Relationships between Somatic Growth and Cognitive Functioning in Young Children with Sickle Cell Disease

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Objective Children with sickle cell disease (SCD) exhibit poor somatic growth due to nutritional and metabolic effects, but potential relationships between growth and other areas of development are unclear. We examined whether growth is related to cognition and whether growth might be one marker of neurocognitive risk. Methods Sixty-four children with SCD and eighty-one demographically similar controls, ages 4 to 8 years, completed cognitive and anthropometric measures. Results Height-for-age partially accounted for cognitive decrements related to SCD on all cognitive measures. Higher body-mass-index was a significant predictor of higher visual-motor and academic achievement scores in children with SCD, but not in controls. Conclusions In some children with SCD, especially those with HbSS and Hb Sβ0, low height-for-age may help to explain neurocognitive risk. Higher body-mass-index may be related to better cognitive outcomes in children with SCD. Nutrition deficits in SCD could explain the association between somatic growth and cognitive deficits.

Key words sickle cell; children; cognitive; somatic growth; height; body mass index.

Sickle cell disease (SCD) can have developmental consequences, including somatic growth deficits and decrements in cognitive functioning. In this study, we examined whether the growth and cognitive consequences of SCD may be interrelated, as both may be influenced by the metabolic and endocrine effects of the disease. SCD is a genetic disorder characterized by hemoglobin defects that affect red blood cells; these cells are less effective in distributing oxygen and form vaso-occlusions that cause pain and organ damage (Frank, Allison, & Cant et al., 1999). Homozygous SS disease is the most common form of SCD, referred to as sickle cell anemia (SCA). Other common genotypes include: SC disease (SC), S-beta-zero thalassemia (Sβ0), and S-beta-plus thalassemia (Sβ+). SS and Sβ0 subtypes are associated with higher rates of neurologic problems, including stroke and silent infarcts (Ohene-Frempong et al., 1998; Pegelow et al., 2002; Wang et al., 2001), and poorer cognitive functioning in early childhood (Schatz & Roberts, 2007).

Numerous studies have documented lower height, weight, and body mass index (BMI) in children with SCA (Barden et al., 2000; Barden, Kawchak, Ohene-Frempong, Stallings, & Zemel, 2002; Henderson, Sauvedra, & Dover, 1994; Pellegrini Braga, Kerbady, & Fishberg, 1995). One study further documented growth deficits across SCA, SC, Sβ+, and Sβ0 subtypes (Platt, Rosenstock, & Espeland, 1984). Children with SCA and Sβ0 showed larger deficits, suggesting that growth is more affected in higher risk subtypes. Growth delays in SCA can begin early and become more severe during development (Stevens et al., 1986; Zemel et al., 2007). Several studies have documented deficits persisting into adulthood (Barden et al., 2002; Henderson et al., 1994), while others have documented catch up growth (Platt et al., 1984; Thomas et al., 2000). There is certainly variability, with some children remaining on a typical growth trajectory (Thomas et al., 2000). SCD treatments may also influence growth. In the Stroke Prevention Trial for Sickle Cell Anemia Study (STOP trial; Wang et al., 2005), children receiving transfusions showed improvements in growth. Similarly, children in the phase II hydroxyurea trial (HUG-KIDS) showed growth improvements growth after 4 to 6 years of hydroxyurea (Wang et al., 2002).
Cognitive effects of SCD vary among children with the disease. In some, cognitive decrements are results of overt stroke or silent infarcts (Armstrong et al., 1996; see Schatz & Puffer, 2006 for review). However, some children with SCD and no history of stroke also exhibit cognitive decrements, most often on measures of general IQ, attention/executive functioning, verbal ability, language skills, and memory (for review, see Schatz, Finke, Kellett, & Kramer, 2002). Children with SCA can exhibit deficits by age two years (Thompson, Gustafson, Bonner, & Ware, 2002) and deficits can progress with age (Wang et al., 2001). Some data suggest that the same SCD treatments that can improve growth also may have cognitive benefits. In the STOP trial (Lee et al., 2006), transfusion therapy was shown to prevent stroke, and hydroxyurea has been associated with higher cognitive scores (Puffer, Schatz, & Roberts, 2007).

Causes of cognitive decrements in SCD are not fully understood, though abnormal patterns of brain maturation may play a role. Subtle structural brain differences have been detected, including abnormalities in tissue density and volumetric growth (Steen et al., 2004). PET and perfusion data also have shown localized tissue dysfunction (Hogan et al., 2006; Oguz et al., 2003). In some studies, cognitive scores have correlated with hematocrit (Hogan et al., 2006; Oguz et al., 2003). In some studies, cognitive scores have correlated with hematocrit (Bernaudin et al., 2000; Brown et al., 1993; Steen et al., 2003). Data further suggest that cognitive decrements in young children vary by SCD subtype, with some decrements observed only in SS and Sβ0 disease (Schatz, Puffer, Sanchez, Stancil, & Roberts, 2009). Together, evidence suggests links between SCD disease processes, brain functioning, and cognitive outcomes, but the specific factors responsible for these associations are not well understood.

