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Examining Biopsychosocial Factors in Relation to Multiple Pain Features in Pediatric Sickle Cell Disease

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Abstract

Objective To examine biopsychosocial variables in relation to multiple pain features in pediatric sickle cell disease (SCD). **Methods** 76 children with SCD ($M = 14.05$, $SD = 3.26$), ages 8–19 years, and 70 caregivers completed measures of coping, mood, and family functioning and reported on multiple pain features via retrospective interviews during routine hematological visits. Sickle cell genotype and health care utilization were collected via medical record review. Using hierarchical regression, biological (genotype), child psychological (coping and mood), and social factors (caregiver coping and family functioning) were evaluated in relation to multiple pain features. **Results** Genotype was associated with pain intensity, and child psychological factors were associated with pain frequency. Multiple biopsychosocial factors were related to health care utilization. **Conclusions** Biopsychosocial factors may have distinct relationships with pain features in pediatric SCD. Understanding these relationships may refine the biopsychosocial model and inform integrated medical and psychosocial approaches in SCD.

Key words: children; pain; sickle cell disease.

Sickle cell disease (SCD) is a group of inherited blood disorders characterized by recurrent vaso-occlusive pain episodes. The unpredictable and debilitating nature of pain in SCD exerts a significant toll on children and their families. Although the vast majority of pain episodes are managed at home, children may experience four to five episodes on average that require medical attention over a 9- to 12-month period. Of these episodes, one to two typically require inpatient hospitalization (Gil et al., 1993; Gil, Williams, Thompson, & Kinney, 1991; Schatz et al., 2015). Recurrent and severe pain may lead to decrements in quality of life and reduced psychological well-being, including frequent school absences, academic attainment problems, reduced opportunity for physical recreation and social activities, and symptoms of depression and anxiety (Anie, 2005; Edwards et al., 2005).

A distinct obstacle to effective pain management in SCD is the substantial heterogeneity of pain in children, including the frequency, intensity, duration, and extent of disability from pain (Dampier et al., 2004; Gil et al., 2000; Jacob et al., 2003; Platt et al., 1991). Previous studies of children with SCD have predominantly focused on biopsychosocial perspectives of children's functional disability and psychosocial adjustment to pain. Models such as the transactional stress and coping framework, the risk-resistance model, and the disease impact model have focused on how illness-related factors (e.g., pain, disease severity) interact with important stress-processing factors

(e.g., child and caregiver coping, family functioning) to influence functional outcomes (e.g., activity disruption, psychological well-being) in children with SCD (Brown et al., 2000; Palermo, 2000; Thompson, Gil, Burbach, Keith, & Kinney, 1993). These biopsychosocial perspectives have been important for illustrating how psychosocial factors influence adjustment in children with SCD; however, these models have been less widely used to examine *pain variability* in SCD, despite the fact that many of these same stress-processing factors are hypothesized to be linked to pain perception. Specifically, modern perspectives of pain, including gate control theory and descending modulation of pain, emphasize that variability in pain perception may be explained by a combination of physiological, cognitive, and emotional processes (Edwards, Campbell, Jamison, & Wiech, 2009; Keefe & France, 1999). Furthermore, social learning theory suggests that children's responses to pain may be altered by the social environment through modeling and reinforcement (Craig, Lilley, & Gilbert, 1996).

Previous research in pediatric SCD has implicated a range of biological and psychosocial variables in relation to pain. The largest epidemiological studies to date have found that SCD genotype and hematological markers (e.g., hematocrit, fetal hemoglobin) are associated with pain frequency and health care utilization (Brousseau, Owens, Mosso, Panepinto, & Steiner, 2010; Gill et al., 1995; Platt et al., 1991), though these relationships have been less consistently found in smaller studies (Barakat et al., 2007; Dampier et al., 2004; Logan, Radcliffe, & Smith-Whitley, 2002). In terms of genotype, patients with SCD in the United States predominantly fall into four genotypes, ordered here according to their estimated prevalence: HbSS (sickle cell anemia; ~60% of patients), HbSC (~30% of patients), and $HbS\beta^0$ and $HbS\beta^+$ thalassemia (~10% of patients) (Hassell, 2010). HbSS and $HbS\beta^0$ are considered higher-risk subtypes versus HbSC and $HbS\beta^+$ in terms of pain and disease severity (Dampier, Ely, Brodecki, & O'Neal, 2002a; Gill et al., 1995; Platt et al., 1991).

