ORIGINAL RESEARCH

Nutritional Epidemiology and Public Health

CURRENT DEVELOPMENTS IN NUTRITION

Weight-for-Height *Z*-score Gain during Inpatient Treatment and Subsequent Linear Growth during Outpatient Treatment of Young Children with Severe Acute Malnutrition: A Prospective Study from Uganda

Jolly GK Kamugisha,[1,2] Betty Lanyero,[3] Nicolette Nabukeera-Barungi,[4] Christian Ritz,[2] Christian Mølgaard,[2] Kim F Michaelsen,[2] André Briend,[2,5] Ezekiel Mupere,[4] Henrik Friis,[2] and Benedikte Grenov[2]

[1]Mwanamugimu Nutrition Unit, Department of Pediatrics, Mulago National Referral Hospital, Kampala, Uganda; [2]Department of Nutrition, Exercise, and Sports, University of Copenhagen, Frederiksberg C, Denmark; [3]World Health Organization, Ethiopia Country Office, UNECA Compound, Addis Ababa, Ethiopia; [4]Department of Pediatrics and Child Health, College of Health Sciences, Makerere University, Kampala, Uganda; and [5]Center for Child Health Research, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

ABSTRACT

Background: Linear catch-up growth after treatment of severe acute malnutrition (SAM) is low, and little is known about the association between ponderal and subsequent linear growth.

Objective: The study assessed the association of weight-for-height *z*-score (WHZ) gain with subsequent linear growth during SAM treatment and examined its modifiers.

Methods: This was a prospective study, nested in a trial (ISRCTN16454889), among 6–59-mo-old children treated for SAM in Uganda. Weight, total length (TL), and knee-heel length (KHL) were measured at admission, weekly during inpatient therapeutic care (ITC), at discharge, and fortnightly during outpatient therapeutic care (OTC) for 8 wk. Linear regression was used to assess the association between WHZ gain during ITC and linear growth during OTC.

Results: Of 400 children, 327 were discharged to OTC and 290 were followed up for 8 wk. Mean WHZ gains were 0.45 in ITC and 1.24 in OTC, whereas mean height-for-age *z*-score (HAZ) declined by 0.41 during ITC and increased by 0.14 during OTC. WHZ gain during ITC was positively associated with HAZ, TL, and KHL gains during OTC [regression coefficients (β) (95% CI): 0.12 (0.09, 0.15) *z*-score; 3.1 (2.4, 3.8) mm and 0.5 (0.1, 0.7) mm, respectively]. The regression coefficients were highest for the middle tertile of WHZ gain with respect to HAZ and TL. Admission diarrhea and low plasma citrulline reduced the association between WHZ gain during ITC and HAZ and TL gain during OTC ($P < 0.001$). In contrast, pneumonia ($P = 0.051$) and elevated plasma C-reactive protein ($P < 0.001$) increased the association with TL gain, but reduced the association with KHL gain ($P < 0.001$).

Conclusions: Among children admitted with SAM, considerable WHZ gain during ITC was followed by very modest linear catch-up growth during OTC, with no indication of a WHZ gain threshold, above which linear growth was higher. To optimize linear growth in these children, early treatment of infections and conditions affecting the gut may be necessary. *Curr Dev Nutr* 2021;5:nzab118.

Keywords: stunting, linear growth, severe acute malnutrition, children, Uganda

Manuscript received May 20, 2021. Initial review completed September 4, 2021. Revision accepted September 9, 2021. Published online September 25, 2021.
Supported by Chr. Hansen A/S, University of Copenhagen, and Innovation Fund Denmark.
Author disclosures: The authors report no conflicts of interest. The sponsor did not have any role in the design, data collection, data analysis, or interpretation of the work presented.
Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/cdn/.

Address correspondence to JGKK (e-mail: jolly_kamugisha@yahoo.com).

Abbreviations: CRP, C-reactive protein; HAZ, height/length-for-age *z*-score; IGF-I, insulin-like growth factor I; ITC, inpatient therapeutic care; KHL, knee-heel length; MNU, Mwanamugimu Nutrition Unit; MUAC, mid-upper arm circumference; NCHS, National Center for Health Statistics; OTC, outpatient therapeutic care; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; TL, total length; WHZ, weight-for-length/height *z*-score.

Introduction

Stunting, defined as a height-for-age *z*-score (HAZ) below −2 of the median of the WHO child growth standards, affects approximately 144 million children of <5 years old globally (1). Moreover, many more children are affected by some degree of linear growth faltering (2, 3).

Stunting is associated with increased risks of infectious diseases, mortality, reduced cognitive and physical development, adverse

maternal reproductive outcomes, as well as noncommunicable diseases and reduced productivity in adulthood (2, 4–7). In addition, studies of children with severe acute malnutrition (SAM) have shown that SAM and stunting often co-exist in the same child (4, 8–16), and that >40% of these children are severely stunted (17–19).

While SAM and stunting are individually associated with an increased risk of mortality, children with multiple anthropometric deficits are at a greatly increased risk of mortality (4, 20). However, the current WHO treatment protocols for SAM (21) aim to rapidly restore weight-for-length/height *z*-score (WHZ) and/or midupper arm circumference (MUAC) deficits (22), with limited attention given to restoration of linear growth, even though the current targets of the World Health Assembly aim to reduce childhood stunting by 40% by 2025 (23). It is even more disturbing that studies of children recovering from SAM have failed to demonstrate catch-up in linear growth (9, 11, 13, 17, 18, 24–27).

Being wasted has recently been shown to increase the risk of subsequent stunting by 3-fold, while being stunted increases the risk of subsequent wasting by 1.5-fold (28). This highlights the need to better understand the relation between ponderal and linear growth in children with SAM. In addition, ponderal and linear growth is influenced by a number of dietary and environmental factors as well as infectious diseases (29, 30). Thus, knowing which factors modify the associations between WHZ and subsequent linear growth among children treated for SAM could help identify those at high risk of poor linear growth, for whom more attention may be needed.

The association between growth in weight and length in children with SAM has been studied before, but the findings are inconsistent (11, 12, 17, 18). In a study of hospitalized Jamaican children with SAM, Walker and Golden (11) showed that two-thirds of the children reached a weight-for-length of 85% of National Center for Health Statistics (NCHS) median before linear growth occurred and that most of the children reached a critical threshold WHZ of −1.3 prior to growth in length. However, concurrence of growth in both WHZ and HAZ has been reported in Bangladesh (12), while in Kenya, increase in WHZ was not associated with linear growth (17).

Knemometry is a method that measures knee-heel length (KHL), including length of the tibia and the soft tissues at both ends. It is a precise and sensitive measure of linear growth over short periods of time, detecting smaller differences with less variation than total length (TL) (31). Apart from a study of Bangladeshi hospitalized children with SAM that found a significant correlation between KHL growth and change in WHZ over time (12), data on association of WHZ and subsequent KHL growth in children with SAM remain limited.

The objective of this study was to assess the association of WHZ gain during inpatient therapeutic care (ITC) with subsequent linear growth during outpatient therapeutic care (OTC) and to identify possible modifiers. The main hypothesis was that children need to gain in WHZ before linear growth can take place, and that the association between WHZ gain and subsequent linear growth is modified by sex, edema, inflammation, or gut function at admission. We also hypothesized that these factors primarily modify the association with growth of the lower leg.

Methods

Study design, setting, and population

The study was a prospective cohort nested in a randomized clinical trial (www.isrctn.com, ISRCTN16454889), conducted among 400 children with SAM at Mwanamugimu Nutrition Unit (MNU), Mulago National Referral Hospital, Kampala, Uganda, from March 2014 to October 2015.

Inclusion and exclusion criteria

Children aged 6–59 mo old with complicated SAM, whose caregivers gave written informed consent were included. Complicated SAM was defined as WHZ <3 or MUAC <11.5 cm or bipedal pitting edema, plus any medical complications requiring hospitalization as per WHO guidelines (21).

