersplenism, autosplenectomy, gallstones and cholecystitis.

^bMusculoskeletal complications: dactylitis, avascular necrosis and osteomyelitis.

^cAutoimmune/Inflammatory complications: deep venous thrombosis, lupus, rheumatoid arthritis, gout and sarcoidosis.

^dCentral nervous system complications: stroke and intracranial bleeding.

^eGenitourinary complications: priapism, chronic kidney disease and end stage renal failure.

^fCardiovascular complications: pulmonary arterial hypertension and left ventricular dysfunction.

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mortality in SCD [32]. In addition, higher fetal hemoglobin levels has been associated with increased survival in SCD [1]. Our finding of elevated fetal hemoglobin in females, with and without hydroxyurea use, may contribute to the increased survival in women with SCD. Further studies are needed to determine other causes of elevated fetal hemoglobin in females. Despite the elevated fetal hemoglobin, females reported lower hydroxyurea use. Reasons for lower hydroxyurea use among females identified in the literature include the proven teratogenic effects of the drug in animals; which deters use during pregnancy [33] and has led to recommendations to discontinue hydroxyurea when attempting to become pregnant, during pregnancy or while breast feeding [13]. A key consideration that needs to be taken into account in the interpretation of our findings is that our data on hydroxyurea was self-reported and lacks indicators of adherence. The possibility that males self-reported hydroxyurea use, but may not be adherent cannot be ruled out. Additional investigations into reasons for less hydroxyurea use in females and the association between self-reported hydroxyurea use and adherence in SCD populations are warranted.

Except for autoimmune diseases, females had significantly less prevalence of chronic end-organ complications than their male counterparts [34]. A study by Ngo et al [34] revealed a higher prevalence of autoimmune diseases in females compared to males [34]. The higher prevalence may be attributed to gender specific hormones and the role of those hormones during the various reproductive stages of a woman [34]. Flare up of autoimmune diseases such as systemic lupus erythematosus are influenced by the age of menarche, menopause or the use of oral contraceptives [34]. Gender-specific hormones may account for the higher occurrence of autoimmune complications among females in our registry.

Males had significantly more complications associated with increased mortality, including skin ulcers, acute chest syndrome, musculoskeletal, genitourinary and cardiovascular complications. Our findings are also consistent with Platt et al [1] findings that males have a lower median age at death than females and individuals with symptomatic SCD have higher

Table 3. Association between participant demographics and sickle cell disease complications.

Variable	P value	OR (95% CI)
Acute chest syndrome		
Age	< .0001	0.96 (0.95–0.97)
Sex	0.002	
Female (ref)		
Male		1.4 (1.14–1.73)
Hydroxyurea use	0.05	
No (Ref)		
Yes		0.8 (0.64–0.99)
Medical insurance	< .0001	
Private (Ref)		
None		0.92 (0.54–1.55)
Medicare, Medicaid or government-sponsored		1.8 (1.44–2.27)
SCD genotype	< .001	
Hb SC (Ref)		
Hb SS		1.73 (1.33–2.26)
Hb S beta+ thalassemia		0.59 (0.35–0.96)
Hb S beta0 thalassemia		2.04 (1.14–3.7)
Other variants		1.04 (0.41–2.6)
Cardiovascular complications		
Age	< .0001	1.06 (1.04–1.08)
Sex	< .0001	
Female (Ref)		
Male		1.70 (1.32–2.21)
Medical Insurance	< .0001	
Private (Ref)		
None		1.17 (0.46–2.56)
Medicare, Medicaid or government-sponsored		1.93 (1.40–2.72)
SCD genotype	0.003	
Hb SC (Ref)		
Hb SS		2.68 (1.82–4.09)
Hb S beta+ thalassemia		0.95 (0.37–2.14)
Hb S beta0 thalassemia		1.82 (0.77–3.93)
Other variants		1.79 (0.40–5.72)
Musculoskeletal complications		
Age	< .0001	1.05 (1.03–1.06)
Sex	0.0034	
Female (Ref)		
Male		1.33 (1.10–1.62)
SCD genotype	0.006	
Hb SC (Ref)		
Hb SS		1.57 (1.21–2.05)
Hb S beta+ thalassemia		1.05 (0.64–1.70)
Hb S beta0 thalassemia		1.46 (0.85–2.46)
Other variants		0.81 (0.26–2.12)
Hydroxyurea current use	0.0083	
No (Ref)		
Yes		0.76 (0.63–0.93)

