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Brief Screening Measures Identify Risk for Psychological Difficulties Among Children with Sickle Cell Disease

Short Title: Screening for Risk Children SCD

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Abstract

Children with sickle cell disease (SCD) experience disproportionately high rates of psychological problems. Our goal was to examine the clinical utility of psychological screening measures to identify children with such problems in medical settings. Caregivers completed screening measures assessing social-emotional problems, ADHD symptoms, executive dysfunction, and health-related quality of life (HRQOL) for children with SCD (receiving either chronic blood transfusion or hydroxyurea) and their siblings. Our findings demonstrated that screening measures identified clinically elevated symptoms in children with SCD that had not been previously reported. Scores for siblings were for the most part in the normal range. The number of days hospitalized (but not cerebral infarct status) predicted higher scores, emphasizing the challenges associated with SCD complications. Overall, our findings support the notion that screening measures reduce the need for reliance on medical provider judgment for psychological referrals and increase equitability in access to services. Early identification resulting in early intervention has contributed substantially to improved psychological functioning in many contexts, and it is thus likely that such improvements would also be achieved in this uniquely vulnerable population.

Key words: sickle cell disease; children, behavior; executive dysfunction, quality of life; transfusion; hydroxyurea

Sickle cell disease (SCD) is a chronic genetic disorder characterized by the production of abnormal hemoglobin in the red blood cells and affects approximately 100,000 Americans (Rees, Williams, & Gladwin, 2010). Children with SCD face life-threatening medical (Redding-Lallinger & Knoll, 2006) and neurologic (DeBaun & Kirkham, 2016) challenges, but in comparison to other pediatric chronic illness populations, such as childhood cancer or asthma (Bennett, Shafran, Coughtrey, Walker, & Heyman, 2015), there is less research regarding their psychological functioning (Anie, 2005). This is particularly surprising given the intense chronic treatment regimens, unpredictable painful episodes, and frequent hospitalizations. Children who receive the primary disease modifying treatments for SCD-related complications, such as chronic blood transfusion therapy (CTT) or hydroxyurea therapy (HU), generally have the most acute and chronic complications (Ware, de Montalembert, Tshilolo, & Abboud, 2017), putting them at higher risk for compromised psychological functioning.

Studies of children with SCD indicate that prevalence rates of internalizing disorders are higher than the general population, with symptoms including depressed mood, social isolation, and feelings of helplessness observed most frequently (Barbarin, Whitten, & Bonds, 1994; Benton, Ifeagwu, & Smith-Whitley, 2007; Jerrell, Tripathi, & McIntyre, 2011; Lukoo et al., 2015). Depressive and anxious symptoms are significantly associated with healthcare utilization, as diagnosis of an internalizing disorder is related to an increased number of hospital admissions and length of hospital stay for children with SCD (Jonassaint, Jones, Leong, & Frierson, 2016; Myrvik, Burks, Hoffman, Dasgupta, & Panepinto, 2013). Further, depressive and anxious symptoms also increase during hospitalizations for pain episodes (Dampier et al., 2016).

The possibility of cognitive dysfunction for children with SCD receiving disease modifying treatments must be strongly considered by medical providers. These children have a

high prevalence of stroke and silent cerebral infarct (SCI) (DeBaun & Kirkham, 2016), which can contribute to cognitive impairment. Additionally, prior studies have shown that children with SCD with and without prior history of stroke or SCI have higher rates of developmental disabilities (Ashley-Koch, Murphy, Khoury, & Boyle, 2001) and more cognitive deficits than the general population, siblings, and peers (Schatz, Finke, Kellett, & Kramer, 2002). Attention and executive functioning are two domains in which children with SCD have particular difficulty (Berkelhammer et al., 2007; Prussien, Jordan, DeBaun, & Compas, 2019), with prevalence rates of attention-deficit/hyperactivity disorder (ADHD) between 19 and 40% in the United States (Acquazzino, Miller, Myrvik, Newby, & Scott, 2017; Benton, Boyd, Ifeagwu, Feldtmose, & Smith-Whitley, 2011; Lance, Comi, Johnston, Casella, & Shapiro, 2015). Cognitive challenges can be a barrier to adherence to care, further affecting SCD-related complications.

SCD-related medical complications and associated treatments have also been shown to contribute to poorer health-related quality of life (HRQOL), as have greater disease severity (Panepinto, O'Mahar, DeBaun, Rennie, & Scott, 2004) and pain (Dampier et al., 2010; Ludwig, Sil, Khowaja, Cohen, & Dampier, 2018; Schlenz, Schatz, McClellan, & Roberts, 2012). Additionally, although adherence to disease-modifying treatments is associated with fewer hospitalizations (Badawy et al., 2017; Hilliard et al., 2018), children with SCD remain high healthcare utilizers, with more frequent hospital contacts to maintain adequate clinical care. However, little is known about the psychological functioning and HRQOL of children with SCD who have the greatest disease severity.

In an effort to increase identification of psychological problems by medical providers, mental health screeners and standardized protocols have been utilized and have improved recognition and treatment of psychological difficulties (Croghan & Brown, 2010; Unützer &

Park, 2012). Across all pediatric populations, a key challenge in medical settings is that psychological problems are often under-identified and under-treated (Unützer & Park, 2012; Williams, Klinepeter, Palmes, Pulley, & Foy, 2004). Illustrative of this issue, Olson and colleagues (2001) found that nearly half of pediatricians felt uncertain about diagnosing depression in children and adolescents.

Medical providers have indicated that, in addition to lacking confidence, they may not make psychology referrals to avoid stigmatizing patients because they lack knowledge about the diagnostic criteria for psychological disorders, have limited expertise regarding psychological treatment, and have a shortage of time (Croghan & Brown, 2010; Liu, Lu, & Lee, 2008; Olson et al., 2001). Specific to the pediatric SCD population, pica is a psychological disorder characterized by an appetite for non-nutritive substances which has a high prevalence in youth with SCD (Ivascu et al., 2001). Previous research has demonstrated that implementation of a screening program for pica in a large SCD clinic identified that 28% of patients had pica symptoms that had not previously been identified by medical providers (Reed-Knight et al., 2015).

Given the disproportionately high rates of social-emotional problems, ADHD symptoms, executive dysfunction, and poorer HRQOL, it is imperative that we determine effective ways to screen children with SCD within hospital and primary care settings for psychological problems. Of particular importance is the need to screen children with SCD who are high healthcare utilizers due to increased SCD-related complications that require chronic treatment therapies. Thus, the primary goal of the present study was to determine the practicality of using well-validated psychological screening measures to identify patients with SCD who exhibit need for psychological intervention. To achieve this goal, we compared the percentage of children with

SCD who had psychological diagnoses or difficulties noted in their medical records to the percentage identified as being at risk for psychological diagnoses or difficulties based on our screening measures. Identifying whether relatively brief and easily administered tools can be used to identify children with SCD in need of psychological and/or neuropsychological referrals would reduce reliance on medical provider judgment and increase equitability in access to services.