Those in shock, severe respiratory distress, weighing <4.0 kg, having significant disabilities that affect response to nutritional therapy, as well those who had been admitted with SAM 6 mo prior to the study were excluded.

Patient management

Patients were managed based on the WHO (21) and the Ugandan integrated management of acute malnutrition (IMAM) protocols (32), as reported elsewhere (33–36). Briefly, children received therapeutic diets consisting of F-75, ready-to-use-therapeutic food (RUTF; Plumpy'nut®) or F-100 (Nutriset) and intravenous antibiotics, commonly ampicillin and gentamycin. During the stabilization phase, F-75 feeds were given at 100–130 mL/kg per day based on severity of edema. Where applicable, breastfeeding in-between the therapeutic feeds was supported. Rehydration Solution for the Malnourished (ReSoMal; Nutriset) was given to those with diarrhea based on WHO protocol (21). Once a child was stabilized, feeds were transitioned from F-75 to RUTF or F-100 according to WHO recommendations. During the rehabilitation phase of ITC, children received RUTF or F-100, plus a nutritious local dish (*kitobeero*). The feeds were increased based on the child's body weight and appetite, and provided between 150 to 200 kcal/kg per day. The children who met the WHO 2013 (21) criteria for discharge were given a 2-wk supply of RUTF and transferred to OTC. Caregivers and their children returned for follow-up at 2, 4, 6, and 8 wk. During follow-up, for each child, a clinical examination was conducted, anthropometry taken, and RUTF refilled. Discharge criteria from OTC was based on WHO 2013 guidelines (21), as detailed elsewhere (36).

Data collection

At admission, the child's sociodemographic information and breastfeeding and medical history were obtained. A study nurse collected data on the household and, where possible, on the mothers' age, education, occupation, and marital status. The study nurse also collected data on food insecurity using the Household Food Insecurity Access Scale (HFIAS) (37). A study medical doctor performed a full physical examination. Anthropometry during ITC and OTC was measured by nutritionists who were specifically recruited and trained by the parent trial management team. A caregiver was requested to completely or partially undress the child depending on the nature of the measurements to be taken. Child body weight, MUAC, and TL were measured in triplicate at admission, weekly during hospitalization, at discharge, and during OTC visits in accordance with WHO guidelines (21), and KHL was

measured 5 times at the same time points. Single body-weight measurements were also taken between 07:00 and 08:00 h during ITC. Body weight was measured to the nearest 100 g using a digital scale (Seca 813; Hamburg, Germany). MUAC was assessed to the nearest 1 mm using standard non-elastic color-coded tapes for children aged <5 y (Child 11.5 red/pac-50; UNICEF). Measurements were performed on the left arm. TL (encompassing both recumbent and standing height) was measured using an infant length board (Infant/Child Shorr-Board®; Maryland, USA) to the nearest 1 mm (standing height was measured for children ≥24 mo of age). KHL was measured on the left lower leg with a digital hand-held caliper with a resolution of 0.01 mm (Mitutoyo, Germany) mounted with knee and heel caps cast in hard plastic (38). The set of 5 measurements, each aimed at the same position (highest spot of lateral femoral condyle on the knee and under the heel straight down from lateral malleolus of fibula) and same applied pressure, was performed and then a print-out of statistical calculations (mean, SD, SE, minimum and maximum values) was instantly available by use of a mobile field printer attached to the knemometer. If the SD was >1 mm, the set of 5 measurements was repeated. Mothers' anthropometry was measured on admission only. Triple body-weight measurements were taken using a digital scale (Seca 813; Hamburg, Germany) to the nearest 100 g and height, using an adult height board (adult Shorr-Board®; Maryland, USA) to the nearest 1 mm, with no shoes and extra clothes. The average was calculated in case of repeated measurements. WHO Anthro version 3.2.2 (15) was used to calculate WHZ and HAZ. BMI for the mother was calculated as weight (kg)/height squared (m^2) (39).

Study pediatricians and nutritionists were responsible for clinical and nutritional assessment of the patients, respectively, and jointly decided on patient management.

Laboratory tests

Four milliliters of venous blood was collected into EDTA-treated Vacutainer tubes (Becton Dickinson; Franklin lakes, NJ USA). Samples for complete blood counts were analyzed using a Coulter counter at the Uganda Cancer Institute laboratory. HIV sero-status was assessed at the MNU side laboratory using Determine HIV-1/2 (Abbot Laboratories USA) rapid tests and HIV-1/2 Stat-Pak Dipstick Assay kit for children aged ≥18 mo. For those <18 mo of age, their HIV status was confirmed using an HIV DNA/polymerase chain reaction (PCR) test done at Baylor HIV clinic. Plasma was obtained by centrifuging at 1300–2200 *g* at ambient temperature for 10 min, and stored at −80°C prior to shipment on dry ice to the University of Copenhagen, Denmark. Plasma C-reactive protein (CRP) was analyzed by the high-sensitivity kit on an ABK Pentra 400 (Horiba; Montpellier, France). Detection of plasma citrulline has been described in detail elsewhere (40). Briefly, the LC-MS method (41) was used. Samples were processed with Sirocco protein precipitation plate (Waters) and separated on an ACQUITY UPLC HSS T3 Column (Waters) using an ultra-performance LC in tandem with triple quadrupole detector MS. L-Citrulline-4,4,5,5-d4 (Sigma-Aldrich) was used as an internal standard. Quantification of citrulline was carried out using QuanLynx (Waters).

Ethical issues

The study followed the Helsinki Declaration and the Ugandan guidelines. Ethical approval was obtained from Makerere University School of Medicine Research Ethics Committee, the Uganda National Council for Science and Technology, as well as Uganda National Drug Authority and a consultative approval from the Danish National Committee of Health Research Ethics. All parents or legal guardians provided written informed consent before their child was enrolled in the study. Caregivers were given oral and written detailed explanations regarding the study and procedures to be conducted. Regardless of participation in the study, all children received standard routine medical and nutritional therapy. Caregivers received a modest transport compensation.

Study outcomes

The main study outcomes were gains in HAZ, TL, and KHL from discharge to 8 wk during OTC. Other outcomes were weight gain during OTC, plus HAZ, TL, and KHL gain during ITC.

The main exposure variable was WHZ gain during ITC (from admission to discharge). Other exposures of interest were WHZ at admission, WHZ at discharge, age, sex, and HIV status, as well as edema, pneumonia, diarrhea, plasma CRP, and citrulline at admission.

Gains in TL, KHL, WHZ, and HAZ during ITC or OTC were calculated as assessments at discharge minus assessments at baseline or assessments at 8 wk minus assessments at discharge, respectively. Gains in TL, KHL, WHZ, and HAZ per week during ITC or OTC were calculated as assessments at discharge minus assessments at baseline or assessments at 8 wk minus assessments at discharge/number of weeks from baseline to discharge or from discharge to 8 wk, respectively. Weight gain (grams) during ITC was calculated as (discharge weight − minimum weight) in kilograms × 1000. Because all children had no edema or diarrhea and/or dehydration at discharge, weight gain (grams) during OTC was calculated as (weight at 8 wk − discharge weight) in kilograms × 1000. Weight gain (grams/kilograms per day) during ITC or OTC was calculated as weight gain (grams)/minimum weight or discharge weight (kilograms)/number of days from minimum weight to discharge or from discharge to 8 wk, respectively.

