

# Pain catastrophizing is associated with poorer health-related quality of life in pediatric patients with sickle cell disease

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**Background:** Sickle cell disease (SCD) is an inherited disorder of the red blood cells and is associated with chronic multisystem involvement. While SCD has been associated with poorer health-related quality of life (HRQoL), there is a paucity of data on the relationship of psychological covariates other than anxiety and depression and quality of life (QoL) in children with SCD.

**Materials and methods:** We performed a cross-sectional study of psychological factors, HRQoL, and pain-related outcomes in participants with SCD and race-matched controls as part of a larger study of experimental pain phenotyping.

**Results:** Pain catastrophizing was inversely correlated with HRQoL measured by the PedsQL™ Generic Core Scale in children with SCD, while this was not noted in control participants. Psychological factors, such as anxiety and depressive symptoms, were also associated with poorer HRQoL in both children with SCD and controls. We did not find an association of psychological factors with prior health care utilization. Psychological factors such as anxiety and depressive symptoms were inversely correlated with pain interference, but not pain intensity in SCD.

**Conclusion:** Catastrophizing is associated with poorer HRQoL in SCD, but in this study, it was not associated with pain intensity or interference and health care utilization in children with SCD. Further studies are needed to fully define the association of psychological factors including catastrophizing with QoL, pain burden, and SCD outcomes.

**Keywords:** pain, depressive symptoms, catastrophizing, sickle cell disease, PROMIS, quality of life

## Background

Sickle cell disease (SCD) affects ~100,000 people in the USA.<sup>1</sup> Sickle hemoglobin results from a mutation in codon 6 of the beta-globin gene where glutamic acid is substituted by valine. In its deoxygenated state, sickle hemoglobin polymerizes and leads to decreased deformability of the red cell and a sickle-shaped red cell. Vaso-occlusive episodic pain is the hallmark of SCD,<sup>2</sup> and pain is the major cause of morbidity, impaired health-related quality of life (HRQoL), health care utilization, and increased mortality in SCD.<sup>2,3</sup> In the biopsychosocial model of pain proposed by Turk and Flor, the dynamic and reciprocal interaction between biologic, psychological, and sociocultural variables shapes a person's response to pain.<sup>4</sup> Psychological variables play a prominent role in the multidimensional experience of pain.<sup>5</sup> They play a significant role in the experience, maintenance, and exacerbation of chronic pain,<sup>6</sup> and are predictive of disability.<sup>7</sup> As in other pain conditions, psychological factors are believed to play a role in pain in SCD. Anxiety and depression, the comorbidities prevalent in patients with SCD,<sup>8</sup> have been associated with increased pain, increased interference, and distress from pain and poorer quality of life in adults

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with SCD.<sup>8</sup> Mahdi et al reported that severe or extremely severe anxiety is independently associated with increased frequency and duration of vaso-occlusive crisis.<sup>9</sup> Children with SCD with these disorders have longer hospitalizations for vaso-occlusive crisis.<sup>10</sup> Pain catastrophizing, broadly conceived as an exaggerated negative “mental set” brought to bear during actual or anticipated pain experience,<sup>11</sup> is a multidimensional construct that represents the dimensions of rumination, magnification, and helplessness.<sup>12</sup> In adults with SCD, mean catastrophizing scores are high and have been associated with greater depression and poorer quality of life (QoL) as measured by the Short Form-36 in all domains.<sup>13</sup> Catastrophizing is also observed to be increased during pain episodes in adult SCD patients.<sup>14</sup> Increased clinical pain has been reported with greater catastrophizing behavior in adults with SCD.<sup>15</sup> In children with SCD, higher catastrophizing is associated with increased risk of disability.<sup>16</sup> While anxiety and depression are associated with poorer QoL in children with SCD,<sup>17</sup> there are no data on the relationship between catastrophizing and HRQoL, and data are limited regarding the relationship of psychological factors with pain intensity and pain interference. The objective of this study was to interrogate the association of psychological factors, such as catastrophizing, somatization, anxiety, and depressive symptoms, with HRQoL and other patient-reported outcomes related to pain in children with SCD.

