REGULAR ARTICLE

blood advances

Risk factors in underweight older children with sickle cell anemia: a comparison of low- to high-income countries

Lauren Jane Klein,[1,2] Shehu Umar Abdullahi,[3] Safiya Gambo,[4] Virginia A. Stallings,[5] Sari Acra,[1] Mark Rodeghier,[6] and Michael R. DeBaun[2,7]

[1]D. Brent Polk Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN; [2]Vanderbilt Institute for Global Health, Vanderbilt University Medical Center, Nashville, TN; [3]Department of Pediatrics, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria; [4]Department of Pediatrics, Murtala Mohammed Specialist Hospital, Kano, Nigeria; [5]Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, The Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA; [6]Rodeghier Consultants, Chicago, IL; and [7]Department of Pediatrics, Vanderbilt-Meharry Center of Excellence in Sickle Cell Disease, Vanderbilt University Medical Center, Nashville, TN

Key Points

- Children aged 5 to 12 years with sickle cell anemia (SCA) living in low- and high-income settings are at risk of being underweight.
- Lower hemoglobin levels and older age are associated with being underweight in children with SCA, irrespective of the setting.

Previously, we demonstrated that older children with sickle cell anemia (SCA) living in Nigeria are at increased risk of death if they are underweight (weight-for-age z score < −1). We now conducted a cross-sectional study in low- and high-income settings to determine the risk factors for being underweight a in children aged 5 to 12 years with SCA. The children from low- and high-income settings were eligible participants for the Primary Prevention of Stroke in Children with Sickle Cell Disease in Nigeria (SPRING; N = 928) and the Silent Cerebral Infarct (SIT, North America/Europe; N = 1093) trials, respectively. The median age in the SPRING and SIT cohorts was 8.1 and 8.5 years, respectively (P < .001). A total of 87.9% (n = 816) of participants in the SPRING trial (low-income) met the study criteria for being underweight (weight-for-age z score < −1), and 22.7% (n = 211) for severely underweight (weight-for-age z score < −3), significantly higher than the SIT (high-income) cohort at 25.7% underweight (n = 281) and 0.7% severely underweight (n = 8; P < .001 for both comparisons). In the combined cohort, older age (odds ratio [OR], 1.24; P < .001) and lower hemoglobin level (OR, 0.67; P < .001) were associated with being underweight. Age and hemoglobin level remained statistically significant in separate models for the SPRING and SIT cohorts. Older age and lower hemoglobin levels in children aged 5 to 12 years with SCA are associated with being underweight in low- and high-income settings.

Introduction

Children with sickle cell anemia (SCA) are at increased risk of undernutrition from insufficient caloric intake along with higher energy requirements associated with increased protein turnover and synthesis, increased erythropoiesis, elevated myocardial expenditure, and a proinflammatory state.[1-3] Anthropometric values, including weight, height, and body mass index (BMI), indicate nutritional status.[4,5] BMI considers weight relative to height. Children with SCA have lower heights than an age- and sex-matched comparison group.[6-8] Thus, BMI may not optimally capture overall nutritional status,

Submitted 17 January 2023; accepted 10 September 2023; prepublished online on *Blood Advances* First Edition 27 September 2023; final version published online 16 November 2023. https://doi.org/10.1182/bloodadvances.2023009711.

Fully anonymized data are available to any qualified investigator with an approved study and data-transfer agreement between Vanderbilt University Medical Center and the institution on request from the corresponding author, Lauren Jane Klein (lauren.klein@vumc.org).

The full-text version of this article contains a data supplement.

especially chronic malnutrition.[9] However, weight is a biomarker for both acute and chronic malnutrition.[10] In the general population, in children aged <5 years, a weight-for-age z score < −2 identifies all children with concurrent moderate wasting and stunting,[11,12] a group that is at a 12-times greater risk of mortality in the absence of treatment than children with normal anthropometric measurements.[13] Weight as a screening measure alone also has the advantage over BMI because it requires only 1 quick measure that is reproducible without requiring specialized training or equipment associated with additional anthropometric measurements.[14]

The nutritional status of children is a potentially modifiable risk factor for reducing SCA mortality among children living in sub-Saharan Arica, where most children with SCA are born.[15] We recently demonstrated that children aged 5 to 12 years with SCA who are underweight (weight-for-age z score < −1) are at increased risk of mortality in a low-income setting.[16] Among 431 children aged 5 to 12 years with SCA who were followed up prospectively, weight-for-age z score was the sole determinant of death.[16] This association between undernutrition and SCA mortality further supports the observation that underweight children with SCA are at increased risk of hospitalization.[17] However, the risk factors for being underweight, irrespective of living in a low-income vs a high-income setting, remain unexplored.[4,5] We completed a pooled secondary analysis of 2 stroke prevention trials conducted in the low-income setting of northern Nigeria and the high-income countries of North America and Europe to test the hypothesis that there are common biologically associated risks of being underweight (weight-for-age z score < −1) in children aged 5 to 12 years old with SCA.

