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ORIGINAL ARTICLE OPEN ACCESS

Linear Growth During Treatment With a Simplified, Combined Protocol: Secondary Analyses of Severely Wasted Children 6–59 Months in the ComPAS Cluster Randomized Controlled Trial

Grace Heymsfield[1] | Kevin Stephenson[2] | Zachary Tausanovitch[1] | André Briend[3,4] | Marko Kerac[5,6] | Heather Stobaugh[7,8] | Jeanette Bailey[1] | Suvi T. Kangas[1]

[1]International Rescue Committee, New York City, New York, USA | [2]Department of Medicine, Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA | [3]Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark | [4]Center for Child Health Research, Faculty of Medicine and Health Technology, Arvo Building, Tampere University, Tampere, Finland | [5]Department of Population Health, London School of Hygiene and Tropical Medicine, London, UK | [6]Centre for Maternal, Adolescent, Reproductive, & Child Health, London School of Hygiene & Tropical Medicine, London, UK | [7]Action Against Hunger, New York City, New York, USA | [8]Tufts University, Boston, Massachusetts, USA

Correspondence: Grace Heymsfield (grace.heymsfield@rescue.org)

Received: 10 June 2024 | **Revised:** 28 October 2024 | **Accepted:** 5 November 2024

Funding: The ComPAS study was funded by the United States Agency for International Development Office of U.S. Foreign Disaster Assistance (https://www.usaid.gov/who-we-are/organization/bureaus/bureau-democracy-conflict-and-humanitarian-assistance/office-us), grant number AID-OFDA-G-14-00208 awarded to the International Rescue Committee, and the Children's Investment Fund Foundation (https://ciff.org/) grant reference title 'Reinventing community management of acute malnutrition' awarded to Action Against Hunger.

Keywords: acute malnutrition | Kenya | linear growth | secondary analyses | South Sudan

ABSTRACT

A simplified, combined protocol treats children with moderate acute malnutrition (MAM), defined by mid-upper arm circumference (MUAC) of < 125 and ≥ 115 mm and no oedema, with 1 daily sachet of ready-to-use therapeutic food (RUTF) and those with severe acute malnutrition (SAM), defined by MUAC < 115 mm and/or oedema, with two daily sachets of RUTF. This protocol was previously shown to result in non-inferior recovery compared to standard treatment that used higher, weight-based RUTF dosing among children with SAM and ready-to-use supplementary food (RUSF) for MAM in a cluster-based randomised controlled trial in Kenya and South Sudan. We conducted a secondary analysis of this trial to compare linear growth among children admitted with MUAC < 115 mm. Linear and ponderal growth were calculated from admission to discharge and visualised using aggregate growth curves. HAZ change adjusted for admission characteristics was negative across the course of treatment but similar across arms [-0.21 ± 0.18 *SE* in the standard arm, -0.24 ± 0.18 *SE* in simplified; difference (95% confidence interval) 0.03 (-0.12, 0.18)]. The unadjusted mean $\pm$ *SE* linear growth velocity from admission to discharge was 1.8 ± 0.7 mm/week in the standard arm compared to 1.7 ± 0.7 mm/week in the simplified arm [difference = 0.09 (-0.36, 0.53)] and similar in adjusted analysis. MUAC and weight gain velocities were not significantly different by treatment arm. Reducing the RUTF dose prescribed to children during SAM treatment does not appear to affect linear growth or other growth velocities during treatment.

Summary

- Linear growth during acute malnutrition treatment is an understudied outcome, despite evidence suggesting a bidirectional relationship between stunting and wasting.
- We performed secondary data analysis of a randomised controlled trial of a simplified, MUAC-based dose for acute malnutrition among children 6–59 months in Kenya and South Sudan, investigating the effect of the intervention on linear growth during treatment.
- Linear growth observed in this sub-population was not sufficient to prevent a similar loss in HAZ in both arms.
- Reducing the RUTF dose prescribed to children during SAM treatment does not appear to affect linear growth or other growth velocities during treatment.
- Overall, this study adds to a growing body of evidence that suggests SAM can be treated effectively and result in similar anthropometric growth when treated with a simplified, MUAC-based dose of RUTF and a standard weight-based dose of RUTF.

1 | Introduction

At any one time, an estimated 45 million children under 5 worldwide are affected by wasting, a life-threatening condition caused by inadequate dietary intake and recurring illness (UNICEF, WHO, and World Bank 2023). Nearly two decades ago, the World Health Organization (WHO) endorsed the community-based management of acute malnutrition (CMAM) model to address the condition. Today, CMAM includes the outpatient treatment of children with uncomplicated acute malnutrition, i.e., children with wasting and/or nutritional oedema who do not have medical complications (WHO 2023). While CMAM has improved global coverage, an estimated 80% of affected children still go untreated, in part due to inadequate supply of therapeutic and supplementary foods (Action Against Hunger 2014; No Wasted Lives Coalition 2018; WHO 2019).

Under the standard CMAM model, the severe and moderate forms of acute malnutrition are often managed in separate facilities, using different food products and protocols (WHO 2023). Children with SAM typically receive weight-based doses of ready-to-use therapeutic food (RUTF), whereas children with moderate acute malnutrition (MAM) may receive one sachet of ready-to-use supplementary food (RUSF) per day (WHO 2023). These two nutritional products are similar in nutritional content and total energy, but can have different sources of protein and amounts of micronutrients (WFP 2016).

In an effort to simplify treatment protocols and/or assess whether the dose of therapeutic food could be safely reduced, previous studies tested the use of novel RUTF dosing for both SAM and MAM treatment (Bailey et al. 2018; Daures et al. 2019; Maust et al. 2015). In South Sudan and Kenya, the ComPAS trial simplified treatment to using two RUTF sachets per day for SAM treatment, as opposed to weight-based dosage, and one RUTF sachet per day for MAM treatment, as opposed to one sachet of RUSF per day (Bailey et al. 2018, 2020). In this study, both SAM and MAM were defined by MUAC thresholds and the presence of oedema, while weight-for-height *z*-score (WHZ) was not used as a criterion (Bailey et al. 2018; WHO 2023). Compared to standard treatment, the ComPAS trial demonstrated non-inferior recovery rates among children admitted with a MUAC < 125 mm and/or oedema and without medical complications (Bailey et al. 2018, 2020).