The disease processes of SCD that affect brain development and cognition could overlap with disease processes affecting somatic growth. Knight, Singhal, Thomas, & Serjeant (1995) found preliminary evidence that growth and cognition are related in SCD, showing that height-for-age during childhood was a stronger predictor of IQ during adolescence than many other risk factors, including hematocrit. The potential growth-cognition relationships in SCD have not been further examined despite this finding and evidence that growth and cognition are related in other pediatric conditions that have commonalities with SCD, such as growth hormone deficiency (Creyghton, van Dam, & Koppeschaar, 2004) and undernutrition (Liu, Raine, Venables, Dalais, & Mednick, 2003). In these conditions, it is hypothesized that somatic growth deficits and problems in brain development are caused by related mechanisms. The same may be true in SCD.

Multiple mechanisms could underlie growth-cognition relationships in SCD. Two possible pathways involve undernutrition and endocrine abnormalities—consequences of SCD that have been associated with co-occurring problems in growth, brain development, and cognition in other populations. Specifically, children with SCD have elevated metabolic rates that can result in protein-energy deficits (Akohoue et al., 2007; Singhal et al., 2002) and deficiencies in micronutrients, especially zinc (Pellegrini Braga et al., 1995). Malnutrition has been linked to brain growth abnormalities and cognitive deficits, which co-occur with height and weight deficits resulting from inadequate calories and protein (Grantham-McGregor & Baker-Henningham, 2005; Winick & Rosso, 1969). Zinc also plays important roles in brain development (Salgueiro et al., 2002) and physical growth and may protect the brain from oxidative stress-related damage that can affect cerebrovascular health (Chan, Chow, & Chiu, 1999). Zinc supplementation has been shown to improve growth and cognitive outcomes (Zemel, Kawchak, Fung, Ohene-Frempong, K., & Stallings, 2002). Further, abnormal growth hormone (GH) release is found in some children with SCD (Soliman et al., 1997). GH is believed to play an important role in brain development in addition to regulating growth (Scheepens, Modersheim, & Gluckman, 2005), which may contribute to cognitive deficits in children with GH deficiency (Skuse, Lawrence, & Tang, 2005). Therefore, nutrition and endocrine factors could mediate associations between growth and cognition in SCD.

The purpose of this study was to examine potential relationships between growth and cognitive consequences of SCD in young children. We assessed growth and cognitive measures among children with varying SCD status: those with more severe SCD (i.e., SS and Sβ0), referred to as “high risk” in this paper, children with “low risk” subtypes (i.e., SC and Sβ+), and a control group without SCD. This is the first study to our knowledge that examines the interrelationships between growth and cognitive development in younger children with SCD. Additionally, in contrast to Knight et al. (1995), we included children with various SCD subtypes and a control group to compare growth-cognition relationships between these populations. Our goals were to determine whether growth may be a useful clinical indicator of neurocognitive risk for some children and to increase our understanding of the interrelationships between these developmental processes in SCD. Early identification of children at risk for cognitive deficits is important and understanding links between growth and the range of cognitive abilities measured in this study may help to disentangle specific relationships
between disease processes that may impact brain function and specific areas of cognitive deficit (see Schatz & Puffer, 2006).

We included three dimensions of growth: height, weight, and BMI (weight/height²), a body composition measure that takes into account both height and weight. These are measured routinely in clinics, and growth deficits in SCD have been documented using these measures. Additionally, various measures of growth likely reflect different physiological processes. Height has been associated with long-term nutritional and health factors (Cogill, 2001; Gorstein et al., 1994), while weight and BMI have been associated with acute nutritional and health changes (Gorstein et al.). Therefore, we included these measures to observe potentially meaningful differences between height-cognition and weight/BMI-cognition relationships in SCD.

In our first hypothesis, we predicted that growth would be a partial mediator in the relationships between SCD status (i.e., high risk, low risk, or control) and cognitive outcomes. We expected growth to partially explain the variance in cognitive scores across groups. Scores were expected to be highest among controls, lower in the low risk SCD group, and lowest in the high risk group; growth status was expected to account for a significant portion of these differences. Mediation was predicted for global cognitive, language, and processing resources abilities, as studies have documented SCD-related decrements in these areas. Analyses also were conducted for academic achievement and visual-motor scores because these are important to understand in young children who are beginning school and expected to develop early reading, math, and writing skills. However, these were not included in a priori predictions because they have not been associated with SCD as consistently as other abilities (Schatz et al., 2002).

The second hypothesis predicted that relationships between somatic growth and cognitive outcomes would differ based on SCD status. We predicted that the association between growth and cognitive scores would be largest in children with high risk SCD, smaller in low risk SCD, and non-existent in controls. That is, we predicted that SCD status would moderate relationships between growth and cognition. Higher growth status was expected to predict higher cognitive scores in the SCD risk group, and non-existent in controls. That is, we predicted that SCD status would moderate relationships between cognitive scores and growth would be at least as large as the associations between cognitive scores and other variables that may indicate level of risk: hematocrit and SCD subtype. We expected that growth status would provide as much or more information about neurocognitive risk than these variables.