## Materials and methods

We performed a cross-sectional study of psychological factors in participants enrolled in a study of psychophysical pain phenotyping using Quantitative Sensory Testing.<sup>18</sup> This paper represents an analysis of a subset of the data relating to psychological covariates and HRQoL. The study was approved by the Institutional Review Board at the University of Pittsburgh. Written informed consent and assent were obtained prior to all procedures from the participants or the parent/legal guardian as applicable.

## Participant selection

The participants with SCD in this study were followed by the Comprehensive Sickle Cell Clinic at the Children’s Hospital of Pittsburgh in Pittsburgh, Pennsylvania. Patients were eligible for the study if they were between 8 and 21 years of age and had a diagnosis of SCD of any genotype, and did not meet any exclusion criteria. Eligible patients with SCD were approached about participation in the study either during a health care visit or over the telephone after determining eligibility. A study-related Institutional Review Board–approved advertisement was also placed in the annual SCD newsletter. If patients expressed interest in participation, in-person written informed

consent was obtained prior to the conduct of any study procedures. According to the Quantitative Sensory Testing protocol, participants underwent the study procedures including collection of questionnaires when they were >2 weeks from the most recent episode of emergency room visit or hospitalization for an SCD-related pain episode. Individuals with sensory disorders, history of an overt stroke, history of recent major procedures including pain interventional procedures in the past 3 months, recent injury to proposed testing sites, significant cognitive impairment, or active major psychiatric or mood disorder were excluded. The control participants were healthy African-American people aged 8–21 without any major self-reported medical, psychiatric, neurologic, or pain-related diagnosis and not receiving pain medications. They were typically either siblings of SCD patients or unrelated controls recruited to the study through flyers placed in the community.

## Measures

HRQoL was measured using two instruments: 1) PedsQL™ Generic Core Scale<sup>19–24</sup> and 2) Peds QL SCD module<sup>25,26</sup> to measure SCD-specific HRQoL. The Peds QL SCD module was administered only to children with SCD. In controls without SCD, HRQoL was measured only using the PedsQL Generic Core Scale. Both modules were based on a 1-month recall period. Total scores on both modules range from 0 to 100. These modules have evidence of validity and reliability in the general population, in chronic illness as well as in SCD.<sup>26–</sup>

<sup>28</sup> We measured the pain intensity, pain interference, anxiety, depressive symptoms, sleep, fatigue, and peer relationships using the appropriate National Institutes of Health–Patient-Reported Outcomes Measurement Information System (PROMIS) short forms or item banks.<sup>29–31</sup> NIH-PROMIS instruments employ a 7-day recall period. All instruments except for sleep and pain intensity were administered using respective pediatric item banks using computerized adaptive testing (CAT) on the PROMIS Assessment Center, an online secure research management tool that enables collection of responses on PROMIS instruments.<sup>32</sup> Sleep and pain intensity measures were administered using the appropriate adult short form instruments because pediatric versions of these instruments are not available. CAT is based on item response theory and can potentially decrease the respondent burden.<sup>33</sup> PROMIS measures a T-score (a standardized score with a mean of 50 and an SD of 10), where higher T-scores indicate greater presence of a trait. PROMIS instruments capture patient-reported outcomes relevant across common medical conditions<sup>34</sup> and measure subjective experience of disease and treatment outcomes, which are important to patients. They have been validated in SCD.<sup>35,36</sup> Pain catastrophizing

was measured using the Pain Catastrophizing Scale (PCS).<sup>12,37</sup> The PCS is a 13-item scale comprising three subscales, rumination, magnification, and helplessness, and subscales are scored and added to obtain a total score. Scores range from 0 to 52, with higher scores indicating greater pain catastrophizing. Both total and subscale scores are calculated. The PCS has been validated in children aged 8–16 years in community samples as well as in children with chronic pain.<sup>12,37–39</sup> Somatization was measured using the Revised Child Somatization Inventory-24 (CSI-24).<sup>40</sup> Since several features of somatization overlap with disease manifestations of SCD, we calculated a somatization score using 19 items and excluding the pain-related items, including pain in chest/heart, lower back, abdominal pain, knees/elbow/joint pain, and arms/legs, as previously described.<sup>41,42</sup> In this manuscript, we have referred to it as Somatization-19. Each item has a maximum possible score of 4. Scores on the 24-item version could potentially range from 0 to 96, and those on the 19-item version could range from 0 to 76. Scoring was done as per the developer's recommendations. If <18 items were answered on the CSI-24 or CSI-19, the scores were regarded as missing. CSI-24 has been validated in a large number of pediatric patients with chronic abdominal pain<sup>40</sup> and has a high internal consistency in children with SCD.<sup>41</sup>

