1-1-2024

Biopsychosocial factors associated with pain and pain-related outcomes in adults and children with sickle cell disease: A multivariable analysis of the GRNDaD multicenter registry

Martha O Kenney
Duke University
Sana Saif Ur Rehman
Washington University School of Medicine in St. Louis
et al.

USASP
US ASSOCIATION FOR THE STUDY OF PAIN

PUBLISHED BY
ELSEVIER

The Journal of Pain, Vol 25, No. 1 (January), 2024: pp 153–164
Available online at www.jpain.org and www.sciencedirect.com

Biopsychosocial Factors Associated With Pain and Pain-Related Outcomes in Adults and Children With Sickle Cell Disease: A Multivariable Analysis of the GRNDaD Multicenter Registry

Martha O. Kenney,[*] Samuel Wilson,[†,‡] Nirmish Shah,[§] Andrey Bortsov,[¶] Wally R. Smith,[‖] Jane Little,[†,‡] Sophie Lanzkron,[**] Julie Kanter,[††] Susan Padrino,[‡‡] Amma Owusu-Ansah,[§§] Alice Cohen,[¶¶] Payal Desai,[‖‖] Deepa Manwani,[***] Sana Saif Ur Rehman,[†††] Ward Hagar,[‡‡‡] and Francis Keefe[§§§]

[*]*Department of Anesthesiology, Division of Pediatric Anesthesiology, Duke University, Durham, North Carolina,* [†]*Department of Medicine, Division of Hematology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina,* [‡]*UNC Blood Research Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina,* [§]*Departments of Pediatrics & Hematology, Duke University, Durham, North Carolina,* [¶]*Center for Translational Pain Medicine, Duke University, Durham, North Carolina,* [‖]*Division of General Internal Medicine, Department of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond, Virginia,* [**]*Department of Medicine, Division of Hematology, Johns Hopkins University School of Medicine, Baltimore, Maryland,* [††]*Division of Hematology and Oncology, University of Alabama, Birmingham, Alabama,* [‡‡]*School of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio,* [§§]*Department of Pediatrics, Division of Pediatric Hematology Oncology, University Hospitals Rainbow Babies & Children's Hospital, Cleveland, Ohio,* [¶¶]*Division of Hematology and Oncology, Newark Beth Israel Medical Center, Newark, New Jersey,* [‖‖]*Levin Cancer Institute, Atrium Health, Charlotte, North Carolina,* [***]*Department of Pediatrics, Albert Einstein College of Medicine and the Children's Hospital at Montefiore (CHAM), Bronx, New York,* [†††]*Department of Medicine, Division of Hematology, Washington University School of Medicine, St. Louis, Missouri,* [‡‡‡]*Department of Pediatrics, UCSF Benioff Children's Hospital, Oakland, California,* [§§§]*Pain Prevention and Treatment Research Program, Department of Psychiatry and Behavioral Science, Duke University, Durham, North Carolina*

Abstract: Pain is the primary symptomatic manifestation of sickle cell disease (SCD), an inherited hemoglobinopathy. The characteristics that influence pain experiences and outcomes in SCD are not fully understood. The primary objective of this study was to use multivariable modeling to examine associations of biopsychosocial variables with a disease-specific measure of pain interference known as pain impact. We conducted a secondary analysis of data from the Global Research Network for Data and Discovery national SCD registry. A total of 657 children and adults with SCD were included in the analysis. This sample was 60% female with a median age of 34 (interquartile range 26–42 years) and a chronic pain prevalence of 64%. The model accounted for 58% of the variance in pain impact. Low social ($P < .001$) and emotional ($P < .001$) functioning, increasing age ($P = .004$), low income ($P < .001$), and high acute painful episodes ($P = .007$) were most strongly associated with high pain impact in our multivariable model. Additionally, multivariable modeling of pain severity and physical function in 2 comparable samples of registry participants revealed that increasing age and low social functioning were also strongly associated with higher pain severity and low physical functioning. Overall, the results suggest that social and emotional functioning are more strongly associated with pain impact in individuals with SCD than previously studied biological modifiers such as SCD genotype, hemoglobin, and percentage fetal hemoglobin. Future research using longitudinally collected data is needed to confirm these findings.

Received March 20, 2023; Received in revised form July 25, 2023; Accepted July 28, 2023
Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.
Address reprint requests to Martha O. Kenney, MD, Division of Pediatric Anesthesiology, Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, NC 27710. E-mail: martha.kenney@duke.edu
1526-5900/$36.00

https://doi.org/10.1016/j.jpain.2023.07.029

Perspective: ***This study reveals that psychosocial (ie, social and emotional functioning) and demographic (ie, age) variables may play an important role in predicting pain and pain-related outcomes in SCD. Our findings can inform future multicenter prospective longitudinal studies aimed at identifying modifiable psychosocial predictors of adverse pain outcomes in SCD.***

Key Words: *Sickle cell disease, chronic pain, biopsychosocial pain model, pain severity, pain interference*

Sickle cell disease (SCD) is an inherited red blood cell disorder that affects approximately 100,000 people in the United States and millions worldwide. Pain is the hallmark of SCD and is associated with poor quality of life, premature mortality, and health care costs exceeding $1.1 billion/year in the United States alone, thus representing a major public health concern.[1–3] Episodes of recurrent acute pain, or vaso-occlusive episodes (VOEs), are prominent in childhood; however, more than 50% of individuals with SCD have chronic or persistent pain by late adolescence and young adulthood.[4,5] SCD pain, both acute and chronic, poses unique challenges for clinicians for several reasons. 1) The pathophysiology is poorly understood.[6,7] 2) Development of chronic SCD pain does not directly correlate with traditionally quoted biological markers of SCD severity.[7] 3) Pain experiences and prognoses in SCD vary tremendously, even within so-called severity categories.[7,8] 4) Individuals living with SCD experience VOEs both before and after developing chronic pain.[7] 5) Chronic SCD pain is multimechanistic and does not respond to disease-modifying treatments in a predictable manner.[9] 6) SCD disproportionately impacts minoritized groups from socioeconomically disadvantaged backgrounds, and thus, systemic and interpersonal racism has contributed to disparities in pain outcomes.[10] These challenges have impacted the assessment and management of pain in individuals with SCD. Those who are at risk for adverse pain outcomes (ie, severe and disabling pain) are rarely identified early in their SCD pain trajectories. Further, unlike other acute-on-chronic painful conditions, opioids have remained the mainstay for treating *all* SCD pain for decades despite the limited evidence for the effectiveness of opioids for chronic noncancer pain.[9] Understanding predictors of adverse pain outcomes in SCD is an essential step toward improving quality of life for individuals living with SCD, and developing new, effective nonopioid therapies.

The biopsychosocial model of pain emphasizes that pain is a complex, multidimensional phenomenon that is influenced by biological, psychological, and social mechanisms.[11,12] In a previous publication, we introduced an explanatory model for sickle cell pain[13] that is grounded in the neuromatrix framework proposed by pain psychologist, Ronald Melzack.[14] Consistent with the biopsychosocial model of pain, our explanatory model emphasizes the complex interplay between biological, psychological, and social factors in the perception and modulation of pain in SCD. Moreover, this pain model advocates for a holistic approach to managing SCD pain, addressing not only biological aspects of pain but also targeting psychological and social contributors to pain experiences in SCD.