(Continued)

Table 3. (Continued)

Variable	P value	OR (95% CI)
Employment	0.0006	
Employed (Ref)		
Not employed by choice		1.63 (1.23–2.15)
Not employed, other		1.41 (1.13–1.76)
Depression		
Age	0.02	1.02 (1.00–1.04)
Sex	0.0381	
Female (Ref)		
Male		0.77 (0.60–0.99)
Medical Insurance	0.03	
Private (Ref)		
None		0.56 (0.23–1.20)
Medicare, Medicaid or government-sponsored		1.33 (0.98–1.82)
Employment	0.02	
Not employed, other (Ref)		
Employed	0.514	1.14 (0.77–1.66)
Not employed by choice	0.006	1.50 (1.12–2.00)
Anxiety		
Employment* sex	0.02	
Not employed by choice vs Employed gender = Female	0.8811	0.97 (0.60–1.54)
Not employed, other vs Employed gender = Female	0.0049	1.72 (1.18–2.51)
Not employed by choice vs Employed gender = Male	0.1717	1.46 (0.85–2.51)
Not employed, other vs Employed gender = Male	0.9066	1.03 (0.63–1.69)

Model includes all variables with $p < 0.1$ in univariate analysis.

Interaction between sex and other covariates were not significant and were eliminated from the final model.

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mortality [1]. For instance, respiratory complications, such as acute chest syndrome, are the leading cause of morbidity and mortality amongst individuals with SCD [35], and more males in our sample had a diagnosis of acute chest syndrome. Males in our sample also had significantly more skin ulcers than females, which has also been previously reported [36]. The higher odds of SCD complications in males could be associated with the higher lab values in males, such as liver enzymes. Although lab values were within normal ranges, this may suggest a higher pro-inflammatory state among men, which has been well reported in SCD [37,38]. Close monitoring of lab values, particularly among males, is warranted to screen for and prevent the occurrence of disease complications that lead to early mortality. Our results support the need for further research to uncover the reasons for a higher incidence of chronic end-organ damage amongst males with SCD and determine if specific social and medical interventions may improve the lifespan of males living with SCD.

Importantly, females had more frequent diagnoses of anxiety and depression than males, consistent with the general population [39,40]. In 2008, using data from the Pain in Sickle Cell Epidemiology Study (PiSCES) study, Levenson et al [41] found that individuals with SCD reporting depressive symptoms and high anxiety had significantly more incidence of pain and also experienced more distress and interference from pain in their daily lives [41]. This is consistent with our findings that females with SCD had significantly more frequent and severe pain in addition to depression and anxiety diagnoses compared to males with SCD. Depression and anxiety is known to exacerbate pain and other physical complications of SCD [41]. In

Table 4. Laboratory measures.