## Statistical methods

Descriptive statistics were used for sociodemographic, clinical, psychological, QoL, and pain characteristics. Given the small sample size, we used nonparametric methods for analyses.

## Results

Data from 33 patients with SCD and 27 controls were analyzed. With the exception of a few participants, the study sample has been previously described in reports of the larger study of experimental pain sensitivity.<sup>18</sup> Demographic data, HRQoL, and psychological characteristics are described in Table 1. Where all questionnaires were not completed, the number of completed questionnaires is indicated. As described in our prior publication,<sup>18</sup> high catastrophizing scores were noted in participants with SCD, and differences were not noted in measures of other psychological assessments between the two groups. Similar to previous reports, PedsQL Generic Core Scale scores were lower in participants with SCD as compared to controls.<sup>27</sup> Lower scores were obtained both in the physical functioning domain and in the psychosocial health domain (combination of emotional, social, and school functioning). Overall, we also noted that

**Table 1** Baseline demographic data, psychological characteristics, and HRQoL

|   | SCD (n=33)         | Controls (n=27)     |
|---|--------------------|---------------------|
| Age (years), median (IQR)   | 15 (10–19)         | 14 (11–18)          |
| Female sex, n (%)   | 23 (69.7)          | 19 (70.37)          |
| PROMIS measures (n=32 SCD)  |                    |                     |
| Pain intensity  | 37.8 (30.7–43.25)  | 37.7 (30.7–43.8)    |
| Pain interference   | 49.4 (32.2–56.4)   | 46.9 (38–53)        |
| Anxiety   | 43.95 (35–51.3)    | 42 (35.8–51.2)      |
| Depression  | 45.3 (32.6–53.85)  | 45.2 (37–54.3)      |
| Sleep disturbance   | 46.7 (38.35–52.9)  | 43.5 (37.4–51)      |
| Fatigue   | 45.15 (37.45–55.1) | 45.3 (35.4–55.8)    |
| Peer relationships  | 47.2 (41.35–53.05) | 48 (43.2–51.8)      |
| Pain Catastrophizing Scale (n=32 SCD)                                   |                    |                     |
| Total score***  | 28.5 (15.5–32)     | 14 (7–24)           |
| Rumination***   | 12.5 (9.5–15)      | 8 (4–12)            |
| Magnification*  | 4 (2–5)            | 1 (0–4)             |
| Helplessness***   | 9 (4–13.5)         | 4 (0–7)             |
| Somatization-revised CSI-24 (n=27 SCD, n=23 Control)                    | 12 (3–31)          | 8 (3–14)            |
| Somatization-revised CSI-24 without pain items (n=26 SCD, n=22 control) | 8.5 (3–20)         | 5 (2.1–7)           |
| QoL: PedsQL™  |                    |                     |
| Generic Core Scale  |                    |                     |
| Total score*  | 73.9 (57.6–89.1)   | 86.96 (78.26–91.5)  |
| Physical function subscale**  | 71.9 (53.1–90.03)  | 90.6 (78.125–93.75) |
| Emotional function subscale (n=32 SCD)                                  | 70 (52.5–92.5)     | 75 (65–95)          |
| Social function subscale*   | 90 (70–100)        | 100 (90–100)        |
| School function subscale*   | 65 (50–80)         | 85 (70–90)          |
| Psychosocial health summary score*                                      | 73.3 (58.33–90)    | 88.3 (75–93.3)      |
| SCD-specific QoL: PedsQL™ SCD Module                                    |                    |                     |
| Total score   | 59.88 (51.16–77.9) |                     |
| Pain and hurt subscale  | 66.7 (52.78–91.66) |                     |
| Pain impact subscale  | 50 (37.5–75)       |                     |
| Pain management subscale  | 50 (50–100)        |                     |

**Notes:** \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .

**Abbreviations:** CSI-24, Child Somatization Inventory-24; HRQoL, health-related quality of life; IQR, interquartile range; PROMIS, Patient-Reported Outcomes Measurement Information System; SCD, sickle cell disease.

scores on the Generic Core Scales and PedsQL SCD modules were highly correlated (Spearman's  $\rho = 0.77$ ).