A secondary goal of this study was to determine whether there were differences in psychological problems between children with SCD receiving CTT versus HU given the differences in hospital contacts and disease severity. To achieve this goal, we assessed differences in the percentage of children in each group who had clinically elevated scores, as well as differences in group mean scores. Gaining a better understanding of which children to screen uniformly will help target limited resources to the most vulnerable in the pediatric SCD population. Finally, we also examined relationships between treatment factors (i.e., hospitalizations, length of time receiving CTT or HU) and psychological functioning in children with SCD.

Method

Participants

Recruitment occurred through the sickle cell clinic at St. Louis Children's Hospital as part of a larger study assessing cognitive functioning (Hood et al., 2019). Inclusion criteria for children with SCD were age 4 to 18 years, diagnosis of SCD identified through newborn screening or laboratory testing, and treatment with either CTT or HU for at least 6 months prior to study.

Exclusion criteria for children with SCD were milder disease severity (e.g., HbSC

genotype), history of bone marrow transplant, severe developmental disability (e.g., autism), and concurrent treatment with CTT and HU. Children with SCD receiving neither CTT nor HU were excluded because they were not the focus of the larger study. That said, children receiving CTT or HU generally represented the patients who attended the SCD clinic most frequently. All children with SCD receiving CTT who met eligibility criteria were approached to be in the study, and 80% agreed to participate.

We also recruited a control sample comprising siblings of the children with SCD. These controls were recruited during clinic visits or were contacted if they had participated in previous studies. Because siblings have the greatest similarity in terms of social and familial environments, this comparison group helped determine the influence of SCD-related disease factors on psychological functioning. Our overall sample comprised 72 children with SCD and their siblings. Previous diagnoses for children included attention and learning disabilities (1 SCD and 1 sibling control, respectively).

Caregivers who completed study measures ranged in age from 26 to 75 years (M = 40.4, SD = 9.0). Most self-identified as African-American/Black (92%), followed by White (6%), and mixed-race (2%). Yearly income was available for 75% of families, with values ranging from $1,750 to $198,000 ($M$ = 30,278, SD = 34,450). Mother's education level was as follows: 16% neither completed high school nor received an equivalent diploma, 6% received a GED, 20% graduated from high school, 16% received an associate degree, 28% completed some college with no degree, 8% received a bachelor's degree, and 6% received a master's degree.

Procedures

The institutional review board at Washington University in St. Louis approved this study. Caregivers provided informed consent in accordance with the Declaration of Helsinki. Caregivers completed psychological screening measures in a private room, with administration on either an iPad or using paper and pencil. Caregivers completed measures for children with SCD receiving transfusion within 3 days after a transfusion. Completion of all measures took approximately 20 - 30 minutes. For their efforts, families were provided with a small monetary gift.

Materials

Behavioral and Emotional Screening System (BESS) (Reynolds & Kamphaus, 2015). The BESS is a 28-item rating scale that assesses function across an array of psychological areas, including internalizing and externalizing problems, issues in school, and adaptive skills. Scores from these four areas were combined to yield a composite T score indicative of psychological risk. Caregivers indicated how child participants had behaved in the last several months. Items were rated on a 4-point scale of "Never" to "Almost Always." T-scores (M = 50, SD = 10) and clinical classifications (normal to extremely elevated) were used in analyses.

Conners 3rd Edition-Short Form (Conners-3) (Conners, Pitkanen, & Rzepa, 2011). The Conners-3 is a 43-item rating scale that assesses symptoms related to ADHD and its most common co-morbid problems in children. Caregivers reported how well items described child participants or how frequently an event had happened in the past month. Items were rated on a 4-point scale of "Not true at all" to "Very much true." For the present study, scores from the inattention and hyperactivity/impulsivity subscales were averaged to create an ADHD symptom

composite. T-scores (M = 50, SD = 10) and clinical classifications (low to very elevated) were used in analyses.

Behavior Rating Inventory of Executive Function Screener (BRIEF-2) (Gioia, Isquith, Guy, & Kenworthy, 2015). The BRIEF-2 screener is a 12-item rating scale that assesses everyday behaviors of executive function. Caregivers reported how well items described child participants or how frequently an event had happened in the past six months. Items were rated on a 3-point scale of "Never," "Sometimes," and "Often." Raw scores and clinical ranges (average to clinically elevated) were used in analyses.

Pediatric Quality of Life Inventory Sickle Cell Disease Module (PedsQL) (Panepinto et al., 2013). The PedsQL is a 43-item multi-dimensional rating scale that assesses HRQOL in individuals with SCD. The present study used a modified version of the PedsQL that included 5 of the 9 dimensions (i.e., pain and hurt, pain management and control, worry I and II, and emotions). Caregivers rated how much of a problem an issue had been for child participants over the past 24 hours on a 5-point scale of "Never" to "Almost Always." Responses were reverse-scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Total scores were then computed as the sum of the items divided by the number of items answered. Total scores and clinical classifications (81 – 100 = high levels of HRQOL, 61 – 80 = intermediate levels HRQOL, and 0 – 60 = poor HRQOL related to pain) were used in analyses (Beverung, Varni, & Panepinto, 2015).

Higher scores on the BESS, Conners-3, and BRIEF-2 were of greater clinical concern, whereas lower scores on the PedsQL indicated poorer HRQOL. Internal consistency for the

BESS, Conners-3, BRIEF-2, and PEDSQL caregiver reports were greater than .85, representing excellent internal consistency.

General Health Questionnaire. Caregivers completed a general questionnaire that provided demographic, health, and education information about child participants and their families. Responses were primarily yes/no, with some free responses.

Medical Record Review. Information was extracted through a retrospective medical record review regarding current psychological diagnoses and difficulties, length of time receiving CTT or HU, number of days hospitalized within the past year, and history of stroke or SCI identified through MRI and neurologic examination.

Statistical Analyses

Analyses were conducted in the R environment (R Core Team, 2017). One-sample z-tests assessed differences in percentages between medical record review diagnoses and screening measures. Welch Independent Samples t-tests, Pearson's Chi-square Test of Independence, and Analysis of Variance (ANOVA) identified differences between groups (i.e., SCD-CTT, SCD-HU, siblings). Post hoc pairwise comparisons were corrected using the false discovery rate. Pearson correlations assessed relationships between screening measures and treatment factors. Hierarchical linear regression models were used to determine whether treatment factors predicted scores on screening measures for children with SCD.

Cohen's *d* and *h* were the measures of effect size used for z-tests, t-tests, and post hoc comparisons, with .2, .5, and .8 representing small, medium, and large effect sizes, respectively. Cramer's V (ϕ_C) and Phi (ϕ) were the measures of effect size for chi squared tests, with .07 to .20, .20 to .35, and ≥ .35 representing weak, moderate, and strong associations, respectively. Partial eta squared (η_p^2) was the measure of effect size used for ANOVA analyses, with .01, .09, and .25 representing small, medium, and large effects, respectively (Cohen, 1988). All effect sizes are reported using bootstrapped bias corrected and accelerated 95% confidence intervals (CI), as they adjust for possible bias and skewness in the bootstrap distribution.