Children with concurrent wasting and low height-for-age, or stunting, are among the most vulnerable of all malnourished children, with a higher mortality risk than either wasting or stunting alone, and about a 12 times greater risk of mortality in the absence of treatment than those with normal anthropometry (McDonald et al. 2013). Despite this, height-for-age *z*-scores (HAZ) and other height outcomes are typically not used to monitor a programme's efficacy alongside weight and MUAC. Poor linear growth is seen during and after acute malnutrition treatment, and evidence suggests acute wasting preludes future stunting (Richard et al. 2012; Ashraf et al. 2012; Stobaugh et al. 2018). Recovery in weight appears to precede linear growth in children treated for SAM (Isanaka et al. 2019; Walker and Golden 1988; Ngari et al. 2019). Improvements in WHZ may reflect rapid weight gain during treatment in comparison to linear growth (Kerac et al. 2014, Kamugisha et al. 2021).

By reducing the RUTF dose for some children with SAM, modified protocols such as the ComPAS protocol reduce nutrients essential for linear growth compared to the standard protocol, especially in heavier children for whom fixed-dose RUTF provides fewer nutrients per kilogram of body mass (Ministry of Medical Services and Ministry of Public Health and Sanitation Kenya 2009; The Republic of South Sudan Ministry of Health 2017; Golden 1995). The original publication did not report on linear growth in the new protocol, but this has since been identified as a priority research need in the newly issued WHO guidelines considering evidence to date (WHO 2023).

The primary aim of this analysis was to compare linear growth in ComPAS among severely wasted children treated with the simplified versus standard protocols. We also aimed to explore changes in additional anthropometrics and programmatic outcomes in this subset of children.

2 | Methods

2.1 | Study Design

This study comprises a secondary data analysis of a dataset collected as part of the ComPAS cluster randomised controlled trial, a multi-site non-inferiority trial conducted in 12 health facilities in 3 urban sub-counties of Nairobi, Kenya and 12 health facilities in a rural, agropastoral region of South Sudan from 2017 to 2018 (Bailey et al. 2018). The study design, procedures, and main results of all children admitted have been described in full previously (Chase et al. 2020, Bailey et al. 2018, 2020), and results from two secondary analyses published (Bailey et al. 2021; Lelijveld et al. 2021). Briefly, the trial found non-inferior recovery in children admitted with less RUTF required for a child with severe malnutrition to reach full recovery in the combined protocol, as well as improved cost-effectiveness (Bailey et al. 2020).

2.2 | Original Study

In the ComPAS intervention arm, a simplified, combined protocol admitted children with both SAM and MAM for treatment in a unified programme, with eligible children receiving RUTF according to their MUAC and/or oedema status: (a) 2 RUTF sachets (1000 kcal total) per day for children with MUAC < 115 mm or bilateral pitting oedema until reaching MUAC ≥ 115 mm for 2 consecutive visits and with 1 RUTF sachet (500 kcal) thereafter, and (b) 1 sachet per day for children admitted with MUAC 115–124 mm. In the control arm, (a) children with MUAC < 115 mm were treated with a weight-based RUTF dose until reaching a MUAC ≥ 115 mm for 2 visits and with 1 RUSF sachet (500 kcal) per day thereafter while children admitted with MUAC 115–124 mm were treated with 1 sachet of RUSFper day. The differences between the standard and simplified protocols, including procedures and dosages, are summarised in Supporting Information S3: File 1 and reported in full (Bailey et al. 2018).

The MUAC-based ComPAS dosage entails a reduction in RUTF for all children with SAM compared to the former WHO guidelines, which recommended treatment of children with SAM with a higher weight-based RUTF dose until full recovery (World Health Organization 2013). Compared to the updated 2023 guidelines (WHO 2023), which suggest a reduction in RUTF starting in the MAM phase, the ComPAS protocol entails a reduction in energy provided to heavier children and those with a WHZ < -3 but MUAC ≥ 115 mm. ComPAS also prescribed a reduction in dose during the SAM phase of treatment as compared with the country protocol in South Sudan for children ≥ 5 kg and in Kenya for children ≥ 5.5 kg (The Republic of South Sudan Ministry of Health 2017, Ministry of Medical Services and Ministry of Public Health and Sanitation Kenya 2009). For children originally diagnosed with SAM who then reached MAM MUAC, and children originally diagnosed with MAM, there was no difference in energy provided between the intervention and control arms; however, RUTF and RUSF differ in their micronutrient composition and protein source (UNICEF 2022a; UNICEF 2022b).

2.3 | Outcomes

The primary outcome for this specific study was height-for-age (HAZ) change from admission to discharge of children admitted with severe wasting to the ComPAS trial. Linear growth in terms of linear growth velocity (mm/week) and change in height from admission to discharge in absolute mm are also presented. Secondary outcomes included change in WHZ, MUAC (in absolute mm and mm/week), and weight gain (in absolute grams and grams per kilograms per day) as well as recovery and length of stay (LoS) in days.

Primary and secondary outcomes were assessed for all children enroled and then for those who fully recovered. Sub-analyses were conducted for the SAM phase of treatment and through 17 weeks of treatment, as the non-response cutoff in the main analysis was extended to 17 weeks to evaluate the status of MAM children who would not have come for a visit at 16 weeks (Bailey et al. 2020).

2.4 | Data Management and Analysis

The dataset was prepared using Stata/IC v.13.1 (StataCorp 2013). We used R version 4.2.3 for the analyses (R Core Team 2023), with the extension packages tidyverse, gtsummary, splines, lme4, mice, zscorer, and emmeans.

Baseline characteristics of the study population are summarised as percent (n) or mean $\pm$ *SD* or median (interquartile range [IQR]) if non-normally distributed. The Wilcoxon rank-sum test tests for continuous variables and Chi-squared test of independence for categorical variables with all expected cell counts ≥ 5 were used to assess baseline differences by treatment arm.

Children with a missing height at discharge but a height recorded on a previous visit had their discharge height imputed on the basis of sex, age, timepoint in treatment, and any previous height measurements using multiple imputation with the mice package for Multivariate Imputation by Chained Equations (MICE) (van Buuren and Groothuis-Oudshoorn 2011). Children with identical admission and discharge height (i.e., copied admission height at exit) but who demonstrated growth on follow-up visits also had their exit height imputed with the same methods. In total, 64 (6.3%) exit heights were imputed. Imputed data remained comparable to non-imputed data, with no significant differences when excluding and including imputed values (Table S1). Anthropometric *z*-score outliers at admission, follow-up, and discharge were omitted per the WHO guidelines for analyses of WAZ (< -6 or > 5), WHZ (< -5 or > 5), and HAZ (< -6 or > 6) (World Health Organization (WHO) 2006).