Methods

Study design and population

We conducted a cross-sectional study as a secondary data analysis of deidentified data sets from the baseline data of children with SCA (homozygous hemoglobin S or hemoglobin Sβ^0 thalassemia) who were screened for 2 previous trials, the Primary Prevention of Stroke in Children with Sickle Cell Disease in Nigeria (SPRING) trial (#NCT02560935) and the Silent Cerebral Infarct (SIT) multicenter clinical trial (#NCT00072761). The legal guardians of all prospective trial participants provided signed informed consent for SPRING or SIT trial screening procedures.

The SPRING trial was a National Institute of Health–funded multicenter phase 3 randomized controlled trial conducted from July 2016 to April 2020 at a low-income region of northern Nigeria at Aminu Kano Teaching Hospital and Murtala Mohammad Specialist Hospital, with referrals from Hasiya Bayero Pediatric Hospital and Muhammad Abdullahi Wase Teaching Hospital, all at Kano, Nigeria, and Barau Dikko Teaching Hospital, Kaduna, Nigeria.[18,19] The institutional review board of Vanderbilt University Medical Center, Nashville, TN, and the respective ethics committees of the local Nigerian participating sites approved the SPRING trial.

The SIT trial was an National Institute of Health–funded multicenter phase 3 randomized, 2-arm controlled clinical trial from December 2004 to November 2013 in 29 clinical centers in the United States, Canada, France, and the United Kingdom.[20] Institution-specific institutional review board approval was obtained at each participating institution.

Children aged 5 to 12 years with SCA (hemoglobin SS or hemoglobin Sβ^0 thalassemia) screened for the SPRING and SIT trials were included in this secondary analysis. Participants aged ≥13 years in the SIT cohort were excluded for comparability between cohorts. Given that the primary outcome was underweight status, children with incomplete data on height, weight, or age were excluded from the study.

We used the World Bank classifications of countries' income levels during the respective studies. Nigeria is a lower-middle–income country.[21] However, Kano, northern Nigeria, is considered a low-income region. All study sites for SIT were located in high-income countries.

Data collection and definitions

Demographic and baseline laboratory values were collected. Study nurses or physicians performed anthropometric measurements, including height (cm) and weight (kg) according to standard protocol[22] as part of the initial research visit. BMI (kg/m^2) was calculated from height and weight measurements. We converted anthropometric measurements to age- and sex-specific z scores based on the World Health Organization growth reference.[4,5] To calculate weight-for-age z scores for children aged >10 years, we used the Canadian Pediatric Endocrine Group growth charts. The Canadian Pediatric Endocrine Group growth charts extend the weight-for-age z scores using the same core data set as the World Health Organization reference for school-aged children and adolescents.[23]

Underweight, stunting, and wasting were classified based on weight-for-age, height-for-age, and BMI z scores, respectively.[4,5] Degrees of undernutrition were delineated into z scores between ≤ −2 and < −1, ≤ −3 and < −2, and < −3 as mild, moderate, and severe, respectively. Our primary analysis focuses on underweight, defined as weight-for-age z score < −1, given the association with mortality in children aged <5 years[24] and children aged 5 to 12 years with SCA.[16]

Statistical analysis

Summary statistics for continuous variables were summarized as means and standard deviations or as medians and interquartile ranges for variables not normally distributed. Categorical variables and prevalence were reported as numbers and percentages. A χ^2 test was used for percentages, a *t* test for means, and a Mann-Whitney *U* test for medians. We used multivariable linear and logistic regression to assess several biological factors (age, sex, hemoglobin, and white blood cell count) likely associated with weight-for-age z score and underweight status. Odds ratios (ORs) with a 95% confidence interval (CI) were used to characterize risk factors associated with being underweight. An interaction term was added for hemoglobin level with cohort based on initial model results. A 2-sided *P* value < .05 was considered significant. Data analysis was performed using SPSS 28.0 (IBM, Armonk, NY) and Stata 15 (StataCorp, College Station, TX).

Results

Characteristics of SPRING and SIT trial participants

Of the children with SCA screened for the SPRING and SIT trials, 97% (928 of 934 total participants) and 98% (1093 of 1119 total

participants), respectively, had complete anthropometric values, and age and sex data to calculate anthropometric z scores, and were included in the analysis (Table 1). The median age of children with SCA in the SIT trial (8.5 years) was higher than that of the SPRING cohort (8.1 years; $P < .001$). In both cohorts, approximately half of the children were male (SPRING: 49.0%; SIT: 50.8%; $P = .434$). The mean hemoglobin level was lower in the SPRING cohort (7.5 g/dL) than in the SIT cohort (8.1 g/dL; $P < .001$), whereas the mean white blood cell count was higher in the SPRING cohort (14.7 × 10^9/L vs 12.4 × 10^9/L, respectively; $P < .001$).

The prevalence of undernutrition is higher in the low-income cohort than in the high-income cohort

All measures of nutritional status were significantly lower in the SPRING cohort than in the SIT cohort. (Tables 1 and 2). The mean weight-for-age z scores were negative for both the SPRING (−2.21) and SIT cohorts (−0.33; $P < .001$). In the SPRING cohort, 87.9% of participants were underweight, with 22.7% classified as severely underweight (weight-for-age z score < −3). In comparison, in the SIT cohort, 25.7% of participants were underweight, with 0.7% classified as severely underweight.