However, despite this biopsychosocial model of pain, traditionally, research in SCD pain has focused primarily on examining the influence of biological variables, such as SCD genotype, total hemoglobin, or fetal hemoglobin level, on pain outcomes. In recent years, the body of literature examining the association between psychosocial variables (e.g. anxiety, depression, fatigue, and pain catastrophizing) and SCD pain has grown significantly, particularly within the pediatric SCD population. Most studies, however, have been limited by a small sample size (less than 100 participants) and recruitment from only 1 institution or sickle cell center.[15–26] Moreover, although the literature has reported a positive association between psychosocial variables and pain in SCD, only a few studies have examined the extent to which psychosocial variables contribute to pain impact and severity when compared to traditional markers of disease severity, such as SCD genotype or hemoglobin.[15,25,27] Thus, the specific biopsychosocial variables that are most important in predicting pain and pain-related outcomes in SCD have not been clearly elucidated. Cross-sectional and longitudinal studies that include large participant samples from multiple sickle cell centers are required to gain a greater understanding. Given that extensive evidence from other chronic pain conditions indicates that targeted psychologically based interventions aimed at improving social and emotional functioning can reduce pain-related distress and pain impact,[12,28,29] the contributions of these psychological variables to pain in SCD should be further explored.

Additionally, very little is known about the prevalence of pain-specific variables in SCD, such as pain variability and widespread pain distribution, and how these variables influence pain outcomes. Psychological distress and widespread pain are characteristics of central or nociplastic pain, a mechanistic pain type that is most responsive to psychologically based interventions but not to opioids.[29]

We conducted a secondary analysis of data collected from participants enrolled in the Global Research Network for Data and Discovery (GRNDaD) national sickle cell registry (most common SCD genotypes, age greater than or equal to 8 years). Our primary objectives were to use multivariable modeling to examine the strength of associations of psychosocial and biological variables with pain impact, an SCD-specific measure of pain interference. We hypothesized that psychosocial variables (eg, social and emotional functioning) and pain-specific variables (eg, number of pain locations) would have a stronger association with pain impact than biological variables (eg, SCD genotype and hemoglobin).

Methods

Participants and Procedures

This study used data from GRNDaD[30] research registry (https://grndad.org), a multicenter registry that aims to prospectively collect relevant data on individuals with SCD, including patient-reported outcomes (PROs), labs, imaging, and other clinical data. Participants of all ages are eligible for inclusion in the GRNDaD registry if they have documentation of laboratory diagnosis of SCD. For this current study, participants were included if they met the following criteria: 1) diagnosis of SCD with genotypes SS, Sβ-thalassemia, or SC, 2) age 8 years or older, and 3) completion of at least 1 pain or pain-related PRO relevant to the outcomes of interest at the time of data collection (April 2022). We restricted the age to 8 years or older because SCD pain is not a significant burden in early childhood.

Fifteen SCD centers had contributed data to GRNDaD at the time of this study. Regulatory approval for GRNDaD was obtained from a single institutional review board (Johns Hopkins University School of Medicine). GRNDaD study personnel at each SCD center consent and enroll eligible participants, and collect baseline data, which is stored in a secure manner via the Research Electronic Data Capture database.

GRNDaD centers are required to collect sociodemographic, laboratory, and clinical data that are relevant to SCD care and complications, but pain-related PRO collection varies across centers (and is not required as part of the minimum data set). The availability of research funding to collect and transfer data to Research Electronic Data Capture is the primary determinant of whether a center includes additional PROs beyond what is required for participation in the registry. At the time of this analysis, 2104 participants, 8 years old or older, were enrolled in the GRNDaD registry. Of these, 723 participants completed at least 1 pain-related survey of interest—the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me)[31] pain subscales, the Brief Pain Inventory Short Form (BPI),[32] or the Patient-Reported Outcomes Measurement Information System Physical Function Short Form 8b[33] (PROMIS physical function). A total of 657 participants from 10 sickle cell centers had completed the ASCQ-Me pain subscales, which assess pain impact (pain impact sample [Fig 1]). A total of 403 participants completed the BPI measure of pain intensity (the pain severity sample), and 267 participants completed the PROMIS physical function questionnaire (the physical function sample), respectively (Fig 1). Two hundred and three participants had completed all 3 questionnaires (ASCQ-Me, BPI, and PROMIS physical function) and, thus, were included in all 3 samples. The pain impact sample represents the primary sample for the analysis that is described in this study. Separate analyses were conducted for the pain severity sample and the physical function sample.

Measures

Self-report measures included sociodemographic information (ie, education and income) on enrollment to the registry and specific measures of pain severity, pain locations, frequency of sickle cell pain episodes, pain impact, emotional functioning, social functioning, and use of hydroxyurea. The presence of chronic pain was obtained via a self-report measure that was based on a published definition of chronic SCD pain.[7] For participants younger than 18 years old, PRO data was obtained by parental proxy. Clinical and laboratory measures such as hemoglobin and fetal hemoglobin percentage (HbF%) were obtained from participant medical records by GRNDaD study personnel. Laboratory values and PRO measures were obtained within the same calendar year, and the majority of participants had lab values collected within 1 month of PRO collection. For participants who completed multiple pain-related PROs since enrollment in GRNDaD, we used the most recent PRO available in the database.

Pain Outcomes

We examined pain and pain-related outcomes that correlate with early mortality or poor quality of life in SCD,[3] and/or are included in consensus guidelines on chronic pain studies in adults and children.[34,35] The primary outcome was pain impact, as measured by the ASCQ-Me[31] Pain Impact Short Form, a 5-item subscale that assesses pain interference over a 7-day recall period.[31] This subscale has been demonstrated to strongly correlate with the PROMIS

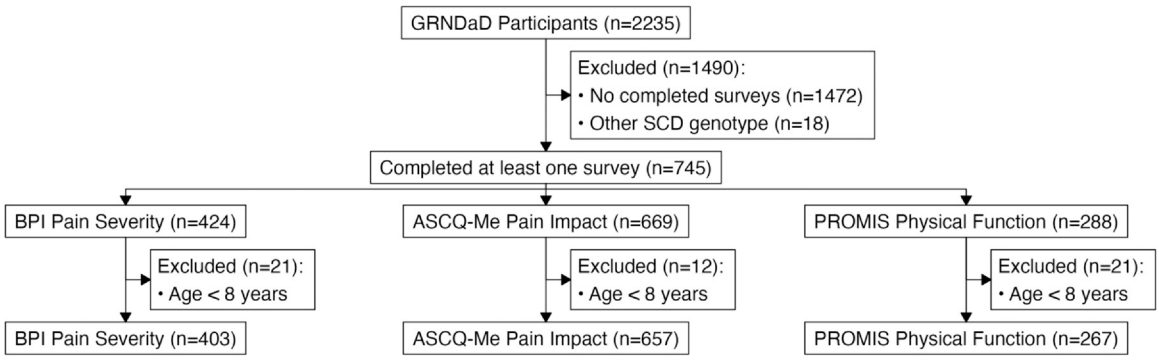

Figure 1. Flow diagram for inclusion of participants in pain impact, pain severity, and physical function models.