Results

Preliminary Analyses

Table 1. reports demographic and disease related factors. On average, children with SCD (CTT and HU) were 12 years of age, 53% female, and the majority identified as African American/Black with the HbSS genotype. Initial analyses indicated that children with SCD and siblings were similar in age, gender, and race, $p > .05$ in all instances. The SCD-CTT and SCD-HU groups were similar regarding genotype (HbSS) and length of time receiving disease modifying treatment, $p > .05$. However, children in the SCD-CTT group had greater disease severity than children in the SCD-HU group, as they were hospitalized for significantly more days within the past year and significantly more children in this group had at least one stroke or SCI (see Table 1).

With respect to psychological functioning for children with SCD, medical record review identified 6/51 (12%) children as having at least one social-emotional problem (i.e., depression,

anxiety, pica, behavior concern), 3/51 (6%) as having a diagnosis of ADHD or attentional difficulties, and 6/51 (12%) as having a learning or language difficulty.

Social-Emotional Problems

Regarding social-emotional problems on the BESS, 22% of all children with SCD had elevated or extremely elevated scores. One sample z-tests revealed that the percentage of problems reported on the BESS was significantly more than the 12% of problems documented in the medical record, $\chi^2(1, N = 49) = 5.06$, $p = .02$, $h = .30$, 95% CI [-.26, 86], small effect.

At the group level, 32% of children in the SCD-CTT group and 17% of children in the SCD-HU group had elevated or extremely elevated scores on the BESS, compared to only 10% of siblings. Chi squared analyses revealed significant differences between groups, $\chi^2(4, N = 70) = 16.77$, $p = .002$, $\phi_C = .17$, 95% CI [.05, .28], medium effect. Specifically, pairwise comparisons showed that the percentage of children with social-emotional problems in the greater disease severity SCD-CTT group was greater than that of siblings, $p = .002$, $\phi_C = .27$, 95% CI [.16, .41], medium effect. However, the percentage of children with social-emotional problems in the milder disease severity SCD-HU group was similar to that of siblings, $p = .29$. The percentage of children in the SCD-CTT group with social-emotional problems trended toward being greater than that of children in the SCD-HU group, $p = .06$, $\phi_C = .18$, 95% CI [.06, .31], small effect (see Figure 1 panel a).

All children with SCD and siblings had mean T scores on the BESS in the typical range (< 60). With respect to mean differences between groups, the T scores of children in the SCD-CTT group (M = 57.3, SD = 10.4) were almost 1 SD above the normative mean. In contrast, children in the SCD-HU group (M = 51.8, SD = 10.9) and siblings (M = 46.9, SD = 10.9) had

scores that were in the average range and relatively consistent with published norms (M = 50, SD = 10).

ANOVA showed significant between-group differences in T scores for social-emotional problems, $F(2, 67) = 4.6$, $p = .01$, $\eta_p^2 = .12$, 95% CI [.01, .27], medium effect. Post hoc analyses showed that children in the SCD-CTT group had mean T scores that were 10 points significantly higher than those of siblings, $p = .01$, $d = 1.08$, 95% CI [.38, 1.77], large effect. Children in the SCD-HU group had mean T scores that were 5 points higher than siblings, $p = .12$, $d = .46$, 95% CI [-.12, 1.04], small effect. Further, children in the SCD-CTT group had mean T scores that were 5.5 points higher than the SCD-HU group, $p = .12$, $d = .59$, 95% CI [-.02, 1.21], medium effect; however, these absolute differences did not reach statistical significance (see Figure 2 panel a).

ADHD Symptoms

Regarding ADHD symptoms on the Conners-3, 22% of all children with SCD had elevated or extremely elevated scores. One sample z-tests revealed that the percentage of ADHD symptoms reported on the Conners-3 was significantly more than the 6% of ADHD diagnoses and attentional difficulties documented in the medical record, $\chi^2(1, N = 49) = 23.50$, $p < .001$, $h = .48$, 95% CI [.09, 1.05], medium effect.

At the group level, 32% of children in the SCD-CTT group and 17% of children in the SCD-HU group had elevated or extremely elevated scores on the Conners-3, compared to only 5% of siblings. Chi-squared analyses revealed significant differences between groups, $\chi^2(4, N = 70) = 37.32$, $p < .001$, $\phi_C = .25$, 95% CI [.14, .35], medium effect. Pairwise comparisons showed that the percentage of children with ADHD symptoms in the SCD-CTT ($p < .001$, $\phi_C = .38$, 95%

CI [.28, .50], large effect) and SCD-HU ($p < .001$, $\phi_C = .31$, 95% CI [.12, .37], medium effect) groups was greater than that of siblings. Additionally, the SCD-CTT group had a higher percentage of ADHD symptoms than the SCD-HU group, $p < .001$, $\phi_C = .23$, 95% CI [.20, .44], medium effect (see Figure 1 panel b).

All children with SCD and siblings had mean T scores on the Conners-3 in the typical range (< 60). With respect to mean differences between groups, children in the SCD-CTT (M = 59.9, SD = 13.1) and SCD-HU (M = 57.5, SD = 11.6) groups were almost one SD above the normative mean. In contrast, siblings had average T scores (M = 50.5, SD = 11.2) that were consistent with published norms (50 ± 10).

ANOVA revealed significant between group differences in T scores for ADHD symptoms, $F(2, 67) = 3.3$, $p = .04$, $\eta_p^2 = .09$, 95% CI [.001, .22], medium effect. Post hoc analyses showed that children in the SCD-CTT group had mean T scores that were 9 points significantly higher than those of siblings, $p = .05$, $d = .78$, 95% CI [.11, 1.46], medium effect. Children in the SCD-HU group had mean T scores that were 7 points higher than those of siblings, $p = .07$, $d = .54$, 95% CI [-.04, 1.133], medium effect; however, this absolute difference did not reach statistical significance. Regarding children with SCD, the SCD-CTT and SCD-HU groups had similar T scores (2 point difference), $p = .51$, $d = .28$, 95% CI [-.32, .89], small effect (see Figure 2 panel b).

Executive Dysfunction

Regarding executive dysfunction on the BRIEF-2, 52% of all children with SCD had potentially or clinically elevated scores. One sample z-tests revealed that the percentage of executive dysfunction reported on the BRIEF-2 was significantly greater than the 12% of

learning and language difficulties documented in the medical record, $\chi^2(1, N = 48) = 73.03$, $p < .001$, $h = .90$, 95% CI [.30, 1.49], large effect.