Clinical characteristics of the participants with SCD were gathered using retrospective chart review and are described in Table 2.

## Pain catastrophizing is associated with poorer HRQoL in SCD, but not in control participants

Pain catastrophizing was associated with poorer HRQoL in children with SCD, but not in controls. Both anxiety and depressive symptoms were associated with poorer HRQoL in SCD as well as in controls, and the relationship of HRQoL

**Table 2** Clinical characteristics of participants with SCD (n=33)

|  |                   |
|--|-------------------|
| Genotype, n (%)  |                   |
| Hemoglobin SS  | 16 (48.5)         |
| Hemoglobin SC  | 13 (39.4)         |
| Hemoglobin S-β + thalassemia   | 4 (12.1)          |
| Number of episodes of health care utilization for pain (emergency room visit/inpatient admissions), median (IQR) |                   |
| 6 months before  | 1 (0–2)           |
| 1 year before  | 1 (0–3)           |
| 3 years before   | 4 (2–6)           |
| Hydroxyurea use, n (%)   | 25 (75.7)         |
| Receiving long-acting opioid therapy or adjunctive medications for pain or on chronic transfusion, n (%)         | 3 (9)             |
| Hematologic parameters   |                   |
| Hemoglobin (g/dL)  | 11.1 (9.9–11.6)   |
| Red blood cell mean corpuscular volume (fL)  | 89.6 (87.2–104.8) |
| Hemoglobin F (%) (n=27)  | 8 (2.2–17.4)      |

**Abbreviations:** IQR, interquartile range; SCD, sickle cell disease.

with somatization was significant in SCD. The strongest association between the pain subscales on the SCD-specific QOL scores was with pain catastrophizing and anxiety, and not with depressive symptoms. These associations are shown in Table 3.

We also found that psychological factors were associated with each other. In SCD, depressive symptoms, catastrophizing, and somatization correlated with anxiety and somatization was associated with depressive symptoms. In controls, depressive symptoms and somatization were correlated with anxiety, but we did not find a significant association between catastrophizing and anxiety. We also did not find a

**Table 3** Association of HRQoL with pain catastrophizing and other psychological characteristics (Spearman's Rho)

| SCD (n=32)                            | PCS     | Anxiety  | Depressive symptoms | CSI-19 (n=26) |
|---------------------------------------|---------|----------|---------------------|---------------|
| Generic QoL module (total score)      | −0.43*  | −0.6***  | −0.49**             | −0.39*        |
| Physical functioning domain           | −0.48** | −0.45**  | −0.25               | −0.23         |
| Psychosocial health summary score     | −0.34^  | −0.61*** | −0.61***            | −0.48*        |
| SCD specific QoL module (total score) | −0.52** | −0.59*** | −0.31^              | −0.39*        |
| Pain and hurt subscale                | −0.23   | −0.44*   | −0.21               | −0.46*        |
| Pain impact subscale                  | −0.53** | −0.50**  | −0.23               | −0.04         |
| Pain management subscale              | −0.44*  | −0.40*   | −0.29               | 0.01          |
| Controls (n=27)                       | PCS     | Anxiety  | Depressive symptoms | CSI-19 (n=22) |
| Generic QoL module (total score)      | −0.27   | −0.49*   | −0.50**             | −0.40^        |
| Physical functioning domain           | 0.002   | −0.41*   | −0.44*              | −0.41^        |
| Psychosocial health summary score     | −0.35^  | −0.55**  | −0.48*              | −0.23         |

**Notes:** \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , ^ $0.05 > p > 0.1$ .

**Abbreviations:** CSI-19, Child Somatization Inventory-19; HRQoL, health-related quality of life; PCS, Pain Catastrophizing Scale; SCD, sickle cell disease.

relationship between somatization and depressive symptoms in controls.

