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Growth and body composition 5-years after treatment for severe-acute malnutrition: a 5-year prospective matched cohort study in Ethiopian children

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Abstract:	Background Short-term anthropometric outcomes have been well documented for children treated for severe acute malnutrition (SAM). However, anthropometric recovery may not necessarily indicate full restoration of healthy body composition. Objective

	This study evaluated long-term effects of SAM on growth and body composition of children 5-years after discharge from community-based management of acute malnutrition (CMAM). Method We conducted a 5-year prospective cohort study enrolling children aged 6 to 59 months discharged from CMAM (post-SAM) (n=203) and their non-malnourished matched controls (n=202) in 2013, from Jimma Zone, Ethiopia. Anthropometric and body composition data (measured by body circumferences and bio-electric impedance analysis) were collected. Multiple linear regression models were fitted to compare differences in growth z-scores for height (HAZ), weight (WAZ) and BMI (BAZ) and body composition (fat-free mass and fat mass) between groups. Result Post-SAM children had higher prevalence of stunting than controls at baseline [82.2% vs 36.0%; p<0.001], 1-year [80.2% vs 53.7%; p<0.001] and 5-year post-discharge [74.2% vs 40.8%; p<0.001]. Post-SAM children remained 5 cm shorter throughout the study follow-up indicating no catch-up in HAZ. No catch-up in WAZ and BAZ was observed either. Post-SAM children had lower calf, hip, waist, mid-upper arm circumference and lower-limb length at 5-year post-discharge (p<0.001 for all). They had larger waist-to-hip (p=0.001) and waist-to-height ratios (p=0.002). Post-SAM children had a persistent deficit in fat-free mass index at baseline, 6-month, and 5-year post-discharge (p<0.001 for all). No difference was detected in head circumference, sitting height, or fat-mass index. Conclusion Five years after SAM treatment, children still had deficits in HAZ, WAZ, BAZ, and fat-free mass, with preservation of fat-mass, sitting height and head circumference at the expense of leg length, a pattern coherent with ‘thrifty growth’. Research is urgently needed to identify the most effective clinical and public health interventions to mitigate these consequences of malnutrition.
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Dear Editors

Re: **Growth and body composition following treatment for uncomplicated severe-acute malnutrition: a 5-year prospective matched cohort study in Ethiopian children**

I would be grateful if you would kindly consider the above manuscript for publication in the *American Journal of Clinical Nutrition*. Our study constitutes new evidence on the childhood consequences of recovery from severe-acute malnutrition (SAM) conventionally defined as wasting.

SAM is a life-threatening and major cause of child morbidity and mortality worldwide. In 2020, 13.6 million were severely wasted, primarily in sub-Saharan Africa and Asia. Although there have been many studies following up treatment over the short-term, the longer-term outcomes of SAM survivors have received less attention. In adults, survivors of childhood SAM demonstrate elevated risk of non-communicable disease, but the preceding childhood growth patterns have not been clarified.

Our paper describes a 5-year prospective cohort study, involving children discharged from community-based management of acute malnutrition (CMAM; n=203) and matched controls (n=202), from Jimma Zone, Ethiopia. We report outcomes for anthropometry and body composition by bio-electrical impedance analysis at 5-years post-discharge. Our study showed variable effects, depending on the outcome. Compared to controls, post-SAM children were 5cm shorter, indicating no catch-up in height z-score, or in weight or BMI z-score. They had smaller body circumferences, shorter leg length, but larger waist-to-hip ratio, due to smaller hips rather than larger waist. They had a persistent deficit in fat-free mass index. However, no difference was detected in head circumference, sitting height percentile, or fat mass index.

Overall, these results indicate a pattern of ‘thrifty growth’, whereby post-SAM children maintain prominent deficits in height, BMI, leg length and fat-free mass, but preserve sitting height and head circumference. These patterns may indicate long-term constraint of traits that are important for the metabolic capacity for homeostasis, which may contribute to elevated adult non-communicable disease risk. There is no indication at this age of elevated adiposity.

we believe our findings will be of interest to clinicians, dieticians, nutritionists and other readers of the AJCN, demonstrating the need to develop interventions that improve long-term outcomes following SAM. We look forward to hearing from you.

Yours sincerely
Getu Gizaw

Growth and body composition 5-years after treatment for severe-acute malnutrition: a 5-year prospective matched cohort study in Ethiopian children

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Competing Interests: The authors have declared that no competing interests exist.

Abstract

Background: Short-term anthropometric outcomes have been well documented for children treated for severe acute malnutrition (SAM). However, anthropometric recovery may not necessarily indicate full restoration of healthy body composition.

Objective: This study evaluated long-term effects of SAM on growth and body composition of children 5-years after discharge from community-based management of acute malnutrition (CMAM).

Method: We conducted a 5-year prospective cohort study enrolling children aged 6 to 59 months discharged from CMAM (post-SAM) (n=203) and their non-malnourished matched controls (n=202) in 2013, from Jimma Zone, Ethiopia. Anthropometric and body composition data (measured by body circumferences and bio-electric impedance analysis) were collected. Multiple linear regression models were fitted to compare differences in growth z-scores for height (HAZ), weight (WAZ) and BMI (BAZ) and body composition (fat-free mass and fat mass) between groups.

Result: Post-SAM children had higher prevalence of stunting than controls at baseline [82.2% vs 36.0%; $p<0.001$], 1-year [80.2% vs 53.7%; $p<0.001$] and 5-year post-discharge [74.2% vs 40.8%; $p<0.001$]. Post-SAM children remained 5 cm shorter throughout the study follow-up indicating no catch-up in HAZ. No catch-up in WAZ and BAZ was observed either. Post-SAM children had lower calf, hip, waist, mid-upper arm circumference and lower-limb length at 5-year post-discharge ($p<0.001$ for all). They had larger waist-to-hip ($p=0.001$) and waist-to-height ratios ($p=0.002$). Post-SAM children had a persistent deficit in fat-free mass index at baseline, 6-month, and 5-year post-discharge ($p<0.001$ for all). No difference was detected in head circumference, sitting height, or fat-mass index.

Conclusion: Five years after SAM treatment, children still had deficits in HAZ, WAZ, BAZ, and fat-free mass, with preservation of fat-mass, sitting height and head circumference at the expense of leg length, a pattern coherent with ‘thrifty growth’. Research is urgently needed to identify the most effective clinical and public health interventions to mitigate these consequences of malnutrition.

Keywords: Severe acute wasting, un-complicated, body composition, bio-electrical impedance analysis, growth, community-based management of acute malnutrition, long-term effect

Abbreviations used:
Bioelectric Impedance Analysis, BIA; CMAM, Community-based Management of Acute Malnutrition; Fat-Free Mass, FFM; Fat-Free Mass Index, FFMI; Fat mass, FM; Fat Mass Index, FMI; Household Food Insecurity Access Scale, HFIAS; Ready-to-Use Therapeutic Food, RUTF; Sitting Height, SH; SAM, Severe Acute Malnutrition

Introduction

Severe acute malnutrition (SAM) in children remains a major cause of morbidity and mortality (1,2). SAM is defined by severe wasting [Mid Upper Arm Circumference (MUAC) <11.5 cm and/or weight-for-height z-score (WHZ) < -3 standard deviations (SD) from World Health Organization (WHO) child growth standard] and/or presence of nutritional edema (3). Children with wasting, especially severe wasting, have weak immunity, are susceptible to long-term developmental delays (4). In 2020, 45.4 million children under 5 years of age had wasting, of which 13.6 million were severely wasted (5). In Ethiopia, acute malnutrition is a major public health problem and in 2019, 7% children under 5 years are found to be wasted (6).