Methods
Participants and Procedures

Participants were 145 children, 4–8 years of age including children with high risk SCD (n = 39), low risk SCD (n = 25), and without SCD (n = 81). In the high-risk group, 37 had SS and 2 had Sβ0. In the low risk group, 15 had SC, and 8 had Sβ+. Children with history of overt stroke or a major developmental disability were excluded. Children with SCD were recruited from clinics as part of a monitoring program in which children receive developmental and cognitive evaluations at ages 1, 3, 5, and 7 years of age (Schatz et al., 2009). Because some children attend visits only every six months and there are occasional missed appointments, we tested children as early as 4 years, 9 months or as late as 8 years, 3 months to ensure that every child had the opportunity to participate. Approximately 80% of children with SCD in the catchment area attend these clinics. For this sample, seventy-four consecutive children were asked to participate and sixty-four completed testing. Among the ten non-participants, eight parents reported interest but had scheduling difficulties; two families declined the screening. All participants gave permission for data to be used for research. Control participants were recruited from schools and after-school programs providing tutoring and recreation. Parents were invited to enroll children through phone calls, letters, and in-person contact at program sites. Potential control participants with chronic health conditions or developmental disabilities were excluded.

Informed consent and assent were obtained from caregivers and children respectively. Children’s height and weight were measured, and each child completed a battery of cognitive tests administered in a single, 60- to 90-minute session. Medical record reviews were conducted for children with SCD. For the SCD group, assessments were completed in the clinic during routine appointments by licensed psychologists or graduate students trained in

unrelated to brain development. Moderator effects were predicted for global cognitive, language, and processing resources abilities. Again, analyses also were conducted with academic achievement and visual-motor scores, though these were not included in a priori hypotheses.
administration of the measures. For controls, assessments were conducted at the school program sites by graduate students or undergraduate research assistants trained and supervised in the administration of the measures by the first two authors. Caregivers received letters with results and a phone call to discuss recommendations, such as further psychoeducational testing, if results suggested possible cognitive difficulties (i.e. any scores below the average range). Children were given books as compensation. All procedures were approved by university and hospital institutional review boards and by the administrations of the schools and programs involved.

**Measures**

Height and weight were measured to the nearest .1 cm, and .1 kg, respectively. In the SCD group, nurses measured growth with electronic or beam scales and stadiometers. For controls, a Seca 880 scale and a Shorr board were used. To assess reliability, 30 children were measured with clinic and research instruments; measurements were highly correlated for height ($r = .99, r_c = .99$) and weight ($r = .97$ and $r_c = .94$).

Cognitive testing included measures of language abilities, processing resources, visual-motor ability, and academic skills, and standard scores ($M = 100; SD = 15$) were generated. Language abilities were assessed with the Spoken Language Quotient of the Test of Language Development – Primary Version, Third edition, chosen for good psychometric properties, high internal consistency, reliability for African American children, and low cultural and gender bias (Newcomer & Hammill, 1997). Processing resources was measured with subtests of the Woodcock-Johnson Test of Cognitive Abilities, 3rd edition (WJ-III; McGrew & Woodcock, 2001): Decision Speed and Memory for Words. In the WJ-III, these are used to compute a Cognitive Efficiency Index, sometimes referred to as processing resources (Case, 1985). Visual-motor ability was measured with the Beery-Buktenica Developmental Test of Visual Motor Integration (Beery & Beery, 2004) and the Hand Movements subtest of the Kaufman Assessment Battery for Children (Kaufman & Kaufman, 1983). Because these have been shown to load onto a general domain of visual processing / visual-motor ability in factor analytic work (McGrew & Flanagan, 1998), they were combined to generate a composite score for this domain. Academic skills in reading and math were measured with WJ-III Tests of Achievement subtests: Letter-Word Identification and Applied Problems. A global cognitive ability index was estimated by calculating the mean of composite scores generated for all domains; in previous work, this has yielded scores correlated with WISC-III Full Scale IQ at $r = .85$ (Schatz, 2004a).

**Statistical Analysis Plan**

Descriptive statistics were generated for demographic variables, and we used t-tests or chi-square analyses to look for group differences. Raw height and weight data were used to calculate BMI (weight/height$^2$). Age-adjusted z-scores for height, weight, and BMI were then calculated using a program from the National Center for Chronic Disease Prevention and Health Promotion (Centers for Disease Control and Prevention, 2005), yielding height-for-age, weight-for-age, and BMI-for-age values. Calculations were based on growth charts from the National Health and Nutrition Examination Survey (Centers for Disease Control and Prevention, 2000). Data were examined for outliers by examining standardized residuals and data were evaluated to ensure that all regression assumptions were met.

For Hypothesis 1, we calculated correlations between variables included in the mediation models. We then used regression to test for mediation with the causal steps method (Baron & Kenny, 1986). Partial mediation was supported if the direct effect of SCD status on the cognitive score decreased after adding growth. As this does not provide a direct significance test and is under-powered with small samples (McCarteny, Burchinal, & Bub, 2006), we used the PRODCLIN procedure (distribution of the PROduct Confidence Limits for Indirect effects; MacKinnon, Fritz, Williams, and Lockwood, 2007) that tests the product of the coefficients, yielding confidence limits estimating the indirect effect; limits not including 0 indicate significant mediation.

