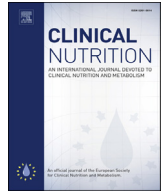




Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: <http://www.elsevier.com/locate/clnu>

Original article

Body composition during outpatient treatment of severe acute malnutrition: Results from a randomised trial testing different doses of ready-to-use therapeutic foods

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ARTICLE INFO

Article history:

Received 15 November 2019

Accepted 28 February 2020

Keywords:

Body composition

Bioelectrical impedance analysis

Severe acute malnutrition

Children

Ready-to-use therapeutic food

Burkina Faso

SUMMARY

Background & aims: Treatment of children with uncomplicated severe acute malnutrition (SAM) is based on ready-to-use therapeutic foods (RUTF) prescribed based on body weight and administered at home. Treatment performance is typically monitored through weight gain. We previously reported that a reduced dose of RUTF resulted in weight gain velocity similar to standard dose. Here we investigate the change in body composition of children treated for SAM and compare it to community controls, and describe the effect of a reduced RUTF dose on body composition at recovery.

Methods: Body composition was measured via bio-electrical impedance analysis at admission and recovery among a sub-group of children with SAM participating in a clinical trial and receiving a reduced or a standard dose of RUTF. Non-malnourished children were measured to represent community controls. Linear mixed regression models were fitted.

Results: We obtained body composition data from 452 children at admission, 259 at recovery and 97 community controls. During SAM treatment the average weight increased by 1.20 kg of which 0.55 kg (45%) was fat-free mass (FFM) and 0.67 kg (55%) was fat mass (FM). At recovery, children treated for SAM had 1.27 kg lower weight, 0.38 kg lower FFM, and 0.90 kg lower FM compared to community controls. However, their fat-free mass index (FFMI) was not different from community controls ($\Delta 0.2 \text{ kg/m}^2$; 95% CI $-0.1, 0.4$). No differences were observed in FFM, FM or fat mass index (FMI) between the study arms at recovery. However, FFMI was 0.35 kg/m^2 higher at recovery with the reduced compared to standard dose ($p = 0.007$) due to slightly lower height ($\Delta 0.22 \text{ cm}$; $p = 0.25$) and higher FFM ($\Delta 0.11 \text{ kg}$; $p = 0.078$) in the reduced dose group.

Conclusions: Almost half of the weight gain during SAM treatment was FFM. Compared to community controls, children recovered from SAM had a lower FM while their height-adjusted FFM was similar. There was no evidence of a differential effect of a reduced RUTF dose on the tissue accretion of treated children when compared to standard treatment.

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1. Introduction

Severe acute malnutrition (SAM) affects 19 million children under 5 years of age globally and at any time, contributing to over 500 000 annual deaths [1]. Children presenting with SAM without medical complications are treated as outpatients [2] with a routine

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<https://doi.org/10.1016/j.clnu.2020.02.038>

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Abbreviations

CMAM	community-based management of acute malnutrition
FFM	fat-free mass
FFMI	fat-free mass index
FM	fat mass
FMI	fat mass index
HAZ	height-for-age z-score
MAM	moderate acute malnutrition
MUAC	mid-upper arm circumference
PA	phase angle
R	resistance
R/h	resistance per height
RUTF	ready-to-use therapeutic food
SAM	severe acute malnutrition
WAZ	weight-for-age z-score
WHO	World Health Organisation
WHZ	weight-for-height z-score
Xc	reactance
Xc/h	reactance per height

antibiotic regimen and Ready-to-Use-Therapeutic-Food (RUTF) prescribed according to body weight [2]. RUTFs are highly fortified energy-dense pastes intended to fulfil 100% of the nutritional needs of children during recovery from SAM to enable a quick regain of lost body tissues while providing sufficient micronutrients to replenish diminished body stores [3]. However, outpatient treatment of SAM has not reached the same rate of weight gain as observed in inpatient treatment despite offering the same quantity of RUTF [4]. It has been assumed that this is due to incomplete consumption of RUTF by the treated child [5–7]. The cost of RUTFs and the large quantity administered per child have sparked attempts to reduce the dose [8,9].