In 2002, the government of Ethiopia adopted CMAM programs for identifying and treating uncomplicated SAM in children (7,8). This strategy allows early identification of cases (9), reduces case fatality (8,10–12), increases coverage (13,14), is cost-effective (15–18) and increases recovery rate (9). However, optimal programs for treating SAM in children should also improve long-term outcomes, including catch up growth and restoration of body composition among children who recover.

Evidence on long-term growth outcomes after treatment for SAM remains inconsistent. Some studies showed catch-up growth (19,20) whereas others found persistent growth deficits (21–23). Furthermore, it has been suggested that children who achieve catch up growth may develop high body fatness and insufficient repletion of muscle and visceral protein, increasing risk of metabolic diseases later in life (23–28). This evidence is mainly based on children hospitalized for therapeutic feeding, before the adoption of CMAM programs. To our knowledge, only one study in Malawi has investigated long-term effects of exposure to SAM after the adoption of CMAM programs. These SAM survivors had deficits in growth and lean mass compared to controls, however the children were enrolled from a tertiary referral medical institution that was likely to admit a large majority of children with complicated SAM, who likely had advanced metabolic dysfunctions (23). Therefore, the findings are limited in representing children treated in out-patient therapeutic care for severe acute malnutrition without complications in CMAM programs.

We have conducted a matched prospective cohort study evaluating short-term health and nutrition outcomes in children with uncomplicated SAM treated under a CMAM program in Jimma Zone, southwest of Ethiopia (29). We found that the burden of common morbidities and nutritional relapse was higher among SAM survivors compared to control children in the first year post-discharge. In the current study, we hypothesized that among SAM survivors, linear growth velocity would continue at the same rate, resulting in no catch-up growth from 1- to 5-year post-discharge and that SAM in children could result in a hierarchical preservation of some tissues relative to others (30). Moreover, this phenotype may continue post malnutrition (31–34). Therefore, the aim of this study was to evaluate the long-term effects of SAM in children on growth and body composition over 5 years of discharge from CMAM.

Methods

Study participants, setting, and design

A matched prospective cohort study was conducted involving children in the rural population of Jimma Zone, southwest of Ethiopia. The study cohort, established in September 2013, has previously been described in detail (29). In brief, the study enrolled post-SAM children aged 6-59 months who were treated for SAM in CMAM programs and discharged as cured according to the Ethiopian national SAM management guideline (35). For each post-SAM case, an age (± 3 months) and sex-matched neighbor was enrolled as a control. The controls were apparently healthy and had no history of an episode of acute malnutrition. The current study in 2018 assessed these children from the first-year follow-up in 2013 that were traced by local health extension workers. Mother or caregiver of all traced children were requested to patriate. For all those given their consent, child socio-demography and anthropometric data were collected at home and invited to come to the nearby health post for body composition measurement in next day.

Data collection and measurements

Data collection procedures during the initial follow-up are described elsewhere (29). In brief, data on socio-demographic and household characteristics at baseline and monthly child anthropometry and morbidity data were collected during the first-year follow-up. Additionally, body composition was measured using bioelectric impedance analysis on a subset of children at enrollment and the 6-month follow-up visit.

At the 5 years post-discharge follow-up visit, we also collected data on socio-demographic and household characteristics using a structured questionnaire. Household food security status was evaluated using Household Food Insecurity Access Scale (HFIAS) (36), and the UNICEF/WHO water and sanitation tool was employed to assess access to safe drinking water and sanitation (37). Household wealth status was generated using wealth index score based on availability of household assets, facilities, and housing conditions (38).

Weight, height, sitting height (SH), lower-limb length, and mid upper-arm- , head-, calf-, hip- and waist-circumferences were done according to standards (39). Height was measured to the nearest 0.1 cm using a height board and weight was measured to the nearest 0.1 kg (SECA 874, Hamburg, Germany). Sitting height and lower-limb length were measured when seated on a specially designed chair that accommodates the base of the wooden height board and has adjustable footrests. Calf-, hip-, waist-, and head- circumferences were measured by rollfix-Hoechstmass to the nearest 0.1 cm. MUAC was measured to the nearest 0.1cm. Each instrument was calibrated according to the manufacturer’s instructions daily before measurement.

Body composition was assessed using whole-body bioelectric impedance analysis (BIA) using Quadscan 4000 analyzer (Bodystat Ltd, UK) per the manufactures protocol (40). Three measurements at 50 KHz were taken 5 minutes apart. All the raw BIA parameters were immediately transcribed from the machine.

Study outcomes

The primary study outcomes are anthropometry indices of growth and various body composition indices at 5-year after discharge from SAM treatment. Secondary outcome included the change in the anthropometry indices from 1-year after discharge to 5-year after discharge. In a subsample of children, we also compared body composition indices cross-sectionally at baseline and 6 months after discharge, and the changes from baseline to 6-month and from 6-month to 5-year to see recovery in lost fat mass (FM) and fat-free mass (FFM) over time.

Growth indices of HAZ, WAZ and BAZ were calculated based on the WHO (2006) child growth standards using the zscore06 and anthroplus commands in Stata (41–43). Furthermore, to test our hypothesis that post-SAM children follow a thrifty growth pattern, we evaluated fat mass, head circumference, sitting height percentile and a lower-limb length between groups. Various indices of body composition were calcuated according to the recommendation by Wells & Fewtrell (44). For anatomical markers of tissue distribution, MUAC, hip and calf circumferences, were considered as indicator of peripheral fat and waist circumference, as an indicator of abdominal fat. In addition, waist-to-hip and waist-to-height ratios were calculated to provide markers of relative fat distribution. Furthermore, a two-compartment model for body composition was derived using data generated from BIA to compare fat mass (FM) and fat-free mass (FFM) between post-SAM and contol groups. Fat mass and fat-free mass were positively correlated with height, hence to be most informative, comparisons between groups require its confounding effect to be removed. We adjusted for height to give fat mass index (FMI) and fat-free mass index (FFMI).

To derive the FM and FFM from BIA parameters, different researchers have developed empirical equations using weight, age, sex, ethnic ancestry, and other variables in addition to resistance and height (45–47). In the absence of a specific BIA equation for our study population, a proxy for fat-free mass index (FFMI) was calculated as one over impedance 1/Z, based on the validation study by Wells et al, 2007 (48). 1/Z behaves statistically the same as FFMI, but the units are abstract (cm/ohms) rather than kg/m^2. We multiplied values by 1000 to make them easier to evaluate. The age range in our study population at baseline was wide; from 6-59 months. Hence, we initially tested for an association between 1/Z and age. There was an association between 1/Z and age by sex **(Figure 1).** Therefore, to understand the post-SAM versus control differences, we calculated age and sex-standardized regression residuals for 1/Z. Similarly, standardized regression residuals were obtained regressing BMI on 1/Z, to provide a proxy for fat mass index (FMI) as validated previously (48).