For Hypothesis 2, we used hierarchical regression to test whether SCD status moderated relationships between growth and cognitive outcomes. The general equation was: $Y = b_0 + b_1(X) + b_2(Z) + b_3(XZ) + e$, where $Y$ is the cognitive variable, $X$ is growth status, $Z$ is SCD status, and $XZ$ is the interaction term (growth x SCD status). Analyses were conducted for each cognitive score. Growth was entered in Step 1, SCD status in Step 2, and the interaction term in Step 3. A significant change in $R^2$ after Step 3 indicated significant moderation. To test Hypothesis 3, we used a correlation matrix to compare relationships between cognitive scores and growth to those between cognitive scores, hematocrit, and SCD status. For all hypotheses, SCD status was entered as a quasi-interval variable with the three levels coded to reflect increasing severity (i.e., control = 0, low risk = 1, and high risk = 2). Power was estimated based on medium-sized relationships between growth, SCD and cognitive scores (Knight et al., 1995).
For power of .80 in regression, 67 participants are required per independent variable (Cohen, 1998); since two variables were entered, the required sample size was 134. For PRODCLIN, 74 were required (Fritz & MacKinnon, 2007). Thus, the sample size was adequate to detect medium-sized effects.

**Results**

**Demographics**

The groups demonstrated adequate overlap on age, gender, and income at an alpha level of .05 (Table I), and all participants were African American. Within the SCD group, 34% of those with high risk subtypes had a history of a major disease complication (e.g., splenic sequestration, acute chest syndrome, aplastic crisis), and the average hematocrit was 23.8%. Of participants with low risk subtypes, 16% had a history of a major complication, and the mean hematocrit was 31.5%. As mentioned earlier, the variability of ages at which the children were tested was due to the necessary flexibility scheduling of participants. A correlation matrix was conducted to examine relationships between age and the outcome variables of interest. Age was not significantly correlated with any of the growth or cognitive outcomes (all r < .16) and was therefore not included as a covariate in the analyses.

**Somatic Growth Indices and Cognitive Outcomes**

Growth and cognitive measures showed variability across levels of SCD status (Table II). Controls had significantly higher mean height-for-age, weight-for-age, and BMI-for-age than those with high risk SCD. Growth differences between children with low risk SCD and controls were non-significant. BMI-for-age was correlated significantly with weight-for-age (r = .80) across groups, but not with height-for-age (r = .25); therefore, BMI-for-age and height-for-age were analyzed separately. On cognitive measures, the control group’s scores were significantly higher than those with high risk SCD on all tests, with differences of approximately 9 to 12 standard score points. Controls also scored significantly higher than the low risk SCD group on visual-motor ability, but not on other domains. The low risk SCD group scored significantly higher than the high risk group on language, academic, and global cognitive abilities.

**Hypothesis 1: Height-for-age as a Mediator in SCD–Cognition Relationships**

SCD status was correlated significantly with height-for-age, BMI-for-age, and cognitive scores; height-for-age was significantly correlated with all cognitive scores (see Supplementary Data, Table VI). Regression analyses for the causal steps method supported partial mediation effects of height-for-age for all cognitive outcomes (Tables III and IV). PRODCLIN analyses confirmed significant partial mediation effects. Confidence limits for mediation effects were estimated to be between: β = −1.27 and −0.13 for global cognitive ability, β = −1.52 and −0.10 for language ability, β = −11.79 and −0.73 for processing resources, β = −1.22 and −0.05 for academic achievement, and β = −1.32 and −0.11 for visual-motor ability.

BMI-for-age was correlated significantly only with academic achievement scores; therefore, mediation analyses were not conducted with scores in other domains. SCD status was a significant, negative predictor of academic achievement scores and BMI-for-age. However,