Cross-sectional and intervention studies of psychological variables in children with SCD have found that child coping is associated with laboratory pain sensitivity and health care utilization for pain (Anie, Steptoe, Ball, Dick, & Smalling, 2002; Gil et al., 1991, 1997, 2001). Moreover, daily diary studies suggest that child mood is associated with pain intensity (Gil et al., 2003; Valrie, Gil, Redding-Lallinger, & Daeschner, 2008; Zempsky, Palermo, et al., 2013). Finally, cross-sectional research evaluating family processes for children with SCD suggests that caregivers are likely involved in development of coping strategies for pain, given consistent associations between caregiver and child coping, and may reinforce specific pain responses in children with SCD (Gil et al., 1991; Kliewer & Lewis, 1995; Lutz, Barakat, Smith-Whitley, & Ohene-Frempong, 2004; Peterson & Palermo, 2004). Caregiver responses to pain and family functioning may also play a more direct role in pain variability via decision making around home-based management of pain and health care utilization (Barakat et al., 2007; Logan et al., 2002).

The purpose of the present study was to examine biological (SCD genotype), psychological (child coping and mood), and social factors (caregiver coping and family functioning) in relation to multiple pain features to determine their relative and combined associations with pain in children with SCD. Specifically, the present study evaluated biopsychosocial factors in relation to pain frequency, intensity, and duration as well as health care utilization for pain. This information was intended to inform a biopsychosocial perspective of pain in SCD and to complement previous models of adaptation in pediatric SCD by suggesting pain outcomes that may be modifiable by combined medical and psychosocial intervention. Based on previous research specific to SCD, the following hypotheses were made: (1) biological risk will be associated with pain frequency (Brousseau et al., 2010; Gill et al., 1995; Platt et al., 1991), (2) child psychological variables will be associated with pain intensity (Gil et al., 2003; Valrie et al., 2008; Zempsky, Palermo, et al., 2013), and (3) biological, child psychological, and caregiver psychological variables will be associated with health care utilization (Anie et al., 2002; Barakat et al., 2007; Brousseau et al., 2010; Gil et al., 1991, 2001; Gill et al., 1995; Logan et al., 2002; Platt et al., 1991). We made no hypothesis for pain duration because of the absence of literature linking this particular pain outcome to specific biopsychosocial factors.

Methods

Participants

This study included 76 children with SCD, ages 8–19 years, and 70 caregivers (see Table I). Youth aged ≥18 years were given the choice of participating with or without a caregiver, as they were more likely to attend hematological visits independently. Families were recruited during routine health maintenance visits at the Children's Center for Cancer and Blood Disorders (CCBD) at Palmetto Richland Children's Hospital in Columbia, South Carolina. Study recruitment and enrollment occurred between April 2012 and June 2013. Eligibility was determined by examining the child's medical chart. The hematologist (C.W.R.) asked families about their interest in the study, and an investigator followed up with the family after the visit or via phone to set up a time to complete procedures (typically at the child's next hematological visit). During the study period, 129 families were approached for participation, and 53 did not participate. Six families were not

Table I. Demographic and Medical Characteristics of Children With Sickle Cell Disease and Their Caregivers

Children ($N = 76$)		Caregivers ($N = 70$)	
Age (*M*, *SD*)	14.05, 3.26	Caregiver relation to child (*n*)	
Gender (*n*)		Mother	62
Male	44	Father	4
Female	32	Grandparent	4
Race[a] (*n*)		Caregiver race[a] (*n*)	
African American	76	African American	70
African International	1	African International	1
White	1	White	1
American Indian/Alaska Native	3	American Indian/Alaska Native	5
Ethnicity (*n*)		Ethnicity (*n*)	
Hispanic, Latino, or Spanish Origin	2	Hispanic, Latino, or Spanish Origin	1
Insurance Status		Caregiver Education (*n*)	
Medicaid only	47	Some high school	6
Medicaid and private insurance	13	High school diploma	22
Private insurance only	16	Some college	28
Sickle Cell Subtype (*n*)		College degree	13
HbSS	48	More than college degree	6
HbSC	19		
$HbS\beta^0$	4		
$HbS\beta^+$	5		
Hematocrit (*M*, *SD*)	27.51, 4.96		
Fetal hemoglobin (*M*, *SD*)	11.27, 9.82		
Currently taking hydroxyurea (*n*)	41		

[a]Participants were able to mark multiple selections.

interested [not a good time ($n = 4$), not enough time at appointments ($n = 1$), and no reason ($n = 1$)]. Of the 44 families who were interested, 19 did not return for their follow-up visits, 18 had infrequent visits and could not return on a separate day, 5 did not have time at their visits, and 2 did not participate because of psychosocial concerns. Participants and nonparticipants did not significantly differ based on age, t (1, 127) = 0.49, $p = .623$; however, nonparticipants were more likely to be male versus participants, χ^2 (1) = 4.17, $p = .041$.

