BPR MCS Bulletin of Pioneering Researches of Medical and Clinical Science

Bulletin of Pioneering Researches of Medical and Clinical Science

Available online: https://bprmcs.com
2022 | Volume 2 | Issue 2 | Page: 42-49

WHO Growth Reference Overestimates Severe Malnutrition in African Children with Sickle Cell Disease

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Abstract

Anthropometric indicators are frequently used to monitor children's nutritional and health status. This study investigated whether the 2007 WHO growth reference inflates estimates of severe malnutrition in children with sickle cell anemia (SCA) compared to a reference tailored specifically for this population. We evaluated children aged 5–12 years with SCA from northern Nigeria enrolled in the SPRING trial (Primary Prevention of Stroke in Children with SCA in sub-Saharan Africa), comparing the prevalence of severe malnutrition (BMI Z-score <−3) and its relationship with mean hemoglobin levels and abnormal transcranial Doppler (TCD) velocities (>200 cm/s) using both references. A total of 799 participants were analyzed (median age 8.2 years, interquartile range 6.4–10.4). Application of the WHO reference produced lower average BMI (−2.3) than the SCA-specific reference (−1.2; $p < 0.001$) and indicated a markedly higher rate of severe malnutrition (28.6 percent vs. 6.4 percent; $p < 0.001$). These results reveal that the WHO reference substantially overestimates severe malnutrition in children with SCA. Notably, severe malnutrition, whether defined by the WHO or SCA-specific reference, was not associated with reduced hemoglobin levels or abnormal TCD findings.

Keywords: Severe malnutrition, Growth references, Sickle cell disease

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How to Cite This Article: Zibi RDN, Dongmo LF, Mbopi PY. WHO Growth Reference Overestimates Severe Malnutrition in African Children with Sickle Cell Disease. Bull Pioneer Res Med Clin Sci. 2022;2(2):42-9. https://doi.org/10.51847/qJPRebuccB

Introduction

Sickle cell anemia (SCA) is a widespread inherited blood disorder [1] that disproportionately affects populations in sub-Saharan Africa, particularly Nigeria. Of the estimated 305,000 children born globally with SCA each year [2], nearly half—around 150,000—are born in Nigeria [3], in stark contrast to roughly 1,300 births in the United States [4]. The influence of sickle cell disease (SCD) on growth and nutrition was first recognized in the mid-20th century [5, 6], with children suffering from SCD, like those with other chronic illnesses, frequently experiencing delayed growth and later onset of puberty [7–9]. Evidence from the Cooperative Study of Sickle Cell Disease (CSSCD), which tracked over 2,000 individuals across different sickle genotypes, showed that children with HbSS or HbSβ⁰ thalassemia (collectively considered SCA) had reduced weight and height compared to children with HbSC or HbSβ⁺ thalassemia. Across all SCD genotypes, growth parameters were below the norms for African American children [8]. A synthesis of 46 anthropometric studies, including both cross-sectional and longitudinal designs, confirmed that growth failure is a global characteristic among children with SCD [9].

In pediatric chronic illnesses, nutritional status is most accurately assessed using reference data from children with the same disease [10–16]. Despite this, most SCD studies rely on World Health Organization (WHO) growth charts, which are derived from healthy children without SCD. Condition-specific growth references exist for disorders such as Down syndrome [12,15,16], Turner syndrome [10, 14], and cystic fibrosis [11, 13]. For SCA, Wolf *et al*. created reference percentiles for weight, height, and blood pressure in children aged five to 15 years [17], but these charts did not include body mass index (BMI) percentiles, which are the standard for assessing severe malnutrition [18]. The lack of SCA-specific growth charts, particularly in low-resource settings, can lead to misclassification of nutritional status and inefficient allocation of limited treatment resources. Until such references become available, WHO growth charts continue to be used for children with SCA.

To address this gap, we examined whether WHO growth standards [18] overestimate the prevalence of severe malnutrition in children with SCA compared to disease-specific growth curves based on longitudinal data from children in high-income countries [17]. We further evaluated whether severe malnutrition in this population correlates with lower hemoglobin levels or elevated transcranial Doppler velocities (>200 cm/s).

Materials and Methods

Study design and participants

This cross-sectional study involved 850 children with SCA, aged 5–12 years, residing in northern Nigeria, a resource-limited region. The study aimed to evaluate nutritional status using both disease-specific and WHO growth standards.