Linear growth in HAZ, absolute mm, and linear growth velocity, weight change in absolute grams and grams per kilograms per week, and MUAC change in absolute mm and mm per week were calculated from admission to discharge for all exit categories and children who recovered using mixed linear models. Random effects were treatment site and country. Fixed effects were treatment group, age, sex, and outcome measures at admission where relevant. Sensitivity analyses comparing a model with complete cases (no imputed variables) and admission HAZ as a fixed effect were also conducted (Deichsel, Tickell, and Rogawski McQuade 2023). Significant differences with either are reported.

Growth curve modelling (i.e., non-linear mixed effect models) was used to fit aggregate growth curve models for change from baseline HAZ, WHZ, WAZ and MUAC. Missing anthropometric measures were imputed on the basis of sex, age, timepoint of treatment, and any previous or subsequent anthropometric measurements for analysis of growth curves using multiple imputation with the mice package for MICE (van Buuren and Groothuis-Oudshoorn 2011). Random effects were treatment site, participant ID, and country. Fixed effects were treatment group, age, sex, and the outcome measure at admission. Least-square means for change from baseline were obtained for treatment follow up at weeks 4, 8, 12 and 16 by treatment arm. Sensitivity analyses comparing complete cases (no imputation) and a model with admission

HAZ as a fixed effect were also conducted (Deichsel, Tickell, and Rogawski McQuade 2023). Significant differences with either are reported.

The percent of children who recovered was defined as MUAC of ≥ 125 mm and no oedema for two consecutive visits. We calculated the percent of children who transitioned to the MAM phase of treatment as those who achieved the MAM criterion per their treatment arm and successfully transitioned to MAM dosage. We calculated the LoS as the duration of the total treatment and the LoS in the SAM phase as the days from enrolment until the MAM transition. We reported outcomes for total LoS in treatment and outcomes through the 17-week cut-off are included in supplemental analyses. Differences in outcomes between total LoS in treatment and by 17 weeks are reported.

Interaction of selected variables with growth velocities and programmatic outcomes were tested including by age category at admission (< 12 months vs. ≥ 12 months; < 24 months vs. ≥ 24 months), sex, WAZ category at admission (WAZ < −3 vs. ≥ −3), WHZ category at admission (WHZ < −3 vs. ≥ −3), HAZ category at admission (HAZ < −3 vs. ≥ −3), and weight at admission (< 5 kg vs. ≥ 5 kg in South Sudan, and < 5.5 kg vs. ≥ 5.5 kg in Kenya, corresponding to reduced dosage in RUTF from admission compared to standard protocol). Only significant interaction terms led to subgroup analyses. P values were regarded as statistically significant if < 0.05.

2.5 | Ethical Consideration

The original ComPAS trial is registered at ISRCTN: trial number ISRCTN30393230 (http://www.isrctn.com/ISRCTN30393230). All procedures involving study participants were approved by the Kenya Medical Research Institute (reference non-KEMRI 551). The Internal Review Board of the Ministry of Health in South Sudan (approved 21 November 2016), and the ethics committee of the London School of Hygiene and Tropical Medicine (reference 11826). The analyses conducted for this paper comply with these ethical approvals. Written informed consent was obtained from the caretakers of all patients or by a witness who could attest to the caretaker's verbal consent.

3 | Results

3.1 | Inclusion in Secondary Analyses

Of the 4078 children admitted with MUAC < 125 mm and/or oedema included in the ComPAS trial dataset (2017 standard protocol, 2062 simplified) (Bailey et al. 2020), 3064 were excluded from this secondary analysis for the following reasons: 2852 were admitted with MUAC greater than or equal to 115 mm, 94 were missing height at discharge, 24 had implausible HAZ scores at admission then 16 at discharge (World Health Organization WHO 2006), and 16 with a HAZ change of 3 *SD* or more. A total of 1014 children were available for this secondary analysis. Of these 1014 children, 533 were in the standard arm and 481 were in the control arm (Figure 1).