Inclusion and Exclusion Criteria

Eligible children must have received their primary hematological care through the CCBD. Youth between the ages of 8 and 21 were eligible to participate; however, older youth (ages 20 and 21) tended to be in the process of transitioning to adult care and were no longer receiving consistent care at the CCBD. Children with major developmental disorders (e.g., intellectual disability) or neurologic disease (e.g., stroke, silent stroke) were excluded, as these conditions would limit the validity of the self-report data. These determinations were made by the primary investigators of the study, which included a doctoral student in clinical psychology, a licensed clinical psychologist, and the child's hematologist. The child's medical history, current school placement, and previous developmental, psychoeducational, and neuropsychological evaluations were used to make determinations of inclusion or exclusion. Participants could not be experiencing pain requiring opioid-based drugs on the day of participation, as this may have influenced their ability to complete self-report data. If opioid drugs were used, families were asked to participate on another day or during their next routine visit. Children undergoing chronic transfusion therapy were excluded because this treatment is typically used for treating or preventing major SCD morbidity other than pain and alters the natural course of pain (Miller et al., 2001). In contrast, children receiving hydroxyurea, a treatment that moderates the pain severity in SCD (Strouse & Heeney, 2012), were not excluded, as this treatment is frequently used among children with severe pain, and this exclusion would bias the sample toward those with less severe pain.

Measures

Background Information

Caregivers completed a brief demographic questionnaire that requested information on their child's race and ethnicity as well as the caregiver's relation to the child, race, ethnicity, family demographics, and education.

Pain and Disease Information

Disease characteristics can be found in Table I. Table II provides means and standard deviations for the pain outcomes.

Pain History Interview. The pain history interview is a modified version of the Structured Pain Interview (SPI) validated in children with SCD ages 7–18 years and their caregivers (Gil et al., 1991). The interview assesses recent pain status through child and caregiver interviews, including pain frequency and health care utilization (previous 12 months), average duration (in days), and average intensity (on a scale from 0 to 10).

Table II. Descriptive Statistics for Measures of Psychosocial Variables and Pain Outcomes

Measures	α	*M (SD)*
Psychosocial variables		
Child variables		
Coping Strategies Questionnaire for sickle cell disease		
Coping attempts	.91	81.27 (31.09)
Negative thinking	.89	53.90 (25.62)
Positive and Negative Affect Scale for children		
Positive mood	.90	3.48 (0.93)
Negative mood	.86	1.68 (0.58)
Caregiver variables		
Coping Strategies Questionnaire–Revised		
Active coping	.90	58.74 (18.77)
Passive coping	.77	25.77 (7.96)
Family functioning		
General functioning	.84	1.68 (0.45)
Pain outcomes		
Child and caregiver report		
Pain frequency (total; previous 12 months)		7.52 (12.27)
Average pain intensity (0–10; previous 12 months)		7.20 (1.70)
Average pain duration (in days; previous 12 months)		2.53 (1.89)
Medical record		
Health care utilization (previous 24 months)		
Total		3.41 (4.02)
Hospitalizations		1.64 (2.53)
Emergency room visits		1.07 (1.80)
Outpatient visits/calls to physician		0.70 (1.84)

For health care utilization, children and caregivers reported on hospitalizations, emergency room visits, and outpatient contacts (e.g., calls or visits to the clinic) for pain. The original interview was found to have moderate to large correlations between adolescents and caregivers for pain intensity and duration, moderate to large correlations between caregivers and the medical record, and moderate stability of caregiver ratings over a 9–12-month period. Caregiver and adolescent ratings were only weakly associated for pain frequency. In contrast to the SPI, we provided a standard definition of an episode for pain frequency. Specifically, an episode was defined as pain lasting for at least 4 hr and believed to be caused by SCD (Ballas et al., 2010). Families were then asked to provide frequencies of episodes that did and did not involve a medical visit, and these totals were combined for the pain frequency score. In the present sample, child and caregiver ratings were moderately associated for pain frequency ($r = .32$, $p = .009$), intensity ($r = .30$, $p = .015$), and duration ($r = .31$, $p = .010$). Caregiver and child reports were viewed as complementary ratings and were averaged to avoid over- or underestimation of pain.