In the combined cohorts, 27.2% were underweight, with stunting and wasting, representing 49.4% and 8.3% of the SPRING and SIT cohorts, respectively. All participants with wasting and stunting were also underweight. Conversely, except for 8 participants (0.4%), all participants who were underweight were either stunted, wasted, or both (Table 3).

Characteristics associated with being underweight

In both the SPRING and SIT cohorts, the median age of children classified as underweight was older than those children who were not underweight (SPRING: 8.3 vs 6.7 years, $P < .001$; SIT: 9.5 vs 8.1 years, $P < .001$). Compared with children who were not underweight, children who were underweight had higher white blood cell counts and lower hemoglobin levels in the combined cohort (Table 4). The association between lower hemoglobin and being underweight remained significant in the SIT cohort ($P < .001$). However, there was no significant difference in hemoglobin levels or white blood cell count in the SPRING trial between participants who were underweight and those who were not underweight ($P = .738$ and $P = .140$, respectively; Table 4).

Biological factors predict underweightness in both the low- and high-income cohorts

Predetermined plausible biological factors postulated to be associated with being underweight (weight-for-age z score < −1) were analyzed in a multivariable logistic regression in the combined cohorts. The model also included an interaction term between hemoglobin level and cohort. Among all participants, for every additional year of age, the odds increased of being underweight (OR, 1.24; 95% CI, 1.17-1.31; $P < .001$; Table 5; Figure 1). Increasing hemoglobin level was associated with decreased odds of being underweight in each cohort (combined cohort: OR, 0.67; 95% CI, 0.6-0.75; $P < .001$; Table 5). There was an interaction between hemoglobin level and cohort ($P = .007$), in which the association between the hemoglobin level and being underweight was dependent on the cohort, with an increase in the hemoglobin level having a greater effect for lower hemoglobin levels in the SIT cohort but at higher hemoglobin levels for the SPRING cohort (Table 5; Figure 2). The participants in the SPRING cohort were more likely to be underweight at all hemoglobin levels (Figure 2).

We then constructed a multivariable logistic regression with the same covariates except group, to assess the model in each cohort separately (the interaction term was not required). Older age (SPRING: OR, 1.38; 95% CI, 1.24-1.53; $P < .001$; SIT: OR, 1.19; 95% CI, 1.11-1.27; $P < .001$) and lower hemoglobin level (SPRING: OR, 0.82; 95% CI, 0.68-0.99; $P = .042$; SIT: OR, 0.59; 95% CI, 0.51-0.68; $P. < .001$) remained associated with being underweight (weight-for-age z score ≥ −1; supplemental Table 1).

Multivariable linear regression was used to assess the association of age, sex, hemoglobin, and white blood cell count with weight-for-age z score at baseline. Age ($\beta = -0.14$; $P < .001$), male sex ($\beta = 0.12$; $P = .008$), and hemoglobin level ($\beta = 0.22$; $P < .001$) were associated with weight-for-age z score for the combined

Table 1. Characteristics of the children with SCA screened for the SPRING (low-income) and SIT (high-income) trials

Variable	SPRING cohort (n = 928)	SIT cohort (n = 1093)	*P* value*
Age (y), median (IQR)	8.1 (6.3-10.3)	8.5 (6.8-10.6)	<.001
Sex (male), n (%)	455 (49.0)	555 (50.8)	.434
Hemoglobin (g/dL), mean (SD)	7.5 (1.1) (n = 913)	8.1 (1.1) (n = 1092)	<.001
White blood cell count (×10^9/L), mean (SD)	14.7 (5.1) (n = 913)	12.4 (3.9) (n = 1088)	<.001
Weight (kg), mean (SD)	19.5 (4.4)	27.3 (7.9)	<.001
Height (cm), mean (SD)	119.3 (11.6)	127.9 (12.7)	<.001
BMI (kg/m^2), mean (SD)	13.6 (1.7)	16.3 (2.3)	<.001
Weight-for-age z score, mean (SD)	−2.21 (1.1)	−0.33 (1.1)	<.001
Height-for-age z score, mean (SD)	−1.59 (1.3)	−0.53 (1.1)	<.001
BMI z score, mean (SD)	−1.93 (1.4)	−0.06 (1.1)	<.001

IQR, interquartile range; SD, standard deviation.
*χ^2 test for percentages, *t* test for means, and Mann-Whitney *U* test for medians.