At the group level, 53% of children in the SCD-CTT group and 51% of children in the SCD-HU group had potentially or clinically elevated scores on the BRIEF-2, compared to 15% of siblings. Chi-squared analyses revealed significant differences between groups, $\chi^2(4, N = 69) = 42.05$, $p < .001$, $\phi_C = .26$, 95% CI [.15, .37], medium effect. Pairwise comparisons showed that the percentage of children with executive dysfunction in the SCD-CTT ($p < .001$, $\phi_C = .41$, 95% CI [.29, .53], large effect) and SCD-HU ($p < .001$, $\phi_C = .40$, 95% CI [.29, .53], large effect) groups was higher than that of siblings. However, there were similar percentages of executive dysfunction in the SCD-CTT and SCD-HU groups, $p = .50$ (see Figure 1 panel c).

Average raw scores on the BRIEF-2 for children in the SCD-CTT (M = 21.4, SD = 4.4) and SCD-HU (M = 19.9, SD = 4.6) group were in the potentially clinically elevated range (> 19.5). Siblings had average scores (M = 16.1, SD = 4.6) that were within normative expectations (< 19.5). ANOVA revealed significant group differences in executive dysfunction $F(2, 66) = 7.4$, $p = .001$, $\eta_p^2 = .18$, 95% CI [.02, .35], large effect. Post hoc analyses showed that children in the SCD-CTT group had raw scores that were 5 points higher than those of siblings, $p = .002$, $d = 1.25$, 95% CI [.53, 1.96], large effect. Children in the SCD-HU group had raw scores nearly 4 points higher scores than those of siblings, $p = .007$, $d = .83$, 95% CI [.23, 1.43], large effect. Regarding children with SCD, the SCD-CTT and SCD-HU groups had similarly high scores (1.5 point difference), $p = .29$ (see Figure 2 panel c).

Health-related Quality of Life

Scores on the PedsQL were only available for children with SCD. Regarding HRQOL, 65% of children in the SCD-CTT group and 48% of children in the SCD-HU group had scores in the poor range. Additionally, 35% of children in the SCD-CTT and 52% of children in the SCD-HU group had scores in the intermediate range. No caregiver reported high levels of HRQOL for children with SCD. Chi squared analyses revealed that children in the SCD-CTT group were more likely to have poor HRQOL than children in the SCD-HU group, $\chi^2(1, N = 48) = 4.8$, $p = .03$, $\phi_C = .16$, 95% CI [.02, .30], small effect (see Figure 1 panel d).

In addition, children in the SCD-CTT (M = 50.4, SD = 17.9) and SCD-HU (M = 54.9, SD = 18.9) groups had mean scores indicating poor HRQOL (< 60). With respect to mean differences between groups, ANOVA indicated that the SCD-CTT and SCD-HU groups had similarly poor scores (4.5 point difference), $F(1, 48) = .68$, $p = .40$, $\eta_p^2 = .01$, 95% CI [.00, .13], negligible effect (see Figure 2 panel d).

Overall, screening measures pointed to clinical scores indicative of psychological risk that was not previously noted in the medical records of children with SCD. Specifically, children with SCD, particularly those in the greater disease severity SCD-CTT group, had scores indicating greater risk for social-emotional problems, ADHD symptoms, and exhibited more behaviors indicative of executive dysfunction than siblings. Effect sizes generally ranged from medium to large, suggesting clinically meaningful differences between groups. In addition, poor HRQOL was found for both the SCD-CTT and SCD-HU groups, with no caregiver reporting that children with SCD had high HRQOL.

Relationships Between Measures

We next sought to determine the relationships among social-emotional problems, ADHD symptoms, executive dysfunction, HRQOL, and treatment factors (i.e., length of treatment [either CTT or HU], number of days hospitalized in the past year) in children with SCD (see Table 2). Correlation analyses revealed that scores from all screening measures were strongly correlated with one another, indicating that caregivers who reported more problems in one area of psychological functioning reported more problems in the other areas. In terms of treatment factors, scores from the ADHD symptoms, executive dysfunction, and HRQOL screening measures were significantly related to number of days hospitalized, *ps* < .05, medium effects; there was also a trend toward a significant relationship with social-emotional problems. In contrast, scores from none of the screening measures were significantly related to length of time receiving treatment, *ps* > .05, negligible small effects.

We next conducted four linear regressions to determine whether hospitalizations predicted social-emotional problems, ADHD symptoms, executive dysfunction, or HRQOL. The mean number of days hospitalized was 4.3 (SD = 8.0) for children with SCD. As previously noted, the SCD-CTT group had significantly more children who had at least one stroke or SCI than the SCD-HU group. By entering stroke/SCI status as an independent variable in our regressions before number of days hospitalized, we were able to determine the influence of number of days hospitalized beyond that attributable to stroke/SCI status. Results revealed that stroke/SCI status did not predict scores on any screening measure for children with SCD, *ps* > .05 in all instances. After the influence of stroke/SCI status was taken into account, the number of days hospitalized did not predict social-emotional problems for children with SCD, $F(1, 42) = 2.81$, $p = .10$, $\eta_p^2 = .06$, 95% CI [.006, .23], small effect. However, after stroke/SCI status was taken into account, number of days hospitalized

significantly predicted ADHD symptoms, $F(2, 42) = 6.25$, $p = .02$, $\eta_p^2 = .13$, 95% CI [.003, .39], executive dysfunction, $F(2, 41) = 4.74$, $p = .04$, $\eta_p^2 = .10$, 95% CI [.001, .28], and HRQOL, $F(2, 41) = 4.16$, $p = .05$, $\eta_p^2 = .09$, 95% CI [.001, .27], all with medium effects.

Based on these regressions, the estimated mean T score for ADHD symptoms was 54.50, with every .50 days hospitalized predicting a 1 point increase in T score. The estimated mean raw score for executive dysfunction was 19.43, with every .18 days hospitalized predicting a 1 point increase. Finally, the estimated mean score for HRQOL was 55.50, with every .71 days hospitalized predicting a 1 point decrease (i.e., poorer HRQOL).

Discussion

Previous studies have demonstrated that children with SCD have disproportionately high rates of social-emotional problems (Benton et al., 2007), ADHD symptoms (Acquazzino et al., 2017), and executive dysfunction (Berg, Edwards, & King, 2012), as well as poor HRQOL (Ojelabi, Graham, & Ling, 2017). We found similarly high rates in the present study using relatively brief and easily administered screening measures. Most strikingly, approximately one-half of children with SCD (receiving either CTT or HU) in our study exhibited behaviors indicative of executive dysfunction, which is consistent with rates seen in other chronic-illness populations (Gioia et al., 2015). Of clinical significance, group mean scores were approximately 1 SD above the normative mean, with greater executive dysfunction than siblings. In addition, approximately one-third of children with SCD receiving CTT had social-emotional problems and ADHD symptoms (both of which were greater than those of siblings), replicating findings from earlier studies in which lengthier clinical interviews were administered (Barbarin et al., 1994;

Benton et al., 2011). Overall, in contrast to children with SCD, siblings were generally rated as having few psychological problems, suggesting that the problems experienced by children with SCD were largely disease related rather than a function of the social and familial challenges they share with their siblings.