Data handling and statistical analysis

Data were double-entered into Epidata version 3.1 and analysis was performed using R version 3.5.1 (R Core Team, 2017), with the extension packages plyr, dplyr, and multcomp. Baseline characteristics were summarized using means ± SDs for normally distributed continuous variables or median (IQR) for non–normally distributed continuous variables, and percentages (*n*) for categorical variables. Both for ITC and OTC, a 2-sample *t* test was used to examine differences in mean gain in weight, TL, KHL, WHZ, and HAZ between sex and edema at admission. Chi-square test was used to compare the percentage of KHL relative to TL at baseline, discharge, and end of follow-up between sex and edema at admission. Associations between WHZ gain during ITC, WHZ at admission, or WHZ at discharge and HAZ, TL, and KHL gain during OTC were investigated using linear regression. In addition, these associations were investigated within strata defined by tertiles of WHZ gain during ITC, WHZ at admission, and WHZ at discharge. Both overall and strata-specific analyzes were controlled for age, sex, edema at admission, and HIV status. Furthermore, modifiers of the associations between WHZ gain during ITC and HAZ, TL, and KHL gain during OTC were investigated by fitting linear regression models that included interaction terms between WHZ gain during ITC and each of the following variables: sex, edema, pneumonia, diarrhea, plasma CRP, and

TABLE 1 Baseline characteristics of 400 children admitted with severe acute malnutrition[1]

Characteristic	*n*	Values
Child		
Age, mo	400	15.0 (11.2; 19.2)
Male sex	400	230 (58%)
Midupper arm circumference, cm	392	11.6 ± 1.5
Total length, cm	398	71.2 ± 6.2
Knee-heel length, mm	380	186.8 (173.9; 202.6)
Weight, kg	399	6.7 (5.7–7.9)
Weight-for-length/height *z*-score	387	−2.9 (−3.7; −1.5)
Length/height-for-age *z*-score	387	−3.1 ± 1.4
Currently breastfeeding	374	54 (14%)
Edema present	399	
No		138 (35%)
Yes		261 (65%)
Diarrhea	400	241 (60%)
Pneumonia	400	68 (17%)
HIV status	368	
Positive		43 (12%)
Negative, exposed		72 (20%)
Negative		253 (69%)
Plasma C-reactive protein	352	
<10 mg/L		134 (38%)
≥10 mg/L		218 (62%)
Hemoglobin, g/dL	298	8.9 (7.8; 10.1)
Plasma citrulline	296	
<10 μmol/L		235 (79%)
≥10 μmol/L		61 (21%)
Mother		
Age, y	356	24.0 (21.0; 28.0)
BMI, kg/m^2	334	22.7 (20.9; 25.3)
Education	385	
Primary		181 (47%)
Secondary or higher		153 (40%)
HIV positive	340	109 (32%)
Household	389	
Household Food Insecurity Access Scale score[2]		5.8 ± 7.0

[1]Values are number of children with data and medians (IQR) or means ± SDs or *n* (%).
[2]A measure of food insecurity in the household in the past 4 wk on a scale from 0 to 27; the higher the score, the more food insecure the household has been.

citrulline at admission, controlled for age, sex, edema at admission, and HIV status. *P* values were regarded as statistically significant if <0.05.

Results

Of the 400 children enrolled, the median (IQR) age was 15.0 (11.2, 19.2) mo, 42% were female, and 65% presented with edema (**Table 1**). Of these, 293 (73%) were followed up at 8 wk, of whom 290 (99%) were included in the analysis of outcomes (**Figure 1**).

During ITC, the children had a mean (± SD) weight gain of 719 (± 501) g or 6.6 (± 5.0) g/kg/d (**Table 2**). The weight gain was lower in children with edema at admission. The mean gains in TL and KHL were slightly negative, and lower in those with edema at admission. During OTC, the mean (± SD) weight gain of 1177 (± 796) g or 3.1 (± 2.2) g/kg per day was accompanied by a 19-mm gain in TL, of which 8 mm was KHL. There was no difference in weight, TL, KHL, WHZ, and HAZ gain by sex or edema at admission. The gains in weight and length translated into a 0.45 increase in WHZ and a 0.41 decrease in HAZ during ITC and a 1.24 increase in WHZ and 0.14 increase in HAZ during OTC, respectively (**Table 3**). **Figure 2** shows weekly (in ITC) and fortnightly (in OTC) changes in absolute WHZ and HAZ. Mean absolute WHZ decreased from approximately −2.62 *z*-score at week 0 (admission) to approximately −2.90 *z*-score after 3 wk in ITC, while mean absolute HAZ decreased from approximately −3.09 *z*-score to approximately −3.45 *z*-score (Figure 2A). In contrast, during OTC, mean absolute WHZ increased steadily from approximately −2.07 *z*-score at week 0 (discharge) and peaked at approximately −0.82 *z*-score after 8 wk, and HAZ decreased slightly from approximately −3.55 *z*-score to approximately −3.39 *z*-score (Figure 2B). At baseline, discharge, and end of follow-up, KHL comprised 27% of TL, with no differences by sex or edema at admission ($P > 0.7$; data not shown).

Association between ponderal and subsequent linear growth

As shown in **Table 4**, after adjusting for age, sex, edema at admission, and HIV status, overall WHZ gain in ITC was positively associated with HAZ, TL, and KHL gain during OTC ($P < 0.001$). The regression

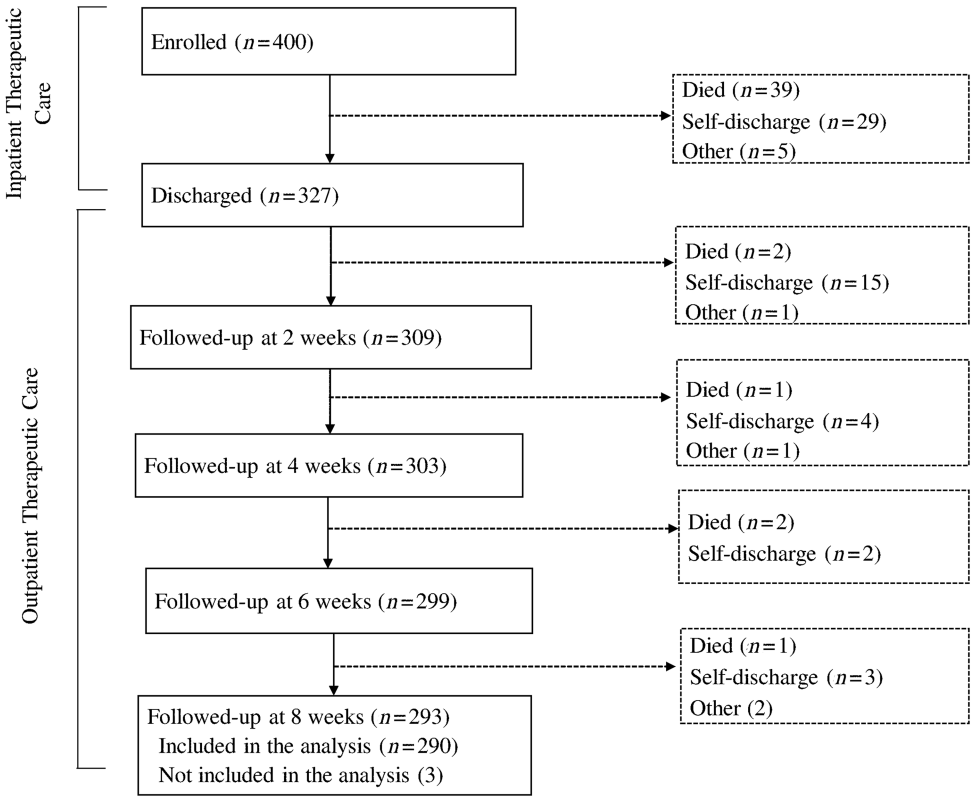

FIGURE 1 Flow chart of study participants.

coefficients reflect that, for each 1-unit higher WHZ gain during ITC, there was a 0.12-unit higher increase in HAZ, corresponding to 3.1-mm higher increase in TL, of which 0.5 mm was KHL gain during OTC. When stratified by tertile, the associations were again positive among those in the lower tertile. With regard to the middle and upper tertiles, there were positive associations with HAZ and TL gain during OTC, and the regression coefficients were higher among those in the middle tertile than in the upper tertile. In contrast, WHZ at admission (overall and tertiles) was negatively associated with all the 3 length measurements ($P < 0.001$). There were no associations between overall WHZ at discharge and linear growth during OTC. However, there were positive associations with TL gain among children in the lower tertile, and with HAZ and TL gain among those in the middle and upper tertiles. Unadjusted analyses are shown in **Supplemental Table 1**.