Participants were originally enrolled as part of the NIH-funded Primary Prevention of Stroke in Children with SCA in sub-Saharan Africa (SPRING Trial, NCT02560935) from July 2016 to July 2017. Recruitment took place in two northern Nigerian states, home to an estimated 32,000 children with SCA out of a combined population of 2,828,861 (2006 census) [19].

Ethical approval was secured from all participating institutions, and informed consent was obtained from each participant. The study was coordinated by Vanderbilt University Medical Center, USA, with local clinical support from five hospitals: Aminu Kano Teaching Hospital (AKTH), Murtala Muhammad Specialist Hospital (MMSH), Hasiya Bayero Pediatric Hospital (HBPH), Muhammad Abdullahi Wase Specialist Hospital (MAWSH), all in Kano, and Barau Dikko Teaching Hospital (BDTH) in Kaduna.

- AKTH is a 500-bed tertiary facility. Its pediatric SCD clinic manages a patient population of approximately 2,010, with around 80 children with SCA seen weekly by a pediatrician and nurse.
- MMSH, an AKTH-affiliated high-volume clinic less than 3 miles away, operates Monday–Friday, with over 17,810 registered children with SCA, and sees at least 400 children weekly.
- HBPH is a 90-bed pediatric hospital located 2.5 miles from AKTH, operating a weekly SCD clinic serving over 11,129 children. Nurses and community health workers see over 100 children daily, with pediatricians attending weekly.
- MAWSH, a 320-bed multispecialty hospital 5 miles from AKTH, has approximately 470 children with SCA on its roster. Weekly consultations include about 42 children with SCA.
- BDTH, Kaduna State University's teaching hospital, hosts a weekly SCD clinic with roughly 1,200 registered children and 40 consultations per week.

SCA-Specific growth reference

Reference percentiles for weight, height, and BMI in children with SCA were obtained from the Silent Cerebral Infarct Multi-Center Clinical (SIT) trial (NCT00072761) [20]. This trial included children aged 5–15 years with SCA and silent cerebral infarcts, randomized to three years of chronic transfusion therapy or observation. Participants were recruited between December 2004 and November 2013 from the United States, Canada, France, and the United Kingdom.

Wolf *et al.* used serial anthropometric measurements from 949 participants (median age 8.2 years, IQR 6.4–10.4) with a median follow-up of 3.2 years (IQR 1.8–4.7, range 0–12.9) to generate percentiles. Each child had a median of five height and weight measurements (IQR 3–7, range 1–12). Quantile regression was applied to derive sex- and age-specific growth percentiles [17].

WHO 2007 growth reference

The WHO 2007 growth charts provide standardized growth benchmarks for school-aged children and adolescents (5–19 years) [18]. These charts were created using three U.S. datasets. The first two were from the Health Examination Survey (HES) Cycle II (ages 6–11, n = 7,417) and Cycle III (ages 12–17, n = 7,514). The third dataset drew from the National Health and Nutrition Examination Survey (NHANES) Cycle I, including only children aged 5–12 years (n = 2,878). The final dataset used for BMI-for-age curves included 30,018 observations (15,103 boys and 14,915 girls) [18].

Data collection and definitions

For all participants, information on demographic characteristics, socioeconomic status, and baseline clinical and laboratory measures—including hemoglobin, white blood cell count (WBC), mean corpuscular volume

(MCV), and blood pressure—was collected. Height (cm) and weight (kg) were measured by study personnel, including nurses, physicians, or trained administrators, and used to calculate body mass index (BMI, kg/m²). These anthropometric data were transformed into Z-scores for weight-for-height (WHZ) using both SCA-specific [17] and WHO growth references [18]. Nutritional categories were defined using BMI Z-scores as follows: wasting (BMI Z < −2), moderate malnutrition (BMI Z between −2 and −3), and severe malnutrition (BMI Z < −3). Overweight children were those with BMI-for-age between the 85th and 94th percentile (BMIZ >2 and <3), and obesity was defined as BMI ≥95th percentile. Children below the 5th percentile were classified as underweight, while those between the 5th and 84th percentiles were considered to have normal weight.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation when normally distributed or as median with interquartile range for non-normal data. Categorical variables were expressed as counts and percentages, and prevalence measures were reported as proportions. Malnutrition prevalence—including wasting, moderate and severe malnutrition, overweight, and obesity—was assessed in children aged 5–12 years from the SPRING cohort using both WHO 2007 standards and SCA-specific growth references. Paired sample t-tests were used to compare continuous outcomes (e.g., BMI Z-scores), while McNemar's test was applied to paired categorical outcomes (e.g., malnutrition prevalence). For comparisons of continuous or ordinal variables between two groups, ANOVA or the Mann–Whitney test was employed, depending on data distribution. Associations between malnutrition and transcranial Doppler (TCD) measurements were evaluated using median quantile regression to account for non-normal TCD distribution, adjusting for age and other covariates. Statistical significance was set at $p < 0.05$ (two-sided). Analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA).