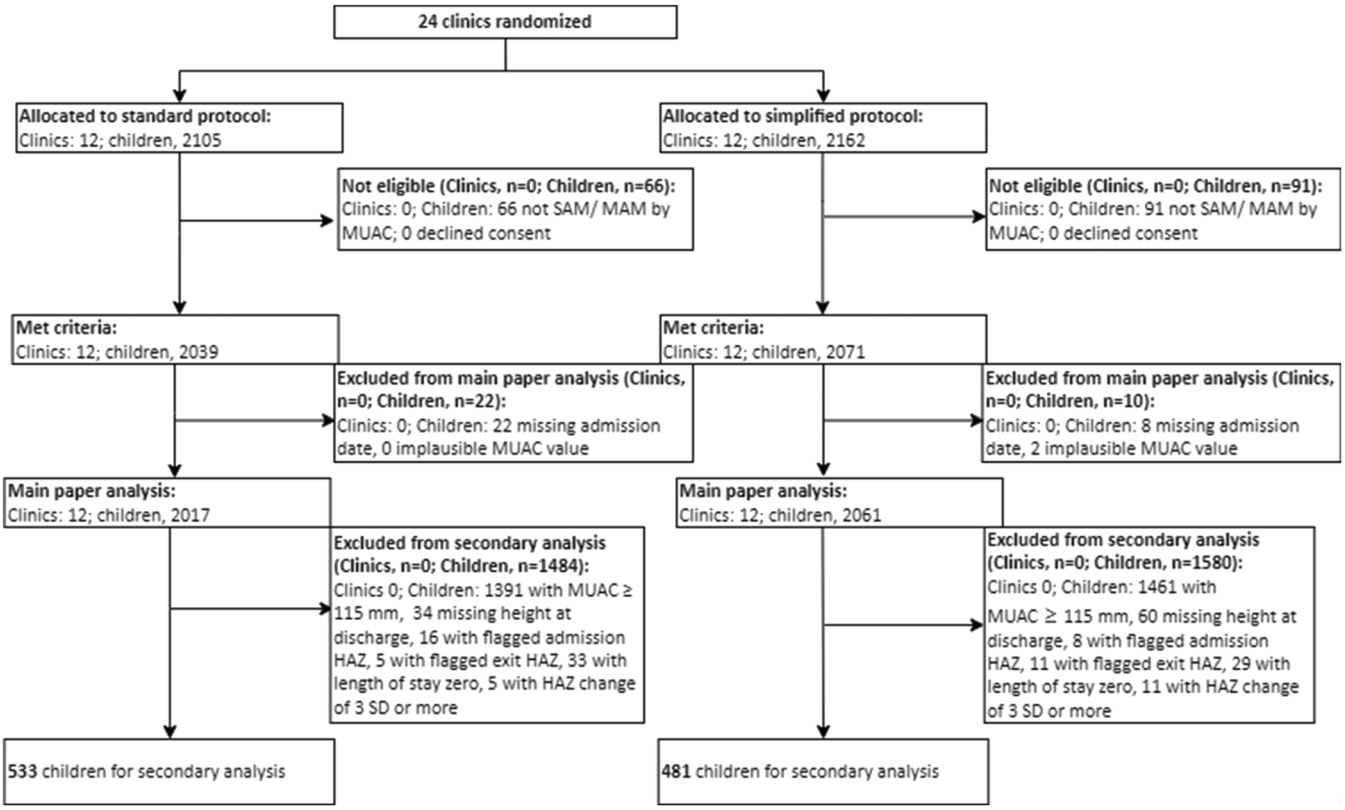


FIGURE 1 | Inclusion of children to the analysis of linear growth during simplified versus standard malnutrition treatment among severely wasted children.

3.2 | Characteristics on Admission

Of the 1014 children in this secondary analysis, 793 were enroled in South Sudan (78.2%). Median age at enrolment was 13 months (IQR: 9–24), 422 (41.6%) were male, and only 13 (1.3%) were enroled with oedema (Table 1). While MUAC and WHZ at admission were similar across groups, mean ± *SD* HAZ at enrolment was −2.3 ± 1.4 in the standard arm, compared to −2.6 ± 1.5 in the simplified arm. Mean ± *SD* WAZ at enrolment was also slightly higher in the standard arm: −3.4 ± 0.9, compared to −3.6 ± 1.0 in the simplified arm. A lower percentage of children in the standard arm lived in households reporting open water as their main water source and severe hunger in the household per the Household Hunger Scale (HHS) (Table 1) (Ballard et al. 2021).

TABLE 1 | Admission characteristics among children with MUAC < 115 mm randomised to simplified versus standard malnutrition treatment analyzed for linear growth.

	All children		Treatment arm		
	***N* not missing**	***N* (%)**	**Standard, *N* = 533**	**Simplified, *N* = 481**	***p*-value**
Country	1014				0.86
Kenya, *n* (%)		221 (21.8%)	115 (21.6%)	106 (22.0%)	
South Sudan, *n* (%)		793 (78.2%)	418 (78.4%)	375 (78.0%)	
Sex and age					
Male, *n* (%)	1014	422 (41.6%)	213 (40.0%)	209 (43.5%)	0.26
Age (months), median (IQR)	1014	13 (9.0, 24.0)	12.0 (9.0, 24.0)	14.0 (9.0, 24.0)	0.24
Age category, % (*n*)	1014				0.45
6 to < 12 months		412 (40.6%)	226 (42.4%)	186.0 (38.7%)	
12 to < 24 months		317 (31.3%)	164.0 (30.8%)	153.0 (31.8%)	
≥ 24 months		285 (28.1%)	143.0 (26.8%)	142.0 (29.5%)	
Anthropometrics at admission					
Edema, % (*n*)	1014	13 (1.3%)	9 (1.7%)	4 (0.8%)	0.23
MUAC (mm), mean ± *SD*	1014	110.4 ± 4.1	110.3 ± 4.3	110.5 ± 3.9	> 0.9
Weight (kg), mean ± *SD*	1014	6.7 ± 1.4	6.7 ± 1.4	6.7 ± 1.4	0.54
Height (cm), mean ± *SD*	1014	72.0 ± 8.4	72.1 ± 8.4	72.0 ± 8.4	0.80
WHZ, mean ± *SD*	1001	−3.1 ± 0.9	−3.1 ± 0.9	−3.2 ± 1.0	0.13
HAZ, mean ± *SD*	1014	−2.4 ± 1.5	−2.3 ± 1.4	−2.6 ± 1.5	**< 0.001**
WAZ, mean ± *SD*	1001	−3.5 ± 0.9	−3.4 ± 0.9	−3.6 ± 1.0	**< 0.001**
Co-morbidities[a]					
Fever, % (*n*)	1013	493 (48.7%)	246 (46.2%)	247 (51.4%)	0.10
Diarrhea, % (*n*)	1014	362 (35.7%)	194 (36.4%)	168 (34.9%)	0.63
Cough, % (*n*)	1014	412 (40.6%)	229 (43.0%)	183 (38.0%)	0.11
Household characteristics					
Maternal educational achievement - none, *n* (%)	1012	693 (68.5%)	355 (66.6%)	338 (70.6%)	0.18
Open defecation, *n* (%)	1013	486 (48.0%)	258 (48.4%)	228 (47.5%)	0.77
Water source: Open water, *n* (%)	1014	89 (8.8%)	24 (4.5%)	65 (13.5%)	**< 0.001**
Fishing or farming as main source of income	1014	436 (43.0%)	233 (43.7%)	203. (42.2%)	0.63
HHS	990				**< 0.001**
Little to no hunger in the HH		423 (42.7%)	250 (49.0%)	173 (36.0%)	
Moderate hunger in the HH		509 (51.4%)	238 (46.7%)	271 (56.5%)	
Severe hunger in the HH		58 (5.9%)	22 (4.3%)	36 (7.5%)	

Note: Bold indicates significance at *p*-value < 0.05.
Abbreviations: HAZ, height-for-age *z*-score; HH, household; HHS, Household Hunger Scale; MUAC, mid-upper-arm circumference; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.
[a]Reported by caregiver; recall period 1 week before admission.

3.3 | Outcomes

3.3.1 | Linear Growth

Mean change in HAZ between enrolment and discharge was negative in both the simplified (−0.26; $SE = 0.12$) and standard protocol arms (−0.27; $SE = 0.12$) (Table 2). There were no differences in change in HAZ between simplified and standard protocols, either in adjusted (difference = −0.017 z-scores; 95% confidence interval [CI]: −0.2 to 0.1; $p = 0.81$) or adjusted analyses (difference = 0.03 z-scores; 95% CI: −0.1, 0.2; $p = 0.65$) (Table 2). Linear growth velocity did not differ between arms in either unadjusted (difference = 0.09 mm/w; 95% CI: −0.4 to 0.5; $p = 0.69$) or adjusted (difference = 0.13 mm/w; 95% CI: −0.3, 0.5; $p = 0.55$) analyses, nor did absolute change in height. Analyses of linear growth and linear growth velocity adjusted for admission HAZ yielded similar results and are found in Table S2. The intra-class correlation coefficient (ICC) for HAZ change and linear growth velocity were 0.06 and 0.12, respectively (Supporting Information S1: Figures). Intervention arm and age interacted significantly when assessing absolute linear growth from admission to discharge ($p = 0.015$). Children 12 months and older in the standard arm had non-statistically significant higher linear growth from admission to discharge than the simplified arm (difference = 3.6 mm; 95% CI: −0.4, 7.6; $p = 0.08$).