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### Table I. Demographic Data by Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>High-risk SCD (n = 39)</th>
<th>Low-risk SCD (n = 25)</th>
<th>Control (n = 81)</th>
<th>Statistical comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>M = 74.89</td>
<td>M = 79.39</td>
<td>M = 80.63</td>
<td>F (2, 144) = 2.61</td>
</tr>
<tr>
<td></td>
<td>SD = 12.83</td>
<td>SD = 13.36</td>
<td>SD = 12.87</td>
<td>p = .077</td>
</tr>
<tr>
<td></td>
<td>F = 55.6–97.8</td>
<td>F = 61.7–100.7</td>
<td>F = 55.7–103.0</td>
<td></td>
</tr>
<tr>
<td>Gender (Male: Female)</td>
<td>15: 24</td>
<td>16: 9</td>
<td>38: 43</td>
<td>χ² (2, N = 145) = 4.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p = .134</td>
</tr>
<tr>
<td>Income (&lt;$10K)</td>
<td>12 (31%)</td>
<td>5 (20%)</td>
<td>16 (20%)</td>
<td>χ² (4, N = 145) = 10.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p = .265</td>
</tr>
<tr>
<td>&lt;$10–20K</td>
<td>12 (31%)</td>
<td>10 (40%)</td>
<td>16 (20%)</td>
<td></td>
</tr>
<tr>
<td>$20–30K</td>
<td>4 (10%)</td>
<td>4 (16%)</td>
<td>17 (21%)</td>
<td></td>
</tr>
<tr>
<td>$30–40K</td>
<td>5 (13%)</td>
<td>1 (4%)</td>
<td>9 (11%)</td>
<td></td>
</tr>
<tr>
<td>&gt;$40K</td>
<td>6 (15%)</td>
<td>5 (20%)</td>
<td>23 (28%)</td>
<td></td>
</tr>
<tr>
<td>Preterm birth (n)</td>
<td>9 (23%)</td>
<td>3 (12%)</td>
<td>9 (11%)</td>
<td>χ² (2, N = 145) = 3.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p = .203</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>M = 23.79</td>
<td>M = 31.55</td>
<td>Not applicable</td>
<td>F (1, 60) = 70.35</td>
</tr>
<tr>
<td></td>
<td>SD = 3.82</td>
<td>SD = 3.00</td>
<td></td>
<td>p = .000</td>
</tr>
<tr>
<td></td>
<td>R = 17.8–35.3</td>
<td>R = 25.0–37.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: SCD = Sickle Cell Disease. SD = Standard Deviation. R = Range.
BMI-for-age did not predict academic achievement scores after controlling for SCD status (β = −0.012, t (2,144) = −0.147, p = 0.883. Therefore, results did not support the hypothesis that BMI-for-age mediates relationships between SCD status and cognitive outcomes.

**Hypothesis 2: SCD Status as a Moderator in Growth-Cognition Relationships**

Results did not support the hypothesis that SCD status moderated relationships between height-for-age and cognitive outcomes. Results also did not support the hypothesis that SCD status moderated relationships between BMI-for-age and global cognitive ability, language ability, or processing resources scores. However, analyses showed a significant moderator effect of SCD status in the relationship between BMI-for-age and visual-motor scores, and a borderline significant moderator effect of SCD status in the relationship between BMI-for-age and academic achievement scores; these relationships were not predicted in a priori hypotheses.

For visual-motor ability, the addition of the interaction term led to an R² change of .027 (p = .035), suggesting that the interaction between BMI-for-age and SCD status explained an additional 2.7% of the variance in scores. A scatter plot (see supplementary material online) showed a positive relationship between BMI-for-age and visual-motor scores in both SCD groups, but a negative relationship between BMI-for-age and visual-motor scores in controls. Increased BMI-for-age was associated with lower scores among controls and with higher scores in the SCD group. For academic achievement, the addition of the interaction term explained an additional 2.3% of the variance and data showed the same pattern; relationships between BMI-for-age and academic achievement were positive for both SCD groups, but negative for controls.

**Hypothesis 3: Correlations Between SCD Risk Variables and Cognitive Scores**

A correlation matrix (Table V) showed that among disease-related factors, hematocrit and SCD subtype were
Table III. Summary of Multiple Regression Analyses for Height-for-age as a Mediator Between SCD Status and Cognitive Outcomes

<table>
<thead>
<tr>
<th>Outcome/Model</th>
<th>Causal Step</th>
<th>Predictor → Outcome</th>
<th>B</th>
<th>SE B</th>
<th>CI for B</th>
<th>β</th>
<th>t</th>
<th>p</th>
<th>Adjusted R²</th>
<th>Cohen's f²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Cognitive Index (GCI)</td>
<td>SCD 1</td>
<td>SCD → GCI</td>
<td>−4.81</td>
<td>0.88</td>
<td>−6.50 to −3.07</td>
<td>−42</td>
<td>−5.48</td>
<td>.00</td>
<td>.17</td>
<td>.20</td>
</tr>
<tr>
<td>SCD 2</td>
<td>SCD → Height</td>
<td>−2.83</td>
<td>0.11</td>
<td>−0.49 to −0.08</td>
<td>−22</td>
<td>−2.69</td>
<td>.01</td>
<td>.04</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>SCD + Height 3</td>
<td>Height → GCI</td>
<td>2.14</td>
<td>0.68</td>
<td>0.80 to 3.48</td>
<td>24</td>
<td>3.17</td>
<td>.00</td>
<td>.22</td>
<td>.28</td>
<td></td>
</tr>
<tr>
<td>SCD + Height 4</td>
<td>SCD → GCI</td>
<td>−4.20</td>
<td>0.87</td>
<td>−5.93 to −2.47</td>
<td>−36</td>
<td>−4.81</td>
<td>.00</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Language Ability