Laboratory measure	Females		Males		P-value
	n	Median or mean (Q1-Q2 or SD)	n	Median or mean (Q1-Q2 or SD)	
Hemoglobin g/dl, mean (SD)	1183	9.3 (1.70)	930	10.0 (2.10)	<0.0001
Hb A2%, median (Q1-Q2)	921	3.5 (3.0–4.1)	725	3.6 (3.0–4.5)	0.1
Hb F % with hydroxyurea use, median (Q1-Q2)	445	9.6 (5–16.9)	451	8.5 (3.5–16)	0.03
Hb F % without hydroxyurea use, median (Q1-Q2)	521	3 (1.3–8)	306	2.2 (1–5.4)	0.0005
Platelet count 10 ⁹ /l, mean (SD)	1180	345 (141.0)	926	337 (149.0)	0.2
MCV fl, mean (SD)	1179	88.9 (13.5)	927	90.1 (14.5)	0.07
MCH pg, mean (SD)	1182	31.0 (5.9)	928	31.5 (5.6)	0.1
MCHC g/dl, mean (SD)	1175	34.6 (1.5)	925	34.7 (1.6)	0.1
Reticulocyte Count 10 ³ /mm ³ , median (Q1-Q2)	588	0.5 (0.1–2)	439	0.5 (0.1–2)	0.15
White Blood Cells 10 ³ /mm ³ , mean (SD)	1180	10.6 (4.5)	929	10.1 (4.1)	0.01
Neutrophils segmented and band %, mean (SD)	1116	55.9 (12.5)	889	53.4 (12.8)	<0.0001
Lymphocytes %, mean (SD)	1128	31.7 (11.4)	902	31.9 (11.8)	0.7
Monocytes %, mean (SD)	1127	8.5 (4.5)	898	9.8 (5.1)	<0.0001
Serum BUN mg/dL, median (Q1-Q2)	1155	7.0 (5.0–9.0)	910	9.0 (7–11)	<0.0001
Serum Creatinine mg/dL, median (Q1-Q2)	1158	0.6 (0.5–0.7)	916	0.8 (0.6–0.9)	<0.0001
Bilirubin serum total mg/dL, median (Q1-Q2)	1153	2.0 (1.2–3.2)	912	2.4 (1.5–4.1)	<0.0001
Bilirubin serum direct mg/dL, median (Q1-Q2)	602	0.4 (0.3–0.7)	460	0.4 (0.3–0.7)	0.8
AST U/L, median (Q1-Q2)	1150	31.0 (22.0–45.0)	907	35.0 (26.0–49.0)	<0.0001
ALT U/L, median (Q1-Q2)	1150	19.0 (13.0–29.0)	908	22.0 (15.0–31.0)	<0.0001
Alkaline Phosphatase U/L, median (Q1-Q2)	1153	75.0 (60.0–100.0)	907	89.0 (70.0–116.0)	<0.0001
Total Protein g/dL, mean (SD)	1146	7.6 (0.70)	906	7.7 (0.7)	0.07
Albumin g/dL, mean (SD)	1146	4.1 (0.50)	902	4.3 (0.5)	<0.0001

Missing values were not included in the comparison. The p-values reported represent strength of associations between variables.

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addition to impacts on physical and mental quality of life, depression has also been associated with a significant increase in total health care costs for individuals with SCD (\$13,016 for no depression diagnosis vs \$30,665 for depression diagnosis $p = 0.01$) [42]. Despite higher rates of depression and anxiety, we found females were more likely to have higher education. Interestingly, we also found females reported a lower household income than male participants with SCD. Income inequality has been associated with an increased risk of depression [43].

Our study has several limitations. All the individuals with SCD that participated in the study were recruited through comprehensive SCD care settings where they receive care from sickle cell specialists. Thus, this sample is not representative of individuals who do not have access to SCD experts. Only individuals that had literacy in English were included and our findings are not generalizable to individuals who have low literacy levels or who are non-English speaking. Next, we did not collect information on psychosocial factors (e.g. social support) and lifestyle factors (e.g. smoking, alcohol, diet, exercise) that are linked to quality of life and lifespan [20,44–46]. We were also unable to account for the impact that gender socialization may have on individuals' behaviors, such as disease self-management. For instance, prior studies have associated femininity with engagement in health promotion [47]. Findings from a recent study by Blake et al [48] suggest that health promotion in SCD is linked to gender socialization; as parents or parental proxies of adolescents with SCD tended to underestimate their male adolescents emotional and social functioning, while overestimating for female adolescents.⁴⁶ Finally, this study is limited due to the use of a cross-sectional design. The timing of individuals completing the surveys and having their medical records abstracted may not be

representative of the sex-based differences in the manifestations and complications of SCD that exists across the lifespan. We abstracted data entered by healthcare providers in the participant's medical records and could not fully ascertain that there was a gender differential in the measurements and recording of those data in the participants' medical records.

Despite those limitations, our study has a large sample size and utilizes data from a consortium with eight geographically diverse comprehensive SCD care settings and continues to follow these participants through the prospective registry. Our sample size had sufficient power to detect statistically significant differences between males and females. Additionally, validated instruments were used to collect self-report data.

Conclusion

Our findings suggest key sex differences in the presentation of SCD, with males having more life-threatening chronic end-organ complications and females having higher rates of depression and anxiety. Future research is required to determine how sex influences the mechanisms underpinning clinical outcome differences.