Statistical analysis

Data entry and consistency checks were done using Epi Data version 3.2 (49). Statistical analyses were conducted using Stata 14 and two-sided statistical significance is considered at $p < 0.05$ (50). Baseline characteristics of study participants were described using means ± SDs and medians (IQR) for the continuous variables and using frequencies and percentages for the nominal variables. Study outcomes were checked for normality of distribution using histogram and Q-Q plots of the outcomes values and the residual terms. We corrected the effect of regression to the mean using STATA command *rtmci* developed by Ariel Linden in 2013 (51) Unadjusted and adjusted group differences in anthropometric and body composition indicators were estimated between the post-SAM and control groups. Study groups were compared cross-sectionally at baseline, 6 months, 1-year and 5-year post-discharge. Furthermore, changes in body composition indicators from baseline to 6-month and from 6-month to 5-year were compared between study groups. Similarly, changes in the HAZ from 1-year to 5-year post-discharge were analysed. We fitted linear regression models to estimate the mean difference between the case and control group for each study outcome. Adjusted differences were estimated using multiple linear regression models containing potential confounders including age, sex, WASH, household food security status, and wealth index. Furthermore, for adjusted models of the anthorpometry outcomes, cross-sectional comparisons at 1-year were adjusted baseline measuremenst and comparisons at 5-year were adjusted for measurements at 1-year.

To evaluate the level of catch-up growth, children were categorized by the change in HAZ (Δ HAZ) from 1-year post-discharge to 5-year post-discharge. Accelerated linear catch-up growth was considered when children had a Δ HAZ of at least ≥ 0.67 z-score based upon the widely used definition of catch-up growth proposed by Ong et al (52). Then, chi-squared test was applied to compare the post-SAM and control group by the occurrence of catch-up growth. To evaluate the level of catch-up in body composition (FFMI and FMI), we conducted a conditional growth model (53). Conditional measures express how an individual child deviates from its own previous body composition trajectory; thus, expressing acceleration or deceleration in body composition. These were calculated as the residuals from linear regressions from FFMI or FMI at a given time on prior FFMI or FMI. For example, a positive residual at 6 months indicates that a child grew more rapidly from baseline to 6-month post-discharge than was predicted from his/her FFMI or FMI at baseline. Then, linear regression was fitted to estimate difference in body composition accretion between groups. All models were evaluated for the goodness of fit, collinearity, and influential outliers.

Ethical considerations

Ethical clearance was obtained from Jimma University ethical review board, reference number IHRPGD/458/2018. The caretakers of study children provide informed consent.

Results

Cohort profile and characteristics

From September 2013 to September 2014, 430 children aged 6-59 months were screened for eligibility and 405 (n=203 post-SAM, n=202 controls) were enrolled into the study **(Figure 2).** From this, 391 (96.5%) completed the 12-months follow-up and 291 (71.9%) were traced at the 5-year follow-up. Between enrollment and 12-month, 14 (*n*: post-SAM = 10; control = 4) children were lost-to-follow up due to death (*n* = 6) and left the study area (*n* = 8). Between the 12-month and 5-year follow-up, 100 children were lost-to-follow up, *n*=14 due to death, *n*=18 left the study area, *n*=17 declined participation, or *n*=51 could not be traced.

More than two-thirds of household heads in post-SAM and control group did not attend formal school at baseline and the 5-year follow-up **(Table 1).** Both at enrollment (p=0.002) and at the 5-year follow-up (p=0.02), mothers of control children had higher MUAC than mothers of post-SAM children (Table 1). There was no statistically significant difference in most baseline characteristics of traced children and the lost-to-follow-up in both groups at the 5-year follow-up **(supplementary table 1).** Only wealth index quartile was better in the traced control children than in the lost-to-follow controls (p=0.02).

Child growth

Post-SAM children remained 5 cm shorter throughout the study follow-up than control children; at 1-year (ES: -5.50 cm; 95% CI: -7.21, -3.58; *P* < 0.001) and 5-year (ES: -4.90 cm; 95% CI: -6.80, -3.07; *P* < 0.001) post-discharge from CMAM **(Table 2).** After adjustment for baseline height, the group difference at 1-year has become non-significant (ES: -0.79 cm; 95%

CI: -1.89, 0.29; *P* < 0.15). On the other hand, after adjustment for height at 1-year, group difference at the 5-year follow-up remained statistically significant (ES: -2.09 cm; 95% CI: -3.70, -0.49; *P* = 0.01). Group differences in HAZ at 1-year and 5-year followed similar pattern as the height measurement. Stunting prevalence was higher in post-SAM children than their controls at baseline (P<0.001), 1-year (P<0.001) and 5-year post-discharge (P<0.001) **(Figure 3).** When both groups are combined, 106 (49%) children had linear catch-up growth between 1-year to 5-year follow-ups. There was statistically non-significant trend towards higher proportion of children achieving catch-up linear growth in the post-SAM than the control group (post-SAM vs control: 53.8% vs 46.2%); p=0.108). Moreover, the majority of catch-up growth observed at 5-year post-discharge occurred among stunted children at 1-year (93.4%). Among the children who were stunted (HAZ < -2 SD) at the 1-year follow-up, the mean ± SD change in HAZ at 5-year was 1.03 ± 1.14 z-score in post-SAM children compared to 1.25 ± 1.20 z-score in the control children.

Post-SAM children had significantly lower weight than their control both at 1-year (ES: -1.60 kg; 95% CI: -2.01, -1.17; *P* <0.001) and 5-year (ES: -1.80 kg; 95% CI: -2.41, -1.21; *P* <0.001) post-discharge. When adjusted for baseline and 1-year measurements, the difference in weight at 1-year (ES: -0.53 kg; 95% CI: -0.86, -0.21; *P* = 0.01) and at 5-year (ES: -0.88 kg; 95% CI: -1.48, -0.17; *P* = 0.005) were decreased but remained statistically significant. Similarly, both unadjusted and adjusted differences in WAZ were statistically significant at 1-year and 5-year follow-ups. No difference in BAZ was observed in the first 1-year post-discharge. However, at 5-year post-discharge, post-SAM children had significantly lower BMI-for-age than control children (ES: -0.40 kg; 95% CI: -0.70, -0.11; *P* = 0.009) **(Table 2).**

Child body composition

At the 5-year follow-up, post-SAM children (*n* = 134) had smaller calf (p<0.001), MUAC (p<0.001), hip (p<0.001), and waist (p<0.001) circumferences but not head circumference (p=0.134) as compared to the controls (*n* = 142) **(Table 3).** In addition, post-SAM children had shorter lower-limb length (p<0.001) than controls. However, sitting height percentile did not differ between the group (p=0.17). Conversely, post-SAM had larger waist-to-hip ratio (p=0.001) and larger waist-to-height ratio (p=0.002) than controls.

Five years after treatment under the CMAM program, a total of 211 children were assessed for body composition. Post-SAM children (*n* = 99) had significantly lower FFMI than controls (*n* = 112) (p<0.001). However, post-SAM children and controls had comparable FMI (p=0.40) at 5-year post-discharge **(Figure 4).** In the subsample of children with body composition measurements at baseline (*n* = 184) and 6-month (*n* = 177), post-SAM children had significantly lower FFMI (p<0.001) than the controls at baseline; even if not reached statistically significant lower FMI (p=0.65) was observed in post-SAM children than controls. At 6-month post-discharge, post-SAM children still had significantly lower FFMI (p<0.001) than the controls; whereas FMI (p=0.55) was higher in post-SAM children than the controls. When looking at conditional growth model, the FFMI deficit persisted over the subsequent 6-month (p=0.008) and also between the 6-month and 5-year even if not significant (p=0.70) as there was no catch-up. Though statistically insignificant, the post-SAM children had FMI catch-up between baseline to 6-month post-discharge (p=0.51). Of note, the post-SAM group had significantly higher FMI increment than controls between the 6-month and 5-year (p=0.03) **(Table 4).** The catch-up in lost fat tissue during exposure to SAM was occurred in the 5-year follow up resulting in comparable FMI at 5-year post discharge as shown in figure 4.