Modifiers of the association between ponderal and subsequent linear growth

Table 5 shows how age-sex-edema-HIV adjusted associations between WHZ gain during ITC and HAZ, TL, and KHL gain during OTC are modified. The associations with HAZ, TL, and KHL gain during OTC were reduced by male sex ($P < 0.001$), whereas they were increased by edema at admission ($P = 0.002$). Also, the associations with HAZ and TL gain were reduced by admission diarrhea and low plasma citrulline ($P < 0.001$). In contrast, both pneumonia ($P = 0.051$) and elevated plasma CRP ($P < 0.001$) increased the associations with TL gain, but reduced the associations with KHL gain ($P < 0.001$). Unadjusted analyses are shown in **Supplemental Table 2**.

Discussion

This study found that there was minimal change in HAZ during SAM treatment. Yet, there was a positive association between WHZ gain during ITC and subsequent linear growth during OTC, but there was no indication of a WHZ gain above which there was accelerated linear growth. There was a relatively large KHL gain during OTC (41% of TL gain). Admission diarrhea and low plasma citrulline reduced the association between WHZ gain during ITC and HAZ and TL gain during OTC. In contrast, pneumonia and elevated plasma CRP increased the association with TL gain but reduced the association with KHL gain.

Ponderal and subsequent linear growth

Overall WHZ gain during ITC was positively associated with HAZ, TL, and KHL gain during OTC. Furthermore, similar associations with gains in all 3 length measurements were seen among those in the lower tertile of WHZ gain (≤ 0). However, among those in the middle and upper tertiles with WHZ gain >0, positive associations were seen with HAZ and TL only, indicating that the greater the WHZ gain during ITC, the greater the subsequent linear growth of the trunk, but not KHL, among children in these tertiles. Similar to results of the current study, 2 studies in Jamaica and Niger found that recovery in WHZ precedes

TABLE 2 Weight, length, and knee-heel length gain during in- and outpatient therapeutic care among children admitted with severe acute malnutrition, both overall and stratified by sex and edema at admission[1]

	Inpatient therapeutic care						Outpatient therapeutic care					
Weight gain	***n***	**g**	***P***	***n***	**g/kg per day**	***P***	***n***	**g**	***P***	***n***	**g/kg per day**	***P***
Total	326	719 ± 501		325	6.6 ± 5.0		291	1177 ± 796		290	3.1 ± 2.2	
Sex[2]			0.736			0.564			0.525			0.333
Male	192	727 ± 453		191	6.5 ± 4.3		173	1153 ± 845		172	3.0 ± 2.3	
Female	134	708 ± 562		134	6.8 ± 5.8		118	1212 ± 716		118	3.2 ± 2.1	
Edema[2]			0.080			0.001			0.281			0.751
No	107	791 ± 522		107	8.0 ± 5.3		92	1105 ± 759		92	3.1 ± 2.3	
Yes	219	684 ± 487		218	5.9 ± 4.6		199	1211 ± 811		198	3.0 ± 2.2	
Total length gain	***n***	**mm**	***P***	***n***	**mm/wk**	***P***	***n***	**mm**	***P***	***n***	**mm/wk**	***P***
Total	323	−5.3 ± 12.5		322	−2.2 ± 6.3		291	19.3 ± 14.1		290	2.4 ± 1.7	
Sex[2]			0.812			0.732			0.591			0.604
Male	190	−5.4 ± 11.1		189	−2.3 ± 5.3		172	19.7 ± 13.7		171	2.4 ± 1.7	
Female	133	−5.1 ± 14.2		133	−2.1 ± 7.5		119	18.8 ± 14.6		119	2.3 ± 1.8	
Edema[2]			0.001			0.013			0.531			0.480
No	219	−2.2 ± 10.7		218	−1.1 ± 4.9		92	18.6 ± 13.9		92	2.3 ± 1.7	
Yes	104	−6.7 ± 13.0		104	−2.8 ± 6.8		199	19.7 ± 14.2		198	2.4 ± 1.7	
Knee-heel length gain	***n***	**mm**	***P***	***n***	**mm/wk**	***P***	***n***	**mm**	***P***	***n***	**mm/wk**	***P***
Total	315	−0.1 ± 5.8		314	0.0 ± 3.0		279	8.0 ± 5.1		278	1.0 ± 0.6	
Sex[2]			0.304			0.274			0.534			0.551
Male	183	0.2 ± 6.9		182	0.2 ± 3.6		165	8.1 ± 4.9		164	1.0 ± 0.6	
Female	132	−0.4 ± 3.8		132	−0.2 ± 1.9		114	7.7 ± 5.5		114	1.0 ± 0.7	
Edema[2]			< 0.001			0.007			0.521			0.492
No	105	1.3 ± 3.0		105	0.5 ± 1.6		89	7.7 ± 5.0		89	0.9 ± 0.6	
Yes	210	−0.7 ± 6.7		209	−0.2 ± 3.5		190	8.1 ± 5.2		189	1.0 ± 0.6	

[1] Values are means ± SDs unless otherwise indicated. The median (IQR) duration of in- and outpatient therapeutic care was 17 (12–22) and 56 (42–58) days, respectively; the latter was predetermined by the parent trial.
[2] *P* values were derived by using a 2-sample *t* test.

TABLE 3 Weight-for-height and height-for-age *z*-score gain during in- and outpatient therapeutic care among children admitted with severe acute malnutrition, overall and stratified by sex and edema at admission[1]

	Inpatient therapeutic care						Outpatient therapeutic care					
	n	*z*-score	*P*	*n*	*z*-score/wk	*P*	*n*	*z*-score	*P*	*n*	*z*-score/wk	*P*
Weight-for-height *z*-score gain												
Total	323	0.45 ± 1.04		322	0.18 ± 0.45		290	1.24 ± 1.13		289	0.15 ± 0.14	
Sex[2]			0.660			0.814			0.733			0.694
Male	190	0.47 ± 0.99		189	0.19 ± 0.42		172	1.22 ± 1.22		171	0.15 ± 0.15	
Female	133	0.41 ± 1.10		133	0.18 ± 0.49		118	1.27 ± 0.98		118	0.16 ± 0.12	
Edema[2]			< 0.001			< 0.001			0.649			0.722
No	105	0.98 ± 0.88		105	0.40 ± 0.36		92	1.29 ± 1.15		92	0.16 ± 0.14	
Yes	218	0.19 ± 1.01		217	0.08 ± 0.44		198	1.22 ± 1.12		197	0.15 ± 0.14	
Height-for-age *z*-score gain												
Total	324	−0.41 ± 0.47		323	−0.16 ± 0.22		291	0.14 ± 0.51		290	0.02 ± 0.06	
Sex[2]			0.685			0.541			0.172			0.172
Male	190	−0.42 ± 0.45		189	−0.17 ± 0.20		172	0.17 ± 0.52		171	0.02 ± 0.06	
Female	134	−0.40 ± 0.51		134	−0.15 ± 0.25		119	0.09 ± 0.49		119	0.01 ± 0.06	
Edema[2]			0.027			0.071			0.100			0.092
No	105	−0.33 ± 0.42		105	−0.13 ± 0.19		92	0.07 ± 0.51		92	0.01 ± 0.06	
Yes	219	−0.45 ± 0.49		218	−0.18 ± 0.24		199	0.18 ± 0.50		198	0.02 ± 0.06	

[1] Values are means ± SDs unless otherwise indicated. The median (IQR) duration of in- and outpatient therapeutic care was 17 (12–22) and 56 (42–58) days, respectively, but the latter was predetermined by the parent trial.