Results

Participant demographics

During the study period from July 2016 to July 2017, 850 children with SCA were screened for the SPRING trial in Nigeria. Of these, 799 children had complete anthropometric data and were included in the analysis **(Figure 1)**. The median age of the cohort was 8.2 years, with males comprising 49.4% of participants **(Table 1)**.

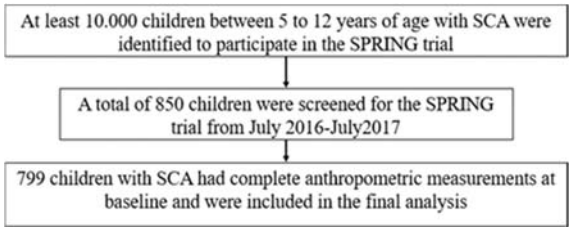


Figure 1. Flow diagram illustrating the recruitment of children with sickle cell anemia screened for the SPRING (Primary Stroke Prevention) trial in Nigeria

Table 1. Baseline characteristics of children with sickle cell anemia (SCA) aged 5–12 years old living in northern Nigeria and screened for the Primary Stroke Prevention in Nigeria (SPRING) trial (n = 799) compared to high-income countries (Silent Cerebral Infarct Multi-Center Clinical (SIT) cohort; n = 1127)

Variable	SPRING Cohort (n = 799)	SIT Cohort (n = 1127)	p-Value #
Age, median (IQR) (years)	8.2 (6.4–10.4)	8.5 (6.7–10.7)	0.001 §
Sex, male, n (%)	395 (49.4)	579 (51.4)	0.402
Weight, median (IQR)(kg)	19.0 (16.0–22.0)	25.9 (22.0–31.9)	<0.001 §
Height, median (IQR)(cm)	120.0 (111.0–128.0)	126.8 (117.9–137.7)	<0.001 §
BMI, mean (SD)	13.7 (1.9)	16.4 (2.7)	<0.001
Hemoglobin, mean (SD) (n = 1909)	7.6 (1.1)	8.2 (2.6)	<0.001
White Blood Count, mean (SD) (n = 1905)	14.7 (5.1)	12.6 (5.2)	<0.001

BMI, body mass index; Hb, hemoglobin; IQR, interquartile range; WBCs, white blood cells. # A p-Value < 0.05 was set for statistical significance. § Mann–Whitney U test.

Higher malnutrition prevalence using WHO growth standards compared to sca-specific references

When evaluated using the WHO growth reference, children exhibited lower mean BMI Z-scores compared with the SCA-specific reference (−2.3 ± 2.0 versus −1.2 ± 1.1, $p < 0.001$). Severe malnutrition was not associated with either mean hemoglobin levels or abnormal transcranial Doppler (TCD) findings, regardless of whether the WHO or SCA-specific growth charts were applied. Baseline characteristics and the overall nutritional profile of the study cohort are summarized in **Table 1**, while mean hemoglobin levels and the proportion of abnormal TCD results stratified by nutritional status are presented in **Table 2** and **Table 3**, respectively.

Table 2. Proportion of children with sickle cell anemia (SCA) aged 5–12 years old in Nigeria (SPRING cohort; n = 799) with abnormal transcranial Doppler (TCD) values (>200 cm/s): World Health Organization (WHO) compared to the SCA-Specific growth reference

Malnutrition	Abnormal TCD, %	*p*-Value #
SCA-Specific Growth Reference *n* = 799		
No malnutrition	14.0	
Moderate malnutrition	7.1	0.034
Severe malnutrition	4.4	
2007 WHO Growth Reference *n* = 799		
No malnutrition	14.8	
Moderate malnutrition	12.3	0.059
Severe malnutrition	7.9	

Abnormal TCD, >200 cm/s; moderate malnutrition, BMI Z-score <−2 and >−3; severe malnutrition, BMI Z-score <−3. # Chi-square. A p-Value < 0.05 was set for statistical significance.