Discussion

This study found that post-SAM children not only failed to reduce their deficits in HAZ, BAZ and WAZ 1-year after discharge from treatment under the CMAM program, but had lower growth rate during the subsequent 4-years. Additionally, the proportion of stunting among post-SAM children was higher than in community controls at baseline, 1-year, and 5-year post-discharge. However, post-SAM children who were stunted at 1-year had catch-up linear growth 5-year post-discharge. Beyond these growth patterns, a "thrifty growth" response to acute malnutrition was evident, demonstrated by a potential "brain sparing growth" - an adaptive phenomenon in which the brain obtains the necessary resources for its development and functioning at the expense of limb growth (23,30,33,54). Finally, a lean mass deficit was observed in post-SAM children from baseline up to 5-year post-discharge compared to controls.

Our results showed that compared to controls, post-SAM children were shorter and had a higher rate of stunting throughout the study. Although stunting prevalence in the post-SAM group decreased by 7% from 1- to 5-year post-discharge, in controls it decreased by 13%. This is the first study to describe long-term associations of exposure to SAM with linear growth covering up to 5-years in the context of an out-patient CMAM program, hampering comparison with other studies. Lelijveld et al (23) evaluated growth and body composition of Malawian children who received CMAM treatment in an inpatient setup. Compared to the controls, children who had recovered from SAM had a significantly higher stunting prevalence at 1-year and 7-year post-discharge. However, within the post-SAM children, stunting prevalence decreased by 40% from 1-year (86%) to 7-year (46%) post-discharge. The larger decrease in stunting prevalence in that study as compared to ours might be explained by a potential "healthy survivor" bias in the Malawi study, with reported mortality rates of 24% between discharge and 1-year and a further 10% between 1- and 7-year. We doubt that at 7-year post-discharge, our children will achieve a similar decrease in stunting prevalence, as HAZ gain we observed occurred mostly in the stunted children at baseline and 1-year post-discharge, whereas those who were not stunted showed impairment of linear growth, with HAZ decreasing by -0.92 z-score over 5-years. This contrasts with the Malawi study where the 10% with the highest HAZ at baseline had stable HAZ during follow-up. Our results suggest that SAM children who were short at admission have exhibited some catch-up linear growth. In general, our result indicates that how fast children grow depends strongly on how tall they are at baseline. Further investigation is needed to identify the underlying factors and mechanisms between wasting and stunting to define an appropriate strategy to promote linear growth.

The stunting of post-SAM children is further explained by their having shorter lower-limb length compared to controls. Sitting height percentage was comparable between the groups, suggesting that torso growth has been preserved and limb lengths compromised, likely because of the SAM episode. SAM children may therefore demonstrate “brain-sparing growth”, consistent with the “thrifty phenotype” hypothesis (33) where growth of vital organs is spared and other growth traits, such as lower-limb length, compromised (33,34). The “thrifty growth” response to SAM is further indicated by preservation of head circumference and favoring fat tissue restoration. A similar finding was documented in the Malawi study (23). Conversely, a long-term effect of exposure to SAM on head circumference was observed in Chilean school-age children (55). The possible explanation is that the Chilean children were exposed to SAM in the first year of life where most post-natal brain development occurs, whereas in our study the majority were older than one year during exposure to SAM.

Post SAM children were observed to have some elements of altered body composition compared to controls after 5-year post-discharge, including lower peripheral mass (calf and hip circumference), lower core fat (waist circumference) and higher core to peripheral fat (waist-to-hip and waist-to-height ratio). The finding of narrower body frame is associated, both with poor physical function, and for women with lower offspring birthweight in later life and with more complications at delivery (56). The interpretation of higher core to peripheral fat needs caution in malnourished children, as in our study it is due to the post-SAM children having short height and small hip circumference, rather than large waist. Thus, we are not confident to say that SAM survivors are at risk of visceral adiposity. Our findings are similar to the study in Malawi (23), where lower hip girth was the main reason for higher waist-to-hip ratio in post-SAM children. Our children are not fully free from ongoing nutrition transition resulting from increased affluence, and a recent study conducted in similar study area Jimma zone found an increase prevalence of obesity among adolescents amongst wealthier coffee farmers (57).

Our study also found significantly lower fat-free mass index in post-SAM children at 5-year post-discharge compared to controls. Interestingly, we did not find a difference in our proxy for fat mass index. Similar findings were observed in Malawian children surveyed at slightly older age and treated at inpatient setup (23), these finding indicate that with or without metabolic derangement, survivors of SAM did not restore their muscle tissue deficit over a long period of time. This incomplete restoring of muscle tissue deficit could lead to avoidable SAM recurrence and/or mortality (58). In addition, the deficit in fat-free mass was continued at adulthood level in a historical cohort of Democratic Republic of Congo (DRC) (59).

Furthermore, the finding of our longitudinal data on subset of children followed from discharged to last visit indicate that post-SAM children restored their deficit in fat that occurred due to fat metabolism in the adaptation to malnutrition. Counterintuitively, the deficit in fat-free mass continued throughout the follow-up period. Similar finding was observed from study done in the DRC by Bahwere et al, 2016 (60). SAM children showed incomplete recovery in fat-free mass during SAM treatment compared to community controls, but full recovery in fat mass. Our findings and the study by Bahwere et al suggests that the rapid increase in body mass during the early phase of nutrition recovery could be safe even if regaining of fat mass rather than fat-free mass mostly occurred. In contrast, a study by Kangas et al in Burkina Faso found that children with severe malnutrition regained more fat-free tissue when rehabilitated (61). This discrepancy might be due to the differences in the study protocols where Kangas et al included children with MUAC <11.5 cm whereas we used the older admission criteria of MUAC <11cm. Thus, the discrepancy may be explained by the fact that the proportion of different tissue accretion depends on nutritional status at admission (62): the level of deficit in our study was higher, which would result in more fat being gained during treatment.

In general, post-SAM children had comparable fat mass index to controls but not in fat-free mass index at both short and long discharge period. The existing data therefore indicates that the use of ready to use therapeutic food (RUTF) in treatment of SAM should not be restricted on the grounds that its high fat content may increase risk of non-communicable diseases (63,64). However, the potential association between SAM with high abdominal fat and risk of non-communicable disease in later life discussed above should not be ignored. Evidence suggests that body composition in infancy can presage adult non-communicable disease risk; in particular, rapid and/or catch-up weight gain in early childhood has been associated with adiposity, insulin resistance, obesity, and non-communicable diseases later in life (65,66). Therefore, without a controlled trial following up treated and untreated cases of SAM, we cannot be sure that treatment with RUTF does not increase the risk. Given the known benefits of RUTF on short term mortality and morbidity, it would be difficult to find a cohort of untreated SAM patients and unethical to proactively study a group of untreated SAM children as controls. Furthermore, deficits in fat-free mass index starting from discharge to 5-year post discharge may have short term implication in functional organs and tissues and long-term effect on other aspect of health and function (67). Improving the composition of therapeutic food provided to treat children with SAM, such as improving the amino acid profile, might benefit regain of fat-free mass (68,69).