SAM treatment success is currently monitored in terms of recovery rates, where recovery is defined by a target weight-for-height z-score (WHZ) and/or mid-upper arm circumference (MUAC). Neither of these anthropometric measures estimates the restoration of the functionally different body components: in particular, fat mass (FM) and fat-free mass (FFM). Most studies that have measured body composition changes during treatment of malnourished children were conducted in inpatient settings on patients with medical complications receiving milk based diets, making it difficult to extrapolate findings to community-based treatment with RUTFs [10–13]. Bahwere et al. (2016) assessed body composition of children at the end of RUTF-based treatment of SAM and concluded that children seemed to present a similar FM but had a deficit of FFM compared to community controls [14]. However, no data were presented for the change in body composition from admission to discharge, preventing the estimation of tissue deposition patterns during treatment. Also, the exclusion of children <24 months of age from the body composition sub-study limits the generalisability of these findings to the full age range of children 6–59 months old eligible for SAM treatment.

We previously reported a non-inferior weight gain velocity with a reduced RUTF dose compared to the standard dose used in outpatient treatment of uncomplicated SAM [15]. The objective of this paper is to assess the change in body composition during SAM treatment and the difference compared to non-malnourished community controls, and explore the effect of a reduced RUTF dose on the body composition of recovered children.

2. Materials and methods**2.1. Study design**

This study was nested in the MANGO trial, a randomized controlled clinical trial comparing the efficacy of a reduced RUTF dose to a standard RUTF dose in the management of uncomplicated SAM in children 6–59 months of age admitted to outpatient care, using a non-inferiority study design. The MANGO trial was performed in accordance with the principles in the Declaration of Helsinki. The research protocol obtained ethical clearance from the national ethics committee (Comité d'éthique pour la recherche en santé (CERS)) and the clinical trials board (Direction Générale de la Pharmacie, du Médicament et des Laboratoires (DGPML)) of Burkina Faso. An independent Data Safety Monitoring Board composed of one paediatrician and one statistician was responsible for monitoring serious adverse events and conducted five complete data reviews during the course of the study. Caregivers provided verbal and written consent prior to enrolment and were made aware of their right to withdraw from the study at any time. The trial was registered at the ISRCTN registry with the number ISRCTN50039021 on 13 May 2016.

2.1.1. The original study

As previously described [15], the study was conducted in the Fada N'Gourma health district in the Eastern region of Burkina Faso where the prevalence of wasting (WHZ < -2) was 10% in 2016 [16].

Study participants were recruited from children presenting with SAM at the 10 participating health centres. Children 6–59 months of age were eligible if: WHZ < -3 and/or MUAC < 115 mm, positive appetite test, and absence of oedema or medical complications. Exclusion criteria included having received treatment for SAM within 6 months, caregiver unable to comply with the weekly check-up schedule, known peanut or milk allergy, or disability affecting food intake.

After confirming eligibility and obtaining consent, children were randomised individually stratified by health centre, as previously described [15]. SAM treatment followed the Burkina national CMAM guidelines except for the RUTF dose: from the third treatment week onwards, children who were randomised to reduced dose received either 1 or 2 sachets per day if weighing <7 kg or ≥7 kg, respectively (Table 1). Children randomised to the standard dose received the standard RUTF dose throughout treatment. Weekly anthropometric measurements and a clinical examination were performed from admission to discharge.

Nutritional recovery was defined as: WHZ ≥ -2 for those admitted with a WHZ < -3 only, MUAC ≥ 125 mm for those admitted with a MUAC < 115 mm only, or WHZ ≥ -2 and MUAC ≥ 125 mm for those admitted with WHZ < -3 and MUAC < 115 mm, on two consecutive visits and absence of any illness. Maximum treatment duration was 16 weeks after which children were classified as non-response to treatment, if the recovery criteria were still not achieved.

2.1.2. The present study

Body composition measurements started 5 months after launch of the main study. The body composition sub-study sample included the main study participants that were enrolled or recovered after February 7, 2017 until the end of the main study in December 2018. Body composition was measured among all children at admission and recovery. In addition, a total of 100 community controls were selected among children presenting for growth monitoring activities in the same 10 health centres and were stratified by sex and age to match the admission distribution of children in the main trial. Community control inclusion criteria

Table 1
RUTF dose in reduced and standard dose groups.