Although HRQOL was only obtained for children with SCD, our results are nonetheless compelling. No child in our study was rated as having high HRQOL. In fact, almost one-half were rated as having poor HRQOL. Poor HRQOL has been demonstrated frequently for children with SCD (Ojelabi et al., 2017), but the very low scores (< 55) observed in our study are not commonplace. Although speculative, it is possible that the proximity of blood transfusion to completion of screening measures could have had a negative influence on caregivers' view of HRQOL. Future research examining the relationship between proximity of blood transfusion to HRQOL ratings will provide further clarity.

With regard to additional factors that could influence psychological function, we believed it was important to consider neurological status, because the children with SCD in our study receiving CTT had a higher incidence of stroke and/or SCI than those receiving HU. Interestingly, neurologic status was not a driving factor in psychological differences between our groups of children with SCD. However, the number of days hospitalized was a strong predictor of psychological problems. Children with SCD experience recurrent and severe pain which can take a significant toll, and frequent hospitalizations for pain are often indicators of challenges with SCD-disease management. In addition, if a patient with a central venous catheter has a fever, they are more likely to be hospitalized to treat possible blood infections with intravenous antibiotics while blood culture findings are pending. Depressive symptoms in children with SCD (which can worsen during hospitalization) are also related to poorer medication adherence

(Badawy et al., 2017) and contribute to increased hospital admissions (Dampier et al., 2016; Myrvik et al., 2013). As such, screening for psychological problems may be particularly crucial for children who have more frequent and/or prolonged hospitalizations.

It is also notable that, compared to findings from our screening measures, considerably lower rates of psychological problems were noted in the medical records of the children in our study. As such, our findings provided support for the use of screening measures as a basis to refer patients for psychological and/or neuropsychological evaluation and subsequent intervention rather than relying solely on the judgment of medical professionals. This approach would reduce the burden on medical professionals who may be less confident in their ability to detect and diagnose psychological problems, as well as ensuring that their patients receive the most comprehensive care possible.

In terms of choosing specific screening measures, we identified high correlations among all of the measures we administered. Thus, at first glance it might appear reasonable to administer only the BESS, as this measure provides a rapid screen of overall psychological functioning. However, if used in isolation it is possible that cognitive problems (e.g., executive dysfunction, ADHD symptoms) may be overlooked. Although it is important to consider limitations on time and resources in a busy medical clinic, inclusion of at least one social-emotional and one cognitive screening measure may be more effective in assessing potential risk for psychological problems. Medical providers could then use the clinical cut-offs associated with the chosen measures to determine who is in need of referral for comprehensive psychological or neuropsychological evaluation. For example, a score of > 65 on either the BESS or BRIEF-2 would indicate clinical risk and trigger referral.

Turning to limitations of the current study, our restricted sample size limited power to address additional questions such as gender differences. We also examined the percentage of psychological problems in relation to findings from the medical record, which serves as only a proxy of medical professional judgment. Additionally, it is unclear whether our results generalize to children with milder disease severity, who have fewer hospitalizations or are not undergoing treatment with transfusion or HU. There are also other variables that contribute to poorer psychological functioning that were not measured in this study, such as the frequency of emergency room visits and absenteeism from school (Myrvik et al., 2013; Schwartz, Radcliffe, & Barakat, 2009). All of these issues will be important points of consideration in future research.

Nonetheless, our study demonstrated that incorporating brief, easily administered, relatively inexpensive psychological screening measures into the clinical care of children with SCD is warranted. Psychological screening is feasible in the medical clinic, as each measure we administered took approximately 5 minutes to complete. For busy medical professionals attempting to treat children with a range of psychological difficulties, psychological screening will add to the comprehensiveness of care, reduce the burden of clinical judgment, and ensure that children receive proper referrals for psychological support.

Conclusion

Medical treatments for children with SCD have shifted from survival to management of this chronic lifelong disease, which makes it essential that we treat comorbid psychological conditions that occur at high rates in this population. Our findings demonstrate that brief screening measures can help determine which patients with SCD need psychological referral.

Early identification of psychological problems and subsequent intervention will contribute to improved well-being in this vulnerable population.

DISCLOSURES OF CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Figure 1. Classifications of clinical risk on caregiver-reported screening measures using the BESS, Conners-3, BRIEF-2, and PedsQL in children with SCD and siblings. BESS = Behavioral and Emotional Screening System; Conners-3 = Conners 3rd Edition-Short Form; BRIEF-2 = Behavior Rating Inventory of Executive Function Screener; PedsQL = Pediatric Quality of Life Inventory Sickle Cell Disease Module; SCD = Sickle cell disease; CTT = Chronic blood transfusion therapy; HU = Hydroxyurea therapy

Figure 2. Differences in group mean scores on caregiver-reported screening measures using the BESS, Conners-3, BRIEF-2, PedsQL in children with SCD (SCD-CTT and SCD-HU) and siblings. Higher scores on the BESS, Conners-3, and BRIEF-2 indicate more clinical concerns; lower scores on the PedsQL indicate poorer HRQOL. BESS = Behavioral and Emotional Screening System; Conners-3 = Conners 3rd Edition-Short Form; BRIEF-2 = Behavior Rating Inventory of Executive Function Screener; PedsQL = Pediatric Quality of Life Inventory Sickle Cell Disease Module; SCD = Sickle cell disease; CTT = Chronic blood transfusion therapy; HU = Hydroxyurea therapy. Error bars represent 95% confidence intervals. † = < .1, * = p < .05, ** = p < .01, *** = p < .001. Dashed line (---) represents cutoff for clinical risk.

References

Acquazzino, M. A., Miller, M., Myrvik, M., Newby, R., & Scott, J. P. (2017). Attention Deficit Hyperactivity Disorder in Children With Sickle Cell Disease Referred for an Evaluation. *Journal of Pediatric Hematology/Oncology*, *39*(5), 350–354.

Anie, K. A. (2005). Psychological complications in sickle cell disease. *British Journal of Haematology*, *129*(6), 723–729.

Ashley-Koch, A., Murphy, C. C., Khoury, M. J., & Boyle, C. A. (2001). Contribution of sickle cell disease to the occurrence of developmental disabilities: a population-based study. *Genetics in Medicine*, *3*(3), 181.

Badawy, S. M., Thompson, A. A., Penedo, F. J., Lai, J., Rychlik, K., & Liem, R. I. (2017). Barriers to hydroxyurea adherence and health- related quality of life in adolescents and young adults with sickle cell disease. *European Journal of Haematology*, *98*(6), 608–614.

Barbarin, O. A., Whitten, C. F., & Bonds, S. M. (1994). Estimating rates of psychosocial problems in urban and poor children with sickle cell anemia. *Health & Social Work*, *19*(2), 112–119.

Bennett, S., Shafran, R., Coughtrey, A., Walker, S., & Heyman, I. (2015). Psychological interventions for mental health disorders in children with chronic physical illness: a systematic review. *Archives of Disease in Childhood*, *100*(4), 308–316.