[2] *P* values were derived by using a 2-sample *t* test.

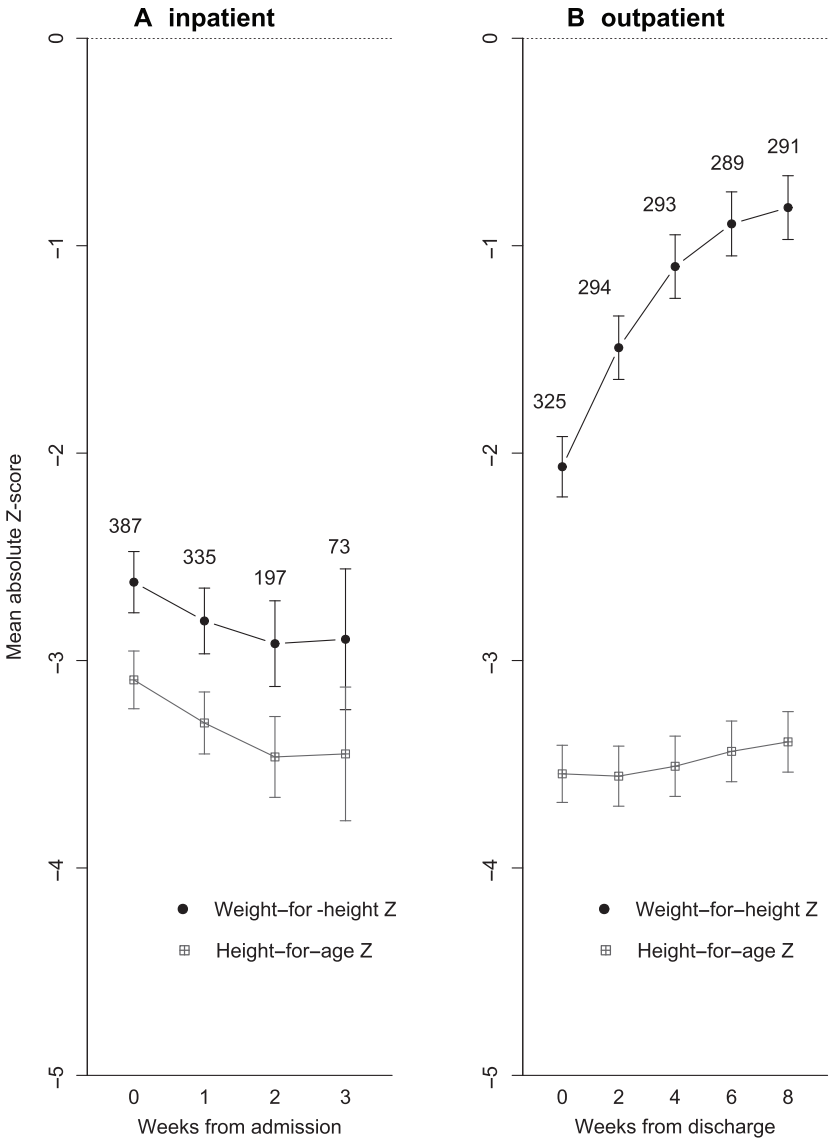

FIGURE 2 Absolute weight-for-height and height-for-age *z*-score during ITC (A) and OTC (B) presented as means (95% CI) for children with severe acute malnutrition. Data are based on the number of children remaining in ITC and OTC at a given time point. ITC, inpatient therapeutic care; OTC, outpatient therapeutic care.

HAZ gain in children treated for SAM (11, 18). In the Jamaican study, among a subgroup mainly consisting of those who were non-edematous and more severely stunted at baseline, it was found that linear growth started after the majority of the children had attained a minimum weight-for-length of 85% of the NCHS median. The same study also found minimal change in HAZ during rehabilitation (11). Similarly, the Niger study of children recovering from wasting (non-edematous SAM) found that nutritional recovery (WHZ ≥ -2 or MUAC ≥ 12.5 cm) preceded gain in HAZ in 77% of those who had catch-up in linear growth. They also demonstrated that, during nutritional rehabilitation, there is a rapid increase in WHZ accompanied by a decline in HAZ and, after rehabilitation, there is a slower increase in WHZ as well as a slower decline in HAZ (18). Absence of a clear threshold of WHZ gain at which there is a start of growth in HAZ has also been reported in 2 other studies of children with SAM in Bangladesh and Kenya (12, 17). However, WHZ and HAZ gains were measured concurrently, unlike in our study. Yet, the Kenyan study (17) found that, between enrollment (after the stabilization phase of ITC) and 1 mo of OTC treatment, WHZ had the largest increase, whereas HAZ had the largest decrease, also indicating that WHZ gain takes precedence over HAZ gain.

On the other hand, the positive association with subsequent TL gain observed in this study concurs with results of a study of 127 Jamaican stunted children, showing that WHZ gain was positively associated with subsequent gain in height (43). However, the regression coefficients were higher than what was seen in this study, perhaps because of the differences in study populations. The Jamaican study (43) involved only stunted children who were not severely acutely malnourished.

TABLE 4 Associations between weight-for-height *z*-score gain during inpatient therapeutic care, weight-for-height *z*-score at admission and at discharge (exposure), and height-for-age *z*-score and total and knee-heel length gain during outpatient therapeutic care (outcome), both overall and stratified by tertile of weight-for-height *z*-score[1]

		Outpatient therapeutic care, β (95% CI)		
Inpatient therapeutic care	***n***	**Height-for-age *z*-score gain**	**Total length gain, mm**	**Knee-heel length gain, mm**
Weight-for-height *z*-score gain				
Overall[2]	323	0.12 (0.09; 0.15)	3.1 (2.4; 3.8)	0.5 (0.1; 0.7)
Tertiles				
Lower (≤0)	108	0.10 (0.03; 0.16)	3.3 (1.5; 5.1)	0.9 (0.2; 1.6)
Middle (>0 to ≤0.9)	108	0.23 (0.11; 0.35)	5.7 (2.4; 9.0)	−0.9 (−2.2; 0.4)
Upper (>0.9)	107	0.13 (0.09; 0.17)	2.9 (1.8; 4.0)	0.3 (−0.2; 0.7)
Admission weight-for-height *z*-score				
Overall	387	−0.06 (−0.09; −0.04)	−1.4 (−2.0; −0.8)	−0.3 (−0.5; −0.1)
Tertiles				
Lower (≤−3.38)	129	−0.07 (−0.09; −0.05)	−1.6 (−2.2; −1.0)	−0.4 (−0.6; −0.1)
Middle (−3.37 to −1.98)	129	−0.08 (−0.11; −0.05)	−1.7 (−2.4; −0.9)	−0.4 (−0.7; −0.1)
Upper (≥−1.96)	129	−0.15 (−0.21; −0.10)	−3.9 (−5.3; −2.4)	−1.1 (−1.7; −0.6)
Discharge weight-for-height *z*-score				
Overall	325	0.01 (−0.02; 0.03)	0.5 (−0.1; 1.1)	−0.0 (−0.3; 0.2)
Tertiles				
Lower (≤−3.38)	110	0.01 (−0.01; 0.04)	0.7 (0.0; 1.3)	−0.1 (−0.3; 0.2)
Middle (−3.37 to −2.0)	108	0.08 (0.04; 0.12)	2.4 (1.3; 3.4)	−0.0 (−0.4; 0.4)
Upper (≥−1.96)	107	0.10 (0.03; 0.17)	2.7 (0.7; 4.7)	−0.8 (−1.5; 0.0)

[1]Values are shown as numbers of children per analysis, regression coefficients (β), and corresponding 95% CIs obtained from linear regression models, adjusted for age, sex, edema at admission, and HIV status.
[2]Discharge value − admission value.