Weight (kg)	Sachets/week			% of reduction
	Standard RUTF dose		Reduced RUTF dose	Reduced RUTF dose
	Admission to discharge	Week 1–2	Week 3 to discharge	from week 1–2 to week 3
3.0–3.4	8	8	7	13%
3.5–4.9	10	10	7	30%
5.0–6.9	15	15	7	53%
7.0–9.9	20	20	14	30%
10.0–14.9	30	30	14	53%

RUTF, ready-to-use therapeutic foods.

included MUAC > 125 mm, a WHZ > -2 and not being ill on the day of the measurements.

Body composition was measured using bio-electrical impedance analysis (BIA) (Nutriguard S, DataInput, Germany). This technique measures Resistance (R), Reactance (Xc), Phase Angle (PA), and hand R and foot R, all at 50 kHz. Electrodes were cut in half lengthwise to better accommodate the small hands and feet of children. The sending electrodes were placed on the dorsal side of the metacarpal and phalange bones on the right side of the body. Receiving electrodes were placed 3 cm from the sending ones towards the arm or the tibia. Each BIA measurement was done twice, and the quality of the measurements was rated by the measurers on a scale from 1 (very poor) to 5 (ideal) in terms of child's position (see S1 Table).

Anthropometrics were measured in duplicate: weight using an electronic scale (SECA 876) to the nearest 100 g, height (recumbent for <24 months of age; standing for ≥24 months of age) using a wooden measuring board (locally made) to the nearest 1 mm, and MUAC using a non-stretchable colourless measuring tape to the nearest 1 mm.

2.2. Outcomes

BIA measurements (R, Xc) were used to estimate body composition. Where two acceptable BIA measurements were available, the mean R and Xc were calculated, otherwise the single measurement was used. Impedance (Z) was calculated as the square root of ($R^2 + Xc^2$). Fat-free mass (FFM) was calculated using an equation predicting FFM from the impedance index ($FFM = 1.93 + 0.669 * (\text{height}^2 / Z)$) in Gambian children measured using another single frequency tetrapolar device (Body Stat, Douglas, Isle of Man), calibrated against the deuterium dilution technique [17]. For this purpose, height was standardised as standing height subtracting 0.7 cm from recumbent measurements. Calculated this way, FFM includes both lean mass and bone. Fat Mass (FM, kg) was calculated as the difference between weight and FFM. FFM and FM were adjusted for height in metres squared to give fat-free mass index (FFMI) and fat mass index (FMI), expressed as kg/m^2 . Impedance index was calculated as height (in cm) squared divided by impedance (cm^2/Z). $1/Z$ was also calculated (multiplied by 1000) as an alternative to FFMI [18].

2.3. Data analysis

Data were collected electronically via tablets using the Open Data Kit (ODK1 software). Baseline characteristics of the study population are summarized as percentage or mean ± standard deviation. Significance tests were conducted for baseline differences between children in the reduced and standard dose arm, as groups are based on non-random sampling of participants included in the main trial. Linear mixed regression models were used to

compare body composition outcomes. Participant id, study sites and research teams were included in the models as random effects. Unadjusted models as well as models adjusted for sex, age and outcome measurements at admission were fitted. Model checking was based on residual plots and normal probability plots.

Interactions between treatment and age group (<12 months vs. ≥ 12 months), sex, MUAC category (<115 vs. ≥ 115 mm), WHZ category (<-3 vs. ≥ -3) and stunting (HAZ < -2 vs. HAZ ≥ -2) at admission, were evaluated for FFM and FM by means of likelihood ratio tests. Only significant interaction terms led to subgroup analyses. A significance level of 0.05 was used. All analyses were performed in STATA 15 (StataCorp, College Station, TX, USA).

3. Results

3.1. Data cleaning and quality

To reduce noise in the body composition data, three data cleaning steps were undertaken. First, BIA measurements with poor hand or foot resistance ($R = 0$ or $R > 300$), as per the Nutriguard manual, were discarded as they indicated poor electrode adhesion resulting in higher overall R and consequently underestimation of FFM ($n = 20$). Second, outliers defined as $R > 1600 \Omega$, $R < 300 \Omega$ or $Xc > 500 \Omega$ were discarded as implausible ($n = 1$). Third, BIA measurements with a quality score < 4 were discarded as they were judged less than optimal in accuracy ($n = 46$). These were labelled erroneous measurements and were 24 in reduced arm, 40 in standard arm and 3 in community controls.