Table 2. Nutritional status in children with SCA screened for the SPRING (low-income) and SIT (high-income) trials

Nutritional status, n (%)	SPRING (n = 928)	SIT (n = 1093)	*P* value*	Combined (N = 2021)
Underweight				
No deficit, weight-for-age z score ≥ −1 (SD)	112 (12.1)	812 (74.3)	<.001	924 (45.7)
Overall underweight, weight-for-age z score < −1 (SD)	816 (87.9)	281 (25.7)		1097 (54.3)
Mild underweight, weight-for-age z score < −1 and ≥ −2 (SD)	279 (30.1)	227 (20.8)		506 (25.0)
Moderate, weight-for-age z score < −2 and ≥ −3 (SD)	326 (35.1)	46 (4.2)		372 (18.4)
Severe underweight, weight-for-age z score < −3 (SD)	211 (22.7)	8 (0.7)		219 (10.8)
Stunted			<.001	
No deficit, height-for-age z score ≥ −1 (SD)	281 (30.3)	731 (66.9)		1012 (50.1)
Overall stunted, height-for-age z score < −1 (SD)	647 (69.7)	362 (33.1)		1009 (49.9)
Mild, height-for-age z score < −1 and ≥ −2 (SD)	301 (32.4)	265 (24.2)		566 (28.0)
Moderate, height-for-age z score < −2 and ≥ −3 (SD)	222 (24.2)	82 (7.5)		304 (15.0)
Severe, height-for-age z score < −3 (SD)	124 (13.8)	15 (1.4)		139 (6.9)
Wasted			<.001	
No deficit, BMI z score ≥ −1 (SD)	232 (25.0)	895 (81.9)		1127 (55.8)
Overall wasted, BMI z score < −1 (SD)	696 (75.0)	198 (18.1)		894 (44.2)
Mild, BMI z score < −1 and ≥ −2 (SD)	274 (29.5)	162 (14.8)		436 (21.6)
Moderate, BMI z score < −2 and ≥ −3 (SD)	228 (24.6)	32 (2.9)		260 (12.9)
Severe, BMI z score < −3 (SD)	194 (20.9)	4 (0.4)		198 (9.8)

SD, standard deviation.
*χ^2 test, comparison of no deficit with the overall category for each condition.

cohort (supplemental Table 2). Age remained significant in both the SPRING and SIT cohorts (SPRING: $\beta = -0.17$, $P < .001$; SIT: $\beta = -0.11$, $P < .001$; supplemental Table 2). Hemoglobin level also remained significant in both cohorts (SPRING: $\beta = 0.12$, $P < .001$; SIT: $\beta = 0.23$, $P < .001$; supplemental Table 2). However, male sex was associated with weight-for-age z score in the SIT cohort ($\beta = 0.24$, $P < .001$; supplemental Table 2).

Discussion

Despite the association of being underweight with increased mortality[16] and hospitalizations,[17] no current studies, to our knowledge, discuss the risk factors for being underweight in children aged >5 years with SCA in both low- and high-income settings. We demonstrate that older age and lower hemoglobin level in children aged 5 to 12 years with SCA in both low- and high-income countries are risk factors for being underweight (weight-for-age z score < −1). As anticipated, the z scores of all anthropometric indices were notably lower among children in the low-income cohort. The presence of common risk factors for undernutrition in both settings underscores the potential for a common biological association for undernutrition in SCA.

Anthropometrical indices to classify children as underweight are proxies for the physiological and functional consequences of the underlying processes of undernutrition and weight loss or the slow

Table 3. Nutritional status classification of participants in the SPRING (low-income), SIT (high-income), and combined cohorts

Nutritional status, % (n)	SPRING (n = 928)	SIT (n = 1093)	Combined (N = 2021)
None	4.3 (40)	56.6 (619)	32.6 (659)
Underweight only	0.3 (3)	0.5 (5)	0.4 (8)
Stunted only	3.0 (28)	12.8 (140)	8.3 (168)
Wasted only	4.7 (44)	4.8 (53)	4.8 (97)
Underweight and stunted	17.3 (161)	12.0 (131)	14.4 (292)
Underweight and wasted	20.9 (194)	4.9 (54)	12.3 (248)
Wasted and stunted	0.0 (0)	0.0 (0)	0.0 (0)
Underweight, stunted, and wasted	49.4 (458)	8.3 (91)	27.2 (549)

Stunted (height-for-age z score < −1.0), underweight (weight-for-age z score < −1.0), and wasted (BMI z score < −1.0) were defined using z scores calculated using the World Health Organization growth reference and Canadian Pediatric Endocrine Group growth charts.
The 0.0 values indicate that all children who were stunted and wasted were also underweight.

Table 4. Characteristics of children with SCA screened for the SPRING (low-income, n = 928), SIT (high-income; n = 1093), or combined (N = 2021) trials according to underweight classifications

Variable	SPRING cohort			SIT cohort			Combined cohort		
	Not underweight (n = 112)	Underweight (n = 816)	*P* value*	Not underweight (n = 812)	Underweight (n = 281)	*P* value*	Not underweight (n = 924)	Underweight (n = 1097)	*P* value*
Age (y), median (IQR)	6.7 (5.5-8.3)	8.3 (6.5-10.5)	<.001	8.1 (6.7-10.4)	9.5 (7.5-11.1)	<.001	8.0 (6.5-10.1)	8.6 (6.7-10.7)	.002
Sex (male), n (%)	59 (52.7)	396 (48.5)	.422	416 (51.2)	139 (49.5)	.610	475 (51.4)	535 (48.8)	.237
Hemoglobin (g/dL), mean (SD)	7.6 (1.2) (n = 111)	7.5 (1.1) (n = 802)	.738	8.2 (1.1) (n = 811)	7.8 (0.9) (n = 279)	<.001	8.2 (1.1) (n = 922)	7.5 (1.1) (n = 1083)	<.001
WBC count (× 10^9/L), mean (SD)	14.9 (5.8) (n = 111)	14.7 (5.1) (n = 802)	.140	12.5 (4.0) (n = 809)	12.2 (3.7) (n = 279)	.254	12.8 (4.3) (n = 920)	14.1 (4.8) (n = 1081)	<.001