## Pain interference, not with pain intensity or health care utilization, is associated with psychological factors in SCD

We observed that in SCD, pain interference, but not pain intensity, was correlated with measures of psychological functioning, such as anxiety and depressive symptoms. We did not find an association between catastrophizing and pain interference in this sample. The magnitude of correlation was greater in SCD as compared to controls (Table 4). We did not find an association between psychological covariates with the number of episodes of health care utilization for pain (emergency room visits or inpatient admissions) in the previous 6 months, 1 year, or 3 years.

## Discussion

This is the first report of the association between pain catastrophizing and HRQoL in children with SCD. Unadjusted analyses presented in this study support the association of psychological factors such as anxiety, depressive symptoms, and somatization with HRQoL and pain interference in pediatric patients with SCD.

**Table 4** Association between patient-reported outcomes of pain and psychological factors, and lack of association of psychological factors with health care utilization for pain (number of emergency room visits or inpatient admissions for pain over a 3-year period prior to the study) (Spearman's rho)

| SCD (n=32)   | PROMIS pain intensity | PROMIS pain interference | Health care utilization for pain (3 years) |
|--|-----------------------|--------------------------|--|
| PROMIS anxiety   | 0.27                  | 0.50**                   | −0.01                                      |
| PROMIS depressive symptoms   | 0.19                  | 0.40*                    | −0.08                                      |
| Pain catastrophizing (n=31 for PROMIS)   | 0.16                  | 0.20                     | 0.01                                       |
| Somatization (pain items excluded) (n=25 for PROMIS, n=26 for health care utilization) | 0.24                  | 0.38^                    | −0.06                                      |
| Controls (n=27)  | PRMOIS pain intensity | PROMIS pain interference |  |
| PROMIS anxiety   | 0.22                  | 0.36^                    |  |
| PROMIS depressive symptoms   | 0.01                  | 0.31                     |  |
| Pain catastrophizing   | −0.10                 | −0.18                    |  |
| Somatization (pain items excluded) (n=22)  | 0.30                  | 0.40^                    |  |

**Notes:** \* $p < 0.05$ , \*\* $p < 0.01$ , ^ $0.05 > p > 0.1$ .

**Abbreviations:** PROMIS, Patient-Reported Outcomes Measurement Information System; SCD, sickle cell disease.

As reported in our previous work,<sup>18</sup> high levels of catastrophizing were noted in children with SCD. The PiSCES study, the largest longitudinal epidemiological study of pain in SCD to date, demonstrated that patients with SCD had high catastrophizing scores, and higher catastrophizing scores were associated with greater depression and poorer QoL.<sup>13</sup> Hollins et al also reported that catastrophizing was increased during painful episodes.<sup>14</sup> While catastrophizing has been associated with poorer HRQoL and depression in adults with SCD, to our knowledge, this is the first observation of the role of catastrophizing on HRQoL in children with SCD. We also did not observe an association between catastrophic thinking and the frequency of prior health care utilization for pain, recent pain intensity, or pain interference. This result was consistent with the results of the PiSCES study where there was no difference between those with high and low catastrophizing scores in pain intensity, distress, interference, and health care utilization, after adjusting for depression.<sup>13</sup> These results were in contrast to those reported by Mathur et al, who reported increased clinical pain with greater catastrophizing behavior in adults with SCD,<sup>15</sup> in contrast to the associations of catastrophizing with chronic pain. Catastrophizing has been associated with more intense pain,<sup>12</sup> emotional distress,<sup>12</sup> disability,<sup>43</sup> pain behaviors,<sup>44</sup> analgesic use,<sup>45</sup> length of hospital stay,<sup>46</sup> and poorer QoL.<sup>47</sup> Pain catastrophizing is one of the factors that is consistently associated with poorer pain outcomes,<sup>48,49</sup> and along with depression, may have an additive effect on the impact of pain in some painful conditions.<sup>50</sup> The authors of the PiSCES study suggested that the lifelong, life-threatening nature of SCD complications and related chronicity of pain over an extended period compared to other chronic pain diseases may have accounted for the lack of relationship between catastrophizing and pain in SCD.<sup>13</sup> In this study, another possible explanation for the lack of correlation between catastrophizing and pain was that the participants were intentionally tested at a time when they were not in pain, except for a small subset that experienced baseline daily pain. We may have missed any pain outside of this period and, therefore, any relationship of pain catastrophizing with pain intensity or pain interference.