Medical Record Review. A structured coding method was used to collect information from the medical chart, including the child's age, gender, sickle cell genotype, and health care utilization for pain. We also collected the child's most recent laboratory results for hematocrit and fetal hemoglobin and whether the child was taking hydroxyurea to characterize the sample. For health care utilization, documented hospitalizations, emergency room visits, and outpatient contacts (e.g., calls or visits to the clinic) for pain during the previous 24 months were recorded (including information documented from caregivers to the hematologist). This information could include health care utilization that occurred at medical centers outside of the CCBD. The child's hematologist consistently documented this information at each health care visit. A second, independent rater reviewed all medical charts, resulting in an interrater agreement of 99.6% for health care utilization. Although the time captured for the medical record differed from the pain history interview (i.e., 24 months vs. 12 months), these measures of health care utilization were strongly related ($r = .67$, $p < .001$). The medical chart measure was used for analyses because it captured a longer period and provided an alternative to the retrospective interviews.

Psychological Variables: Child Completed

Table II provides means, standard deviations, and internal consistency for the psychosocial questionnaires. Internal consistency ranged from good to excellent for the psychosocial questionnaires.

Coping Strategies Questionnaire for Sickle Cell Disease. The Coping Strategies Questionnaire for Sickle Cell Disease (CSQ-SCD) is an 80-item questionnaire validated in children and adolescents with SCD aged 7–17

years (Gil et al., 1991). The CSQ-SCD assesses coping behaviors children use to deal with pain. Each item is rated on a 7-point scale from 0 (*never*) to 6 (*always*) to indicate how often a strategy is used. Factor analysis has supported three broad subscales: Coping Attempts, Negative Thinking, and Passive Adherence. Coping Attempts and Negative Thinking were used in the present study, as these outcomes have been the focus of pain interventions in SCD (Gil et al., 1997, 2001; Schatz et al., 2015). Coping Attempts measures adaptive coping responses, such as cognitive and behavioral distraction (e.g., "I think of things I enjoy doing."), whereas Negative Thinking measures maladaptive coping responses, such as catastrophic thinking (e.g., "It is terrible and I feel it is never going to get any better."). Scores on the Coping Attempts scale ranged from 0 to 180, and scores on the Negative Thinking Scale ranged from 0 to 144, with higher scores representing higher ratings.

Positive and Negative Affect Scale. The Positive and Negative Affect Scale (PANAS-C) is a 27-item scale containing two subscales that assess positive and negative mood states. The PANAS-C was originally validated with children in grades 4 through 8, establishing good internal consistency and convergent validity with measures of anxiety and depression (Laurent et al., 1999). This measure has also been used in children with SCD between the ages of 7 and 21 years (Zempsky, O'Hara, et al., 2013). Children rate the extent to which they have felt different positive and negative emotions in the past week using a 5-point scale ranging from 1 (*very slightly or not at all*) to 5 (*extremely*). Average ratings across positive and negative emotions were used to calculate overall Positive and Negative Mood scale scores. This approach was taken (vs. total score) because some children did not comprehend all of the emotion words (e.g., jittery). Scores ranged from 1 to 5, with higher scores representing higher ratings of positive or negative mood.

Social Variables: Caregiver Completed

Coping Strategies Questionnaire-Revised. The Coping Strategies Questionnaire-Revised (CSQ-R) is a revised 27-item scale that assesses coping strategies adults use to manage pain. The CSQ-R has been validated in a large sample of healthy African American adults, with good to excellent internal consistency (Hastie, Riley, & Fillingim, 2004). Each item is rated on a 7-point scale from 0 (*never*) to 6 (*always*) to indicate how often a strategy is used. Caregivers reported how often they used coping strategies *for their own pain* (e.g., headache). Factor analysis suggests two broad factors: Active and Passive Coping. Active Coping assesses adaptive coping, while Passive Coping assesses maladaptive coping. Scores on the Active Coping scale ranged from 0 to 108, and scores on the Passive Coping scale ranged from 0 to 54, with higher scores representing higher ratings.

McMaster Family Functioning Assessment Device. Caregivers reported on family functioning using the General Functioning (GF) subscale of the Family Functioning Assessment Device (FAD). The GF is a 12-item subscale that assesses the degree to which a family functions well together as a unit. Caregivers rated the extent to which they strongly agree or disagree with 12 statements on a 4-point scale ranging from 1 (*strongly agree*) to 4 (*strongly disagree*). Scores were averaged across the 12 items to produce a GF score that ranged from 1 to 4, with *lower scores* representing *better family functioning*. The GF scale has demonstrated good psychometric properties among a range of pediatric populations, including families of children with SCD (Alderfer et al., 2008). The GF has also established convergent validity with variables thought to indicate familial dysfunction (e.g., caregiver mental health problems; Byles, Byrne, Boyle, & Offord, 1988).