Table 3. Mean hemoglobin of children with sickle cell anemia (SCA) aged 5–12 years old in Nigeria (SPRING cohort; *n* = 799): WHO compared to the SCA-Specific growth reference

Malnutrition	Hemoglobin (g/dL), Mean (SD)	*p*-Value #
SCA-Specific Growth Reference		
No malnutrition	7.5 (1.1)	
Moderate malnutrition	7.6 (1.1)	0.124
Severe malnutrition	7.9 (1.5)	
2007 WHO Growth Reference		
No malnutrition	7.5 (1.2)	
Moderate malnutrition	7.6 (1.1)	0.981
Severe malnutrition	7.6 (1.2)	

Moderate malnutrition: BMI Z-score <−2 and >−3; severe malnutrition, BMI Z-score <−3. # ANOVA. A *p*-Value < 0.05 was set for statistical significance.

When the WHO growth reference was used, the proportion of children identified as wasted (BMI Z-score <−2) was considerably higher than with the SCA-specific growth reference, at 50.7% compared to 22.3% (p < 0.001) **(Figure 2a)**. Severe malnutrition appeared 22.3% more frequently under the WHO criteria than under the SCA-specific reference (28.7% vs. 6.4%, p < 0.001), while moderate malnutrition was slightly more common with the WHO reference, showing a 5.4% difference (21.3% vs. 15.9%, p < 0.001) **(Figure 2b)**. Rates of overweight and obesity were also higher according to the WHO reference, at 1.5%, compared with 0.4% using the SCA-specific reference **(Figure 2a)**.

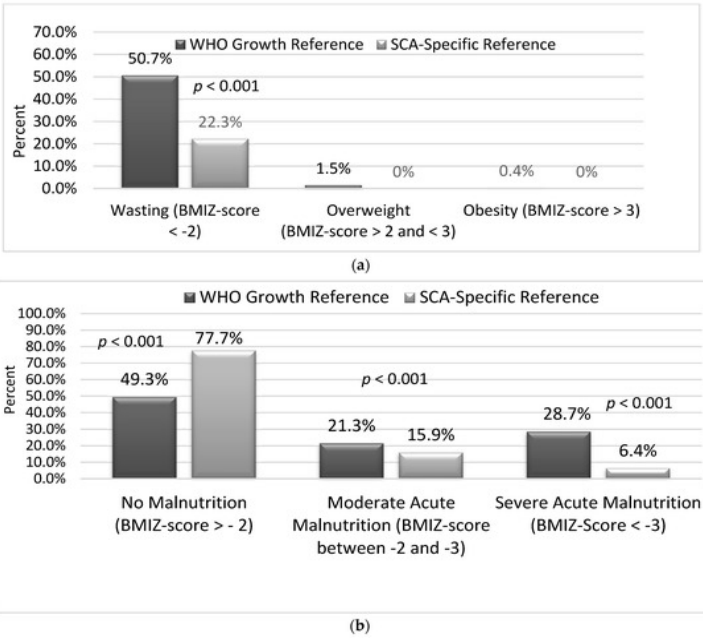


Figure 2. Malnutrition patterns in children with sickle cell anemia (SCA) assessed using WHO and SCA-specific growth charts. (a) Comparison of the proportion of children classified as wasted, overweight, or obese under the two growth references. In children aged 5–12 years from northern Nigeria, the WHO charts substantially overestimated the occurrence of wasting relative to SCA-specific standards. McNemar's test was applied, with p-values <0.05 considered statistically significant. (b) Comparison of moderate (BMI Z-score between −3 and −2) and severe malnutrition (BMI Z-score <−3) using both references. Among SCA children in Kano, Nigeria, the WHO reference overrepresented both moderate and severe malnutrition compared with the SCA-specific charts. Statistical significance was determined using McNemar's test (p < 0.05)

When analyzed by age, mean BMI Z-scores and rates of severe malnutrition were consistently elevated with the WHO reference. **Figures 3** and **4a, b** display the age-specific BMI Z-scores and the prevalence of moderate and severe malnutrition in this pediatric population.