Supporting information

S1 Table. Data variables.

(DOCX)

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References

1. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality In Sickle Cell Disease—Life Expectancy and Risk Factors for Early Death. *N Engl J Med Boston* [Internet]. 1994 Jun 9 [cited 2019 Apr 1]; 330(23):1639–44. Available from: <https://search.proquest.com/docview/1983834366/abstract/E1B961FE1B144C89PQ/1>. PMID: 7993409
2. Hassell KL. Population Estimates of Sickle Cell Disease in the U.S. *Am J Prev Med* [Internet]. 2010 Apr 1 [cited 2020 Jan 14]; 38(4, Supplement):S512–21. Available from: <http://www.sciencedirect.com/science/article/pii/S074937970900960X>. PMID: 20331952
3. Noguchi CT, Schechter AN, Rodgers GP. 3 Sickle cell disease pathophysiology. *Baillieres Clin Haematol* [Internet]. 1993 Mar 1 [cited 2020 Jan 14]; 6(1):57–91. Available from: <http://www.sciencedirect.com/science/article/pii/S0950353605800666>. PMID: 8353318
4. Kato GJ, Hebbel RP, Steinberg MH, Gladwin MT. Vasculopathy in sickle cell disease: Biology, pathophysiology, genetics, translational medicine, and new research directions. *Am J Hematol* [Internet]. 2009 [cited 2020 Jan 14]; 84(9):618–25. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/ajh.21475>. PMID: 19610078
5. Conran N, Franco-Penteado CF, Costa FF. Newer Aspects of the Pathophysiology of Sickle Cell Disease Vaso-Occlusion. *Hemoglobin* [Internet]. 2009 Jan 1 [cited 2020 Jan 14]; 33(1):1–16. Available from: <https://doi.org/10.1080/03630260802625709>. PMID: 19205968
6. Steinberg MH. Management of Sickle Cell Disease. *N Engl J Med* [Internet]. 1999 Apr 1 [cited 2020 Jan 14]; 340(13):1021–30. Available from: <https://doi.org/10.1056/NEJM199904013401307>. PMID: 10099145
7. Hamideh D, Alvarez O. Sickle cell disease related mortality in the United States (1999–2009). *Pediatr Blood Cancer* [Internet]. 2013 [cited 2020 Jan 14]; 60(9):1482–6. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/pbc.24557>. PMID: 23637037