Mean HAZ consistently dropped during follow-up but was not significantly different between treatment arms (Figure 2).

No differences were found in linear growth velocity or HAZ change by treatment arm among children who recovered or through 17 weeks of treatment only (Table 2). While treatment and age interacted significantly when assessing absolute linear growth from admission to discharge, no significant interactions were found between treatment and sex, age, admission weight, WAZ category, WHZ category, or stunting status at admission for linear growth velocity and HAZ change (Table S2).

No differences were found in anthropometry at discharge between treatment arms in the unadjusted and adjusted models (all $p > 0.5$) (Table S3). Analyses adjusted for admission HAZ and through the first 17 weeks of treatment only yielded similar results (Table S3).

3.4 | Programmatic Outcomes

The mean ± SD LoS was higher in the standard protocol (88.0 ± 3.6 days) compared to the simplified protocol (79.4 ± 3.7 days) when adjusting for admission sex and age (difference = 8.6 days; 95% CI: 1.1, 16; $p = 0.027$) (Table 3). Analyses adjusted for admission HAZ and through the first 17 weeks of treatment yielded similar results (Table S4). When adjusting for admission sex, age, and weight, weight gain in grams during treatment was significantly higher in the SAM dosage phase in the standard arm, compared to the simplified arm (difference = 107 g; 95% CI: 8.9, 205; $p = 0.034$) (Table 3). This difference was not significant when further adjusting for admission HAZ (Table S4). No significant interactions were observed between treatment and sex, age, WAZ category, WHZ category, or stunting status at admission for MUAC or weight gain velocity (Table S4).

Unlike HAZ, WAZ and WHZ improved during treatment, though the rate of improvement slowed over the course of treatment in both arms (Figure 3). Change in WAZ and WHZ from baseline did not differ significantly at weeks 4, 8, 12 or 16 between treatment arms. MUAC improved similarly across arms over the course of treatment (Figure 3).

4 | Discussion

In this secondary analysis of children with SAM treated with a simplified versus standard protocol, no significant differences in linear growth from admission to discharge were detected by treatment arm according to HAZ change, linear growth velocity, or absolute linear growth in mm. This suggests that linear growth among severely wasted children may be similar during treatment with a simplified, MUAC-based RUTF dose compared to the standard, weight-based dosing strategy during the SAM phase of treatment.

However, linear growth observed in this sub-population (1.7 ± 1.6 mm/week in the standard arm and 1.6 ± 0.6 mm/week in the simplified arm) was not sufficient to prevent poor linear growth defined as a loss in HAZ from admission to discharge, which was noted across both treatment arms. Our work demonstrates HAZ can deteriorate in relatively short treatment windows with either a standard weight-based or simplified MUAC-based RUTF dose during the SAM phase and with 1 sachet of RUTF or RUSF during the MAM phase of treatment. As negative change in HAZ 1 year after malnutrition treatment is a strong risk factor for relapse to SAM or MAM across all age groups (Stobaugh et al. 2018), our work indicates this deterioration can begin during treatment and should continue to be reported for malnutrition treatment regardless of RUTF dose.

In contrast to two prior studies evaluating reduced and optimised RUTF doses in children with SAM, we did not observe differences in linear growth by treatment arm in ComPAS (Kangas et al. 2019; Stephenson et al. 2021). One key difference between these studies is control arm treatment: in ComPAS, control arm children were given 500 kcal/day of RUSF when they reached MAM criteria, whereas children in the control arms in the prior studies received a full dose of RUTF until full recovery (Bailey et al. 2020; Kangas et al. 2019; Stephenson et al. 2021). This protocol difference may have contributed to the disparate results. In addition, heavier children in the intervention arm of both prior studies of reduced and optimised doses were provided with a higher RUTF dose in the SAM phase than the ComPAS protocol (Kangas et al. 2019; Stephenson et al. 2021).

Previous work has raised questions on optimising the formulation of therapeutic foods to promote long-term linear growth and cognitive development (Lelijveld, Stephenson, and

TABLE 2 | Linear growth from admission to discharge among children with MUAC < 115 mm admitted to simplified and standard malnutrition treatment.

	Unadjusted[a]						Adjusted[b]					
	Standard		Simplified		Difference (95% CI)	*p*-value	Standard		Simplified		Difference (95% CI)	*p*-value
	n	Mean ± *SE*	*n*	Mean ± *SE*			*n*	Mean ± *SE*	*n*	Mean ± *SE*		
HAZ change (*SD*'s)												
All children[c]	533	−0.27 ± 0.12	481	−0.26 ± 0.12	−0.017 (−0.17, 0.13)	0.81	533	−0.21 ± 0.18	481	−0.24 ± 0.18	0.03 (−0.12, 0.18)	0.65
Through 17 weeks[c,d]	533	−0.23 ± 0.14	481	−0.22 ± 0.14	−0.014 (−0.15, 0.12)	0.83	533	−0.17 ± 0.20	481	−0.20 ± 0.20	0.035 (−0.099, 0.17)	0.59
Full recovery[e]	94	−0.16 ± 0.19	105	−0.14 ± 0.20	−0.023 (−0.22, 0.18)	0.81	94	−0.11 ± 0.24	105	−0.14 ± 0.24	0.037 (−0.15, 0.23)	0.69
Linear growth velocity (mm/wk)												
All children[c]	533	1.8 ± 0.7	481	1.7 ± 0.7	0.09 (−0.36, 0.53)	0.69	533	1.7 ± 0.6	481	1.6 ± 0.6	0.13 (−0.31, 0.56)	0.55
Through 17 weeks[c,d]	533	1.8 ± 0.7	481	1.7 ± 0.7	0.07 (−0.37, 0.52)	0.74	533	1.8 ± 0.6	481	1.6 ± 0.6	0.12 (−0.31, 0.55)	0.57
Full recovery[e]	94	1.9 ± 0.8	105	1.8 ± 0.8	0.091 (−0.43, 0.61)	0.72	94	1.8 ± 0.6	105	1.7 ± 0.6	0.16 (−0.38, 0.61)	0.63
Linear growth (mm)												
All children[c]	533	25.7 ± 11.1	481	24.7 ± 11.1	0.96 (−4.0, 5.9)	0.69	533	24.3 ± 8.8	481	23.3 ± 8.8	1.08 (−3.4, 5.6)	0.62
Through 17 weeks[c,d]	533	23.3 ± 9.5	481	23.0 ± 9.5	0.29 (−4.2, 4.8)	0.89	533	22.2 ± 7.4	481	21.7 ± 7.4	0.51 (−3.5, 4.6)	0.79
Full recovery[e]	94	24.5 ± 8.5	105	21.0 ± 8.5	3.50 (−3.1, 10.1)	0.28	94	23.4 ± 5.5	105	19.6 ± 5.6	3.90 (−2.1, 9.9)	0.19
Sub-group analysis by												
Admission age						**0.015**[f]						**0.015**[f]
6 to < 12 months	226	29.9 ± 10.1	186	33.0 ± 10.1	−3.0 (−9.7, 3.7)	0.35	226	30.2 ± 8.8	186	31.8 ± 8.8	−1.6 (−7.7, 4.4)	0.58
≥ 12 months	307	19.2 ± 7.04	295	15.6 ± 7.0	3.6 (−0.4, 7.6)	0.08	307	18.3 ± 6.3	295	14.8 ± 6.2	3.6 (−0.4, 7.6)	0.08