Procedures

All study procedures were conducted by the principal investigators (A.M.S., J.S.). Institutional Review Board approval was obtained from Palmetto Richland Children's Hospital, with concurrent approval from the University of South Carolina. Informed consent was obtained from all caregivers, and assent was obtained from all children. Children and caregivers completed demographic and psychosocial questionnaires and pain interviews in a private clinic room. Questions were read aloud to all children, with the exception of adolescents who indicated a preference for completing measures independently. For child questionnaires, one child did not complete the PANAS-C, and one caregiver did not complete the FAD-GF because of experimenter error. Another child's caregiver was unable to complete caregiver questionnaires because of an acute medical illness; thus, only the child's ratings were used. Electronic and paper medical records were reviewed after the visit.

Data Analyses

Analyses were completed using SPSS, Version 19. With alpha set to .05, the study sample size was designed to detect a small to moderate effect ($\sim f^2 = .11–.12$), consistent with effect sizes reported for SCD genotype and psychosocial factors in relation to pain and health care utilization in previous studies (Barakat et al., 2007; Gil et al., 1991; Logan et al., 2002). Correlations between biopsychosocial variables and pain outcomes were evaluated to determine individual relationships. To evaluate combined

Table III. Correlations Between Biopsychosocial Variables and Multiple Pain Features

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Child age	–													
2. Child gender	.13	–												
3. Sickle cell genotype	.19	−.24*	–											
4. Child coping attempts	−.25*	−.07	−.03	–										
5. Child negative thinking	.14	−.26*	.28*	.25*	–									
6. Child positive mood	−.16	−.06	.07	.36**	−.13	–								
7. Child negative mood	−.02	−.26*	−.02	.31**	.42***	−.21	–							
8. Caregiver active coping	−.12	.19	.02	.17	.07	.22	−.01	–						
9. Caregiver passive coping	.17	.02	−.01	.03	.21	−.10	.05	.27*	–					
10. Family functioning	.21	−.27*	.14	−.03	.26*	−.08	.07	−.11	.27*	–				
11. Pain frequency	.02	−.12	.17	.08	.35**	−.26*	.17	.17	.18	.05	–			
12. Pain intensity	.11	−.11	.25*	.03	.21	−.01	.03	.04	−.07	.08	.18	–		
13. Pain duration	.05	.00	−.06	−.13	.20	−.23*	.15	−.09	.22	−.09	.24*	.15	–	
14. Health care utilization	.15	.07	.23*	−.11	.25*	−.25*	.11	.21	.31**	.04	.50***	.25*	.12	–

*$p < .05$; **$p < .01$; ***$p < .001$.

associations between biopsychosocial factors and pain features, a multiple hierarchical regression approach was used. The latter approach allowed us to examine the unique and combined amount of variance contributed by each factor when multiple biopsychosocial variables were included in the same model. Consistent with the power analysis, a correlation of .20 (a small to moderate effect) was used as the criterion for including variables in the models. The goal was to achieve parsimonious models that captured key variables associated with the pain outcomes. For demographic variables, child age and gender were considered as possible covariates using the same criterion; however, neither variable met this criterion ($r = .02$–$.15$, $p \geq .203$).

Sickle cell genotype was dummy-coded into high- (HbSS and HbSβ^0) versus low-risk groups (HbSC and HbSβ^+). Variables were entered as follows: sickle cell genotype (categorical; first step), child psychological variables (continuous; second step), and caregiver psychological variables (continuous; third step). For the initial correlation analysis, biserial correlations were used for gender and sickle cell genotype, and Pearson correlations were used for the remaining variables. All models were tested to conform to assumptions of multiple regression. Pain frequency was log-transformed because of a nonnormal residual distribution and several influential cases (dfbeta > 1). All other assumptions were met.