8. DeBaun MR, Ghafari DL, Rodeghier M, Maitra P, Chaturvedi S, Kassim A, et al. Decreased median survival of adults with sickle cell disease after adjusting for left truncation bias: a pooled analysis. *Blood* [Internet]. 2019 Feb 7 [cited 2020 May 4]; 133(6):615–7. Available from: <https://ashpublications.org/blood/article/133/6/615/260539/Decreased-median-survival-of-adults-with-sickle>. PMID: 30530750
9. Adamkiewicz TV, Silk BJ, Howgate J, Baughman W, Strayhorn G, Sullivan K, et al. Effectiveness of the 7-Valent Pneumococcal Conjugate Vaccine in Children With Sickle Cell Disease in the First Decade of Life. *Pediatrics* [Internet]. 2008 Mar 1 [cited 2020 Jan 14]; 121(3):562–9. Available from: <https://pediatrics.aappublications.org/content/121/3/562>. PMID: 18310206
10. Halasa NB, Shankar SM, Talbot TR, Arbogast PG, Mitchel EF, Wang WC, et al. Incidence of Invasive Pneumococcal Disease among Individuals with Sickle Cell Disease before and after the Introduction of the Pneumococcal Conjugate Vaccine. *Clin Infect Dis* [Internet]. 2007 Jun 1 [cited 2020 Jan 14]; 44(11):1428–33. Available from: <https://academic.oup.com/cid/article/44/11/1428/476499>. PMID: 17479937
11. Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. *N Engl J Med*. 1986 Jun 19; 314(25):1593–9. <https://doi.org/10.1056/NEJM198606193142501> PMID: 3086721
12. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, et al. Effect of Hydroxyurea on Mortality and Morbidity in Adult Sickle Cell Anemia: Risks and Benefits Up to 9 Years of Treatment. *JAMA* [Internet]. 2003 Apr 2 [cited 2020 Jan 14]; 289(13):1645–51. Available from: <https://jamanetwork.com/journals/jama/fullarticle/196300>. PMID: 12672732
13. National Heart, Lung, and Blood Institute (NHLBI). Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014 | National Heart, Lung, and Blood Institute (NHLBI) [Internet]. 2014 [cited 2020 Jan 20]. <https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/evidence-based-management-sickle-cell-disease-expert-0>.
14. Ballas SK, Pulte ED, Lobo C, Riddick-Burden G. Case series of octogenarians with sickle cell disease. *Blood* [Internet]. 2016 Nov 10 [cited 2020 Jan 14]; 128(19):2367–9. Available from: <https://ashpublications.org/blood/article/128/19/2367/35510/Case-series-of-octogenarians-with-sickle-cell>. PMID: 27702797
15. Barton-Gooden A, Grindley M, Knight-Madden J, Asnani M. Gender influences on the health of adolescents with sickle cell disease. *Psychol Health Med* [Internet]. 2019 Apr 21 [cited 2021 Jul 2]; 24(4):470–80. Available from: <https://doi.org/10.1080/13548506.2018.1533985>. PMID: 30318923
16. Arduini GAO, Trovó de Marqui AB. Prevalence and Characteristics of Priapism in Sickle Cell Disease. *Hemoglobin*. 2018 Mar; 42(2):73–7. <https://doi.org/10.1080/03630269.2018.1452760> PMID: 29745276
17. Boافر TK, Olayemi E, Galadanci N, Hayfron-Benjamin C, Dei-Adomakoh Y, Segbefia C, et al. Pregnancy outcomes in women with sickle-cell disease in low and high income countries: a systematic review and meta-analysis. *BJOG Int J Obstet Gynaecol*. 2016 Apr; 123(5):691–8. <https://doi.org/10.1111/1471-0528.13786> PMID: 26667608
18. Chinegwundoh FI, Smith S, Anie KA. Treatments for priapism in boys and men with sickle cell disease. *Cochrane Database Syst Rev* [Internet]. 2020 Apr 1 [cited 2021 Jul 2]; 4:CD004198. Available from: <https://europepmc.org/articles/PMC7134865>. PMID: 32251534
19. Haddad LB, Curtis KM, Legardy-Williams JK, Cwiak C, Jamieson DJ. Contraception for individuals with sickle cell disease: a systematic review of the literature [Internet]. *Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews* [Internet]. Centre for Reviews and Dissemination (UK); 2012 [cited 2021 Jul 2]. <http://www.ncbi.nlm.nih.gov/books/NBK98267/>.
20. McClish DK, Penberthy LT, Bovbjerg VE, Roberts JD, Aisiku IP, Levenson JL, et al. Health related quality of life in sickle cell patients: the PiSCES project. *Health Qual Life Outcomes*. 2005 Aug 29; 3:50. <https://doi.org/10.1186/1477-7525-3-50> PMID: 16129027
21. McClish DK, Levenson JL, Penberthy LT, Roseff SD, Bovbjerg VE, Roberts JD, et al. Gender differences in pain and healthcare utilization for adult sickle cell patients: The PiSCES Project. *J Womens Health* 2002. 2006 Mar; 15(2):146–54.
22. DiMartino LD, Baumann AA, Hsu LL, Kanter J, Gordeuk VR, Glassberg J, et al. The Sickle Cell Disease Implementation Consortium: Translating Evidence-Based Guidelines into Practice for Sickle Cell Disease. *Am J Hematol* [Internet]. 2018 Dec [cited 2020 Jan 14]; 93(12):E391–5. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6503654/>. PMID: 30203558
23. Masese RV, DeMartino T, Bonnabeau E, Burns EN, Preiss L, Varughese T, et al. Effective Recruitment Strategies for a Sickle Cell Patient Registry Across Sites from the Sickle Cell Disease Implementation Consortium (SCDIC). *J Immigr Minor Health*. 2020 Oct 9.
24. Glassberg JA, Linton EA, Burson K, Hendershot T, Telfair J, Kanter J, et al. Publication of data collection forms from NHLBI funded sickle cell disease implementation consortium (SCDIC) registry.