<table>
<thead>
<tr>
<th>Outcome/Model</th>
<th>Causal Step</th>
<th>Predictor → Outcome</th>
<th>B</th>
<th>SE B</th>
<th>CI for B</th>
<th>β</th>
<th>t</th>
<th>p</th>
<th>Adjusted R²</th>
<th>Cohen's f²</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD 1</td>
<td>SCD → Language</td>
<td>−4.11</td>
<td>1.21</td>
<td>−6.50 to −1.72</td>
<td>−27</td>
<td>−3.40</td>
<td>.00</td>
<td>.08</td>
<td>.08</td>
<td></td>
</tr>
<tr>
<td>SCD + Height 3</td>
<td>Height → Language</td>
<td>2.40</td>
<td>0.94</td>
<td>0.54 to 4.26</td>
<td>21</td>
<td>2.55</td>
<td>.01</td>
<td>.10</td>
<td>.12</td>
<td></td>
</tr>
<tr>
<td>SCD + Height 4</td>
<td>SCD → Language</td>
<td>−3.43</td>
<td>1.22</td>
<td>−5.84 to −1.02</td>
<td>−23</td>
<td>−2.82</td>
<td>.01</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Processing Resources

<table>
<thead>
<tr>
<th>Outcome/Model</th>
<th>Causal Step</th>
<th>Predictor → Outcome</th>
<th>B</th>
<th>SE B</th>
<th>CI for B</th>
<th>β</th>
<th>t</th>
<th>p</th>
<th>Adjusted R²</th>
<th>Cohen's f²</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD 1</td>
<td>SCD → Proc Resources</td>
<td>−4.40</td>
<td>1.27</td>
<td>−6.90 to −1.90</td>
<td>−28</td>
<td>−3.48</td>
<td>.00</td>
<td>.07</td>
<td>.08</td>
<td></td>
</tr>
<tr>
<td>SCD + Height 3</td>
<td>Height → Proc Resources</td>
<td>2.20</td>
<td>0.99</td>
<td>0.24 to 4.16</td>
<td>18</td>
<td>2.22</td>
<td>.03</td>
<td>.10</td>
<td>.11</td>
<td></td>
</tr>
<tr>
<td>SCD + Height 4</td>
<td>SCD → Proc Resources</td>
<td>−3.77</td>
<td>1.28</td>
<td>−6.30 to −1.24</td>
<td>−24</td>
<td>−2.95</td>
<td>.03</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Table IV. Summary of Multiple Regression Analyses for Height-for-age as a Mediator Between SCD Status and Cognitive Outcomes: Additional Analyses

<table>
<thead>
<tr>
<th>Outcome/Model</th>
<th>Causal Step</th>
<th>Predictor → Outcome</th>
<th>B</th>
<th>SE B</th>
<th>CI for B</th>
<th>β</th>
<th>t</th>
<th>p</th>
<th>Adjusted R²</th>
<th>Cohen's f²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic Achievement</td>
<td>SCD 1</td>
<td>SCD → Academic</td>
<td>−5.89</td>
<td>1.05</td>
<td>−7.97 to 3.81</td>
<td>−43</td>
<td>−5.64</td>
<td>.00</td>
<td>.18</td>
<td>.21</td>
</tr>
<tr>
<td>SCD + Height 3</td>
<td>Height → Academic</td>
<td>1.86</td>
<td>0.82</td>
<td>0.24 to 3.48</td>
<td>.17</td>
<td>2.28</td>
<td>.02</td>
<td>.20</td>
<td>.23</td>
<td></td>
</tr>
<tr>
<td>SCD + Height 4</td>
<td>SCD → Academic</td>
<td>−5.36</td>
<td>1.06</td>
<td>−7.35 to −3.37</td>
<td>−39</td>
<td>−5.08</td>
<td>.02</td>
<td>.20</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td>Visual-Motor Ability</td>
<td>SCD 1</td>
<td>SCD → Visual-Motor</td>
<td>−4.83</td>
<td>1.00</td>
<td>−6.80 to −2.83</td>
<td>−38</td>
<td>−4.83</td>
<td>.00</td>
<td>.13</td>
<td>.15</td>
</tr>
<tr>
<td>SCD + Height 3</td>
<td>Height → Visual-Motor</td>
<td>2.14</td>
<td>0.78</td>
<td>0.61 to 3.67</td>
<td>.21</td>
<td>2.76</td>
<td>.01</td>
<td>.17</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>SCD + Height 4</td>
<td>SCD → Visual-Motor</td>
<td>−4.22</td>
<td>1.00</td>
<td>−6.20 to −2.24</td>
<td>−33</td>
<td>−4.22</td>
<td>.00</td>
<td>.17</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Note. SCD = Sickle Cell Disease. SCD Status was coded as: 0 = Control; 1 = Low Risk SCD, 2 = High Risk SCD. NA = Not Applicable.

Discussion

This study was the first to examine relationships between growth and cognitive effects of SCD during early childhood. We included control participants without SCD to examine growth-cognition relationships across both children with common SCD genotypes and children without the disease. Children with SCD showed lower growth and cognitive scores than controls, with the high risk SCD.
Academic Achievement and BMI-for-age are strongly correlated with the other risk factors. This suggests that height-for-age likely provides unique information about neurocognitive risk that cannot be learned from BMI-for-age. Correlational analyses show that height-for-age was not correlated with the lower cognitive scores in children with SCD, particularly those with high risk subtypes. This suggests that low height status is one indicator of neurocognitive risk in young children with SCD. Results further suggest that the relationship between growth and cognitive development is different in children with SCD than in demographically similar children without the disease. The relationship between height and cognitive scores in this study was consistent with findings of Knight et al. (1995) that childhood height was predictive of IQ in adolescents with SCD.