3.2. Baseline

A total of 802 children were initially randomised to reduced ($n = 402$) or standard ($n = 400$) RUTF dose between October 2016 and July 2018. By the time the sub-study was started in February 2017, 140 children (70 in reduced arm and 70 in standard arm) had already been enrolled in the main trial. Thereafter, we obtained successful body composition measurements from a total of 452 (68%, 215 in reduced and 237 in standard arm) out of 661 children admitted after sub-study launch and 259 (64%, 122 in reduced and 137 in standard arm) out of 402 children recovered after sub-study launch (Fig. 1). In total, 179 children had both data points available: 80 in the reduced and 99 in the standard arm. The children included in the body composition sub-study did not differ from those not included in terms of age, sex, anthropometrics and socio-economic factors ($p > 0.05$, data not shown). Community controls were measured between April and November 2018.

At admission, mean age was 14 months, 52% were male, mean weight was 6.3 kg, mean FFM was 4.9 kg and mean FM was 1.4 kg. There were no baseline differences in anthropometrics or body composition characteristics between children receiving the reduced and standard RUTF dose (Table 2).

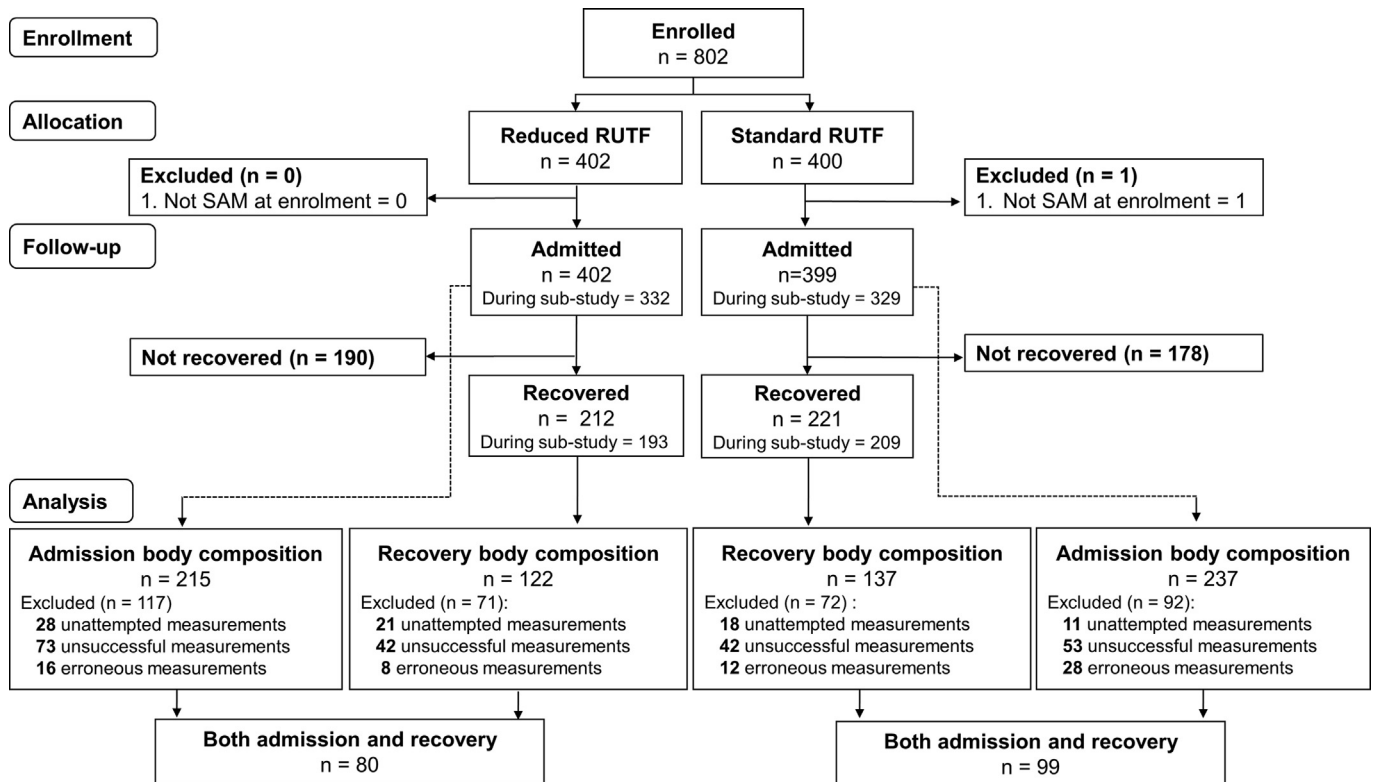


Fig. 1. Patient flow chart. RUTF, ready-to-use therapeutic food.