Underweight defined as weight-for-age *z* score < −1 based on the World Health Organization growth reference and Canadian Pediatric Endocrine Group growth charts.
IQR, interquartile range; SD, standard deviation; WBC, white blood cell count.
*χ^2 test for percentages, *t* test for means, and Mann-Whitney *U* test for medians.

Table 5. Multivariable logistic regression to assess biological risk factors for underweight (weight-for-age z score less than −1) status in the combined cohort of children with SCA screened for the SPRING (low-income) and SIT (high-income) trials

Variable	Combined cohorts (n = 2000)		
	OR	95% CI	*P* value
Age, y	1.236	1.170-1.3056	<.001
Sex (male)	0.816	0.646-1.031	.089
Hemoglobin (g/dL)	0.588	0.506-0.684	<.001
White blood cell count (× 10^9/L)	0.979	0.953-1.007	.134
Group (SPRING)*	1.947	0.314-12.067	.474
Interaction of hemoglobin by group*	1.379	1.03-1.740	.007

Abbreviations are explained in Table 1.
*Reference category is SIT.

rate of weight gain, reflecting a range of possible causative factors, both biological (at child level) and socioeconomic (household and society levels).[10] Children with SCA have higher resting energy expenditure than children without SCA, suggesting that the need for dietary intake of energy and protein for children with SCA is somewhat increased compared with that for children without SCA.[25-27] Children in the low-income cohort were more likely to be underweight, with the dietary and feeding practices remaining suboptimal for these children.[6] There are socioenvironmental factors contributing to the increased malnutrition in the low-income setting, in addition to the biological factors we have investigated. In our low-income cohort, a high percentage of participants were underweight, stunted, and wasted (49.4%). Similar to children aged <5 years without hemoglobinopathies,[28] this group may be at higher risk of death.

Consistent with prior studies, children with lower hemoglobin levels were more likely to be underweight in both cohorts.[6,29] However, these previous studies were in younger children aged <5 years [6] or with small sample sizes (n = 100),[29] and not in both low- and high-income settings.[6,29] In a secondary analysis of the Dissemination and Implementation of Stroke Prevention Looking at the Care Environment cohort (3305 children with SCA and at least 2 anthropometric assessments during study follow-up), low hemoglobin level was associated with low BMI z scores.[30] However, the association with weight-for-age z scores was not addressed, and all study centers were located in the United States, a high-income setting.[30] Chronic anemia is associated with SCA and decreased growth; long-term red blood cell transfusion therapy designed to increase the baseline hemoglobin levels have been noted to increase weight, height, and BMI z scores for children with SCA.[30,31] Some studies suggest that hydroxyurea has no detrimental effects on growth and that it can potentially improve growth in children with SCA.[30,32-35] However, to our knowledge, no trial has tested whether hydroxyurea improves growth, potentially through increasing hemoglobin levels,[36] as a primary hypothesis.

Older age was associated with an increased risk of being underweight in both cohorts. The majority of undernutrition literature focuses on children aged <5 years.[37,38] In a longitudinal study by Zemel et al, in children from birth to aged 18 years, age at enrollment was negatively associated with weight-for-age z scores, and from

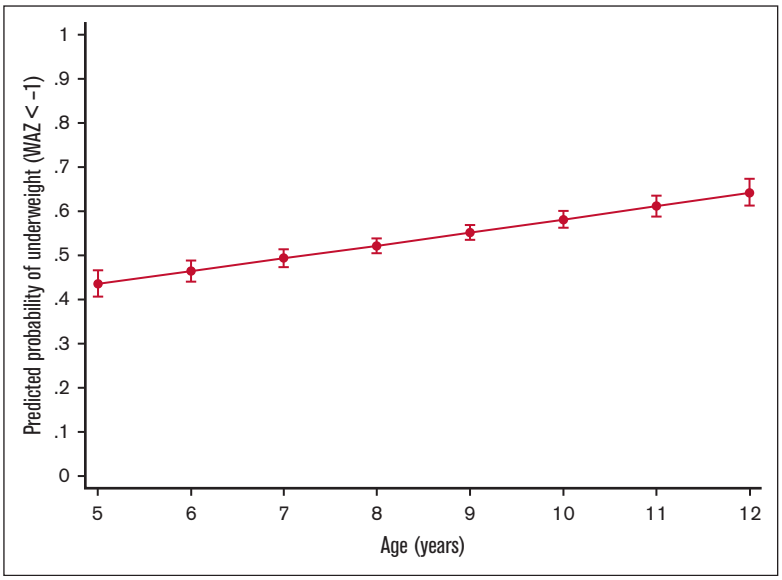

Figure 1. The relationship between age and the predicted probability of being underweight (weight-for-age z score [WAZ] < −1) with 95% CIs from a logistic regression model of the combined cohort (n = 2000) of children with SCA screened for the SPRING and SIT trials. Underweight (WAZ < −1.0) was defined using z scores calculated from the World Health Organization growth reference and Canadian Pediatric Endocrine Group growth charts.