Further, in agreement with this study, Doherty et al. (12) found that KHL gain is positively correlated with WHZ gain in Bangladeshi children recovering from SAM. The authors suggested that KHL gain initially behaves as a ponderal index. However, children in the Bangladeshi study received intensive inpatient nutritional rehabilitation for 15 d and had their WHZ and HAZ measured concurrently (after every 15 d), unlike in this study, where WHZ gain in ITC was associated with KHL gain during OTC. Knemometry has been shown to be a more sensitive measure of linear growth over short periods than measurement of TL (31). As such, the gain in KHL observed in the Bangladeshi study (12) may have been mediated by early recovery in WHZ following the intensive nutritional treatment that the children received during hospitalization. In addition, measurement of KHL gain involves measuring changes in the length of the tibia and fibula plus changes in the soft tissues covering these (31). Thus, changes in tissue edema as well as fat deposition in the suprapatellar and heel-fat pads that take place during nutritional rehabilitation are likely to influence KHL growth.

Furthermore, this study has shown that, during ITC, there is a decline in HAZ, TL, and KHL, with a higher decline seen in those with edema at admission. In contrast, during OTC, there is an increase in all 3 length measurements, with no difference by edema at admission. This finding is quite unexpected as it is often believed that children cannot lose length. This does not seem to be due to measurement error because triple length measurements were taken during both ITC and OTC. However, loss of edema and nearly no fat deposition during ITC may have caused the observed apparent decrease in all 3 length measurements. This finding concurs with those of a study of children admitted with SAM in Jamaica, in which a decrease in HAZ at discharge was reported in a subgroup of those with kwashiorkor (edematous SAM) (11). Likewise, in Kenya, Ngari et al. (17) reported HAZ loss after 1 mo of follow-up in children treated for SAM.

The mechanisms behind the relation between growth in weight and length are unclear, but some studies have reported involvement of leptin (44). In a study of children with mild malnutrition [defined as weight-for-height between 90% and 80% of the median according to Waterlow criteria (45)], Büyükgebiz et al. (44) found a much higher mean leptin concentration in children who showed catch-up in linear growth compared with those who did not, despite the significant weight gain seen in both groups. Moreover, studies of children with SAM in Kenya and Uganda have shown that leptin concentrations are low at admission (46, 47), but increase relative to treatment period (46). Thus, the increased stores of leptin-producing fat cells during recovery from SAM may be one mechanism through which sufficient weight gain could increase bone and linear growth.

Modifiers of associations between ponderal and linear growth

While pneumonia does not modify the association between WHZ gain during ITC and HAZ gain during OTC, it tends to increase the association (nonsignificantly) for TL gain, but reduces it for KHL gain during OTC. Therefore, with pneumonia, the body seems to sacrifice knee-heel growth to maintain trunk growth. Interestingly, we see the same pattern for elevated plasma CRP. This is not surprising, since pneumonia precipitates an acute-phase response (48). Data on modifiers of the relation between weight gain during ITC and subsequent linear growth during OTC in children with SAM are rare. In a recent review, Millward (49) reported that inflammation inhibits endochondral ossification through the action of mediators such as proinflammatory cytokines, the activin A-follistatin system, glucocorticoids, and fibroblast growth factor

TABLE 5 Potential modifiers of association between weight-for-height *z*-score gain during inpatient therapeutic care and height-for-age *z*-score and total and knee-heel length gain during outpatient therapeutic care[1]

	Outpatient therapeutic care								
	Height-for-age *z*-score gain			Total length gain, mm			Knee-heel length gain, mm		
Inpatient therapeutic care	*n*	Δ*β* (95% CI)	*P*	*n*	Δ*β* (95% CI)	*P*	*n*	Δ*β* (95% CI)	P
Sex (male vs. female)	223	−0.08 (−0.10; −0.06)	< 0.001	223	−2.76 (−3.33; −2.20)	< 0.001	212	−0.66 (−0.89; −0.43)	< 0.001
Condition at admission									
Edema (vs. no edema)	223	0.04 (0.02; 0.07)	0.002	223	1.92 (1.18; 2.66)	< 0.001	212	0.78 (0.48; 1.07)	< 0.001
Pneumonia (vs. no pneumonia)	223	0.02 (−0.01; 0.05)	0.169	223	0.74 (−0.00; 1.49)	0.051	212	−0.66 (−0.96; −0.36)	< 0.001
Diarrhea (vs. no diarrhea)	223	−0.04 (−0.07; −0.02)	< 0.001	223	−1.79 (−2.36; −1.23)	< 0.001	212	−0.04 (−0.28; 0.19)	0.716
Elevated plasma CRP (vs. normal)[2]	211	0.10 (0.08; 0.13)	< 0.001	211	2.81 (2.22; 3.39)	< 0.001	202	−0.50 (−0.74; −0.25)	< 0.001
Low plasma citrulline (vs. normal)[3]	223	−0.10 (−0.13; −0.08)	< 0.001	223	−2.87 (−3.54; −2.21)	< 0.001	212	−0.04 (−0.31; 0.23)	0.764

[1]Values are shown as numbers of children per analysis, differences in regression coefficients (Δ*β*) and corresponding 95% CIs and *P* values (for test of no difference in regression coefficients, i.e., no modification) obtained from linear regression models with interaction terms between correlates and weight-for-height *z*-score gain during inpatient therapeutic care (discharge value − admission value), adjusted for age, sex, edema at admission, and HIV status. CRP, C-reactive protein.
[2]Defined as plasma CRP ≥10 mg/L.
[3]Defined as plasma citrulline <10 μmol/L.

21. Also, clinically low-grade inflammation characterized by elevated acute-phase reactants such as CRP is usually accompanied by reduced circulating insulin-like growth factor I (IGF-I), a main growth factor in childhood. A study of Zimbabwean stunted infants found higher concentrations of plasma CRP and other inflammatory markers and lower concentrations of biomarkers of the growth hormone–IGF axis (IGF-I, insulin-like growth factor binding protein 3) among cases compared with controls (50). In the same study, IGF-I was negatively correlated with CRP, indicating that low-grade inflammation resulting from infections likely modulates linear growth through suppression of the growth hormone–IGF axis. Furthermore, elevated plasma CRP has been shown to be associated with loss of appetite and reduced food intake (51–53). Thus, appetite suppression may be another mechanism through which inflammation may modulate linear growth.

In addition, a different pattern was seen for admission diarrhea, whereby the associations of WHZ gain during ITC with HAZ and TL gain during OTC were reduced in those with this condition. This concurs with results of a pooled analysis of data from 9 community-based studies in 5 countries showing that a higher cumulative burden of diarrhea prior to 24 mo of life was associated with an increased prevalence of stunting at 24 mo of age (54). Also, an analysis of longitudinal data from 7 cohort studies found that cumulative diarrhea burden was associated with a small but measurable decrease in linear growth (55). In addition, in this study, low plasma citrulline at admission reduced associations of WHZ gain during ITC with HAZ and TL gain during OTC, similar to what was seen for diarrhea. This is plausible as diarrhea rarely gives a strong acute-phase response, but rather impairs absorption, just like low plasma citrulline (42). These results agree with those of 2 studies in Uganda and Brazil. The Ugandan study, based on the same cohort of children as the current study, demonstrated that children with SAM have significantly reduced plasma citrulline concentrations compared with their community controls (40), indicating reduced enterocyte mass and perhaps increased risk of impaired nutrient absorption in these children. In addition, the Brazilian study of children with wasting or stunting found that higher plasma citrulline concentrations predicted better TL growth in initially stunted girls than in boys (56). Further, in this study, we see an overall negative difference—that is, the association between WHZ gain during ITC and HAZ and TL gain during OTC is weaker in those with both diarrhea and low plasma citrulline at admission.

Taken together, the data suggest that, if absorption capacity is impaired, then weight gained during ITC is not supporting length gain of the trunk. This perhaps indicates that, while macronutrients providing energy are absorbed and deposited, nutrients required for linear growth of the trunk are not. In contrast, if there is inflammation, then weight gained during ITC is leading to accelerated length gain of the trunk but sacrificing leg length growth, maybe reflecting that the gut and absorptive capacity are not primarily affected.