3.3. Change from admission to recovery

Community controls had similar age (13.7 ± 9.7 months) and sex (52% male) distribution, but differed from children with SAM in terms of socio-economic status: they were from wealthier households and living closer to health centre. At admission, children with SAM had on average 2.47 kg lower weight than community controls, with 0.93 kg less FFM and 1.57 kg less FM (Table 3). This corresponds to 15% lower FFM and 59% lower FM, compared to community controls (Fig. 2). During SAM treatment the average weight increased by 1.20 kg with FFM increasing by

0.55 kg and FM by 0.67 kg, representing 45% and 55% of weight gained, respectively. Z decreased by 125Ω (SE = 8Ω) during treatment. The intra-individual variability of Z (SD) in terms of change from admission to recovery was 87Ω and inter-individual variability at each time point was 71Ω . At recovery, children treated for SAM had a 1.27 kg lower weight, 0.38 kg lower FFM, 0.90 kg lower FM and 1.5 kg/m^2 lower FMI compared to community controls, representing 6% lower FFM and 34% lower FM than community controls. However, their FFMI was no longer different from community controls ($\Delta 0.2 \text{ kg/m}^2$; 95% CI $-0.1, 0.4$; $p = 0.14$).

Table 2
Baseline characteristics of 452 children included in the body composition sub-study by intervention group.

Characteristics	RUTF dose		Difference p-value
	Reduced	Standard	
n	215	237	
Age, months	13.6 ± 9.6	14.1 ± 9.8	0.65
Male, % (n)	51.6 (111)	51.5 (122)	0.97
Weight, kg	6.3 ± 1.3	6.3 ± 1.4	0.81
Height, cm	69.3 ± 8.2	69.5 ± 8.6	0.86
Mid-upper arm circumference, mm	113.2 ± 6.8	113.5 ± 6.4	0.67
Weight-for-height z-score	-3.1 ± 0.7	-3.1 ± 0.7	0.84
Height-for-age z-score	-2.4 ± 1.2	-2.5 ± 1.3	0.63
Weight-for-age z-score	-3.5 ± 0.8	-3.6 ± 0.8	0.71
Impedance, Ω	991 ± 133	1001 ± 129	0.44
Impedance index, cm^2/Ω	4.9 ± 1.2	4.8 ± 1.3	0.84
1/Impedance ($\times 1000$), Ω	1.03 ± 0.14	1.02 ± 0.13	0.35
Fat-free mass, kg	5.2 ± 0.8	5.2 ± 0.8	0.84
Fat mass, kg	1.1 ± 0.7	1.1 ± 0.8	0.51
Admission criteria, % (n)			0.46
Weight-for height z-score only	31.2 (67)	26.2 (62)	
Mid-upper arm circumference only	38.6 (83)	39.7 (94)	
Weight-for-height z-score & mid-upper arm circumference	30.2 (65)	34.2 (81)	

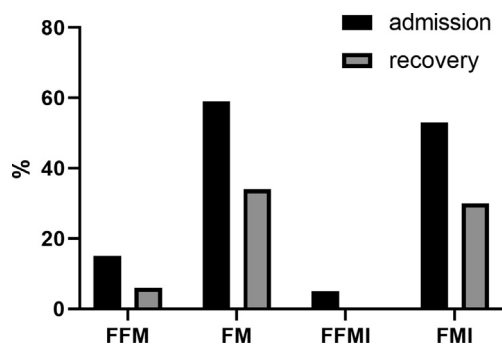
All values are means \pm SD unless otherwise indicated.

Table 3

Comparison of anthropometric and body composition outcomes between children with SAM at admission and at recovery and community controls.