The relationships between height-for-age and cognitive scores in our study were relatively small; a one standard deviation increase in height-for-age z-score was related to increases of approximately 2 standard score points on cognitive tests. This is not trivial given that cognitive decrements in SCD are typically less than 10 standard score points, but indicates that height-for-age cannot be used as a single indicator of neurocognitive risk. Rather, it will be important to identify additional factors to explain more of the variance in cognitive scores. The need to consider height-for-age with additional factors was further supported by correlational analyses, showing that height-for-age, hematocrit, and SCD genotype were correlated with many cognitive outcomes, but that height-for-age was not strongly correlated with the other risk factors. This suggests that height-for-age likely provides unique information about neurocognitive risk that cannot be learned from looking only at other disease characteristics.

A different pattern of relationships was found between BMI-for-age and cognitive scores, suggesting that BMI-cognition relationships may be in opposite directions in children with SCD versus controls for some abilities. For visual-motor ability and academic achievement, higher BMI-for-age predicted higher scores, appearing to be protective in children with SCD. In contrast, higher BMI-for-age seemed to predict poorer performance in children without the disease; this is consistent with studies of child obesity showing an association between high BMI and lower cognitive scores (Datar, Sturm, & Magnabosco, 2004). However, since our control sample did not have a continuous distribution at the lower end of BMI-for-age, we cannot draw strong conclusions about BMI-cognition relationships in children without SCD. These results could suggest that additional weight in children with SCD does not have the negative effects on cognition seen in children without the disease; in fact, it could indicate a protective factor (e.g., better nutritional status and metabolic processing). As these were unexpected results, further research is needed to determine whether higher BMI, or overweight status, affects cognition differently in children with SCD compared to peers without SCD.

It is notable that height-for-age and BMI-for-age differed in their relationships with growth and cognition in children with SCD. This is consistent with evidence discussed earlier showing that height and BMI are determined by distinct underlying mechanisms (Cogill, 2001; Gorstein et al., 1994). Related to SCD, height deficits are likely related to chronic disease processes, such as anemia or increased metabolic rate, which can lead to longstanding deficiencies in macronutrients and micronutrients (e.g., zinc). Additionally, height deficits could be indicative of GH abnormalities that could affect growth and brain development.

### Table V. Correlations between Cognitive Scores and Potential Predictors in SCD Group: Growth, Hematocrit and SCD Subtype

<table>
<thead>
<tr>
<th></th>
<th>Hematocrit</th>
<th>SCD Subtype</th>
<th>Height z-scores</th>
<th>BMI z-scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>1.00</td>
<td>−.737**</td>
<td>205</td>
<td>.390**</td>
</tr>
<tr>
<td>SCD Subtype</td>
<td>−.737**</td>
<td>1.00</td>
<td>−181</td>
<td>−.467**</td>
</tr>
<tr>
<td>Height z-scores</td>
<td>205</td>
<td>−181</td>
<td>1.00</td>
<td>.349**</td>
</tr>
<tr>
<td>BMI z-scores</td>
<td>399**</td>
<td>−.467**</td>
<td>349**</td>
<td>1.00</td>
</tr>
<tr>
<td>Global Cognitive Index&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.256*</td>
<td>−.369**</td>
<td>.354**</td>
<td>.243</td>
</tr>
<tr>
<td>Language Ability&lt;sup&gt;b&lt;/sup&gt;</td>
<td>.285*</td>
<td>−.446**</td>
<td>.261*</td>
<td>.204</td>
</tr>
<tr>
<td>Processing Resources&lt;sup&gt;c&lt;/sup&gt;</td>
<td>.025</td>
<td>−.213</td>
<td>225</td>
<td>.018</td>
</tr>
<tr>
<td>Academic Achievement&lt;sup&gt;d&lt;/sup&gt;</td>
<td>.292*</td>
<td>−.330**</td>
<td>.280*</td>
<td>.270*</td>
</tr>
<tr>
<td>Visual-Motor Ability&lt;sup&gt;e&lt;/sup&gt;</td>
<td>.188</td>
<td>−.213</td>
<td>.314*</td>
<td>.252*</td>
</tr>
</tbody>
</table>

<sup>a</sup>Global Cognitive Index = mean of standard scores for all cognitive tests.
<sup>b</sup>Language Ability = Spoken Language Quotient from the Test of Language Development—Primary Version, 3rd edition.
<sup>c</sup>Processing Resources = mean of standard scores from Woodcock Johnson Tests of Achievement, 3rd edition (WJ-III) Decision Speed and Memory for Words subtests.
<sup>d</sup>Academic Achievement = mean of standard scores on WJ-III Letter-Word Identification and Applied Problems subtests.
<sup>e</sup>Visual-Motor Ability = mean of standard scores on the Beery-Buktenica Test of Visual Motor Integration and the Hand Movements subtest from the Kaufmann Assessment Battery for Children.