Limitations

Although inherent in the hypothesis, it is a potential problem that height is part of both the exposure (WHZ gain during ITC) and outcomes (linear growth during OTC). As such, a high WHZ gain not only reflects a high weight gain but also a low height gain. However, this is not likely to be a major problem given that the exposure and outcomes were measured in different time periods, and linear growth was limited in ITC.

Our study was conducted at a national referral hospital, where patients usually present with advanced disease. Thus, our findings may not be applicable in settings where children are less ill. Finally, we also considered it a limitation that the follow-up was only 8 wk.

Conclusions

Among children admitted with SAM, considerable WHZ gain during ITC was followed by very modest linear catch-up growth during OTC, and there was no indication of a WHZ gain threshold above which there was accelerated linear growth. Also, WHZ gain during ITC was positively associated with linear growth during OTC, and the regression coefficients were highest for the middle tertile of WHZ gain with respect to HAZ and TL gain. Moreover, admission diarrhea and low plasma citrulline reduced the association between WHZ gain during ITC and HAZ and TL gain during OTC, whereas pneumonia and elevated plasma CRP increased the association with TL gain but reduced the association with KHL gain during OTC. There is need to strengthen prevention, early diagnosis, and treatment of infections plus other conditions associated with impaired gut function in children with SAM, as this may be beneficial in recovery of linear growth in these children. In order to optimize recovery in linear growth among children treated for SAM, further research is needed to understand the regulation of ponderal compared with linear growth and to determine factors modifying linear growth of the different body parts.

Acknowledgments

The authors' responsibilities were as follows—JGKK, HF, and BG: contributed to the study design; NN-B, BG, and BL: collected the data; JGKK and CR: conducted data analysis; JGKK, CR, HF, BG, AB, KFM, CM, and EM: were involved in data interpretation; JGKK: prepared the manuscript and had primary responsibility for the final content; and all authors: critically reviewed and read and approved the final manuscript.

References

1. United Nations Children's Fund (UNICEF); World Health Organization; International Bank for Reconstruction and Development/The World Bank. Levels and trends in child malnutrition: key findings of the 2020 edition of the Joint Child Malnutrition Estimates [Internet]. Geneva (Switzerland): World Health Organization; 2020 [cited 2020 Jul 28]. Available from: https://www.who.int/publications/i/item/jme-2020-edition.
2. de Onis M, Branca F. Childhood stunting: a global perspective. Matern Child Nutr 2016;12:12–26.
3. Perumal N, Bassani DG, Roth DE. Use and misuse of stunting as a measure of child health. J Nutr 2018;148:311–5.
4. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, Mathers C, Rivera J. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet North Am Ed 2008;371:243–60.
5. Prendergast AJ, Humphrey JH. The stunting syndrome in developing countries. Paediatr Intl Child Health 2014;34:250–65.
6. Dewey KG, Begum K. Long-term consequences of stunting in early life. Matern Child Nutr 2011;7:5–18.
7. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. Lancet North Am Ed 2007;369:60–70.
8. Burrell A, Kerac M, Nabwera H. Monitoring and discharging children being treated for severe acute malnutrition using mid-upper arm circumference: secondary data analysis from rural Gambia. International Health 2017;9:226–33.
9. Kangas ST, Salpéteur C, Nikièma V, Talley L, Ritz C, Friis H, Briend A, Kaestel P. Impact of reduced dose of ready-to-use therapeutic foods in children with uncomplicated severe acute malnutrition: a randomised non-inferiority trial in Burkina Faso. PLoS Med 2019;16:e1002887.
10. Chase RP, Kerac M, Grant A, Manary M, Briend A, Opondo C, Bailey J. Acute malnutrition recovery energy requirements based on mid-upper arm circumference: secondary analysis of feeding program data from 5 countries, Combined Protocol for Acute Malnutrition Study (ComPAS) stage 1. PLoS One 2020;15:e0230452.
11. Walker SP, Golden MH. Growth in length of children recovering from severe malnutrition. Eur J Clin Nutr 1988;42:395–404.
12. Doherty CP, Sarkar MAK, Shakur MS, Ling SC, Elton RA, Cutting WA. Linear and knemometric growth in the early phase of rehabilitation from severe malnutrition. Br J Nutr 2001;85:755–9.
13. Kerac M, Bunn J, Chagaluka G, Bahwere P, Tomkins A, Collins S, Seal A. Follow-up of post-discharge growth and mortality after treatment for Severe Acute Malnutrition (FuSAM study): a prospective cohort study. PLoS One 2014;9:e96030.
14. Sandige H, Ndekha MJ, Briend A, Ashorn P, Manary MJ. Home-Based treatment of malnourished Malawian children with locally produced or imported ready-to-use food: J Pediatr Gastroenterol Nutr 2004;39:141–6.
15. Ciliberto MA, Sandige H, Ndekha MJ, Ashorn P, Briend A, Ciliberto HM, Manary MJ. Comparison of home-based therapy with ready-to-use therapeutic food with standard therapy in the treatment of malnourished Malawian children: a controlled, clinical effectiveness trial. Am J Clin Nutr 2005;81:864–70.
16. Linneman Z, Matilsky D, Ndekha M, Manary MJ, Maleta K, Manary MJ. A large-scale operational study of home-based therapy with ready-to-use therapeutic food in childhood malnutrition in Malawi. Matern Child Nutr 2007;3:206–15.
17. Ngari MM, Iversen PO, Thitiri J, Mwalekwa L, Timbwa M, Fegan GW, Berkley JA. Linear growth following complicated severe malnutrition: 1-year follow-up cohort of Kenyan children. Arch Dis Child 2019;104:229–35.
18. Isanaka S, Hitchings MDT, Berthé F, Briend A, Grais RF. Linear growth faltering and the role of weight attainment: prospective analysis of young children recovering from severe wasting in Niger Matern Child Nutr 2019;15(4):e12817.
19. Berkley JA, Ngari M, Thitiri J, Mwalekwa L, Timbwa M, Hamid F, Ali R, Shangala J, N Mturi M, Jones KDJ, et al. Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: a multicentre, double-blind, randomised placebo-controlled trial. Lancet Global Health 2016;4:464–73.
20. McDonald CM, Olofin I, Flaxman S, Fawzi WW, Spiegelman D, Caulfield LE, Black RE, Ezzati M, Danaei G; Nutrition Impact Model Study. 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;97:896–901.
21. WHO. Guideline: updates on management of severe acute malnutrition in infants and children [Internet]. Geneva (Switzerland): World Health Organization; 2013 [cited 2019 Apr 25]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK190328/.
22. Barouaca H, Squali F-Z, Hida M. Effect of short-term of nutrition rehabilitation on catch-up growth in marasmus and kwashiorkor children. J Food Nutr Disord 2013;2:1–5.
23. WHO; UNICEF; World Food Program. Global nutrition targets 2025: stunting policy brief (WHO/NMH/NHD/14.3) [Internet]. Geneva (Switzerland): World Health Organization; 2014 [cited 2020 May 27]. Available from: https://apps.who.int/iris/bitstream/handle/10665/149019/WHO_NMH_NHD_14.3_eng.pdf?ua=1.
24. Sigh S, Roos N, Chamnan C, Laillou A, Prak S, Wieringa F. Effectiveness of a locally produced, fish-based food product on weight gain among Cambodian children in the treatment of acute malnutrition: a randomized controlled trial. Nutrients 2018;10:909.