Benton, T. D., Boyd, R., Ifeagwu, J., Feldtmose, E., & Smith-Whitley, K. (2011). Psychiatric diagnosis in adolescents with sickle cell disease: a preliminary report. *Current Psychiatry Reports*, *13*(2), 111–115.

Benton, T. D., Ifeagwu, J. A., & Smith-Whitley, K. (2007). Anxiety and depression in children and adolescents with sickle cell disease. *Current Psychiatry Reports*, *9*(2), 114–121.

516 Berg, C., Edwards, D. F., & King, A. (2012). Executive function performance on the children's
517 kitchen task assessment with children with sickle cell disease and matched controls. *Child*
518 *Neuropsychology*, *18*(5), 432–448.
519 Berkelhammer, L. D., Williamson, A. L., Sanford, S. D., Dirksen, C. L., Sharp, W. G.,
520 Margulies, A. S., & Prengler, R. A. (2007). Neurocognitive sequelae of pediatric sickle cell
521 disease: a review of the literature. *Child Neuropsychology*, *13*(2), 120–131.
522 Beverung, L. M., Varni, J. W., & Panepinto, J. A. (2015). Clinically meaningful interpretation of
523 pediatric health-related quality of life in sickle cell disease. *Journal of Pediatric*
524 *Hematology/Oncology*, *37*(2), 128.
525 Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Lawrence Erlbaum.
526 Conners, C. K., Pitkanen, J., & Rzepa, S. R. (2011). *Conners comprehensive behavior rating*
527 *scale*. Springer.
528 Croghan, T. W., & Brown, J. D. (2010). *Integrating mental health treatment into the patient*
529 *centered medical home*. Agency for Healthcare Research and Quality Rockville, MD.
530 Dampier, C., Jaeger, B., Gross, H. E., Barry, V., Edwards, L., Lui, Y., … Reeve, B. B. (2016).
531 Responsiveness of PROMIS® pediatric measures to hospitalizations for sickle pain and
532 subsequent recovery. *Pediatric Blood & Cancer*, *63*(6), 1038–1045.
533 Dampier, C., Lieff, S., LeBeau, P., Rhee, S., McMurray, M., Rogers, Z., … Wang, W. (2010).
534 Health- related quality of life in children with sickle cell disease: A report from the
535 Comprehensive Sickle Cell Centers Clinical Trial Consortium. *Pediatric Blood & Cancer*,
536 *55*(3), 485–494.
537 DeBaun, M. R., & Kirkham, F. J. (2016). Central nervous system complications and
538 management in sickle cell disease: a review. *Blood*, blood-2015.

539 Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2015). *BRIEF-2: Behavior Rating*
540 *Inventory of Executive Function*. Psychological Assessment Resources.
541 Hilliard, L. M., Kulkarni, V., Sen, B., Caldwell, C., Bemrich- Stolz, C., Howard, T. H., …
542 Lebensburger, J. D. (2018). Red blood cell transfusion therapy for sickle cell patients with
543 frequent painful events. *Pediatric Blood & Cancer*, *65*(12), e27423.
544 Hood, A. M., King, A. A., Fields, M. E., Ford, A. L., Guilliams, K. P., Hulbert, M. L., … White,
545 D. A. (2019). Higher executive abilities following a blood transfusion in children and young
546 adults with sickle cell disease. *Pediatric Blood & Cancer*, *0*(0), e27899.
547 https://doi.org/10.1002/pbc.27899
548 Ivascu, N. S., Sarnaik, S., McCrae, J., Whitten-Shurney, W., Thomas, R., & Bond, S. (2001).
549 Characterization of pica prevalence among patients with sickle cell disease. *Archives of*
550 *Pediatrics & Adolescent Medicine*, *155*(11), 1243–1247.
551 Jerrell, J. M., Tripathi, A., & McIntyre, R. S. (2011). Prevalence and treatment of depression in
552 children and adolescents with sickle cell disease: a retrospective cohort study. *The Primary*
553 *Care Companion to CNS Disorders*, *13*(2).
554 Jonassaint, C. R., Jones, V. L., Leong, S., & Frierson, G. M. (2016). A systematic review of the
555 association between depression and health care utilization in children and adults with sickle
556 cell disease. *British Journal of Haematology*, *174*(1), 136–147.
557 Lance, E. I., Comi, A. M., Johnston, M. V, Casella, J. F., & Shapiro, B. K. (2015). Risk factors
558 for attention and behavioral issues in pediatric sickle cell disease. *Clinical Pediatrics*,
559 *54*(11), 1087–1093.
560 Liu, S.-I., Lu, R.-B., & Lee, M.-B. (2008). Non-psychiatric physicians' knowledge, attitudes and
561 behavior toward depression. *Journal of the Formosan Medical Association*, *107*(12), 921–

931.

Ludwig, N. N., Sil, S., Khowaja, M. K., Cohen, L. L., & Dampier, C. (2018). Executive Functioning Mediates the Relationship Between Pain Coping and Quality of Life in Youth With Sickle Cell Disease. *Journal of Pediatric Psychology*, *43*(10), 1160–1169.

Lukoo, R. N., Ngiyulu, R. M., Mananga, G. L., Gini-Ehungu, J.-L., Ekulu, P. M., Tshibassu, P. M., & Aloni, M. N. (2015). Depression in children suffering from sickle cell anemia. *Journal of Pediatric Hematology/Oncology*, *37*(1), 20–24.

Myrvik, M. P., Burks, L. M., Hoffman, R. G., Dasgupta, M., & Panepinto, J. A. (2013). Mental health disorders influence admission rates for pain in children with sickle cell disease. *Pediatric Blood & Cancer*, *60*(7), 1211–1214.

Ojelabi, A., Graham, Y., & Ling, J. (2017). Health-related Quality of Life Predictors in Children and Adolescents with Sickle Cell Disease: A Systematic Review. *International Journal of TROPICAL DISEASE & Health*, *22*(2), 1–14. https://doi.org/10.9734/IJTDH/2017/31954

Olson, A. L., Kelleher, K. J., Kemper, K. J., Zuckerman, B. S., Hammond, C. S., & Dietrich, A. J. (2001). Primary care pediatricians' roles and perceived responsibilities in the identification and management of depression in children and adolescents. *Ambulatory Pediatrics*, *1*(2), 91–98.

Panepinto, J. A., O'Mahar, K. M., DeBaun, M. R., Rennie, K. M., & Scott, J. P. (2004). Validity of the child health questionnaire for use in children with sickle cell disease. *Journal of Pediatric Hematology/Oncology*, *26*(9), 574–578.

Panepinto, J. A., Torres, S., Bendo, C. B., McCavit, T. L., Dinu, B., Sherman- Bien, S., … Varni, J. W. (2013). PedsQL™ sickle cell disease module: feasibility, reliability, and validity. *Pediatric Blood & Cancer*, *60*(8), 1338–1344.