Despite the median scores of depressive symptoms and anxiety being no higher than average and no different from controls in patients with SCD, we found the relationship between HRQoL and psychological factors in SCD. In previous studies, both depression and anxiety have been found to be associated with a poorer QoL in individuals with or without SCD.<sup>17,51,52</sup> Anxiety disorders such as Generalized Anxiety Disorder<sup>53</sup> have been found in population-based studies to be associated with poorer QoL, with more severe

anxiety symptoms being associated with poorer HRQoL after controlling for sociodemographic factors.<sup>54</sup> Similarly, poorer QoL has been described in depressive disorders.<sup>55</sup> Studies of chronic pain patients have shown that anxiety and depression are associated with persistent or chronic pain.<sup>56,57</sup> Despite these relationships, we did not observe an association between anxiety and depression, and frequency of prior health care utilization. These data are in agreement with the observations by Carroll et al, who did not report increased depressive symptoms in patients with SCD who had high rates of health care utilization,<sup>58</sup> suggesting that health care utilization is likely an incomplete measure of pain-related morbidity in SCD. These data also highlight the need for further study of the role of anxiety in SCD, specifically in relation to SCD pain and HRQoL.

We also found that anxiety and depressive symptoms were associated with pain interference, but not pain intensity in SCD. This is in contrast to the PiSCES study, where pain intensity as well as interference and distress from pain were higher in adults who were depressed as compared to those who were not depressed.<sup>8</sup> Similar results were observed between anxiety and pain intensity as well as interference and distress from pain.<sup>8</sup> To our knowledge, this is the first report of associations between pain interference with anxiety and depressive symptoms in children with SCD. We also noted associations between the total score of HRQoL and anxiety and depressive symptoms. Interestingly, the magnitude of associations was highest for anxiety as compared to other psychological factors. While we showed that somatization, even after exclusion of pain items, was associated with decreased HRQoL, we did not see a direct relationship with pain. Somatization has been shown to be associated with pain intensity<sup>59</sup> and health care utilization in SCD,<sup>41</sup> but we did not observe these associations. We did, however, observe a trend toward significant correlation between somatization and pain interference in SCD.

The limitations of our study include the predominance of female patients and a small sample size. It is also possible that there may have been a selection bias, because patients had volunteered to come for a separate visit exclusively to participate in an ~75-minute study visit that included psychophysical pain phenotyping. Psychological covariates such as anxiety and depressive symptoms were assessed using modules that had a 7-day recall. This may have potentially measured a “state” versus a “trait” symptom. However, PROMIS measures were specifically chosen in our study because of their widespread applicability across various diseases as well as healthy states and the ability to reduce respondent burden using CAT. Clinical pain burden was measured using health care utilization



for pain. This is known to be an insufficient measure of pain burden, but is widely used across SCD studies because of the lack of easily available better measures. It is also unclear if anticipation of undergoing laboratory sensory testing influenced PCS or PROMIS anxiety scores in this study. We explored the influence of multiple psychological factors simultaneously in unadjusted analyses. There is overlap and correlation between these psychological factors; however, due to the small sample size, multiple psychological factors studied, and inadequate data on other clinical complications that influence HRQoL in SCD, we did not attempt an adjusted analysis. Thus, the relationships described here should be investigated in larger studies, and the results of this study must be interpreted in the context of these limitations.

## Conclusion

Catastrophizing is associated with poorer HRQoL in SCD, but in this study, it was not associated with pain intensity or interference and health care utilization in children with SCD. Further studies are needed to fully define the association of psychological factors including catastrophizing with HRQoL, pain burden, and SCD outcomes.

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## Disclosure

The authors report no conflicts of interest in this work.

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