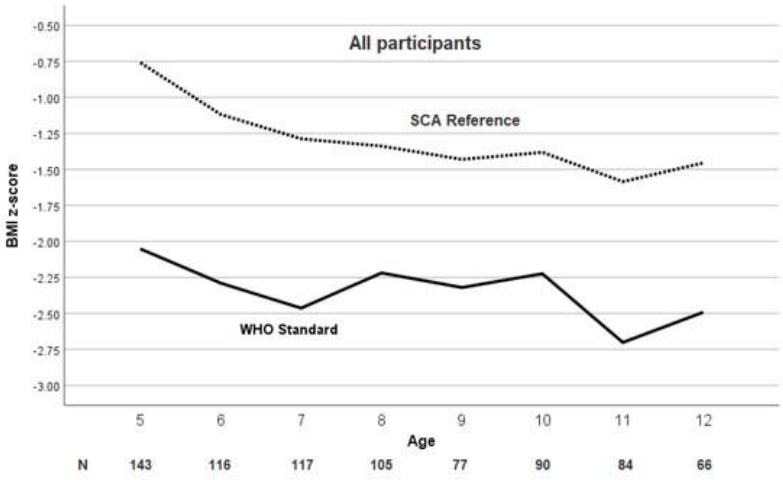
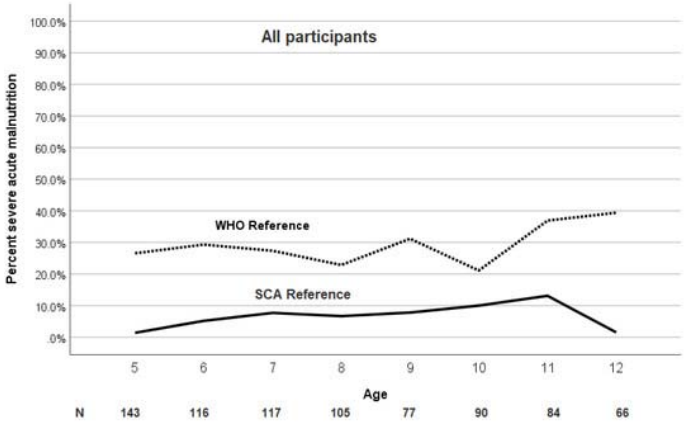
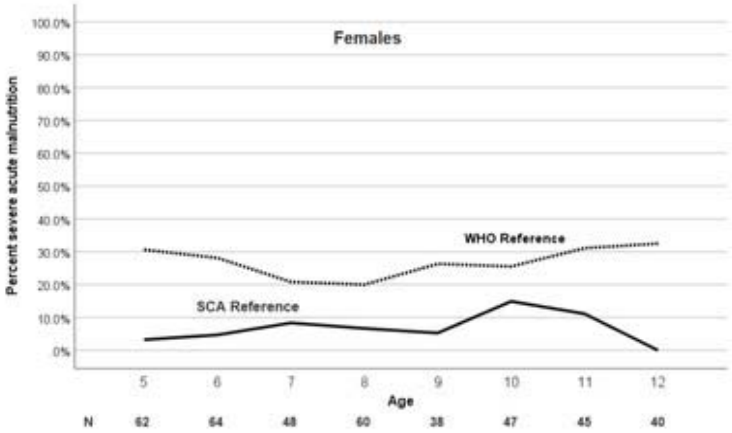


Figure 3. Age-related pattern of BMI Z-scores in children with SCA according to WHO and SCA-specific growth charts. Across all ages (5–12 years), children with sickle cell anemia in Nigeria showed higher mean BMI Z-scores when evaluated using the SCA-specific reference compared with the WHO reference



(a)



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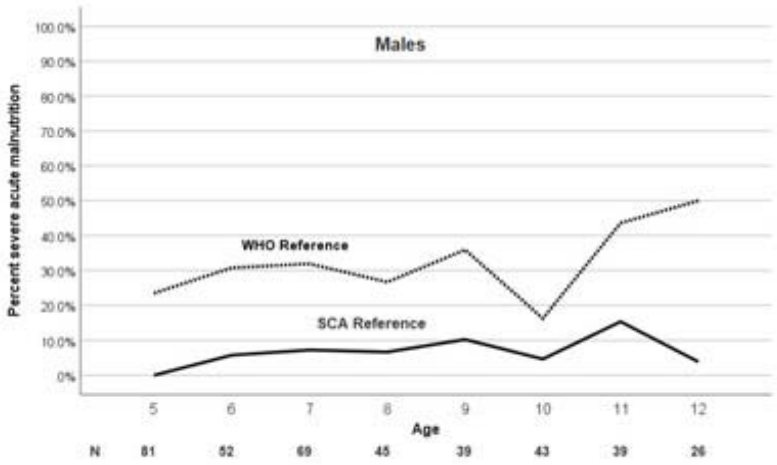