585 Prussien, K. V, Jordan, L. C., DeBaun, M. R., & Compas, B. E. (2019). Cognitive Function in
586 Sickle Cell Disease Across Domains, Cerebral Infarct Status, and the Lifespan: A Meta-
587 Analysis. *Journal of Pediatric Psychology*.
588 R Core Team. (2017). R: A language and environment for statistical computing. Vienna, Austria:
589 R Foundation for Statistical Computing.
590 Redding-Lallinger, R., & Knoll, C. (2006). Sickle cell disease—pathophysiology and treatment.
591 *Current Problems in Pediatric and Adolescent Health Care*, *36*(10), 346–376.
592 Reed-Knight, B., Thompson, B., Bigham, L., Sil, S., Griffin, A., & Johnson, A. (2015).
593 Identification of pica behaviors in youth with sickle cell disease: A quality improvement
594 (QI) project. *Clinical Practice in Pediatric Psychology*, *3*(2), 167.
595 Rees, D. C., Williams, T. N., & Gladwin, M. T. (2010). Sickle-cell disease. *The Lancet*,
596 *376*(9757), 2018–2031.
597 Reynolds, C. R., & Kamphaus, R. W. (2015). BASC-3 Behavioral and Emotional Screening
598 System manual. Circle Pines, MN: Pearson.
599 Schatz, J., Finke, R. L., Kellett, J. M., & Kramer, J. H. (2002). Cognitive functioning in children
600 with sickle cell disease: a meta-analysis. *Journal of Pediatric Psychology*, *27*(8), 739–748.
601 Schlenz, A. M., Schatz, J., McClellan, C. B., & Roberts, C. W. (2012). Responsiveness of the
602 PedsQL to pain-related changes in health-related quality of life in pediatric sickle cell
603 disease. *Journal of Pediatric Psychology*, *37*(7), 798–807.
604 Schwartz, L. A., Radcliffe, J., & Barakat, L. P. (2009). Associates of school absenteeism in
605 adolescents with sickle cell disease. *Pediatric Blood & Cancer*, *52*(1), 92–96.
606 Unützer, J., & Park, M. (2012). Strategies to improve the management of depression in primary
607 care. *Primary Care: Clinics in Office Practice*, *39*(2), 415–431.

Ware, R. E., de Montalembert, M., Tshilolo, L., & Abboud, M. R. (2017). Sickle cell disease. *The Lancet*.

Williams, J., Klinepeter, K., Palmes, G., Pulley, A., & Foy, J. M. (2004). Diagnosis and treatment of behavioral health disorders in pediatric practice. *Pediatrics*, *114*(3), 601–606.

Figure

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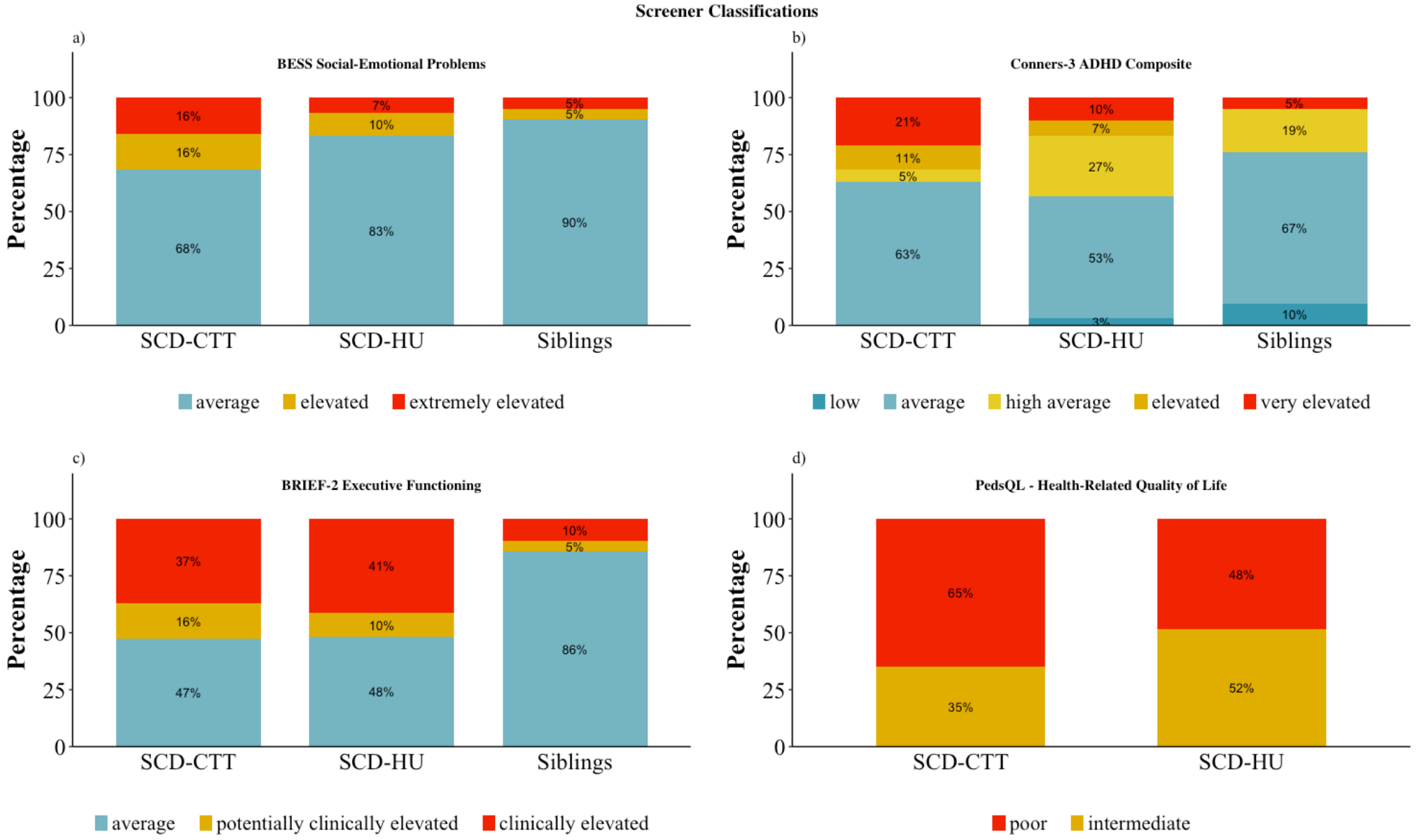