Results

Correlations

Table III provides correlations for sickle cell genotype, child and caregiver psychological factors, and multiple pain features. Sickle cell genotype was significantly associated with pain intensity and health care utilization, such that children with high-risk genotypes had higher pain intensity ratings ($M = 7.48$, $SD = 1.64$) and health care utilization ($M = 4.02$, $SD = 4.09$) versus children with low-risk genotypes ($M = 6.58$, $SD = 1.70$ for intensity; $M = 2.08$, $SD = 3.60$ for health care utilization). Child negative thinking was positively associated with pain frequency and health care utilization and approached significance with pain intensity and duration. Child positive mood was negatively associated with pain frequency, duration, and health care utilization. Caregiver passive coping was positively associated with child health care utilization. Caregiver active coping approached significance as a *positive* correlation with child health care utilization. Family functioning was not associated with the pain outcomes.

Hierarchical Regressions

Table IV provides hierarchical regression results for sickle cell genotype and child psychological variables predicting multiple pain features. For pain frequency, the regression model was statistically significant, $F(2, 72) = 7.15$, $p = .001$, accounting for 17% of the variance overall. Both child negative thinking, $t(1, 73) = 2.95$, $p = .004$, and positive mood, $t(1, 73) = -1.97$, $p = .053$, were significant individual predictors. For pain intensity, the regression model was statistically significant, $F(2, 73) = 3.32$, $p = .042$, accounting for 8% of the variance overall. Sickle cell genotype contributed a significant amount of variance to the model, $\Delta F(1, 74) = 4.79$, $p = .032$, $\Delta R^2 = .06$, whereas negative thinking did not, $\Delta F(1, 73) = 1.80$, $p = .184$, $\Delta R^2 = .02$. For pain duration, the regression model was statistically significant, $F(3, 65) = 2.87$, $p = .043$, accounting for 12% of the variance overall. Child psychological factors contributed a significant amount of variance to the model, $\Delta F(2, 66) = 3.30$, $p = .043$, $\Delta R^2 = .09$. Negative thinking, $t(1, 67) = 1.98$, $p = .052$, was a significant individual predictor, whereas positive mood was not, $t(1, 67) = -1.37$, $p = .175$. The addition of caregiver passive coping did not contribute a significant amount of variance to the model, $\Delta F(1, 65) = 1.92$, $p = .171$, $\Delta R^2 = .03$.

Table IV. Hierarchical Regressions With Biopsychosocial Variables and Multiple Pain Features

Variable	*B*	95% CI	β	ΔR^2	Total R^2
Pain frequency					
Child psychological				.17**	.17
Negative thinking	0.01**	0.00, 0.01	.32		
Positive mood	−0.11*	−0.21, 0.00	−.21		
Pain intensity					
Child biological				.06*	.06
Sickle cell genotype	0.90*	0.08, 1.71	.25		
Child psychological				.02	.08
Negative thinking	0.01	−0.01, 0.03	.16		
Pain duration					
Child psychological				.09*	.09
Negative thinking	0.02*	0.00, 0.03	.23		
Positive mood	−0.31	−0.76, 0.14	−.16		
Caregiver psychological				.03	.12
Passive coping	0.04	−0.02, 0.09	.17		
Health care utilization					
Child biological				.04	.04
Sickle cell genotype	1.69	−0.46, 3.83	.19		
Child psychological				.11*	.15
Negative thinking	0.03	−0.01, 0.06	.17		
Positive mood	−1.22*	−2.24, −0.19	−.27		
Caregiver psychological				.10*	.25
Active coping	0.05	−0.01, 0.10	.21		
Passive coping	0.10	−0.02, 0.22	.20		

Note. Pain frequency was log-transformed because of several influential cases and a nonnormal residual distribution. The models for pain duration and health care utilization included a subset of 70 families with both child and caregiver data.

*$p < .05$; **$p < .01$.

For health care utilization, the regression model was statistically significant, $F(5, 63) = 4.25$, $p = .002$, accounting for 25% of the variance overall. Sickle cell genotype was not a significant predictor, $\Delta F(1, 67) = 2.47$, $p = .121$, $\Delta R^2 = .04$. The addition of child psychological variables contributed a significant amount of variance to the model, $\Delta F(2, 65) = 4.36$, $p = .017$, $\Delta R^2 = .11$. Child positive mood, t (1, 67) = −2.36, $p = .021$, was a significant individual predictor, whereas negative thinking was not, t (1, 67) = 1.43, $p = .157$. The addition of caregiver psychological variables also contributed a significant amount of variance to the model, $\Delta F(2, 63) = 4.33$, $p = .017$, $\Delta R^2 = .10$; however, caregiver active, t (1, 67) = 1.80, $p = .076$, and passive coping, t (1, 67) = 1.71, $p = .092$, were not significant as individual predictors.