- Orphanet J Rare Dis [Internet]. 2020 Jul 7 [cited 2021 Jan 25]; 15. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7341606/>. PMID: 32635939
25. Treadwell MJ, Hassell K, Levine R, Keller S. Adult Sickle Cell Quality-of-Life Measurement Information System (ASCQ-Me): Conceptual Model Based on Review of the Literature and Formative Research. *J Pain*. 2014 Oct; 30(10):902–14. <https://doi.org/10.1097/AJP.000000000000054> PMID: 24300219
 26. Bender R, Lange S. Adjusting for multiple testing—when and how? *J Clin Epidemiol*. 2001 Apr; 54(4):343–9. [https://doi.org/10.1016/s0895-4356\(00\)00314-0](https://doi.org/10.1016/s0895-4356(00)00314-0) PMID: 11297884
 27. Ballas SK, Lusardi M. Hospital readmission for adult acute sickle cell painful episodes: frequency, etiology, and prognostic significance. *Am J Hematol* [Internet]. 2005 [cited 2020 Jan 28]; 79(1):17–25. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/ajh.20336>. PMID: 15849770
 28. de Abood M, de Castillo Z, Guerrero F, Espino M, Austin KL. Effect of Depo-Provera or Microgynon on the painful crises of sickle cell anemia patients. *Contraception*. 1997 Nov; 56(5):313–6. [https://doi.org/10.1016/s0010-7824\(97\)00156-x](https://doi.org/10.1016/s0010-7824(97)00156-x) PMID: 9437560
 29. Smith-Whitley K. Reproductive issues in sickle cell disease. *Blood* [Internet]. 2014 Dec 4 [cited 2020 Mar 18]; 124(24):3538–43. Available from: <https://ashpublications.org/blood/article/124/24/3538/33523/Reproductive-issues-in-sickle-cell-disease>. PMID: 25472967
 30. Yoong WC, Tuck SM. Menstrual pattern in women with sickle cell anaemia and its association with sickling crises. *J Obstet Gynaecol J Inst Obstet Gynaecol*. 2002 Jul; 22(4):399–401. <https://doi.org/10.1080/01443610220141362> PMID: 12521464
 31. Brandow AM, Farley RA, Panepinto JA. Neuropathic pain in patients with sickle cell disease. *Pediatr Blood Cancer*. 2014 Mar; 61(3):512–7. <https://doi.org/10.1002/pbc.24838> PMID: 24167104
 32. Brandow AM, Panepinto JA. Hydroxyurea use in sickle cell disease: the battle with low prescription rates, poor patient compliance and fears of toxicities. *Expert Rev Hematol*. 2010 Jun; 3(3):255–60. <https://doi.org/10.1586/ehm.10.22> PMID: 21082977
 33. Ballas SK, McCarthy WF, Guo N, DeCastro L, Bellevue R, Barton BA, et al. Exposure to Hydroxyurea and Pregnancy Outcomes in Patients With Sickle Cell Anemia. *J Natl Med Assoc* [Internet]. 2009 Oct [cited 2020 Mar 18]; 101(10):1046–51. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0027968415310725>. PMID: 19860305
 34. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. *Front Neuroendocrinol* [Internet]. 2014 Aug 1 [cited 2021 Jul 2]; 35(3):347–69. Available from: <https://www.sciencedirect.com/science/article/pii/S0091302214000466>. PMID: 24793874
 35. Farooq S, Abu Omar M, Salzman GA. Acute chest syndrome in sickle cell disease. *Hosp Pract* [Internet]. 2018 May 27 [cited 2020 Mar 24]; 46(3):144–51. Available from: <https://www.tandfonline.com/doi/full/10.1080/21548331.2018.1464363>. PMID: 29648482
 36. Minniti CP, Eckman J, Sebastiani P, Steinberg MH, Ballas SK. Leg ulcers in sickle cell disease. *Am J Hematol* [Internet]. 2010 Jul 23 [cited 2020 Mar 24]; 85(10):831–3. Available from: <http://doi.wiley.com/10.1002/ajh.21838>. PMID: 20872960
 37. Ataga KI, Moore CG, Hillery CA, Jones S, Whinna HC, Strayhorn D, et al. Coagulation activation and inflammation in sickle cell disease-associated pulmonary hypertension. *Haematologica* [Internet]. 2008 Jan 1 [cited 2020 Mar 26]; 93(1):20–6. Available from: <http://www.haematologica.org/cgi/doi/10.3324/haematol.11763>. PMID: 18166781
 38. Torres LS, Okumura JV, Silva DGH, Mimura KKO, Belini-Júnior É, Oliveira RG, et al. Inflammation in Sickle Cell Disease: Differential and Down-Expressed Plasma Levels of Annexin A1 Protein. *Connes P*, editor. *PLOS ONE* [Internet]. 2016 Nov 1 [cited 2020 Mar 26]; 11(11):e0165833. Available from: <http://dx.plos.org/10.1371/journal.pone.0165833>. PMID: 27802331
 39. McLean CP, Asnaani A, Litz BT, Hofmann SG. Gender Differences in Anxiety Disorders: Prevalence, Course of Illness, Comorbidity and Burden of Illness. *J Psychiatr Res* [Internet]. 2011 Aug [cited 2020 Apr 23]; 45(8):1027–35. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3135672/>. PMID: 21439576
 40. Albert PR. Why is depression more prevalent in women? *J Psychiatry Neurosci JPN* [Internet]. 2015 Jul [cited 2020 Apr 23]; 40(4):219–21. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4478054/>. PMID: 26107348
 41. Levenson JL, McClish DK, Dahman BA, Bovbjerg VE, de A. Citero V, Penberthy LT, et al. Depression and Anxiety in Adults With Sickle Cell Disease: The PiSCES Project. *Psychosom Med* [Internet]. 2008 Feb [cited 2020 Mar 24]; 70(2):192–6. Available from: <http://journals.lww.com/00006842-200802000-00009>. PMID: 18158366
 42. Adam SS, Flahiff CM, Kamble S, Telen MJ, Reed SD, De Castro LM. Depression, quality of life, and medical resource utilization in sickle cell disease. *Blood Adv* [Internet]. 2017 Oct 24 [cited 2020 Mar 24]; 1(23):1983–92. Available from: <https://ashpublications.org/bloodadvances/article/1/23/1983/15709/Depression-quality-of-life-and-medical-resource>. PMID: 29296845