Pain Interference and Pain Behavior questionnaire and, thus, is a disease-specific measure of pain interference.[36] Raw scores were converted to T-scores using conversion tables in the ASCQ-Me User's Manual,[37] with scores ranging from 0 to 100. A higher T-score indicates "better" health or less pain impact.

Given the multidimensional nature of the SCD pain experience, we also explored 2 additional pain-related outcomes—numeric pain severity and physical function—using the BPI questionnaire and PROMIS Physical Function Short Form 8b. The BPI is a self-report questionnaire[32] that has been administered across a variety of pain conditions. To assess pain severity in our sample, we used a composite of the 4 pain items of the severity subscale (ie, a mean severity score), as recommended by the BPI developers.[38] PROMIS Physical Function Short Form 8b is an 8-item questionnaire that measures physical impairments that impact a person's ability to carry out daily activities. Total raw scores were calculated and converted to T-scores using the applicable score conversion table in the PROMIS Physical Function Scoring Manual.[39]

Predictor Variables for Multivariable Modeling

Sociodemographic Variables. Age, gender, education level, income, and race—were self-reported on enrollment.

Pain-specific Variables . They included a number of pain locations, pain variability, and the frequency of SCD pain episodes. The number of pain locations was evaluated using item 2 from the BPI questionnaire, which allows participants to shade or note the areas on a body map where they experience pain. We used this body map to quantify the number of painful sites. The BPI body map lacks a standardized scoring method; therefore, to quantify sites, we considered the number of body areas reported by participants and divided the map into sections with the maximum score corresponding to 22 sites or locations. We assessed short-term intra-individual variability in pain by obtaining the absolute numeric difference between "worst pain in the last 24 hours" and the "least pain in the last 24 hours" from the BPI questionnaire. The frequency of SCD pain episodes was assessed using item 1 from the ASCQ-Me Pain Episodes Frequency and Severity Measure subscale.

Social and Emotional Variables. We assessed 2 psychosocial constructs—social and emotional functioning—using data collected from the ASCQ-Me Social Functioning Impact Measure and Emotional Impact Measure. The ASCQ-Me social functioning domain is a 5-item subscale that assesses respondent participation in social activities and social roles. ASCQ-Me emotional impact is a 5-item instrument that has been shown to strongly correlate with PROMIS depression and anxiety scales.[36] Raw scores were converted to T-scores using conversion tables in the ASCQ-Me User's Manual.[37]

Given that some PROs used in the GRNDaD registry are validated in the adult population, Cronbach's alpha was calculated separately for participants 8 to 17 years old and participants 18 years and older for each of these adult measures (ASCQ-Me social and emotional functioning, ASCQ-Me pain episodes, ASCQ-Me pain impact, BPI pain severity subscale, and PROMIS physical function) to evaluate for internal consistency. The values were greater than .7 for all measures in both the pediatric and adult samples.

Statistical Analyses

Demographics and baseline characteristics of participants were summarized. A multivariable linear regression model was created for our primary outcome of interest—pain impact—using the approach outlined in Frank Harrell's textbook, *Regression Modeling Strategies*.[40] The predictor variables included in the models were age, SCD genotype, gender, income, education level, hemoglobin, HbF%, BPI pain variability, BPI number of pain locations, ASCQ-Me emotional functioning, ASCQ-Me social functioning, ASCQ-Me pain episodes, and use of hydroxyurea. Nonreported variables were assumed to be missing at random. Multiple imputation of each sample was conducted to address missing data, which averaged 10 to 20%, depending on the variable and participant sample. Some variables, such as HbF% had high missing rates (greater than 30%) in the pain impact sample but were ultimately included in the analysis due to sufficient accuracy of the predictors used in the imputation (imputation R^2 = .71). A summary of the imputation performance and missing data is provided in Supplementary Table 1. Multiple imputation was performed with aregImpute, which uses a chained equation approach with bootstrap samples, each of which is imputed using weighted predictive mean matching prior to modeling. As each sample was defined by the availability of the outcome measure, none of the outcomes were imputed, albeit the outcomes were used to impute missing predictors to reduce bias.[40,41] To avoid missing complex, nonlinear relationships between a predictor and an outcome, continuous variables were modeled using restricted cubic splines, with 5 knots for age, hemoglobin, and HbF%, and 3 knots for pain variability, emotional functioning, social functioning, and number of pain locations. Income and education level were simplified into fewer categories to allow for better imputation. Given the relatively few predictors, the large size of each sample, and the goal of effect estimation, all the prespecified predictors were included in the final model with no data reduction. Internal validation of the model was conducted to assess for the degree of overfitting. The relative importance of each predictor variable to the model was derived from the Wald Chi-square analysis of variance of the full model compared to the model without the potential predictor, subtracting the degrees of freedom used by the predictor. Partial effect graphs of the most important predictors in the model were presented, with the other predictors set at the median (continuous predictors) or mode (categorical predictor) values. Statistical analysis was conducted with the R statistical program (R Foundation for Statistical Computing, Vienna, Austria) version 4.2.2, using the RMS package for multiple imputation, linear regression modeling, partial effect prediction, and validation. Graphs were generated

Table 1. Demographic and Clinical Characteristics of Participants From Pain Impact Sample (N = 657)

CHARACTERISTICS	N (%) OR MEDIAN (IQR)
Age	
Median (IQR)	34 (26–42)
Mean ± SD	36 ± 13
Range	9 to 79
8 to 18	26 (4.1%)
19 to 30	236 (37%)
31 to 40	191 (30%)
41 to 50	96 (15%)
51 to 60	57 (8.9%)
61+	31 (4.9%)
Gender	
Male	256 (40%)
Female	380 (60%)
Genotype	
HbSS	397 (67%)
HbSC	123 (21%)
HbSβ^+-thalassemia	42 (7.1%)
HbSβ^0-thalassemia	30 (5.1%)
Hemoglobin (g/dL)	9.50 (8.20–10.88)
Fetal hemoglobin %	6 (2–14)
Hydroxyurea	291 (58%)
Chronic pain (on enrollment)*	380 (64%)
BPI pain variability†	1 (0–3)
BPI number of pain locations‡	
Median (IQR)	6.0 (3.0–8.5)
Mean ± SD	6.7 ± 4.8
Pain episodes	
None	89 (14%)
1	65 (9.9%)
2	107 (16%)
3	122 (19%)
4 or more	273 (42%)
Emotional functioning§	53 (46–60)
Social functioning§	52 (46–60)
Highest level of education completed	
Grades 1 through 11	35 (7.3%)
High school/GED	188 (39%)
Some college/associates	124 (26%)
College degree and above	135 (28%)
Income (enrollment year)	
Less than $12,060	240 (44%)
$12,060 to $16,240	67 (12%)
$16,240 to $20,420	23 (4.2%)
$20,420 to $24,600	28 (5.1%)
$24,600 to $28,780	20 (3.7%)
$28,780 to $32,960	17 (3.1%)
$32,960 to $37,140	19 (3.5%)
$37,140 to $41,320	18 (3.3%)
More than $41,320	113 (21%)
Admissions (enrollment year)	
0	254 (46%)
1 to 3	206 (38%)
4 to 6	51 (9.3%)
7 to 12	29 (5.3%)
More than 12	7 (1.3%)
Race	
Asian	2 (.3%)
Black or African American	544 (92%)
Native Hawaiian/Pacific Islander	0 (0%)
White	6 (1.0%)
More than 1 race	17 (2.9%)
Unknown/not reported	66

Abbreviations: IQR, interquartile range; GED, General Educational Development.
*Self-report measure.
†Defined as the absolute difference between worst and least pain in 24 h (questions 3 and 4 from BPI).
‡Maximum of 22 pain locations.
§T-scores. Higher value indicates better health in the domain.

with the ggplot2 package in R. *P* values and 95% confidence intervals were presented graphically or reported for all statistical tests. A full list of the R packages, model specifications, and regression coefficients is available in the Supplementary document.