25. Ngari MM, Thitiri J, Mwalekwa L, Timbwa M, Iversen PO, Fegan GW, Berkley JA. The impact of rickets on growth and morbidity during recovery among children with complicated severe acute malnutrition in Kenya: a cohort study. Matern Child Nutr 2018;14:1–9.
26. Ashraf H, Alam NH, Chisti MJ, Mahmud SR, Hossain MI, Ahmed T, Salam MA, Gyr N. A follow-up experience of 6 months after treatment of children with severe acute malnutrition in Dhaka, Bangladesh. J Trop Pediatr 2012;58:253–7.
27. Khanum S, Ashworth A, Huttly SR. Growth, morbidity, and mortality of children in Dhaka after treatment for severe malnutrition: a prospective study. Am J Clin Nutr 1998;67:940–5.
28. Schoenbuchner SM, Dolan C, Mwangome M, Hall A, Richard SA, Wells JC, Khara T, Sonko B, Prentice AM, Moore SE. The relationship between wasting and stunting: a retrospective cohort analysis of longitudinal data in Gambian children from 1976 to 2016. Am J Clin Nutr 2019;110:498–507.
29. Richard SA, Black RE, Gilman RH, Guerrant RL, Kang G, Lanata CF, Mølbak K, Rasmussen ZA, Sack RB, Valentiner-Branth P, et al. Wasting is associated with stunting in early childhood. J Nutr 2012;142:1291–6.
30. Martorell R, Young MF. Patterns of stunting and wasting: potential explanatory factors. Adv Nutr 2012;3:227–33.
31. Michaelsen KF. Short-term measurements of linear growth using knemometry. J Pediatr Endocrinol Metab 1994;7:147–54.
32. Ministry of Health Uganda. Integrated management of acute malnutrition guidelines [Internet]. Kampala (Uganda): Ministry of Health; 2010 [cited 2019 Apr 29]. Available from: https://www.ennonline.net/integratedmanagementam.
33. Nabukeera-Barungi N, Grenov B, Lanyero B, Namusoke H, Mupere E, Christensen VB, Michaelsen KF, Mølgaard C, Rytter MJ, Friis H. Predictors of mortality among hospitalized children with severe acute malnutrition: a prospective study from Uganda. Pediatr Res 2018;84:92–98.
34. Lanyero B, Namusoke H, Nabukeera-Barungi N, Grenov B, Mupere E, Michaelsen KF, Mølgaard C, Christensen VB, Friis H, Briend A. Transition from F-75 to ready-to-use therapeutic food in children with severe acute malnutrition, an observational study in Uganda. Nutr J 2017;16:52.
35. Grenov B, Namusoke H, Lanyero B, Nabukeera-Barungi N, Ritz C, Mølgaard C, Friis H, Michaelsen KF. Effect of probiotics on diarrhea in children with severe acute malnutrition: a randomized controlled study in Uganda. J Pediatr Gastroenterol Nutr 2017;64:396–403.
36. Kamugisha JGK, Lanyero B, Nabukeera-Barungi N, Nambuya-Lakor H, Ritz C, Mølgaard C, Michaelsen KF, Briend A, Mupere E, Friis H, et al. Weight and mid-upper arm circumference gain velocities during treatment of young children with severe acute malnutrition, a prospective study in Uganda. BMC Nutr 2021;7:26.
37. Coates J, Swindale A, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for measurement of food access: indicator guide: version 3: (576842013-001). Washington, DC: American Psychological Association; 2007.
38. Fabiansen C, Yaméogo CW, Iuel-Brockdorf A-S, Cichon B, Rytter MJH, Kurpad A, Wells JC, Ritz C, Ashorn P, Filteau S, et al. Effectiveness of food supplements in increasing fat-free tissue accretion in children with moderate acute malnutrition: a randomised 2 × 2 × 3 factorial trial in Burkina Faso. PLoS Med 2017;14:e1002387.
39. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Department of Nutrition Health and Development. Geneva (Switzerland): World Health Organization; 2006.
40. Lanyero B, Grenov B, Barungi NN, Namusoke H, Michaelsen KF, Mupere E, Mølgaard C, Jiang P, Frøkiær H, Wiese M, et al. Correlates of gut function in children hospitalized for severe acute malnutrition, a cross-sectional study in Uganda. J Pediatr Gastroenterol Nutr 2019;69:292–8.
41. Demacker PNM, Beijers AM, van Daal H, Donnelly JP, Blijlevens NMA, van den Ouweland JMW. Plasma citrulline measurement using UPLC tandem mass-spectrometry to determine small intestinal enterocyte pathology. J Chromatogr B 2009;877:387–92.
42. Poole A, Deane A, Summers M, Fletcher J, Chapman M. The relationship between fasting plasma citrulline concentration and small intestinal function in the critically ill. Critical Care 2016;19:16.
43. Walker S, Grantham-McGregor S, Himes J, Powell C. Relationships between wasting and linear growth in stunted children. Acta Paediatr 1996;85:666–9.
44. Buyukgebiz B, Ozturk Y, Yilmaz S, Arslan N. Serum leptin concentrations in children with mild protein-energy malnutrition and catch-up growth. Pediatr Int 2004;46:534–8.
45. Waterlow JC. Note on the assessment and classification of protein-energy malnutrition in children. Lancet North Am Ed 1973;302:87–9.
46. Bartz S, Mody A, Hornik C, Bain J, Muehlbauer M, Kiyimba T, Kiboneka E, Stevens R, Bartlett J, St Peter JV, et al. Severe acute malnutrition in childhood: hormonal and metabolic status at presentation, response to treatment, and predictors of mortality. J Clin Endocrinol Metab 2014;99:2128–37.
47. Njunge JM, Gwela A, Kibinge NK, Ngari M, Nyamako L, Nyatichi E, Thitiri J, Gonzales GB, Bandsma RHJ, Walson JL, et al. Biomarkers of post-discharge mortality among children with complicated severe acute malnutrition. Sci Rep 2019;9:5981.
48. Quinton LJ, Jones MR, Robson BE, Mizgerd JP. Mechanisms of the hepatic acute-phase response during bacterial pneumonia. Infect Immun 2009;77:2417–26.
49. Millward DJ. Nutrition, infection and stunting: the roles of deficiencies of individual nutrients and foods, and of inflammation, as determinants of reduced linear growth of children. Nutr Res Rev 2017;30:50–72.
50. Prendergast AJ, Rukobo S, Chasekwa B, Mutasa K, Ntozini R, Mbuya MNN, Jones A, Moulton LH, Stoltzfus RJ, Humphrey JH. Stunting is characterized by chronic inflammation in Zimbabwean infants. PLoS One 2014;9:e86928.
51. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr 2004;80:299–307.
52. Carrero JJ, Qureshi AR, Axelsson J, Avesani CM, Suliman ME, Kato S, Bárány P, Snaedal-Jonsdottir S, Alvestrand A, Heimbürger O, et al. Comparison of nutritional and inflammatory markers in dialysis patients with reduced appetite. Am J Clin Nutr 2007;85:695–701.
53. Sieske L, Janssen G, Babel N, Westhoff TH, Wirth R, Pourhassan M. Inflammation, appetite and food intake in older hospitalized patients. Nutrients 2019;11:1986.
54. Checkley W, Buckley G, Gilman RH, Assis AM, Guerrant RL, Morris SS, Mølbak K, Valentiner-Branth P, Lanata CF, Black RE, et al. Multi-country analysis of the effects of diarrhoea on childhood stunting. Int J Epidemiol 2008;37:816–30.
55. Richard SA, Black RE, Gilman RH, Guerrant RL, Kang G, Lanata CF, Molbak K, Rasmussen ZA, Sack RB, Valentiner-Branth P, et al. Diarrhea in early childhood: short-term association with weight and long-term association with length. Am J Epidemiol 2013;178:1129–38.
56. Guerrant RL, Leite AM, Pinkerton R, Medeiros P, Cavalcante PA, DeBoer M, Kosek M, Duggan C, Gewirtz A, Kagan JC, et al. Biomarkers of environmental enteropathy, inflammation, stunting, and impaired growth in children in northeast brazil. PLoS One 2016;11:e0158772.