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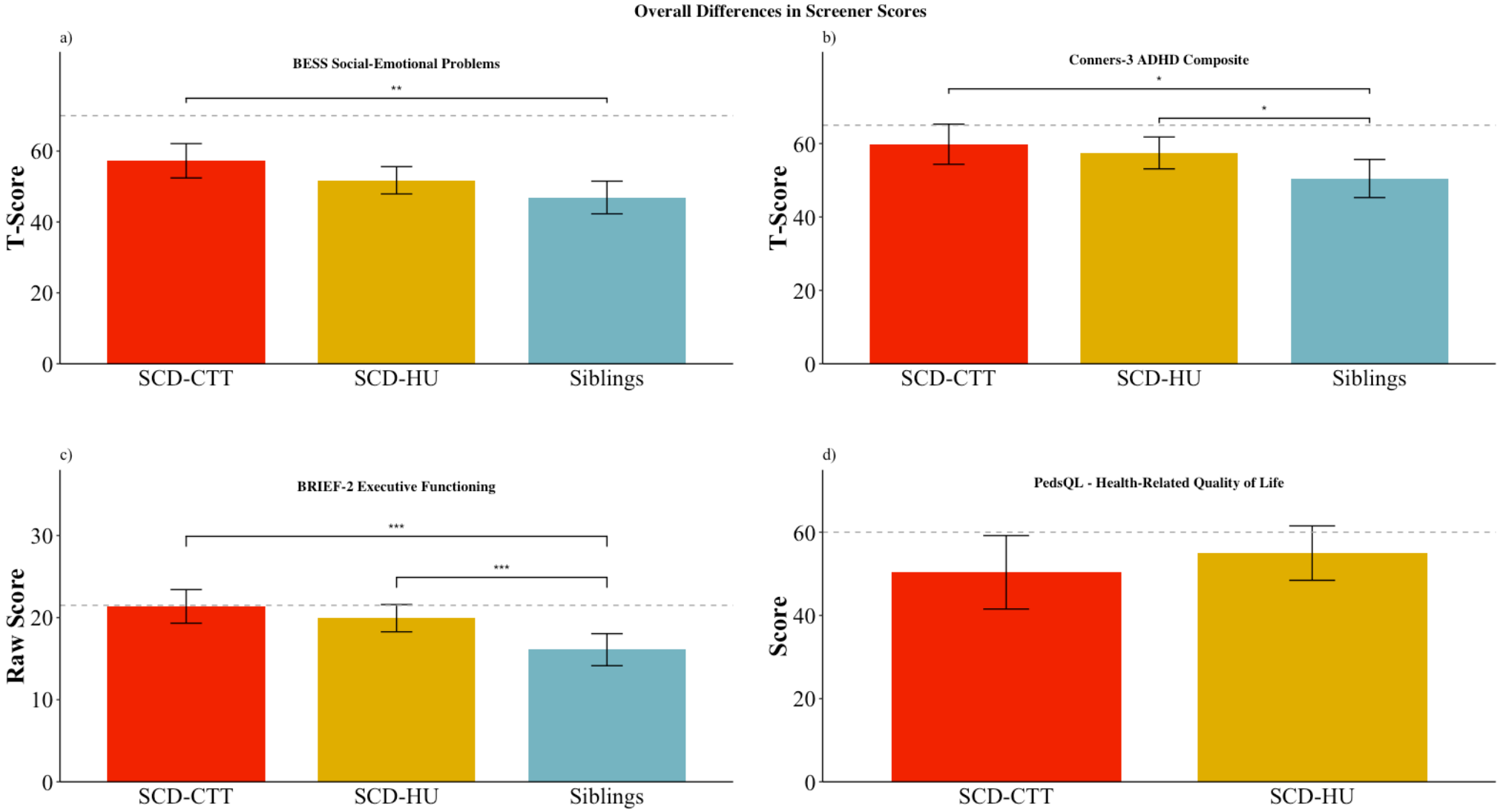

Table 1. Characteristics of children with SCD and siblings

Characteristics	SCD-CTT (n = 20)	SCD-HU (n = 31)	Siblings (n = 21)	Statistic	Effect Size 95 % CI	p value
Demographics						
Mean (SD)						
Age (years)	12.1 (3.7)	11.9 (3.7)	13.4 (4.7)	$F = .16$	$\eta_p^2 = .005$ [.00, .02]	.85
Range	4 - 18	5 - 18	5 - 18			
N (%)						
Race						
Black	20 (100%)	29 (94%)	21 (100%)	$\chi^2 = 2.72$	$\phi_C = .19$ [.00, .41]	.27
Bi-racial (Black/White)	0 (0%)	2 (6%)	0 (0%)			
Gender						
Male	9 (45%)	15 (48%)	9 (43%)	$\chi^2 = .16$	$\phi_C = .05$ [.00, .28]	.92
Female	11 (55%)	16 (52%)	12 (57%)			
Disease Related Factors						
Mean (SD)						
# of days hospitalized in last year	6.5 (11.5)	2.8 (4.0)	—	$t = 1.35$	$d = .40$ [-.20, 1.00]	.01*
Range	0 - 39	0 - 11	—			
Treatment length (months)	46.5 (33.7)	46.9 (9.3)	—	$t = .04$	$d = .01$ [-.59, .56]	.96
Range	6 - 125	6 - 114	—			
N (%)						
Sickle cell genotype						
HbSS	19 (95%)	28 (91%)	—	$\chi^2 = 1.72$	$\phi = .19$ [.02, .50]	.19
HbS-beta thal +	0 (0%)	2 (6%)	—			
HbS-beta thal zero	0 (0%)	1 (3%)	—			
HbSD	1 (5%)	0 (0%)	—			
Stroke Status						
Stroke/SCI	16 (80%)	10 (32%)	—	$\chi^2 = 9.26$	$\phi = .47$ [.22, .69]	.002*
Neither	4 (20%)	21 (68%)	—			

Note: SCD = Sickle cell disease; CTT = Chronic blood transfusion therapy; HU = Hydroxyurea therapy; 95% CI = 95% Confidence Interval; η_p^2 = partial eta squared; ϕ_C = Cramer's V; d = Cohen's D; ϕ = Phi; HbSS = sickle cell anemia; HbS-beta thal + = Hemoglobin beta plus thalassemia; HbS-beta thal zero = Hemoglobin beta zero thalassemia; HbSD = Hemoglobin S-D-Los Angeles; SCI = silent cerebral infarct. * Indicates a significant difference between children in the SCD-CTT and SCD-HU groups.

Table 2. Correlations between screening measures of social-emotional functioning, ADHD symptoms, executive function, quality of life, and treatment factors in children with SCD

Variables	1.	2.	3.	4.	5.
1. BESS – social-emotional functioning					
2. Conners-3 ADHD symptoms	.81**				
3. BRIEF-2 executive functioning	.81**	.67**			
4. PedsQL – health-related quality of life	-.48**	-.47**	-.43**		
5. Number of days hospitalized in past year	.27†	.38*	.33*	-.30*	
6. Length of time receiving CTT or HU	.05	-.08	.04	-.09	.10

Note. BESS = Behavioral and Emotional Screening System; Conners-3 ADHD = Conners 3rd Edition-Short Form - Attention Deficit Hyperactivity Disorder symptoms; BRIEF-2 = Behavior Rating Inventory of Executive Function; PedsQL = Pediatric Quality of Life Inventory Sickle Cell Disease Module; CTT = Chronic blood transfusion therapy; HU = Hydroxyurea therapy. † = < .1, * = p < .05, ** = p < .01.