Supplemental Analysis: Child Versus Caregiver Report of Pain

In the present study, we chose to average child and caregiver ratings of pain to avoid over- or underestimation of pain. Post hoc support for this plan can be found in supplementary analyses, which indicated no consistent pattern of larger correlation values for child report or parent report of pain with demographic or biopsychosocial factors. For example, five of nine key correlation values were larger with child than caregiver report and four of nine were larger with caregiver than child report. Specifically, child gender ($r = -.21$), SCD genotype ($r = .29$), and child negative mood ($r = .20$) appeared to be somewhat more strongly associated with pain frequency for child versus caregiver report ($r = -.05$; $r = .06$; $r = .13$), though direct comparisons of these correlations were not statistically significant (all Steiger's z-scores <1.5). Child negative thinking ($r = .28$) appeared to be somewhat more strongly associated with pain intensity for child versus caregiver report ($r = .06$), whereas SCD genotype ($r = .25$) was more strongly associated with pain intensity on caregiver versus child report ($r = .13$); again, direct comparisons were not statistically significant (z-scores <1.5). Finally, child age ($r = .29$) was more strongly and inversely associated with pain duration on child versus caregiver report ($r = -.15$; $z = 2.68$, $p < .01$), whereas child negative thinking ($r = .20$), child positive mood ($r = -.21$), and caregiver passive coping ($r = .28$) were more strongly and, in some cases inversely, associated with pain duration for caregiver versus child report ($r = .16$; $r = -.08$; $r = -.01$; all z-scores <1.96).

Discussion

This study evaluated biopsychosocial factors in relation to multiple pain features in children with SCD. The results suggest that individual biopsychosocial factors may have distinct relationships with pain

features and may be informative for future intervention studies.

For pain frequency, our hypothesis for sickle cell genotype was not supported. Previous epidemiological studies have demonstrated the importance of genotype in relation to pain frequency; however, these studies have predominantly relied on medical documentation to measure pain (Gill et al., 1995; Platt et al., 1991; Reese & Smith, 1997). Thus, sickle cell genotype may be a better predictor of severe episodes requiring health care utilization versus mild episodes treated at home. In contrast, we found that child psychological variables were significantly related to pain frequency, with both negative thinking and positive mood emerging as important individual factors. Two previous studies with similar samples and methodology failed to find an association between child psychological factors and pain frequency. The reason for the discrepancy is unclear, but may be related to prior studies focusing on coping rather than mood (Anie et al., 2002; Gil et al., 1991). Of note is that these relationships were consistent when caregiver and child ratings were separated.

The findings for pain intensity also differed from our hypothesis. Sickle cell genotype was a significant predictor of pain intensity. For child psychological variables, negative thinking was also related to pain intensity; however, this relationship was no longer significant after controlling for genotype. In addition, genotype and negative thinking were moderately related, such that children with high-risk genotypes had higher levels of negative thinking versus those with low-risk genotypes (Table III). Collectively, these findings suggest that negative thinking may be a consequence of pain intensity in SCD. A prior study examining the temporal precedence of pain intensity and psychological factors found a similar pattern for positive mood. Specifically, a prospective daily diary study found that changes in positive mood were more likely to be a consequence of pain intensity rather than vice versa in adolescents with SCD (Gil et al., 2003). Future studies may benefit from a similar, prospective approach to understand the immediate and temporal effects of negative thinking in relation to pain intensity.

The results for health care utilization demonstrated the most support for our hypothesis. Sickle cell genotype demonstrated a moderate correlation with health care utilization. Genotype was no longer significant in the regression model; however, this was likely the result of reduced power in the model using child and caregiver data. In addition, child positive mood was associated with health care utilization, and the caregiver variables approached significance in the model. These findings are consistent with several previous correlational and longitudinal studies, which have supported the role of both biological risk and psychosocial factors in predicting health care utilization in children with SCD (Gil et al., 1991; Logan et al., 2002; Reese & Smith, 1997). In contrast to previous work by Barakat and colleagues (2007), we did not find support for family functioning in relation to health care utilization; however, our measure of utilization was specific to pain, whereas the prior study focused on broad use of health services. Family functioning was associated with child negative thinking and caregiver passive coping (Table III), suggesting that this variable may serve a more distal role in influencing pain outcomes in SCD. Alternatively, our measure of family functioning may not have captured the specific family dynamics involved in pain management. Future studies may benefit from using measures of family functioning that are more specific to pain management, such as measures of parental response style in relation to pain (Peterson & Palermo, 2004).