43. Patel V, Burns JK, Dhingra M, Tarver L, Kohrt BA, Lund C. Income inequality and depression: a systematic review and meta-analysis of the association and a scoping review of mechanisms. *World Psychiatry* [Internet]. 2018 Feb 1 [cited 2020 Mar 29]; 17(1):76–89. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1002/wps.20492>. PMID: 29352539
44. Palermo TM, Riley CA, Mitchell BA. Daily functioning and quality of life in children with sickle cell disease pain: relationship with family and neighborhood socioeconomic distress. *J Pain*. 2008 Sep; 9(9):833–40. <https://doi.org/10.1016/j.jpain.2008.04.002> PMID: 18550443
45. Martin C, Pialoux V, Faes C, Charrin E, Skinner S, Connes P. Does physical activity increase or decrease the risk of sickle cell disease complications? *Br J Sports Med*. 2018 Feb; 52(4):214–8. <https://doi.org/10.1136/bjsports-2015-095317> PMID: 26701924
46. Cohen RT, DeBaun MR, Blinder MA, Strunk RC, Field JJ. Smoking is associated with an increased risk of acute chest syndrome and pain among adults with sickle cell disease. *Blood*. 2010 May 6; 115(18):3852–4. <https://doi.org/10.1182/blood-2010-01-265819> PMID: 20448118
47. Mayor E. Gender roles and traits in stress and health. *Front Psychol* [Internet]. 2015 Jun 9 [cited 2021 Jul 2]; 6:779. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4460297/>. PMID: 26106354
48. Blake A, Guthrie-Dixon N, Grindley M, Barton-Gooden A, Knight-Madden J, Asnani M. Level of agreement between adolescents' self-assessment and parent proxy report of health-related quality of life in adolescents with sickle cell disease. *Pediatr Blood Cancer*. 2020 Apr; 67(4):e28198. <https://doi.org/10.1002/psc.28198> PMID: 32020725