The main strengths of this study were its controlled design, the large sample size, and the high rate of follow up. Long term follow-up of matched SAM and control children who had likely faced the same environmental influences allowed us to evaluate long-term effects of exposure to SAM on growth and body composition. Only a few studies have examined growth and body composition in the context of treatment of SAM. To our knowledge, no studies have looked long-term at growth and body composition change among uncomplicated SAM children treated under current protocol-CMAM. Having a large sample size helps generalize our finding to all children currently being treated for SAM. In addition, tracing rate was excellent, and this minimized the possibility of bias due to loss to follow up. Finally, the comparison of those traced and not traced strengthen the conclusion of an absence of selection bias due to loss to follow up. However, our finding should not be interpreted without taking into account some limitation. Body composition was assessed using BIA which is not gold standard. In addition, our control children were not fully healthy, and these children have stunting starting from enrollment although not as severe as SAM children.

Conclusions

We identified long-term adverse consequences of exposure to SAM on growth and body composition. SAM survivors did not show catch-up growth up to 5-years post-discharge. Initial weight gain during treatment primarily favoured fat mass accretion, leaving the malnourished children with insufficient restoration of lean tissue. Furthermore, SAM survivors showed some indication of thrifty growth. Given this, there is a need to design a package of interventions that will be systematically offered to children after completing intensive initial treatment for SAM to address the absence of catch-up growth and persistent lean tissue deficit. Research is urgently needed to test different clinical and public health interventions and identify those most effective. Furthermore, research is needed to revise the current discharge criteria for CMAM program by considering restoration of lean mass and also further follow-up is required to evaluate the effect of exposure to SAM in early life on nutrition and health outcomes during the adolescent period.

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Data sharing: Data described in the manuscript, code book, and analytic code will be made available upon request.

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Table 1: Description of selected child and household socio-economic characteristics of the study population at enrollment and 5th-year post-discharge assessment.

	Prospective cohort enrollment in 2013			**Assessment after 5 years in 2018**		
	Post-SAM[1] n[3]= 203	Controls[2] n= 202	p-value[4]	Post-SAM N[5]= 144	Controls n= 153	p-value
Child characteristics						
Age (month)	15 [11; 30]	14 [11; 29]	0.972	71 [64; 84]	70 [64; 85]	0.901
Sex, male	52.3 (110)	49.7 (109)	0.842	47.7 (73)	52.3 (80)	0.784
Sleeping under INT						
Yes	51.3 (102.0)	40.1 (79.0)	0.091	63.9 (87.0)	66.2 (96.0)	0.694
No	48.7 (97.0)	59.1 (118.0)		36.1 (49.0)	33.8 (49.0)	
Household characteristics						
Maternal age (years)	28.0 [25.0; 34.0]	25.0 [22.5; 30.0]	0.001	35.0 [29.0; 39.0]	32.0 [29.0; 38.0]	0.996
Maternal MUAC (cm)	22.1 [22.1; 23.4]	22.8 [21.1; 24.0]	0.002	23.2 [22.0; 24.3]	24.0 [22.3; 25.6]	0.021
Educational status of household head						
Ever attended formal education	26.7 (54.0)	31.3 (62)	0.313	20.6 (40.0)	27.6 (40.0)	0.171
Never attended	73.3 (148)	68.7 (136)		79.4 (108.0)	72.4 (105.0)	
Food insecurity						
No	57.7 (117)	76.5 (153)		45.5 (66.0)	33.8 (46.0)	
Mild	3.0 (6)	3.5 (7)	<0.001	11.7 (17.0)	12.5 (17.0)	0.161
Moderate	8.8 (18)	9.0 (18)		20.0 (29.0)	20.6 (28.0)	
Severe	30.5 (62)	11.0 (22)		22.8 (33.0)	33.1 (45.0)	
Wealth status						
Poorest	26.3 (50)	23.3 (42)		32.3 (30.0)	19.0 (21.0)	
Poorer	24.6 (43)	27.2 (49)	0.642	20.4 (19.0)	28.2 (31.0)	0.170
Middle	24.2 (46)	26.1 (47)		23.7 (22.0)	27.3 (30.0)	
Richer	26.8 (51)	23.3 (42)		23.6 (22.0)	25.5 (28.0)	
Toilet facility						
Improved	47.5 (96)	49.5 (99)	0.690	49.3 (66.0)	61.3 (87.0)	0.045
Un-improved	52.5 (106)	50.5 (101)		50.7 (68.0)	38.7 (55.0)	
Drinking water source						
Improved	91.1 (185)	90.9 (181)	0.952	81.4 (109.0)	84.5 (120.0)	0.485
Un-improved	8.9 (18)	9.1 (18)		18.6 (25.0)	15.5 (22.0)	

Data shown are mean (±SD), median [IQR], or % (n). INT, insecticide-treated bed-net. MUAC= Mid-upper arm circumference. [1]Post-SAM= children recruited at the graduation of treatment for severe acute malnutrition in 2013. [2]Control= non-wasted matched group of post-SAM recruited concurrently in 2013.
[3]n= baseline sample size, [4]t-test for continuous and chi2 test for the categorical variable used to compare post-SAM and control.[5]n= sample size after 5-years post-discharge

Table 2: Comparison of differences in mean of anthropometric parameters between post-SAM and control groups at different follow-up times.

	N[1]	Post-SAM Mean (±SD)	Control Mean (±SD)	Unadjusted[2] Diff	(95% CI)	P-value	Adjusted[3] Diff	(95% CI)	P-value
Height (cm)									
1-year post-discharge	320	78.9 (7.45)	84.4 (8.98)	-5.50	(-7.21; -3.58)	<0.001	-0.79	(-1.89; 0.29)	0.15
5-years post-discharge	235	100.7 (7.31)	105.6 (8.68)	-4.90	(-6.80; -3.07)	<0.001	-2.09	(-3.70; -0.49)	0.011
Weight (kg)									
1-year post-discharge	320	9.6 (2.07)	11.2 (2.19)	-1.60	(-2.01; -1.17)	<0.001	-0.53	(-0.86; -0.21)	0.011
5-years post-discharge	235	14.2 (2.36)	16.0 (2.76)	-1.80	(-2.41; -1.21)	<0.001	-0.88	(-1.48; -0.17)	0.005
Height-for-age z-score									
1-year post-discharge	310	-3.85 (1.47)	-2.71 (1.44)	-1.14	(-1.46; -0.81)	<0.001	-0.20	(-0.54; 0.13)	0.24
5-years post-discharge	216	-3.34 (1.14)	-2.48 (1.187)	-0.86	(-1.13; -0.56)	<0.001	-0.49	(-0.78; -0.19)	0.001
We1ght-for–age z-score									
1-year post-discharge	312	-2.85 (1.15)	-1.64 (1.00)	-1.21	(-1.45; -0.97)	<0.001	-0.34	(-0.60; -0.08)	0.009
5-years post-discharge	220	-3.11 (1.07)	-2.17 (1.07)	-0.94	(-1.19; -0.68)	<0.001	-0.54	(-0.82; -0.26)	<0.001
BMI-for-age z-score									
1-year post-discharge	310	-0.84 (1.72)	-0.55 (1.67)	-0.29	(-0.67; 0.07)	0.12	0.00	(-0.36; 0.36)	0.99
5-years post-discharge	211	-2.21 (1.15)	-1.78 (1.18)	-0.43	(-0.72; -0.13)	0.004	-0.40	(-0.70; -0.11)	0.009

[1] N= sample size at each follow-up timepoints. [2]Un-adjusted difference= based on linear regression used to compare mean difference at 12-month, 5-year post-discharge. [3]Adjusted difference= Multiple linear regression was used to determine overall significant mean difference at 1- year, and 5-year post discharge between post-SAM and control after adjusting potential confounders. Baseline age and anthropometric data, sex was used for 1- year outcome variables; age at 1- year, anthropometric data at 1- year, sex were used to adjusted for 5-years outcome variables. Controls were used as reference group in all analysis.