Multivariable regression models for pain severity and physical function samples were also generated using the statistical approach outlined above.

Results

Description of Sociodemographic and Clinical Characteristics

The pain impact sample was 60% female with a median age of 34 (interquartile range [IQR] 26–42 years). Most of the participants had sickle cell anemia (HbSS genotype [n = 397, 67%])—the predominant genotype in SCD—and the remainder had sickle hemoglobin C disease (HbSC genotype [n = 123, 21%]) or sickle beta-thalassemia disease (HbSβ^+ [n = 42, 7.1%] or Hbβ^0 [n = 30, 5.1%] genotypes). Fifty-eight percent of the participants were on hydroxyurea. The overwhelming majority reported an annual income of less than $41,320, with 44% reporting an annual income of less than $12,060. In terms of clinical pain characteristics, chronic pain was reported in 64% of the sample at the time of enrollment into the registry. The median number of pain locations reported was 6 out of 22 locations (27%). A large number (n = 240, 44%) of participants reported having 4 or more sickle cell pain episodes in the prior 12 months. Most participants had at least 1 hospital admission during the year of enrollment into GRNDaD, and approximately 22% had 4 or more hospital admissions in the enrollment year. The median pain impact score in the sample was 51 (IQR 44–64), and the median PROMIS physical function score was 43 (IQR 38–49). Table 1 details additional clinical and sociodemographic characteristics of the pain impact sample. Descriptive statistics for the pain severity and physical function samples were comparable to the pain impact sample and are presented in Table 2 and Supplementary Table 2.

Variables Associated With High Pain Impact

Overall, for pain impact, our multivariable regression model accounted for 58% of variance ($R^2_{adj} = .58$). In our

Table 2. Descriptive Statistics for Outcome Variables of Interest for the 3 Participant Samples

OUTCOME VARIABLE	*ASCQ-ME PAIN IMPACT*[*] *N = 657*	*BPI PAIN SEVERITY*[†] *N = 403*	*PROMIS PHYSICAL FUNCTION*[‡] *N = 267*
Pain impact			
Median (IQR)	51 (44–64)	51 (44–58)	50 (44–64)
Range	25 to 64	25 to 64	25 to 64
BPI mean severity score			
Median (IQR)	3.29 (1.25–5.25)	3.00 (.75–5.25)	3.25 (1.25–5.00)
Range	0 to 10	0 to 10	0 to 10
Physical function			
Median (IQR)	43 (38–49)	43 (38 – 49)	44 (38–51)
Range	20 to 60	20 to 60	20 to 60

Abbreviation: IQR, interquartile range.
[*]ASCQ-Me Pain Impact, 5-item short form. Higher T-scores indicate better health, that is, less pain impact.
[†]Defined as mean severity score—the composite of questions 3 to 6 (a numerical rating of worst, least, average, and current pain).
[‡]PROMIS Physical Function Short Form 8b; Higher T-scores indicate better health in the domain.

analysis of the relative contribution of each variable in the model for pain impact, we found that social functioning (Wald $X^2 = 87.47$; $P < .001$), emotional functioning (Wald $X^2 = 57.86$; $P < .001$), income (Wald $X^2 = 20$; $P < .001$), age (Wald $X^2 = 15.60$; $P = .004$), and number of sickle cell pain episodes (Wald $X^2 = 13.98$; $P = .007$) had the strongest association with pain impact (Fig 2). The relationships between these variables and pain impact are visually depicted in the prediction graphs found in Fig. 3A to 3E. Regression coefficients for all the variables examined in the model are in the Appendix.

In this multivariable analysis, we found that better social and emotional functioning was associated with lower pain impact (Fig. 3A and 3B). Changes in pain impact were most pronounced at social and emotional functioning T-scores of 45 to 60. Predicted changes in pain impact were minimal outside of this score range for social and emotional functioning.

In our model of pain impact, increasing age was associated with worse pain impact (lower T-scores) (Fig 3D). Examination of the predicted change in pain impact with increasing age showed that changes in pain impact were most pronounced during late adolescence and young adulthood (age 20 to early 30s). Pain impact increases steadily (decreasing T-scores) in late adolescence and young adulthood. From the early to mid-30s, pain impact decreases slightly (increasing T-scores) compared to young adulthood. After age 40, age-associated changes in pain impact are minimal.

Variables Associated With Increased Pain Severity and Worse Physical Function

For the pain severity sample, our multivariable regression model accounted for 48% of variance ($R^2_{adj} = .48$). We found that pain variability (Wald $X^2 = 38.76$;

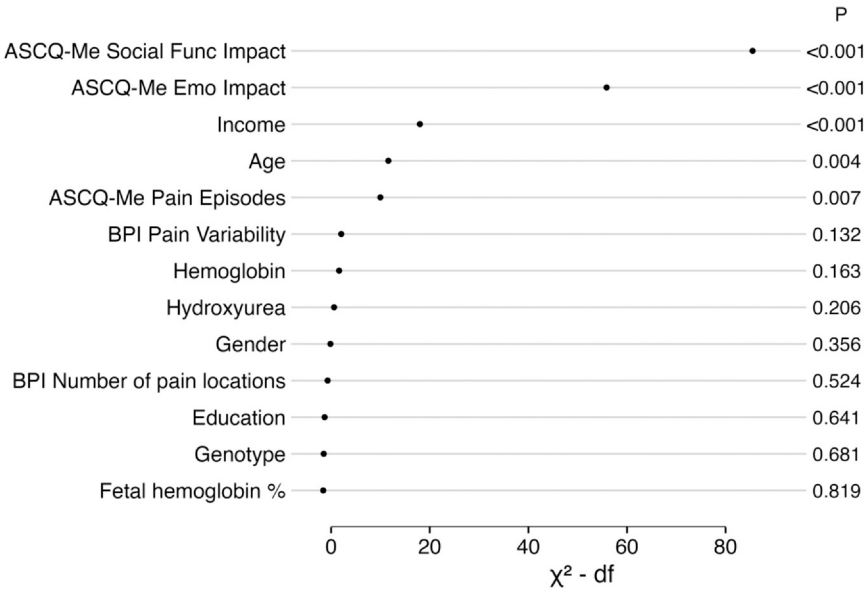

Figure 2. Strength of predictor variables in the multivariable model for pain impact. The relative importance of each predictor variable in the multivariable regression model for pain impact determined by Wald Chi-square (X^2) test. X-axis is represented as Wald chi-square (X^2) minus degrees of freedom (df), which indicates the strength of the predictor variable's impact on the outcome (ie, pain impact) and its explanatory power in the model. A larger X^2 – df value suggests the predictor variable has a stronger impact on the outcome and provides more explanatory power to the model. Corresponding *P*-values < .05, indicates that predictor variable contributes significantly to model. *P*-values > .05 indicates predictor variable does not significantly contribute the model, that is, the variable could be omitted without a meaningful or significant effect on the model. N = 657; $R^2 = .60$, $R^2_{adj} = .58$.