The examination of pain duration was an exploratory aspect of this study. Child and caregiver psychological factors had small to moderate correlations with pain duration. Previous studies have not found significant relationships between child psychological factors and pain duration. This discrepancy may be the result of measurement differences between studies (Anie et al., 2002; Gil et al., 1991). Caregiver passive coping was also associated with pain duration; however, this association was attenuated with the inclusion of child psychological factors in the regression model, suggesting that caregiver passive coping may have been weakened by the inclusion of child psychological factors. The relationships between several variables also differed when child and caregiver ratings were separated. Additional research evaluating biopsychosocial factors and pain duration would be beneficial for understanding the importance of this particular pain feature as an outcome in future intervention studies.

This study should be considered in the context of limitations, including the size and characteristics of the sample, cross-sectional design, and method of pain measurement. First, while the sample size was based on published effect sizes, we were underpowered to detect certain effects, particularly for caregiver psychological variables, which tended to approach significance in both the correlation and regression analysis. In terms of patient characteristics, we included a broad age range; however, previous research suggests that important developmental factors influence the extent to which children rely on different types of strategies to manage pain (Dampier, Ely, Brodecki, & O'Neal, et al., 2002b; Gil et al., 1991, 1993). In terms of generalizability, males were more likely to be underrepresented in the sample compared with nonparticipants. In addition, we suspect that many of the

children who did not participate in the study had milder disease presentations. While our sample characteristics are comparable with those of previous studies (Barakat et al., 2007; Gil et al., 1991, 1993), the findings may best generalize to children who receive consistent and frequent hematological care. Finally, the majority of patients with HbSS disease were taking hydroxyurea. It is possible that correlations between sickle cell genotype and pain were attenuated as the result of this medication, and the results may not generalize to populations in which this medication is infrequently used. Alternative biological predictors apart from SCD genotype were considered as biological risk factors for the analyses; however, hydroxyurea also alters several key hematological markers, including hematocrit and fetal hemoglobin.

Another limitation is the cross-sectional approach, which limits inferences regarding causality. In particular, previous authors have noted that child and caregiver psychological factors may be consequences rather than predictors of pain (Gil et al., 2003). There has been minimal research examining the temporal precedence of these factors in SCD, particularly for pain frequency and duration. Thus, our understanding of this issue is limited. The use of prospective daily diaries and intervention studies that manipulate psychosocial factors in response to pain may provide a more refined understanding of this issue in the future.

Finally, this study predominantly relied on retrospective reports of acute pain. The retrospective reports may have contained measurement error because of inaccuracies in recalling health information over the previous year (Shiffman, Stone, & Hufford, 2008). In addition, previous research suggests that an individual's psychological state can bias retrospective reporting, including for children who are asked to recall pain (Van Den Brink, Bandell-Hoekstra, & Huijer Abu-Saad, 2001). It is notable that child and caregiver psychological factors demonstrated the largest effect size with health care utilization from the medical record, which would not be as impacted by recall bias or the psychological state of the child or caregiver. We also chose to average child and caregiver ratings to avoid over- or underestimation of pain; however, supplemental analyses suggest that the relationships between biopsychosocial variables may differ by reporter, though the majority of these differences were not statistically significant. The measurement of vaso-occlusive pain in children with SCD, including the use of child versus caregiver report, remains an important area of investigation for future studies. Finally, this study was limited to focusing on acute pain in SCD; however, it is increasingly being recognized that SCD results in both acute and chronic pain (Smith & Scherer, 2010). Future studies would benefit from examining whether biopsychosocial factors exert different effects on children with chronic versus acute pain from SCD, particularly given the relatively small effect sizes observed in the current and previous studies.

The present study may inform combined medical and psychosocial intervention for pain in SCD. Previous interventions for pain in SCD have predominantly focused on specific cognitive-behavioral coping strategies for pain, including education, distraction, deep breathing, muscle relaxation, guided imagery, and positive coping statements, and only a few have incorporated caregivers in the intervention approach. These interventions have consistently shown to improve coping attempts for children with SCD, with mixed findings in terms of changes in pain intensity, health care utilization, and activity level. These interventions have also not consistently demonstrated changes in negative thinking or changes on measures of psychological functioning (e.g., depression and anxiety) (Anie & Green, 2012). The current study suggests that more comprehensive intervention approaches that provide the above strategies along with other components (e.g., strategies to address negative thinking and positive mood) may be beneficial for improving children's experiences of pain. A caregiver component may also be warranted (Palermo, Wilson, Peters, Lewandowski, & Somhegyi, 2009). These interventions may in turn assist with improving functional outcomes for children with SCD.

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