Table 3: Comparison of mean difference in body shape and proportion between post-SAM and controls at 5-year post-discharge follow-up

	Post-SAM (n=134)	Controls (n=142)	Unadjusted difference[1]			Adjusted difference[2]		
	Mean (±SD)	Mean (±SD)	Diff[1]	(95% CI)	P-value	Diff	(95% CI)	p-value
Sex, male: %(n)	55 (60)	54 (67)			0.877			
Age (years): median (IQR)	5 (5-6)	6 (5-7)	-0.24	(-0.55; 0.05)	0.107			
lower-limb length (cm)	30.2 (2.89)	31.7 (3.46)	-1.54	(-2.30; -0.78)	<0.001	-1.57	(-2.21; -0.94)	<0.001
Sitting height percentile[3] (cm)	54.3 (2.09)	54.2 (2.47)	0.06	(-0.47; 0.61)	0.83	0.10	(-0.39; 0.60)	0.68
Calf circumference (cm)	19.5 (1.33)	20.7 (1.62)	-1.20	(-1.49; -0.78)	<0.001	-1.14	(-1.47; -0.80)	<0.001
MUAC (cm)	14.5 (10.0)	15.2 (10.3)	-0.66	(-9.08; -4.24)	<0.001	-0.64	(-9.07; -4.21)	<0.001
Head circumference (cm)	50.2 (2.03)	50.7 (3.80)	-0.54	(-1.27; 0.18)	0.15	-0.54	(-1.26; 0.17)	0.13
Waist circumference (cm)	52.3 (3.10)	53.2 (2.83)	-0.93	(-1.69; -0.22)	<0.010	-0.92	(-1.59; -0.23)	<0.001
Hip circumference (cm)	51.3 (3.01)	53.4 (3.36)	-2.14	(-2.90; -1.38)	<0.001	-2.05	(-2.73; -1.36)	<0.001
Waist-to-height ratio (cm)	0.51 (0.04)	0.49 (0.03)	0.012	(0.003; 0.022)	0.008	0.013	(0.004; 0.021)	0.002
Waist-to-hip ratio (cm)	1.01 (0.05)	0.99 (0.06)	0.020	(0.006; 0.033)	0.003	0.021	(0.008; 0.033)	0.001

[1] difference in mean b/n post-SAM and control. [1]Un-adjusted difference= linear regression used to compare mean difference at 5-year post-discharge between post-SAM and control. [2]Adjusted difference= Multiple linear regression was used to determine significant mean difference between post-SAM and control after adjusting for age, sex. Controls were used as reference group. [3]sitting height percentiles= (sitting height / height) *100.

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Table 4: Comparison of cross-sectional mean difference in body composition between post-SAM and control at different follow-up time and conditional body composition change from baseline to 6 months, and from 6-month to 5-year post-discharge follow-up

	N[1]	Post-SAM	Control	Unadjusted[2]			Adjusted[3]		
		Mean (±SD)	Mean (±SD)	Diff	(95% CI)	P-value	Diff	(95% CI)	P-value
1/z[4] (fat-free-mass index): z-score									
At baseline	184	-0.014 (1.04)	0.702 (0.92)	-0.71	(-1.00, -0.43)	<0.001	-0.70	(-0.97; -0.43)	<0.001
6 months post-discharge	177	-0.177 (1.06)	0.526 (0.85)	-0.70	(-0.99; -0.41)	<0.001	-0.69	(-0.97; -0.41)	<0.001
5-years post-discharge	211	-0.035 (0.95)	0.484 (0.99)	-0.52	(-0.78; -0.25)	<0.001	-0.52	(-0.77; -0.26)	<0.001
Conditional 1/z from baseline to 6-month	177	-0.229 (1.07)	0.171 (0.88)	-0.40	(-0.68; -0.11)	0.007	-0.39	(-0.68; -1.04)	0.008
Conditional 1/z from 6-month to 5-year	98	0.044 (1.08)	-0.037 (0.91)	0.08	(-0.32; 0.48)	0.69	0.07	(-0.31; 0.47)	0.69
BMI residual[5] (fat-mass index): z-score									
At baseline	184	-0.025 (0.96)	0.034 (1.05)	-0.05	(-0.35; 0.23)	0.68	-0.06	(-0.35; 0.21)	0.64
6 months post-discharge	176	0.058 (1.04)	-0.031 (0.92)	0.08	(-0.20; 0.38)	0.55	0.08	(-0.16; 0.33)	0.50
5-years post-discharge	211	0.064 (1.03)	-0.051 (0.95)	0.12	(-0.15; 0.38)	0.40	0.51	(-0.15; 0.39)	0.34
Conditional BMI residual from baseline to 6-month	176	0.060 (1.09)	-0.034 (0.89)	0.09	(-0.20; 0.39)	0.53	0.09	(-0.19; 0.39)	0.51
Conditional BMI residual from 6-month to 5-year	98	0.234 (1.01)	-0.198 (0.94)	0.43	(0.04; 0.82)	0.03	0.43	(0.03; 0.82)	0.032

N[1]= sample size in each follows up time. [2]Un-adjusted difference= linear regression used to compare cross-sectional mean difference at baseline, 6-month, 5-year post-discharge and to compare conditional body composition change between post-SAM and control. [3]Adjusted difference= Multiple linear regression was used to determine overall significant mean difference at baseline, 6-month, 5-year and conditional body composition change after adjusting for age and sex. [4]In the absence of a specific BIA equation for our study population that could be used to provide fat-free mas and fat mass estimates, a proxy for fat-free mas index was calculated based on validation study by Wells et al., 2007-dividing 1/impedance (z) then age and sex standardized regression residual used to compare groups. Similarly, [5]standardized regression residual were obtained regressing BMI on [1/z], to provide a proxy for fat mass index, as described by Wells et al., 2007. Controls were used as reference group in all analysis.

Figure 1: Scatterplot showing the association between 1/impedance (Z) with age and sex at baseline. In the absence of a specific BIA equation for our study population that could be used to provide fat-free mas and fat mass estimates, a proxy for fat-free mas index was calculated based on validation study by Wells et al., 2007-dividing 1/impedance (Z). The blue and red lines are fitted value from a linear regression of 1/Z with age and sex. The grey areas are 95% confidence interval of the fitted values.