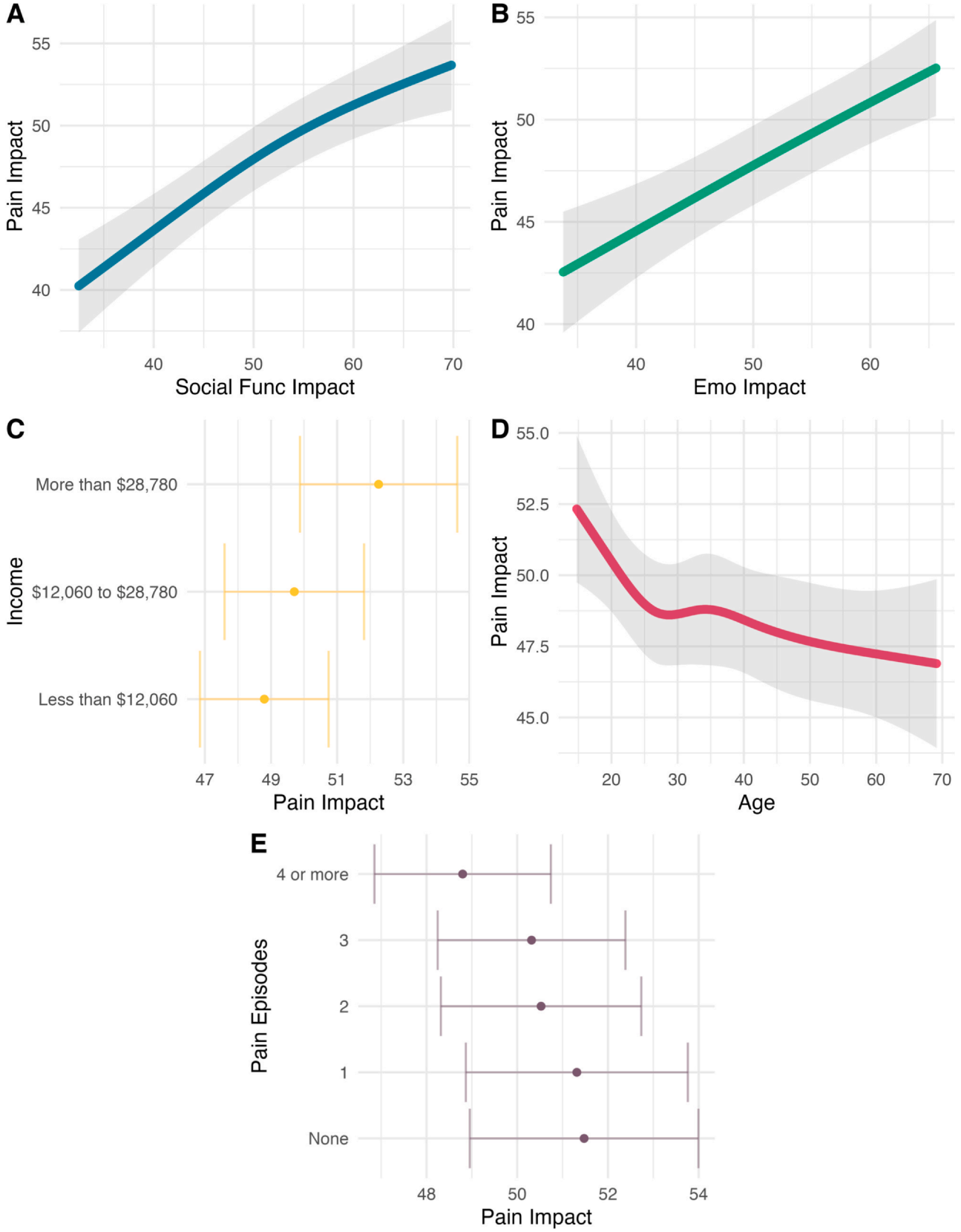

Figure 3. Panels A to E depict the relationship between significant predictor variables and pain impact. Predicted pain impact with 95% confidence intervals for the 4 most influential predictor variables. Pain impact assessed by ASCQ-Me Pain Impact Short Form (5-item questionnaire). Raw scores converted to T-scores. Higher T-scores imply better health or less pain impact. Adjusted to (median/mode): age = 34; genotype = SS; gender = female; income = less than $12,060 annually; education = High school/GED; hemoglobin = 9.5; HbF = 6.3%; BPI pain variability = 1; pain episodes = 4 or more; emotional Impact = 53.3; social functioning impact = 52.2; number of pain locations = 6; and hydroxyurea = yes. GED, General Educational Development.

$P < .001$), age (Wald $X^2 = 17.39$; $P = .002$), social functioning (Wald $X^2 = 15.34$; $P = < .001$), and number of pain locations (Wald $X^2 = 11.58$; $P = .003$) had the strongest association with pain severity in the model (Supplementary Fig 1). Thus, short-term pain variability, increasing age, greater number of pain locations, and lower social functioning were most associated with higher pain severity.

For the physical function sample, our multivariable linear regression model accounted for 55% of the variance in physical function ($R^2_{adj} = .55$). Age (Wald $X^2 = 32.33$; $P < .001$) and social functioning (Wald $X^2 = 18.25$; $P < .001$) were the strongest contributors to physical function in this model (Supplementary Fig 2). Thus, increasing age and lower social functioning had the strongest association with lower physical function.

The prediction graphs for the significant variables in the pain severity and physical function models are presented respectively in Supplementary Fig. 3A to 3D and 4A and 4B. The Appendix contains the regression coefficients for all the variables examined in the pain severity and physical function models.

Conclusions

This study aimed to identify associations between potential biopsychosocial variables and pain impact in children and adults with SCD, using data from the GRNDaD research registry. To our knowledge, this study is one of the few multicenter SCD pain studies that examine the relationships between pain outcomes and biopsychosocial variables. Our results are consistent with prior studies and offer surprising and novel insights into biopsychosocial contributors to pain outcomes in SCD.