Note: Bold indicates significance at *p*-value < 0.05.

[a]Data are mean ± *SE* and mean difference (95% CI) when using linear mixed models with country and treatment site as random effects.

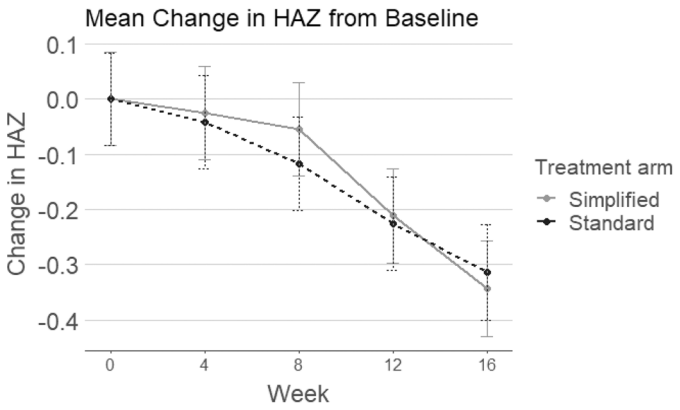
[b]Data are mean ± *SE* and mean difference (95% CI) when using linear mixed models with country and treatment site as random effects and when controlling for admission HAZ (HAZ change) or admission height (linear growth and linear growth velocity), admission age, and sex.

[c]Regardless of outcome or length of stay in treatment.

[d]Growth through 17 weeks of treatment or discharge if LoS < 17 weeks.

[e]≥ 125 mm for two consecutive measurements and no oedema, with 3-week minimum stay.

[f]Significant interaction ($p < 0.05$).



Week	N	Difference: Simplified - Standard	SE	p-value
0	1014	0	0.12	1
4	962	0.02	0.12	0.89
8	772	0.06	0.12	0.61
12	603	0.01	0.12	0.91
16	415	-0.03	0.12	0.82

FIGURE 2 | Mean change in HAZ from baseline among children admitted with MUAC < 115 mm by week of treatment and treatment group. Adjusted for baseline age, sex, and admission HAZ, with treatment site, participant ID, and country as random effects. HAZ, height-for-age *z*-score.

Manary 2022; Potani et al. 2023). While RUTF and RUSF are similar calorically per sachet, RUTF provides a higher percentage of high-quality protein from dairy sources (UNICEF 2022a; UNICEF 2022b). Amino acid composition of therapeutic foods may play an important role in growth: while lower cost, non-dairy and lower-dairy RUTF showed lower weight gain, lower recovery, and lower WAZ at discharge, for example (Potani et al. 2021). Our work does not suggest a difference in linear growth when comparing treatment with RUTF compared to RUSF during the MAM phase; however, the relatively short duration of the MAM phase for children admitted SAM in the control arm (43.2 ± 3.8 days in the SAM phase compared to 89 ± 2.7 days among children fully recovered) should be emphasised as a limitation. Study populations and settings also varied: children with uncomplicated SAM in a rural region of Eastern Burkina Faso (Kangas et al. 2019), rural Sierra Leone (Stephenson et al. 2021), urban Nairobi and rural Aweil East, South Sudan (Bailey et al. 2020). There may be significant differences in underlying determinants of malnutrition in these contexts and populations, for which we lack standardised measures (UNICEF 2021). Compared to the previous studies that report linear growth differences in children treated with reduced doses, severely wasted children in this secondary analysis were older, taller, and thinner per MUAC and WHZ, yet had similar HAZ at admission; therefore, stunting at admission does not explain the discrepancy in findings (Kangas et al. 2019; Stephenson et al. 2021).

Weight gain precedes linear growth (Isanaka et al. 2019; Walker and Golden 1988; Ngari et al. 2019; Bourdon et al. 2024), and improvements in WHZ may reflect rapid weight gain during treatment in comparison to linear growth (Kerac et al. 2014; Kamugisha et al. 2021). Mean weight gain velocity in the intervention arm of this analysis (2.0 g/kg/day) was higher than that seen with a reduced dosage among SAM children who had improved to MAM in Sierra Leone (1.4 g/kg/day) (Stephenson et al. 2021), but lower than many others: in Mali with the ComPAS protocol (5.8 g/kg/day) (Kangas et al. 2022), the MANGO trial in Burkina Faso (3.5 g/kg/day after 2 weeks of treatment) (Kangas et al. 2019), and the OptiMA protocol in Burkina Faso (4.7 g/kg/day) (Daures et al. 2019) and Niger (4.3 g/kg/day) (Phelan et al. 2023). Consistent with other work, this secondary analysis suggests weight gain velocity is similar across children treated with a simplified and standard dosage during treatment (Bailey et al. 2020).