Figure 2: Cohort flow diagram showing enrolment and follow-up of participants from baseline to 5th-year post-discharge.

Figure 3: Comparing trends in stunting prevalence between post-SAM and controls at baseline, 1-year and 5-year post-discharge. Error bars represent 95 % confidence intervals. Significant higher stunting was observed among post-SAM children in all time points than controls.

Figure 4: Comparison of body composition between post-SAM and control at 5-year post-discharge. Left side (1/z) is comparison for fat-free mass index and the right side (BMI residual) is to compare fat-mass index.

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

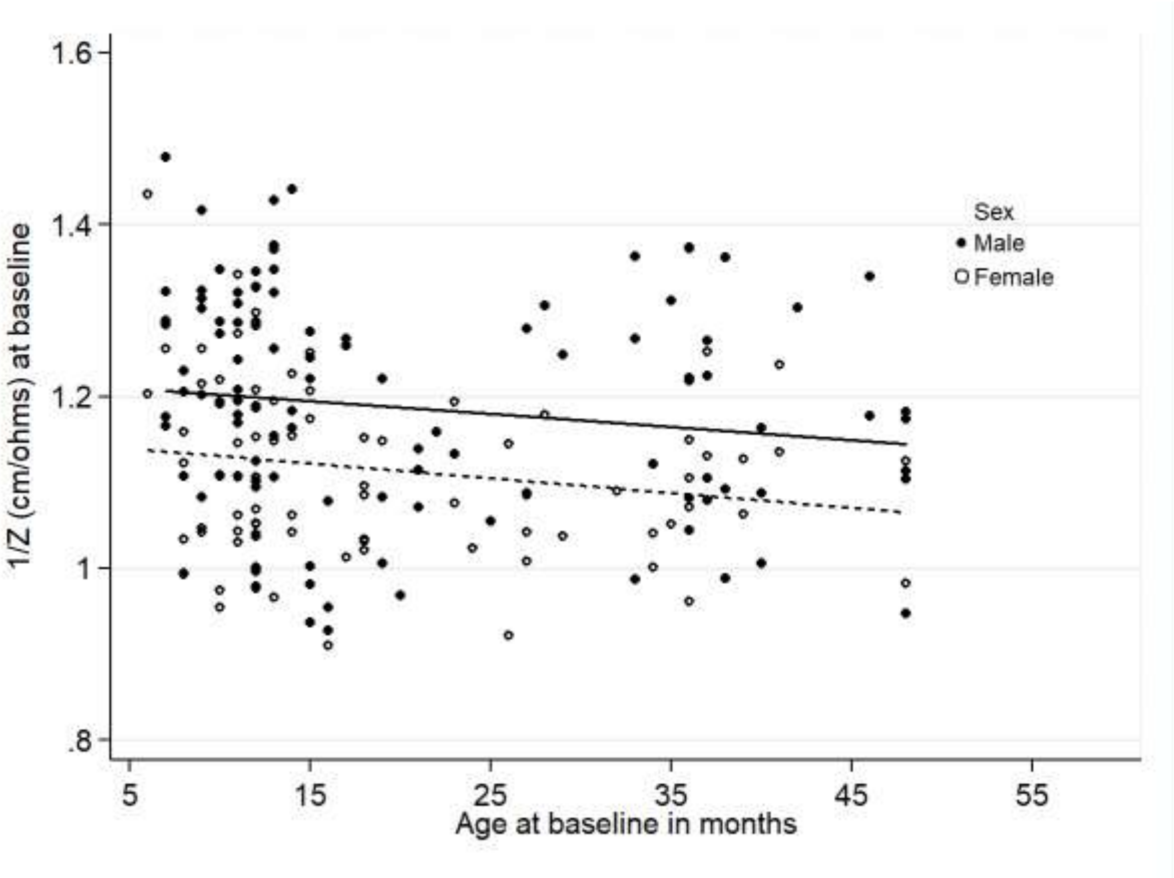
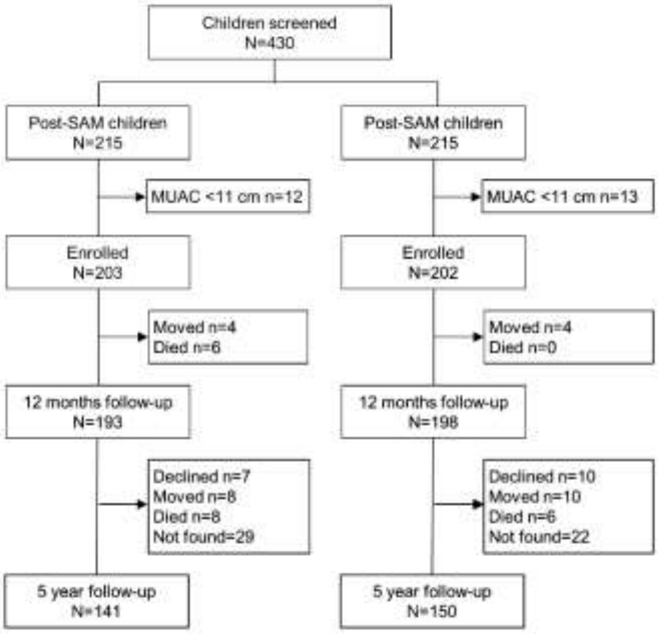


Figure 1: Scatterplot showing the association between 1/impedance (Z) with age and sex at baseline. In the absence of a specific BIA equation for our study population that could be used to provide fat-free mass and fat mass estimates, a proxy for fat-free mass index was calculated based on validation study by Wells et al., 2007-dividing 1/impedance (Z). The solid line for males and short-dash line for females are fitted values from a linear regression of 1/Z with age and sex.



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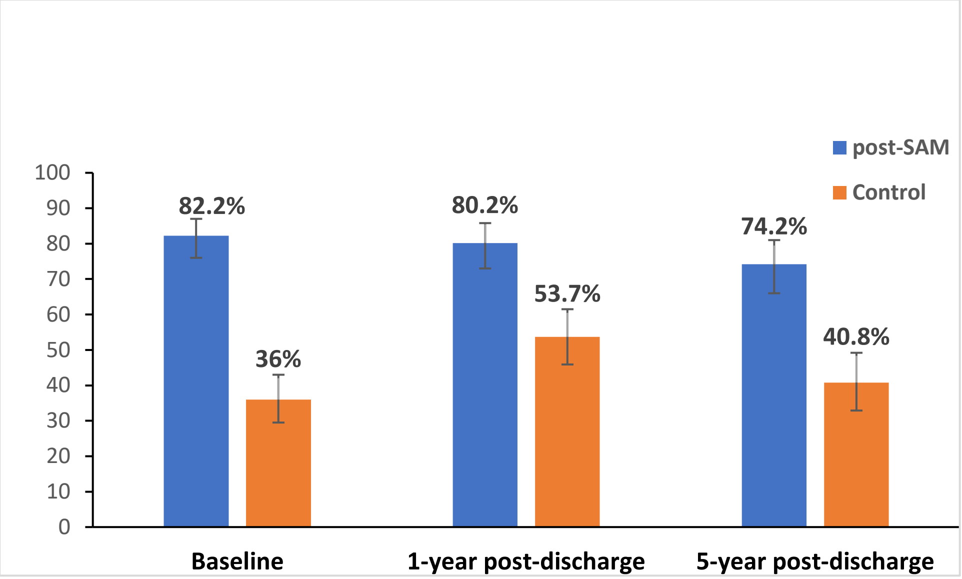

Figure 3: Comparing trends in stunting prevalence between post-SAM and controls at baseline, 1-year and 5-year post-discharge. Error bars represent 95 % confidence intervals. Significant higher stunting was observed among post-SAM children in all time points than controls.