study entry to the last visit, 59% of children with SCA declined in weight-for-age z score.[39] Another study in children aged 6 months to 15 years demonstrated weight-for-age z score reduction across all age groups.[40] Similarly, in Tanzania, in a cohort of patients with SCA with ages ranging from 0.5 to 48 years, the most significant growth deficits were observed during adolescence.[17] Our findings and those of others suggest that growth faltering is associated with increasing age in children with SCA. Growth faltering with age may represent a continued insult from SCA or reflect the effects of increased resting energy expenditure and suboptimal food intake perpetuated by or superimposed on SCA.

As expected, our study has limitations as a secondary analysis of participants screened for 2 large randomized clinical trials in children with SCA. Because of the cross-sectional design, we cannot infer that the relationship between the biological factors is causal. Weight-for-age z score as a continuous variable was also significantly related to lower hemoglobin levels and older age among both individual and combined cohorts, consistent with a dose response. Lower hemoglobin levels may result from the same pathophysiology that causes poor nutritional status, and longitudinal studies should evaluate the change in hemoglobin and weight status over time. Dietary intake, maternal characteristics, access to health care, and household food security should be explored in future work on nutritional status in children with SCA. However, the strength of our study was the ability to combine research-quality anthropometric measures in 2 large populations of children with SCA that differed in location, low-income vs high-income settings.

The consistency of risk factors in low- and high-income settings provides substantial evidence for disease-specific risk factors associated with being underweight. Our findings from this study contribute to our understanding of the factors associated with underweight status in children aged 5 to 12 years with SCA in both low- and high-income settings. A low hemoglobin level is a potentially modifiable risk factor for preventing underweight

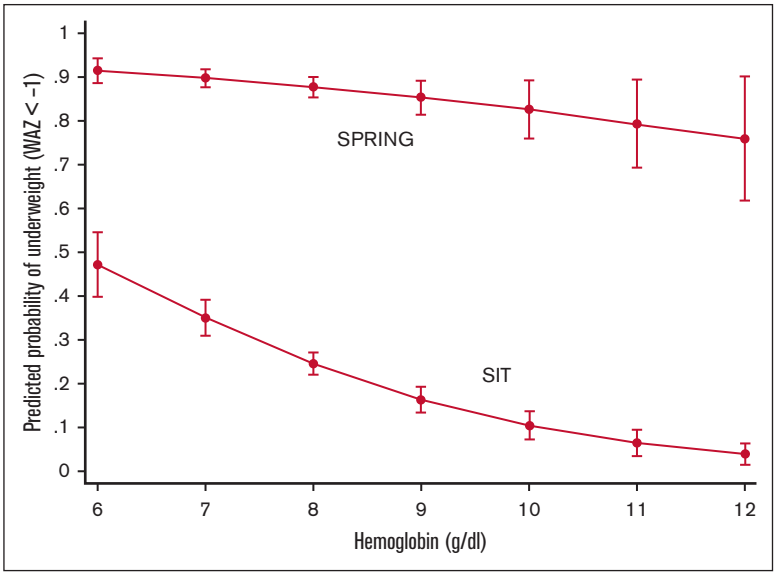

Figure 2. The relationship between hemoglobin and the predicted probability of being underweight (WAZ < −1) with 95% CIs from a logistic regression model of the combined cohort (n = 2000) of children with SCA screened for the SPRING and SIT trials. This is a graphical representation of the interaction term between the hemoglobin level and cohort in the model. Underweight (WAZ < −1.0) was defined using z scores calculated from the World Health Organization growth reference and Canadian Pediatric Endocrine Group growth charts.

status in older children with SCA in both low- and high-income settings.

Acknowledgments

The authors thank Bilya Sani Musa, Mustafa Nateqi, Khadijah Bulama, Murtala Umar, Charity Dooshima Agba-Dooyum, Fahad Usman, Abdulrasheed Sani, Awwal Gambo, Jamila Ibrahim, Gloria Bahago, Jamil Galadanci, Leshana Saint Jean, and Jennifer C. Beck for providing the successful conduct of the research reported in this publication.

The SPRING trial was supported by National Institutes of Health (NIH) grant R01NS094041, NIH/National Center for Advancing Translational Sciences grant UL1 TR000445, and the generous donation of the Phillips family. The SIT trial was supported by grants from the National Institute of Neurological Disorders and Stroke (5U01NS042804 and 3U01NS042804 [American Recovery Reinvestment Act supplementary grant]) (M.R.D.). L.J.K. was supported by the Fogarty International Center; the National Heart, Lung, and Blood Institute of the NIH (D43 TW009337), and the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH (T32DK007673). The sponsors did not have any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The findings and conclusions in this paper are those of the authors and do not represent the official position of the NIH.