MUAC is a proxy for weight gain used in programming to monitor child growth (Roberfroid et al. 2013; Goossens et al. 2012). The age, sex, and baseline anthropometric adjusted mean MUAC gain velocity among severely wasted children was 1.1 mm/week in the standard arm and 1.0 mm/week for in the simplified arm. This is higher than what was found among SAM children treated with an optimised protocol in Sierra Leone (0.5 mm/week) (Stephenson et al. 2021), similar to the OptiMA protocol in Niger (0.25 mm/day) (Phelan et al. 2023), and lower than the MANGO trial in Burkina Faso (1.8 mm/week) (Kangas et al. 2019) and lower than demonstrated in Mali with the simplified protocol (0.4 mm/day) (Kangas et al. 2022). Change in MUAC-for-age *z*-score was identical across treatment arms in both adjusted and unadjusted analyses. Consistent with other work, this secondary analysis suggests MUAC gain is similar across children treated with a simplified and standard dosage during treatment (Bailey et al. 2020). The higher MUAC velocity in our secondary analysis of severely wasted children compared to the main analysis is consistent with previous work demonstrating MUAC gain is highest at lower MUAC's and declines to lower levels of growth at higher MUAC's and as treatment progresses (Chase et al. 2020; Kangas et al. 2019; Goossens et al. 2012).

Strengths of this analysis include robustness and consistency of findings across unadjusted and adjusted analyses, as well as analyses with and without imputed values. The data analyzed come from a cluster randomised controlled trial in two

TABLE 3 | Programme outcomes and anthropometric gain velocities for children with MUAC < 115 mm admitted to simplified and standard treatment.

	Unadjusted[a]				Adjusted[b]			
	Standard	**Simplified**	**Difference (95% CI)**	***p*-value**	**Standard**	**Simplified**	**Difference (95% CI)**	***p*-value**
Total (from SAM to full recovery)[c]	***n* = 94**	***n* = 105**			***n* = 94**	***n* = 105**		
Length of stay, d	89 ± 2.7	80 ± 3.2	8.3 (−0.04, 16.7)	0.051	88 ± 3.6	79 ± 3.7	8.6 (1.1, 16)	**0.027**
Weight gain, g	1539 ± 75.0	1503 ± 90.4	36.3 (−191, 263)	0.74	1589 ± 73.8	1451 ± 86.2	139 (−73.6, 351)	0.19
Weight gain velocity, g/kg/d	2.8 ± 0.4	3.1 ± 0.4	−0.3 (−0.8, 0.2)	0.24	2.9 ± 0.2	2.9 ± 0.2	0.0082 (−0.5, 0.5)	0.97
MUAC gain, mm	18.3 ± 1.7	17.8 ± 1.7	0.48 (−1.8, 2.8)	0.67	18.1 ± 0.6	17.3 ± 0.6	0.80 (−0.9, 2.5)	0.34
MUAC gain velocity, mm/w	1.6 ± 0.2	1.7 ± 0.2	−0.10 (−0.4, 0.2)	0.49	1.6 ± 0.1	1.7 ± 0.1	−0.083 (−0.4, 0.2)	0.54
Total (from SAM to any outcome)	***n* = 533**	***n* = 481**			***n* = 533**	***n* = 481**		
Recovery, % (*n*)	21.1% (94)	23.2% (105)	−0.021 (−0.1, 0.1)	0.60	23.4% (94)	25.0% (105)	−0.016 (−0.1, 0.1)	0.69
Length of stay, d	95.9 ± 12.4	94.9 ± 12.5	0.99 (−11.2, 13.2)	0.87	93.8 ± 10.3	93.4 ± 10.3	0.40 (−11.5, 12.3)	0.98
Weight gain, g	1048 ± 114	1060 ± 114	−12.2 (−181, 157)	0.88	1078 ± 132	1065 ± 133	13.3 (−162, 189)	0.88
Weight gain velocity, g/kg/d	2.1 ± 0.2	2.0 ± 0.2	0.069 (−0.3, 0.5)	0.72	2.2 ± 0.2	2.0 ± 0.2	0.17 (−0.2, 0.6)	0.37
MUAC gain, mm	11.6 ± 2.0	11.6 ± 2.0	−0.027 (−1.7, 1.6)	0.97	11.8 ± 2.2	11.7 ± 2.2	0.10 (−1.5, 1.8)	0.90
MUAC gain velocity, mm/w	1.1 ± 0.1	1.0 ± 0.1	0.023 (−0.1, 0.2)	0.76	1.1 ± 0.1	1.1 ± 0.1	0.041 (−0.1, 0.2)	0.55
SAM phase only[c]	***n* = 533**	***n* = 481**			***n* = 533**	***n* = 481**		
Transitioned to MAM phase, % (*n*)[d]	81.1% (423)	87.6% (417)	−0.065 (−0.2, 0.02)	0.14	81.4% (423)	87.7% (417)	−0.063 (−0.2, 0.03)	0.15
Length of stay SAM phase, d	43.2 ± 3.8	40.8 ± 3.8	2.4 (−4.1, 8.8)	0.45	42.4 ± 2.8	40.3 ± 2.8	2.0 (−4.4, 8.5)	0.51
Weight gain SAM phase, g	678 ± 37	604 ± 38	74.2 (−15.1, 163)	0.097	702 ± 39	596 ± 39	107 (8.9, 205)	**0.034**
Weight gain velocity SAM phase, g/kg/d	3.3 ± 0.3	3.3 ± 0.3	0.03 (−0.7, 0.7)	0.94	3.4 ± 0.3	3.2 ± 0.3	0.17 (−0.6, 0.9)	0.63
MUAC gain SAM phase, mm	7.9 ± 1.2	7.3 ± 1.3	0.66 (−0.3, 1.7)	0.18	8.0 ± 1.2	7.2 ± 1.2	0.759 (−0.08, 1.6)	0.074
MUAC gain velocity SAM phase, mm/w	1.8 ± 0.2	1.7 ± 0.2	0.034 (−0.2, 0.3)	0.78	1.8 ± 0.3	1.8 ± 0.3	0.054 (−0.2, 0.3)	0.67

Note: Bold indicates significance at *p*-value < 0.05.

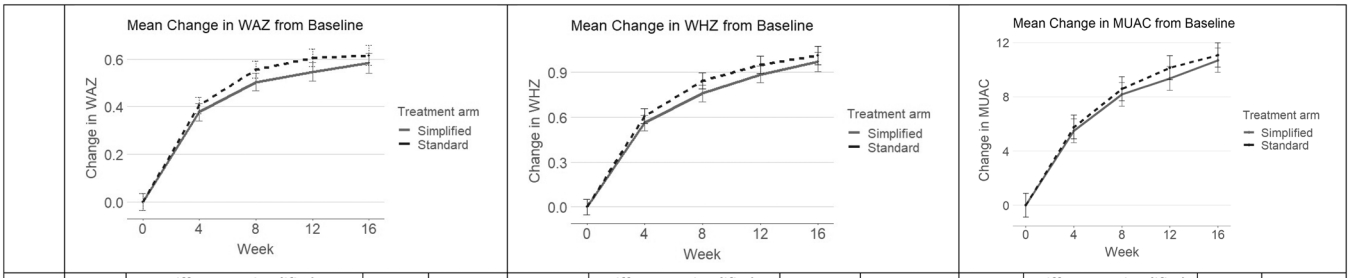
Abbreviations: MAM, moderate acute malnutrition; MUAC, mid-upper arm circumference; SAM, severe acute malnutrition; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.