(c)

Figure 4. Trends in Severe Malnutrition by Age and Sex in Children with SCA Using WHO and SCA-Specific References. (a) The proportion of children with SCA classified as severely malnourished (BMI Z-score <−3) differs depending on the growth chart applied. Across all age groups, the WHO reference consistently identifies a higher prevalence than the SCA-specific standard. (b, c) When examining BMI Z-scores by age and sex, both boys and girls show higher rates of severe malnutrition according to WHO charts, with a noticeable rise after age 10

Severe malnutrition and TCD velocity

Analysis revealed a significant association between malnutrition severity and TAMMV values. Children categorized as severely malnourished under either WHO or SCA-specific references exhibited lower average TCD velocities (WHO: 138.7 vs. 150.2, p = 0.001; SCA-specific: 133.1 vs. 147.6, p = 0.002) **(Table 2)**.

Because TCD velocities tend to decline with age and malnutrition rates increase with age, we applied quantile regression using SCA-specific malnutrition categories (Appendix A, Table A1). Only moderate malnutrition was linked to a statistically significant TCD reduction (−8.6, p = 0.041), after adjusting for age and other factors.

Severe malnutrition, irrespective of the growth reference, did not correspond to lower mean hemoglobin levels **(Table 3)**. Moreover, using the WHO reference, children with severe malnutrition did not exhibit higher rates of abnormal TCD readings compared with those without malnutrition (7.9% vs. 14.8%, p = 0.59). Interestingly, the SCA-specific reference showed that severely malnourished children had fewer abnormal TCD results than their non-malnourished peers (4.4% vs. 14%, p = 0.034).

Discussion

In sub-Saharan Africa, where SCA is widespread and severe malnutrition is common—such as in Nigeria, which records around 150,000 annual SCA births [3] compared to 1,300 in the USA [4]—accurate assessment of nutritional status is essential for effective allocation of scarce resources. Our findings indicate that the WHO growth reference overestimates severe malnutrition among children with SCA aged 5–12 years when compared to SCA-specific charts.

Within our cohort, the prevalence of severe malnutrition varied substantially by reference: 6% according to SCA-specific standards versus 28% by WHO criteria.

Although malnutrition in healthy children often correlates with low hemoglobin levels [21], no such association was observed in our SCA cohort. Similarly, severe malnutrition did not increase the likelihood of abnormal TCD readings, consistent with a prior study in Jamaican children with SCA (n = 358) [22]. This lack of association may reflect the chronic anemia inherent to SCA. Furthermore, including children older than five years could have contributed to the absence of a clear link between severe malnutrition and hemoglobin, as both anemia and malnutrition are more prevalent in children under five.

Within the age span of 5–12 years, our analysis revealed clear inconsistencies in how severe malnutrition is classified depending on the growth reference employed. Using the WHO growth charts, peaks in the proportion of children identified as severely malnourished were evident at ages five and ten for both sexes **(Figure 3a, b)**. The higher prevalence at age five may reflect a gap in support services for children older than five, as most nutritional programs and interventions are focused on those under five. The rise at age ten could be linked to the delayed onset of puberty, which occurs roughly two years later in children with SCA compared to their peers without the condition [23].

Several limitations must be acknowledged. The cross-sectional nature of the study restricts the ability to determine how poor nutritional status influences long-term health outcomes, including morbidity and mortality. While the SCA-specific growth reference was constructed from secondary analyses of the SIT trial, it benefits from serial measurements spanning a median follow-up of 3.2 years (IQR 1.8–4.7; range 0–12.9 years) and encompasses data from over 25 SCA clinics across four high-income countries, representing the most comprehensive dataset currently available. Additionally, we did not include an age-matched cohort of children without SCA from northern Nigeria. However, in settings where severe malnutrition is common, the most appropriate comparator is not children without SCA, but rather children with SCA in resource-limited environments where severe acute malnutrition is rare.

Conclusions

In areas where malnutrition is widespread, accurately identifying children with SCA who are severely malnourished is vital, given the significant resources required for intervention. Our findings indicate that, among older Nigerian children with SCA, reliance on WHO growth references substantially overestimates the prevalence of severe malnutrition when compared to an SCA-specific reference derived from populations in high-income countries.

Acknowledgments: None.

Conflict of interest: None.

Financial support: None.

Ethics statement: None.

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