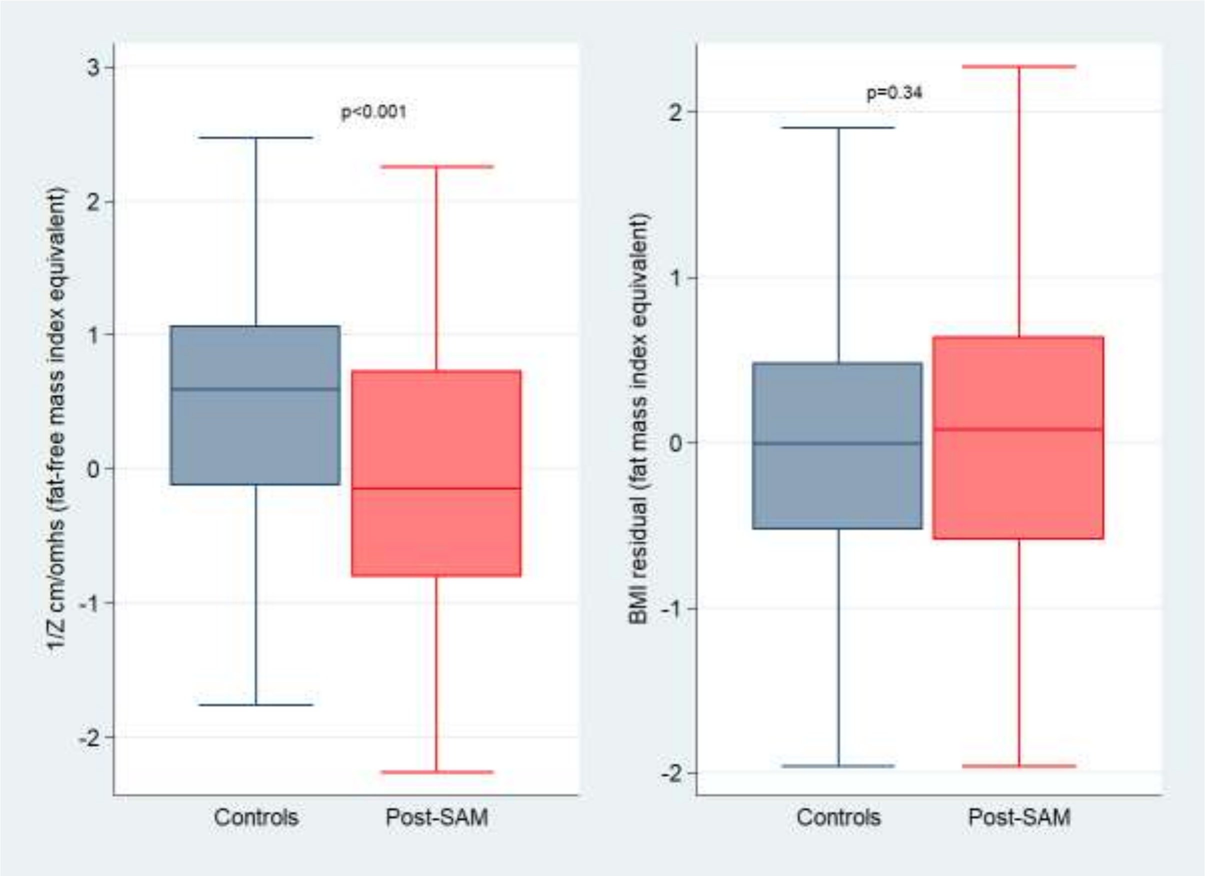

Figure 4: Comparison of body composition between post-SAM and control at 5-year post-discharge. Left side (1/z) is comparison for fat-free mass index and the right side (BMI residual) is to compare fat-mass index.

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Supplementary Table 1: comparison of selected child and household characteristics of missed eligible with assessed children

	Post-SAM[1]			Controls[2]		
	Enrolled[3] n=141	Missed[4] n=52	p-value[5]	Enrolled n=150	Missed n=48	p-value
Child characteristics						
Age (month), Male	15.0 [12.0; 29.0]	15.0 [11.0, 27.0]	0.667	14.0 [11.0; 31.0]	14.5 [12.0; 25.5]	0.714
Sex, male	52.5 (74.0)	59.6 (31.0)	0.430	54.7 (82.0)	54.2 (26.0)	0.952
Household characteristics						
Maternal age (years)	28.0 [25.0; 33.0]	26.0 [25.0; 31.0]	0.207	25.0 [22.0; 30.0]	25.0 [23.0; 30.0]	0.515
Maternal MUAC (cm)	22.0 [21.0; 23.2]	22.5 [21.4; 23.5]	0.171	22.5 [21.5, 24.0]	23.0 [22.0; 23.6]	0.894
Educational status of household head						
Ever attended formal education	28.5 (40.0)	24.1 (14.0)	0.524	31.3 (46.0)	34.0 (16.0)	0.725
Never attended	71.5 (100.0)	75.9 (44.0)		68.7 (101.0)	66.0 (31.0)	
Food insecurity						
No	62.4 (88.0)	50.0 (26.0)		79.9 (119.0)	70.8 (34.0)	
Mild	1.4 (2.0)	3.8 (2.0)	0.223	2.0 (3.0)	8.3 (4.0)	0.051
Moderate	8.5 (12.0)	7.8 (4.0)		9.4 (14.0)	4.2 (2.0)	
Severe	27.7 (39.0)	38.5 (20.0)		8.7 (13.0)	16.7 (8.0)	
Wealth status						
Poorest	23.5 (31.0)	32.6 (17.0)		18.8 (25.0)	40 (18.0)	
Poorer	21.9 (29.0)	26.9 (14.0)	0.123	30.0 (40.0)	20.0 (19.0)	0.021
Middle	24.2 (32.0)	25.0 (13.0)		25.6 (34.0)	26.7 (12.0)	
Richer	30.4 (40.0)	15.5 (8.0)		25.6 (34.0)	13.3 (6.0)	
Toilet facility						
Improved	48.6 (68.0)	46.2 (24.0)	0.796	51.0 (76.0)	43.7 (21.0)	0.382
Un-improved	51.4 (72.0)	53.8 (28.0)		49.0 (73.0)	56.3 (27.0)	
Drinking water source						
Improved	90.0 (127.0)	96.1 (50)	0.127	91.2 (135.0)	91.7 (44.0)	0.923
Un-improved	10.0 (14.0)	3.9 (2.0)		8.8 (13.0)	8.3 (4.0)	

Data shown are mean (±SD), median [IQR], or % (n).[1] =post-SAM children in prospective cohort and eligible for 5th-year post-discharge survey. [2] = control children in prospective cohort and eligible for 5th-year post-discharge survey. [3] =Enrolled children in 5th-year post-discharge survey. 4 =Missed children are those eligible but not assessed in 5th-year post-discharge survey due to different reasons. [5] = t-test for continuous and chi2 test for the categorical variable used to compare post-SAM and control