Authorship

Contribution: L.J.K., M.R., and M.R.D. conceptualized and designed the secondary analysis, had full access to all the data in the study, took responsibility for data integrity and data analyses accuracy, and wrote the initial manuscript; S.U.A. and S.G. conducted the SPRING trial; M.R.D. served as the principal investigator of the SIT trial; L.J.K. and M.R. performed the analyses; M.R.D. and L.J.K. interpreted the results; and all authors reviewed the manuscript and approved its submission.

Conflict-of-interest disclosure: M.R.D. and his institution sponsor 2 externally funded research investigator-initiated projects; Global Blood Therapeutics (GBT) will provide funding for the cost of the clinical studies. GBT was not a cosponsor of either study; did not receive any compensation for the conduct of these 2 investigator-initiated observational studies. M.R.D. is a member of the GBT advisory board for a proposed randomized controlled trial, for which he receives compensation; serves on the steering committee for a Novartis-sponsored phase 2 trial to prevent priapism in men; was a medical adviser in developing the CTX001 Early Economic Model; provided medical input on the economic model as part of an expert reference group for the Vertex/CRISPR CTX001 Early Economic Model in 2020; and consulted for the Formal Pharmaceutical company on sickle cell disease in 2021 and 2022. The remaining authors declare no competing financial interests.

ORCID profiles: L.J.K., 0000-0003-1076-8518; S.U.A., 0000-0001-5567-9629; V.A.S., 0000-0002-7025-7149; S.A., 0000-0003-4447-7233; M.R., 0000-0001-7258-0073; M.R.D., 0000-0002-0574-1604.

Correspondence: Lauren Jane Klein, D. Brent Polk Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Monroe Carell Jr. Children's Hospital at Vanderbilt and Vanderbilt Institute for Global Health, 2525 West End Ave, Suite 750, Nashville, TN 37203; email: lauren.klein@vumc.org.

References

1. Borel MJ, Buchowski MS, Turner EA, Goldstein RE, Flakoll PJ. Protein turnover and energy expenditure increase during exogenous nutrient availability in sickle cell disease. *Am J Clin Nutr*. 1998;68(3):607-614.
2. Nartey EB, Spector J, Adu-Afarwuah S, et al. Nutritional perspectives on sickle cell disease in Africa: a systematic review. *BMC Nutr*. 2021;7(1):9.
3. Hyacinth HI, Gee BE, Hibbert JM. The role of nutrition in sickle cell disease. *Nutr Metab Insights*. 2010;3:57-67.
4. Becker PJ, Nieman Carney L, Corkins MR, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition). *J Acad Nutr Diet*. 2014;114(12):1988-2000.
5. Duggan MB. Anthropometry as a tool for measuring malnutrition: impact of the new WHO growth standards and reference. *Ann Trop Paediatr*. 2010;30(1):1-17.
6. Islam MR, Moinuddin M, Ahmed A, Rahman SM. Association of sickle cell disease with anthropometric indices among under-five children: evidence from 2018 Nigeria Demographic and Health Survey. *BMC Med*. 2021;19(1):5.
7. Barden EM, Kawchak DA, Ohene-Frempong K, Stallings VA, Zemel BS. Body composition in children with sickle cell disease. *Am J Clin Nutr*. 2002;76(1):218-225.
8. Rhodes M, Akohoue SA, Shankar SM, et al. Growth patterns in children with sickle cell anemia during puberty. *Pediatr Blood Cancer*. 2009;53(4):635-641.
9. Bouma S. Diagnosing pediatric malnutrition: paradigm shifts of etiology-related definitions and appraisal of the indicators. *Nutr Clin Pract*. 2017;32(1):52-67.
10. Wells JCK, Briend A, Boyd EM, et al. Beyond wasted and stunted—a major shift to fight child undernutrition. *Lancet Child Adolesc Health*. 2019;3(11):831-834.
11. Thurstans S, Sessions N, Dolan C, et al. The relationship between wasting and stunting in young children: a systematic review. *Matern Child Nutr*. 2022;18(1):e13246.