*SCD subtype was coded as: 0 = Control; 1 = Low Risk SCD, 2 = High Risk SCD.

*p < .05; **p < .001.
development simultaneously over time (Skuse et al., 2005). Therefore, relationships between height and cognitive ability in this study may be related to chronic underlying disease processes. In contrast, BMI-for-age may fluctuate more often with acute changes in anemia and energy deficits. This is consistent with evidence that metabolic rate increases and dietary intake decreases during pain crises (Fung et al., 2001). Therefore, BMI status at any one point in time likely reflects a child’s current state of health and disease severity, whereas height is a more stable measure of growth and is more related to chronic disease severity over the life course.

Relating growth to neurocognitive risk, results suggest that height-for-age may be a more reliable indicator of risk at any one point in time, whereas BMI-for-age might be more predictive of cognitive outcomes when it is tracked over time to observe fluctuations that could have a cumulative effect. We may have failed to observe the complete relationship between BMI and cognitive ability because we measured BMI at one point in time when participants were not experiencing a crisis or other complication. However, height-for-age and BMI-for-age were significantly correlated in the SCD group ($r = .22, p < .01$), indicating some overlap between children with low height-for-age and BMI-for-age, rather than two distinct subsets.

**Clinical Implications**

Growth status may be one of several variables that can be used to help identify children at higher risk for neurocognitive deficits, as most clinics have limited capacity to provide testing and follow-up intervention services. We are not suggesting that growth monitoring alone is sufficient. However, early, consistent growth monitoring may be one important part of a plan to identify children who need early cognitive and pre-academic assessment and/or intervention.

As higher height-for-age and BMI-for-age were associated with higher cognitive scores, promoting early intervention for growth deficits could have a role to play in preventing cognitive decrements associated with poor growth. Interventions for poor growth could include dietary nutritional interventions that carry very low risk of side effects. Additionally, because hydroxyurea is associated with both improved growth and cognitive functioning, it may be beneficial to consider growth and cognitive deficits in weighing the costs and benefits of this treatment. Our results add to the literature supporting the need to provide children who exhibit growth deficits with a range of health assessments, including cognitive assessment. Looking at factors such as growth, anemia, and other measures of disease severity to determine the need for cognitive assessment is important in this younger age range when children are less likely to exhibit clear signs of cognitive problems in daycare or early school settings. Early detection is a necessary for prevention efforts, which are of increasing interest to the public education system.

**Study Limitations and Directions for Future Research**

This study has several limitations, including the correlational design and lack of data related to mechanisms underlying the observed relationships. Given these limitations, it is unclear whether growth is only a general marker for disease risk or whether it shares a close, proximal cause with cognitive deficits. Likewise, our results do not provide specific guidelines related to optimal ranges for height-for-age and BMI-for-age in children with SCD. An additional limitation is that national growth curves may not be well-matched to African American children who exhibit elevated rates of being overweight and obese (Terrell, 2002). This is likely the reason that our control group mean fell well above the national normative group mean and that the SCD group means were at or above the normative population means, with 32% of controls and 14% of the SCD group classified as overweight. Seven of the nine children with SCD who were overweight had low-risk SCD subtypes, suggesting that some children with less severe disease follow growth trajectories similar to their demographically-similar peers; we did not examine specific outcomes for children with SCD who are overweight.

This study focused purposefully on a narrow age range to look at growth and cognition in early childhood. However, future longitudinal studies will be important to examine growth-cognition relationships during later childhood and adolescence. Studies also should include larger samples to examine possible gender differences in growth-cognition relationships. Future studies also should measure a broader range of abilities. Specifically, additional pre-academic measures should be administered, as WJ-III subtests may be less sensitive to variability in academic performance. Studies also should include additional pre-academic measures such as social competence and adaptation (Boni, Brown, Davis, Hsu, & Hopkins, 2001), also could be assessed in future studies.

To examine the mechanisms underlying the growth-cognition link in SCD, future studies should measure nutrition and endocrine factors. As nutrient status and endocrine functioning are not routinely measured in many clinics, this study provides evidence supporting the rationale for adding these measures to future investigations. Intervention studies targeting these factors would...
provide the strongest test of the proposed relationships. Nutrition interventions hold particular promise, as nutrient supplementation, specifically with protein-energy and zinc, has improved both growth and cognition in some populations (Grantham-McGregor & Baker-Henningham, 2005; Heyman et al., 1985; Leonard et al., 1998; Pellegrini Braga et al., 1995).

In addition to physiological factors, the influence of contextual variables on growth-cognition relationships, such as SES, caregiver education, and school environments, should be examined given previous findings on the associations between SES, cognition, and school performance in SCD (Brown et al., 1993; Schatz, Finke, & Roberts, 2004b). By including the contextual factors that may be influencing the growth-cognition relationships seen in this study, we will better understand the range of interventions that are most likely to help mitigate the effects of SCD on physical and cognitive development.

**Supplementary Data**

Supplementary data can be found at: http://www.jpepsy.oxfordjournals.org/.

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