Pain Impact Sample Findings

We found that over 60% of our pain impact sample had chronic pain and that the median physical function score in the overall sample was below the standardized population score of 50. These findings are consistent with prior studies highlighting that chronic pain is a significant burden in SCD and is associated with poor physical functioning and disability.[42,43]

Our multivariable model explained 58% of the variance in pain impact. The strength and findings of this model suggest that psychosocial variables (ie, social functioning and emotional functioning) are more strongly associated with pain impact in individuals with SCD than biological variables such as SCD genotype, hemoglobin, or HbF%. SCD genotype is considered the main determinant of disease severity. The HbSS genotype is generally believed to be the most severe SCD genotype.[4,44] Hemoglobin and fetal hemoglobin are also modifiers of disease severity in SCD. However, in our model, we found that SCD genotype, hemoglobin, and HbF% were less strongly associated with pain impact compared to social and emotional functioning, income, age, and frequency of pain episodes. Selection bias may account for some of these findings, as individuals with the HbSC genotype who are doing well may be less likely to be receiving care at an SCD center and, thus, be enrolled in GRNDaD. Nevertheless, the results of our multivariable regression modeling agree with the tremendous variability in pain experiences that has been observed clinically among individuals with the same SCD genotype.[8] Taken together, these findings underscore the notion that, while SCD genotype, hemoglobin, and fetal hemoglobin are important markers of disease severity and disease-specific complications, other factors, such as patient psychosocial characteristics, may be stronger contributors to pain impact in SCD. We believe that this represents a novel finding that contributes to the literature on SCD pain. Of note, we were limited to the biological/laboratory variables routinely reported in GRNDaD. Indeed, other biological variables associated with increased pain intensity or frequency in SCD (eg, co-inherited α-thalassemia, reticulocyte count, mean corpuscular volume, and serum lactic dehydrogenase values)[44] were not included in our models due to the paucity of reliable data.

Our findings add to the growing body of literature that highlight the influence of psychosocial variables on pain outcomes in SCD. Prior studies have noted that poor pain self-efficacy, poor pain coping, and high pain catastrophizing are associated with increasing pain intensity and pain-related disability.[17,19,20] Other studies have also noted that elevated fatigue, anxiety, and depression are associated with high self-reported pain.[15,21] We believe that our findings extend beyond these prior studies by highlighting that psychosocial variables may have a comparable or even greater influence on pain impact than biological markers of disease severity, such as genotype or hemoglobin. Further exploration of the specific psychosocial variables that hold the most importance is warranted in future prospective studies. Nevertheless, our findings, combined with prior research, suggest that to attain comprehensive pain management in SCD, targeted pain interventions will need to expand to include psychosocial variables alongside biological variables.

Age is a known sociodemographic predictor of disease severity and pain in SCD. Prior reports on SCD have noted a relationship between increasing age and chronic pain intensity and chronic pain disability.[19,21,45] Additionally, health care utilization is highest in the 20 to 30 age group, and overwhelmingly, most of these health care encounters involve pain management.[46] Multiple factors contribute to the vulnerability of the adolescent and young adult (AYA) population, including the lack of structured transition from pediatric to adult care, increase in disease complications as individuals age, and transition from acute to chronic/persistent pain.[6,7] Our results provide greater insights into the pain burden in the AYA sickle cell population. In this study, we used restricted cubic splines for age, which allowed us to model the complex, nonlinear relationships between pain impact and age (as well as pain severity and age in a separate patient sample). For our primary model of pain impact, we found that the

steepest age-related change in pain impact occurred during the 20 to early 30s age group, and pain impact was worse during this period. Consistent with prior studies that report high health care utilization in the AYA sickle cell population, these results emphasize that the AYA group is a critical and vulnerable subgroup of individuals living with SCD. The need to develop interventions that specifically target this subgroup is urgent.

Pain Severity Sample Findings

In addition to psychosocial variables, we examined 2 pain-specific variables (ie, number of pain locations and short-term pain variability), which, to our knowledge, have only been studied in 3 prior predictive SCD studies.[20,47,48] In our pain impact model, neither pain variability nor the number of pain locations appeared to be as important to pain impact as the psychosocial variables. However, in the model for pain severity, these 2 pain-specific variables had strong associations with pain severity. Given that our models for pain impact and pain severity included overlapping, but not identical, patient samples, we cannot make direct comparisons between the 2 models. Age had a significant complex, nonlinear relationship with pain severity, which was greatest in the 20-to-early 30s age group, once again highlighting that the AYA population is the SCD subgroup that is most vulnerable to pain.

Physical Function Sample Findings

Increasing age had the strongest association with worsening physical function compared to the other variables in the model. Prior research has shown that, in SCD, pain is the dominant symptom during young adulthood, while during older ages, complications secondary to organ dysfunction, such as chronic kidney disease and pulmonary hypertension, predominate.[4] Thus, organ complication, rather than pain, is likely the driving force for functional impairment in older individuals (ie, greater than 40 years) with SCD.

Comment on Overall Pattern of Findings From Pain Impact, Pain Severity, and Physical Function Models

The prevalence of our pain-specific variables across the 3 patient samples provides some insight into potential mechanisms that contribute to chronic SCD pain. We found that pain in multiple locations was common across all 3 samples, with the number of pain locations averaging greater than 6 (or 27–30% of 22 locations). This is comparable to findings from the Pain in Sickle Cell Epidemiology Study, a longitudinal study of pain in adults with SCD, which showed that the average number of pain locations reported among the study cohort was 3.3/16 locations (25%).[47] Zempsky et al[48] also found that over 20% of adolescents hospitalized for a VOE reported pain in 7 or more unique body locations. Our findings, along with these from prior studies, suggest that widespread pain is common in SCD and provide a rationale for further investigation of features of centralized pain disorder in SCD. A high prevalence of central pain in SCD warrants additional studies on the role of centrally acting analgesics, nonpharmacologic behavioral interventions, and support for social needs in managing SCD-related pain.[29]

This study leveraged data collected prospectively from a research registry to analyze pain outcomes in large samples of individuals living with SCD. Unlike other chronic pain disorders, SCD is a rare disease in the United States, and recruiting from small populations is challenging, particularly when considering the types of epidemiologic studies required to understand pain outcomes in SCD. The insight gained from our results highlights the important role that research registries, such as GRNDaD, can play in addressing gaps of knowledge in SCD pain. However, to fully leverage the potential of registries like GRNDaD, standardization and systematic collection of PROs within the clinical setting are required. Considering this study's findings, we recommend that all participating centers collect PROs capturing data on participants' mood and pain distribution. PROMIS measures, such as the depression and anxiety scales, would be appropriate given the presence of validated adult and pediatric versions, which would facilitate comparisons across the lifespan. Future efforts should also foster collaboration with SCD centers and streamline the integration of PRO data collection into routine clinical practice and electronic medical records. This concerted approach will ensure that chosen PROs hold both clinical significance and practical feasibility for implementation across different sickle cell centers. By addressing these improvements, registries, such as GRNDaD, can be leveraged to study pain trajectories and outcomes in a longitudinal manner and, thus, advance our understanding of pain outcomes in SCD.

Strengths and Limitations

The results of this study should be interpreted with consideration of a few limitations. The study was a cross-sectional analysis of registry data, and thus, we are unable to establish causality or definitively predict future pain outcomes. Further, the study is limited by the data available in the GRNDaD registry, and as it was also reliant on patient self-report or parental proxy for reporting of outcomes, it may be subject to recall and nonresponse bias. The PROs used in this study (BPI, ASCQ-Me, and PROMIS Physical Function) are adult measures, and given that the validity and reliability of some of these self-reported measures have not been established in the pediatric SCD population, interpretation of pain outcomes in this age group may be limited. ASCQ-Me subscales were used for predictor variables (eg, social functioning, emotional functioning, frequency of pain episodes) and the outcome variable (pain impact) in this study. Although ASCQ-Me is a measurement system that comprises multiple subscales that assess distinct constructs, it is important to acknowledge that shared method variance could potentially introduce bias into the study's findings.