[a]Data are mean ± *SE* (unless otherwise noted) and mean difference (95% CI) when using linear mixed models with country and treatment site as random effects.

[b]Data are mean ± *SE* and mean difference (95% CI) when using linear mixed models with country and treatment site as random effects and when adjusting for outcome at admission (admission MUAC for MUAC change; admission weight for weight change), age, and sex.

[c]Refers to growth until transitioned to MAM dosage.

[d]Reached MAM criterion by protocol.



Wk	n	Difference: Simplified - Standard	SE	p-value	n	Difference: Simplified - Standard	SE	p-value	n	Difference: Simplified - Standard	SE	p-value
0	1014	0	0.05	1	1014	0	0.07	1	1014	0	1.26	1
4	945	-0.03	0.05	0.57	945	-0.05	0.07	0.52	945	-0.27	1.26	0.83
8	751	-0.05	0.05	0.30	751	-0.08	0.08	0.27	751	-0.41	1.27	0.74
12	577	-0.06	0.05	0.28	577	-0.06	0.08	0.42	577	-0.78	1.29	0.53
16	372	-0.03	0.06	0.59	372	-0.04	0.09	0.63	372	-0.39	1.29	0.76

FIGURE 3 | Mean change in growth from baseline among children admitted with MUAC < 115 mm by week of treatment and treatment group. Adjusted for baseline age, sex, and outcome at admission (admission WAZ for WAZ change, admission WHZ for WHZ change, and admission MUAC for MUAC change), with treatment site, participant ID, and country as random effects. MUAC, mid-upper arm circumference; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.

countries, with quality control measures in place during data collection. Children in this analysis were slightly older than previous work studying children admitted by MUAC criterion only (Daures et al. 2019; Kangas et al. 2022; Stephenson et al. 2021). Our findings underscore the importance of understanding individual and contextual drivers of growth. In most cases, anthropometric velocities of children in these secondary analyses were lower than previous CMAM studies of reduced and optimised doses (i.e., for MUAC and weight velocity), but this difference was inconsistent (Stephenson et al. 2021; Kangas et al. 2022; Kangas et al. 2019; Daures et al. 2020; Phelan et al. 2023).

Limitations to this analysis included both statistical and operational constraints. This is a secondary analysis of data from a trial that was not powered for sub-group analyses (Bailey et al. 2020). We detected significant differences in age, admission anthropometrics, and treatment outcomes in the population included in these analyses by country and health facility (Supporting Information S1: Figures). For example, children admitted in Kenya for this sub-analysis were generally younger than in South Sudan. Because analyses were done preserving the original cluster-randomised design at the health facility level, large differences between clusters (ICC for change in HAZ = 0.064) had a negative impact on inferential power (Gupta and Kopper 2021). The lack of power to detect what may be clinically relevant differences in linear growth in this secondary analysis is an inherent limitation (Carlin and Hocking 1999).

We were unable to triangulate our findings with other known determinants of linear growth, including recurrent illnesses, anemia, caregiver characteristics, protein quality in the first 1000 days, and total caloric and micronutrient intake (Bourdon et al. 2024; Kotloff et al. 2012; Ghosh, 2016; Brander et al. 2019; Nikièma et al. 2022). The monthly frequency of height measures during treatment limited the data available for this analysis. As this was a secondary analysis of data collected in 2017–2018, we were unable to directly verify implausible values. While linear growth is notoriously difficult to monitor, especially in young children, the study benefitted from the technical oversight of research staff during implementation (Foote 2014). We excluded outliers consistent with WHO guidance and other research on linear growth (World Health Organization WHO, 2006; Brander et al. 2019). Importantly, we retained biologically implausible linear loss (i.e., linear growth in mm < 0) to avoid overcorrecting for measurement error and positively biasing the results measures. We report the SAM phase until the first achievement of MAM criterion—whereas some children who had transitioned to MAM regressed back to the SAM criterion and were again treated with the higher dose.

Further research is needed with an explicit focus on linear growth during and after SAM treatment, with more frequent and post-discharge height measures. This is true for both standard and modified protocols, as guidance on acceptable linear growth for modified protocols to be compared to is lacking. Previous work regarding optimised doses hypothesised that timing of reduced RUTF may correspond to a window where growth-essential nutrients are accumulated, and that this reduction may contribute to a slower rate of length gain compared to standard treatment (Stephenson et al. 2021). While we did not detect this during treatment, our findings underscore the importance of post-discharge monitoring and interventions to better understand how patterns of growth may differ during and after treatment, as well as how and if this translates into functional developmental outcomes (WHO 2023). Future work must also explore the ideal dose and formulation of therapeutic foods to prevent poor linear growth during and after a wasting episode.

5 | Conclusion

Reducing the RUTF dose prescribed to children during SAM treatment does not appear to affect linear growth during treatment, nor other growth velocities. Overall, this study adds to a growing body of evidence that suggests that children with

SAM can achieve similar anthropometric growth when treated with a reduced and simplified MUAC-based dose of RUTF. Considering the range observed in the context to date, ponderal and linear growth trajectories should continue to be reported in studies testing optimised and reduced RUTF doses for the treatment of SAM.

Author Contributions

André Briend, Marko Kerac, and Jeanette Bailey contributed to the design of the ComPAS research and oversaw implementation. All authors contributed to the statistical analysis plan for the secondary analyses. Grace Heymsfield, Zachary Tausanovitch, and Kevin Stephenson analyzed the data. Grace Heymsfield, Kevin Stephenson and Suvi T. Kangas wrote the manuscript. All authors have critically reviewed the manuscript and contributed to the interpretation of the data. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank all caregivers, study participants and staff at study clinics who generously provided their time and without whom this study would not have been possible. We thank the Ministries of Health in Kenya and South Sudan, the offices of UNICEF and WFP in Kenya and South Sudan, the International Rescue Committee, Action Against Hunger, and the London School of Hygiene and Tropical Medicine for their support of the study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.