12. Myatt M, Khara T, Schoenbuchner S, et al. Children who are both wasted and stunted are also underweight and have a high risk of death: a descriptive epidemiology of multiple anthropometric deficits using data from 51 countries. *Arch Public Health*. 2018;76(1):28-11.
13. McDonald CM, Olofin I, Flaxman S, et al. The effect of multiple anthropometric deficits on child mortality: meta-analysis of individual data in 10 prospective studies from developing countries. *Am J Clin Nutr*. 2013;97(4):896-901.
14. Bailey J, Lelijveld N, Khara T, et al. Response to malnutrition treatment in low weight-for-age children: secondary analyses of children 6–59 months in the ComPAS cluster randomized controlled trial. *Nutrients*. 2021;13(4):1054.
15. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. *Nat Rev Dis Primers*. 2018;4(1):18010-22.
16. Klein LJ, Abdullahi S, Gambo S, et al. Underweight children over 5 years with sickle cell anemia are at risk for early mortality in a low-resource setting. *Blood Adv*. 2023;7(11):2339-2346.
17. Cox SE, Makani J, Fulford AJ, et al. Nutritional status, hospitalization and mortality among patients with sickle cell anemia in Tanzania. *Haematologica*. 2011;96(7):948-953.
18. Abdullahi SU, Jibir BW, Bello-Manga H, et al. Hydroxyurea for primary stroke prevention in children with sickle cell anaemia in Nigeria (SPRING): a double-blind, multicentre, randomised, phase 3 trial. *Lancet Haematol*. 2022;9(1):e26-e37.
19. Abdullahi SU, Wudil BJ, Bello-Manga H, et al. Primary prevention of stroke in children with sickle cell anemia in sub-Saharan Africa: rationale and design of phase III randomized clinical trial. *Pediatr Hematol Oncol*. 2021;38(1):49-64.
20. DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *N Engl J Med*. 2014;371(8):699-710.
21. The World Bank Group. World Bank Country and Lending Groups. 2022. Accessed 23 April 2023. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups
22. Lohman TJ, Roache AF, Martorell R, eds. *Anthropometric Standardization Reference Manual*. Human Kinetics Books; 1988.
23. Rodd C, Metzger DL, Sharma A; Canadian Pediatric Endocrine Group CPEG Working Committee for National Growth Charts. Extending World Health Organization weight-for-age reference curves to older children. *BMC Pediatr*. 2014;14(32):32.
24. Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008;371(9608):243-260.
25. Borel MJ, Buchowski MS, Turner EA, Peeler BB, Goldstein RE, Flakoll PJ. Alterations in basal nutrient metabolism increase resting energy expenditure in sickle cell disease. *Am J Physiol*. 1998;274(2):E357-E364.
26. Hyacinth HI, Adekeye OA, Yilgwan CS. Malnutrition in sickle cell anemia: implications for infection, growth, and maturation. *J Soc Behav Health Sci*. 2013;7(1).
27. Barden EM, Zemel BS, Kawchak DA, Goran MI, Ohene-Frempong K, Stallings VA. Total and resting energy expenditure in children with sickle cell disease. *J Pediatr*. 2000;136(1):73-79.
28. Odei Obeng-Amoako GA, Karamagi CAS, Nangendo J, et al. Factors associated with concurrent wasting and stunting among children 6–59 months in Karamoja, Uganda. *Matern Child Nutr*. 2021;17(1):17.
29. Silva CM, Viana MB. Growth deficits in children with sickle cell disease. *Arch Med Res*. 2002;33(3):308-312.
30. Galadanci NA, Sohail M, Akinyelure OP, Kanter J, Ojesina AI. Treatment-related correlates of growth in children with sickle cell disease in the DISPLACE Cohort. *J Pediatr Hematol Oncol*. 2022;44(5):249-254.
31. Wang WC, Morales KH, Scher CD, et al. Effect of long-term transfusion on growth in children with sickle cell anemia: results of the Stop Trial. *J Pediatr*. 2005;147(2):244-247.
32. Rana S, Houston PE, Wang WC, et al. Hydroxyurea and growth in young children with sickle cell disease. *Pediatrics*. 2014;134(3):465-472.
33. Wang WC, Helms RW, Lynn HS, et al. Effect of hydroxyurea on growth in children with sickle cell anemia: results of the HUG-KIDS study. *J Pediatr*. 2002;140(2):225-229.
34. Adegoke SA, Braga JAP, D Adekile A, Figueiredo MS. Impact of hydroxyurea on anthropometry and serum 25-hydroxyvitamin D among children with sickle cell disease. *J Pediatr Hematol Oncol*. 2018;40(4):e243-e247.
35. Hankins JS, Aygun B, Nottage K, et al. From infancy to adolescence: fifteen years of continuous treatment with hydroxyurea in sickle cell anemia. *Medicine (Baltimore)*. 2014;93(28):e215.
36. Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet*. 2011;377(9778):1663-1672.
37. Victora CG, Christian P, Vidaletti LP, Gatica-Domínguez G, Menon P, Black RE. Revisiting maternal and child undernutrition in low-income and middle-income countries: variable progress towards an unfinished agenda. *Lancet*. 2021;397(10282):1388-1399.
38. Okubo T, Janmohamed A, Topothai C, Blankenship JL. Risk factors modifying the double burden of malnutrition of young children in Thailand. *Matern Child Nutr*. 2020;16(suppl 2):e12910.
39. Zemel BS, Kawchak DA, Ohene-Frempong KO, Schall JI, Stallings VA. Effects of delayed pubertal development, nutritional status, and disease severity on longitudinal patterns of growth failure in children with sickle cell disease. *Pediatr Res*. 2007;61(5 pt 1):607-613.
40. Al-Saqladi AWM, Bin-Gadeen HA, Brabin BJ. Growth in children and adolescents with sickle cell disease in Yemen. *Ann Trop Paediatr*. 2010;30(4):287-298.