The interpretation of this study's findings should also consider the variations in funding, resources, and availability of nonpharmacological treatments (eg, cognitive behavior therapy, acupuncture, and physical therapy) across different SCD centers. These potential differences in

centers were not explored in this study. Moreover, some SCD centers participating in GRNDaD did not administer all 3 questionnaires (ASCQ-Me, BPI, and PROMIS Physical Function); thus, some participants lacked completed questionnaires. This limitation prevented direct comparisons between the 3 pain and pain-related models generated in this study. The presence of missing data is also a limitation that may introduce potential bias and affect the generalizability of the study's findings. Lastly, limitations specific to multivariable regression modeling should also be considered. These include multicollinearity (ie, some of the predictor variables may be correlated) and overfitting, which would affect the generalizability of our models to the broader SCD population.

Despite these limitations, this study provides valuable insights into the factors influencing pain experiences and outcomes in individuals living with SCD. By conducting a secondary analysis of data from a large national, multicenter SCD registry, the study benefits from a substantial sample size, enhancing the generalizability of the findings. The multivariable modeling approach employed in the study is also a strength, as it allowed for the examination of various psychosocial and biological variables simultaneously. Our findings suggest that social and emotional functioning have a stronger association with pain impact in individuals with SCD compared to previously studied biological markers. This novel insight expands our understanding of the complex interplay between psychosocial and biological factors that influence pain perception and modulation in SCD, and thus, highlighting the importance of the biopsychosocial model in SCD pain. Importantly, given the observed increase in pain impact and pain severity during adolescence and young adulthood, this study brings attention to the need for focused and targeted pain interventions in this specific age group.

Insights gained from this study can inform future prospective studies that aim to establish the causal role of psychosocial variables in adverse pain outcomes in SCD. Future studies should also explore the relative contribution of pain-specific psychological variables (eg, pain coping and pain self-efficacy) and sociocultural variables (eg, social support) to pain impact and pain severity compared to biological modifiers SCD severity. By identifying modifiable biopsychosocial predictors of adverse pain outcomes in SCD, such studies can provide insight into the pathogenesis of chronic SCD pain, guide patient selection for trials of nonopioid interventions for SCD pain, and identify "high-risk" individuals for targeted preventive and symptomatic interventions early in their pain trajectory.

Disclosures

N.S. has research funding from GBT; serves as a consultant for GBT, Bluebird bio, Forma, Agios, Vertex, and Novartis; and is a speaker for GBT, Emmaus Pharmaceuticals. D.M. has research funding from Grifol's, and serves as a consultant for GBT, Pfizer, and Novartis. J.L. has research funding from GBT, Bluebird, NASCC, and the NIH, holds a patent on SCD Biochip, and has adjudication for FORMA. J.K. is a consultant for Guide point Global, GLG, Novartis, and Bluebird, has received honorarium from Novartis, Oric, Bausch, Glycomimetics, Chiesi, Bausch, GSK, and Chiesi, and holds research funding from the NHLBI, HRSA, and the CDC (1R01HL133896-01A1, 1RO1HL158807-01A1, U01HL133990-01). W.H. has research funding from Forma Therapeutics, Global Blood Therapeutics, Chiesi USA, National Heart Blood and Lung Institute, California Department of Public Health, Sangamo Therapeutics, and Health Resources and Services Administration. M.O.K is supported by an National Institute of Neurological Disorders and Stroke Diversity Supplement Award (3U24NS114416-01S2).

Appendix A. Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.jpain.2023.07.029.

References

1. Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG: The cost of health care for children and adults with sickle cell disease. Am J Hematol 84:323-327, 2009. https://doi.org/10.1002/ajh.21408

2. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA: Acute care utilization and rehospitalizations for sickle cell disease. JAMA 303:1288-1294, 2010. https://doi.org/10.1001/jama.2010.378

3. Platt OS, Brambilla DJ, Rosse WF, *et al.* Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 330:1639-1644, 1994. https://doi.org/10.1056/nejm199406093302303

4. Kato GJ, Piel FB, Reid CD, *et al.* Sickle cell disease. Nat Rev Dis Primers 4:18010 . https://doi.org/10.1038/nrdp.2018.10, 2018.

5. Smith WR, Penberthy LT, Bovbjerg VE, *et al.* Daily assessment of pain in adults with sickle cell disease. Ann Intern Med 148:94-101, 2008. https://doi.org/10.7326/0003-4819-148-2-200801150-00004

6. Field JJ, Ballas SK, Campbell CM, *et al.* AAAPT diagnostic criteria for acute sickle cell disease pain. J Pain 20:746-759, 2019. https://doi.org/10.1016/j.jpain.2018.12.003

7. Dampier C, Palermo TM, Darbari DS, Hassell K, Smith W, Zempsky W: AAPT diagnostic criteria for chronic sickle cell disease pain. J Pain 18:490-498, 2017. https://doi.org/10.1016/j.jpain.2016.12.016

8. Darbari DS, Ballas SK, Clauw DJ: Thinking beyond sickling to better understand pain in sickle cell disease. Eur J Haematol 93:89-95, 2014. https://doi.org/10.1111/ejh.12340

9. Cooper TE, Fisher E, Gray AL, *et al.* Opioids for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev 7:Cd012538. https://doi.org/10.1002/14651858.CD012538.pub2, 2017.

10. Power-Hays A, McGann PT: When actions speak louder than words - racism and sickle cell disease. N Engl J Med 383:1902-1903, 2020. https://doi.org/10.1056/NEJMp2022125

11. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC: The biopsychosocial approach to chronic pain: scientific

advances and future directions. Psychol Bull 133:581-624, 2007. https://doi.org/10.1037/0033-2909.133.4.581

12. Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD: The role of psychosocial processes in the development and maintenance of chronic pain. J Pain 17:T70-T92, 2016. https://doi.org/10.1016/j.jpain.2016.01.001

13. Kenney MO, Smith WR: Moving toward a multimodal analgesic regimen for acute sickle cell pain with non-opioid analgesic adjuncts: a narrative review. J Pain Res 15:879-894, 2022. https://doi.org/10.2147/jpr.S343069

14. Melzack R: Pain and the neuromatrix in the brain. J Dent Educ 65:1378-1382, 2001

15. Donohoe C, Smith EL: Psychological predictors of pain in children and adolescents with sickle cell disease: a scoping review. J Pediatr Oncol Nurs 36:150-159, 2019. https://doi.org/10.1177/1043454218819457

16. Bakshi N, Lukombo I, Shnol H, Belfer I, Krishnamurti L: Psychological characteristics and pain frequency are associated with experimental pain sensitivity in pediatric patients with sickle cell disease. J Pain 18:1216-1228, 2017. https://doi.org/10.1016/j.jpain.2017.05.005

17. Sil S, Cohen LL, Bakshi N, *et al.* Changes in pain and psychosocial functioning and transition to chronic pain in pediatric sickle cell disease: a cohort follow-up study. Clin J Pain 36:463-471, 2020. https://doi.org/10.1097/ajp.0000000000000827

18. Knisely MR, Tanabe PJ, Yang Q, Masese R, Jiang M, Shah NR: Severe pain profiles and associated sociodemographic and clinical characteristics in individuals with sickle cell disease. Clin J Pain 37:669-677, 2021. https://doi.org/10.1097/ajp.0000000000000957

19. Matthie N, Jenerette C, Gibson A, Paul S, Higgins M, Krishnamurti L: Prevalence and predictors of chronic pain intensity and disability among adults with sickle cell disease. Health Psychol Open 7:2055102920917250. https://doi.org/10.1177/2055102920917250, 2020.

20. Bakshi N, Gillespie S, McClish D, McCracken C, Smith WR, Krishnamurti L: Intra-individual pain variability and phenotypes of pain in sickle cell disease: a secondary analysis from the Pain in Sickle Cell Disease Epidemiology Study (PiSCES). Pain 136:1102-1113, 2021. https://doi.org/10.1097/j.pain.0000000000002479

21. Alberts NM, Kang G, Li C, *et al.* Pain in youth with sickle cell disease: a report from the sickle cell clinical research and intervention program. Clin J Pain 37:43-50, 2021. https://doi.org/10.1097/ajp.0000000000000889

22. Karlson CW, Barajas KG, Seals SR, *et al.* Longitudinal predictors of pain in pediatric sickle cell disease. J Pediatr Psychol 48:553-561, 2023. https://doi.org/10.1093/jpepsy/jsad017

23. Kuisell C, Ploutz-Snyder R, Williams DA, *et al.* Adolescents and young adults with sickle cell disease: nociplastic pain and pain catastrophizing as predictors of pain interference and opioid consumption. Clin J Pain 39:326-333, 2023. https://doi.org/10.1097/ajp.0000000000001119

24. Schneider MB, Manikowski A, Cohen L, Dampier C, Sil S: The distinct longitudinal impact of pain catastrophizing on pain interference among youth living with sickle cell disease and chronic pain. J Behav Med 45:622-631, 2022. https://doi.org/10.1007/s10865-021-00280-4

25. Hood AM, Kölbel M, Stotesbury H, *et al.* Biopsychosocial predictors of quality of life in paediatric patients with sickle cell disease. Front Psychol 12:681137. https://doi.org/10.3389/fpsyg.2021.681137, 2021.

26. Reinman L, Schatz J, Johnston J, Bills S: Fatigue, stress appraisal, and emotional functioning among youth with sickle cell disease: a daily diary study. J Pediatr Psychol 48:562-571, 2023. https://doi.org/10.1093/jpepsy/jsad019

27. Childerhose JE, Cronin RM, Klatt MD, Schamess A: Treating chronic pain in sickle cell disease - the need for a biopsychosocial model. N Engl J Med 388:1349-1351, 2023. https://doi.org/10.1056/NEJMp2301143

28. Sturgeon JA: Psychological therapies for the management of chronic pain. Psychol Res Behav Manag 7:115-124, 2014. https://doi.org/10.2147/prbm.S44762

29. Cohen SP, Vase L, Hooten WM: Chronic pain: an update on burden, best practices, and new advances. Lancet 397:2082-2097, 2021. https://doi.org/10.1016/s0140-6736(21)00393-7

30. Lanzkron S, Manwani D, Desai P, Kanter J, Little J: GRNDaD: big data and sickle cell disease. Blood Adv 6:1088, 2022. https://doi.org/10.1182/bloodadvances.2021005282

31. Keller SD, Yang M, Treadwell MJ, Werner EM, Hassell KL: Patient reports of health outcome for adults living with sickle cell disease: development and testing of the ASCQ-Me item banks. Health Qual Life Outcomes 12:125. https://doi.org/10.1186/s12955-014-0125-0, 2014.

32. Cleeland CS, Ryan KM: Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singap 23:129-138, 1994

33. Rose M, Bjorner JB, Gandek B, Bruce B, Fries JF, Ware Jr. JE: The PROMIS Physical Function item bank was calibrated to a standardized metric and shown to improve measurement efficiency. J Clin Epidemiol 67:516-526, 2014. https://doi.org/10.1016/j.jclinepi.2013.10.024

34. Dworkin RH, Turk DC, Farrar JT, *et al.* Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 113:9-19, 2005. https://doi.org/10.1016/j.pain.2004.09.012

35. McGrath PJ, Walco GA, Turk DC, *et al.* Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. J Pain 9:771-783, 2008. https://doi.org/10.1016/j.jpain.2008.04.007

36. Keller S, Yang M, Treadwell MJ, Hassell KL: Sensitivity of alternative measures of functioning and wellbeing for adults with sickle cell disease: comparison of PROMIS® to ASCQ-Me℠. Health Qual Life Outcomes 15:117. https://doi.org/10.1186/s12955-017-0661-5, 2017.

37. Keller S, Yang M, Evensen C, Cowans T: ASCQ-Me User's Manual. Published December 2017. https://staging.healthmeasures.net/images/ASQMe/ASCQ-Me_Scoring_Manual.pdf Accessed May 27, 2022.

38. Cleeland CS. The Brief Pain Inventory User Guide. Published 2009. https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf Accessed May 30, 2022.

39. Physical Function: A Brief Guide to PROMIS Physical Function Instruments. Published June 10, 2020. https://staging.

healthmeasures.net/images/PROMIS/manuals/PROMIS_Physical_Function_Scoring_Manual.pdf Accessed May 30, 2022.

40. Harrell F. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis; 2015.

41. Moons KG, Donders RA, Stijnen T, Harrell Jr. FE: Using the outcome for imputation of missing predictor values was preferred. J Clin Epidemiol 59:1092-1101, 2006. https://doi.org/10.1016/j.jclinepi.2006.01.009

42. Swanson ME, Grosse SD, Kulkarni R: Disability among individuals with sickle cell disease: literature review from a public health perspective. Am J Prev Med 41:S390-S397, 2011. https://doi.org/10.1016/j.amepre.2011.09.006

43. Lanzkron S, Little J, Field J, *et al.* Increased acute care utilization in a prospective cohort of adults with sickle cell disease. Blood Adv **2**:2412-2417, 2018. https://doi.org/10.1182/bloodadvances.2018018382

44. Quinn CT: Minireview: clinical severity in sickle cell disease: the challenges of definition and prognostication. Exp Biol Med ((Maywood)) 241:679-688, 2016. https://doi.org/10.1177/1535370216640385

45. Brandow AM, Zappia KJ, Stucky CL: Sickle cell disease: a natural model of acute and chronic pain. Pain 158:S79-S84, 2017. https://doi.org/10.1097/j.pain.0000000000000824

46. Fingar KR, Owens PL, Reid LD, Mistry KB, Barrett ML: Characteristics of inpatient hospital stays involving sickle cell disease, 2000–2016. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Agency for Healthcare Research and Quality (US); 2006.

47. McClish DK, Smith WR, Dahman BA, *et al.* Pain site frequency and location in sickle cell disease: the PiSCES project. Pain 145:246-251, 2009. https://doi.org/10.1016/j.pain.2009.06.029

48. Zempsky WT, Wakefield EO, Santanelli JP, *et al.* Widespread pain among youth with sickle cell disease hospitalized with vasoocclusive pain: a different clinical phenotype? Clin J Pain 33:335-339, 2017. https://doi.org/10.1097/ajp.0000000000000403