Characteristic	At admission to SAM treatment (A)	At recovery from SAM (B)	Community control (C)	Deficit at admission (A–C)	Gain during treatment (B–A)	Deficit at recovery (B–C)
n	452	259	97			
Weight, kg	6.33	7.53	8.80	–2.47 (–2.64; –2.31)	1.20 (1.14; 1.26)	–1.27 (–1.44; –1.10)
Height, cm	69.7	70.6	73.6	–3.8 (–4.7; –3.0)	0.9 (0.7; 1.0)	–3.0 (–3.8; –2.1)
Mid-upper arm circumference, mm	113.4	130.2	143.6	–30.3 (–31.8; –28.7)	16.9 (16.1; 17.7)	–13.4 (–15.0; –11.8)
Weight-for-age z-score	–3.5	–2.2	–0.8	–2.8 (–3.0; –2.6)	1.3 (1.3; 1.4)	–1.4 (–1.6; –1.3)
Height-for-age z-score	–2.4	–2.3	–0.9	–1.6 (–1.9; –1.3)	0.1 (0.1; 0.2)	–1.5 (–1.7; –1.2)
Weight-for-height z-score	–3.1	–1.3	–0.3	–2.8 (–3.0; –2.6)	1.8 (1.7; 1.9)	–1.0 (–1.2; –0.8)
Impedance, Ω	999	874	867	132 (107; 156)	–125 (–140; –110)	7 (–19; 32)
Impedance index, cm^2/Ω	4.9	5.7	6.2	0.8 (0.7; 0.9)	–1.4 (–1.6; –1.2)	–0.6 (–0.8; –0.4)
1/Impedance ($\times 1000$), Ω	1.02	1.16	1.17	0.14 (0.12; 0.16)	–0.15 (–0.18; –0.12)	–0.01 (–0.04; 0.02)
Fat-free mass, kg	5.20	5.75	6.13	–0.93 (–1.05; –0.81)	0.55 (0.47; 0.63)	–0.38 (–0.51; –0.25)
Fat mass, kg	1.13	1.80	2.69	–1.57 (–1.70; –1.44)	0.67 (0.60; 0.74)	–0.90 (–1.03; –0.76)
Fat-free mass index, kg/m^2	11.0	11.8	11.6	–0.6 (–0.8; –0.4)	0.7 (0.6; 0.9)	0.2 (–0.1; 0.4)
Fat mass index, kg/m^2	2.2	3.5	5.0	–2.8 (–3.1; –2.6)	1.4 (1.2; 1.5)	–1.5 (–1.7; –1.2)

All values are means or mean differences (95% CI) when using linear mixed models with id, study site and team as random effects and adjusting for sex and age.

**Fig. 2.** Deficit in fat-free mass (FFM), fat mass (FM), fat-free mass index (FFMI) and fat mass index (FMI) at admission to treatment and recovery from SAM compared to community controls when adjusting for age and sex.

3.4. Difference between study arms

No differences were observed between study arms for FFM, FM and FMI at recovery (Table 4): FFM was 5.86 kg with reduced and 5.75 kg with standard RUTF dose at recovery and FM was 1.82 kg with reduced and 1.91 kg with standard RUTF dose at recovery, when adjusting for sex, age and outcome at admission. However, Z and FFMI were higher with the reduced dose. No interactions were observed between treatment arm and sex, age, WHZ category, MUAC category or stunting status at admission.

Table 4

Body composition outcomes at recovery among children treated with reduced and standard RUTF dose.

Outcome	RUTF dose		Difference Values	p-value
	Reduced	Standard		
n	80	99		
Weight, kg	7.69	7.65	0.03 (–0.09; 0.15)	0.59
Height, cm	71.3	71.5	–0.22 (–0.59; 0.15)	0.25
Mid-upper arm circumference, mm	130.5	130.2	0.25 (–0.84; 1.33)	0.65
Weight-for-age z-score	–2.1	–2.2	0.05 (–0.07; 0.17)	0.40
Height-for-age z-score	–2.2	–2.2	–0.05 (–0.13; 0.04)	0.28
Weight-for-height z-score	–1.2	–1.4	0.14 (0.00; 0.28)	0.046
Impedance, Ω	860	895	–35.1 (–58.1; –12.2)	0.003
Impedance index, cm^2/Ω	5.9	5.7	0.2 (–0.1; 0.4)	0.151
1/Impedance ($\times 1000$), Ω	1.18	1.13	0.05 (0.01; 0.09)	0.006
Fat-free mass, kg	5.86	5.75	0.11 (–0.01; 0.23)	0.078
Fat mass, kg	1.82	1.91	–0.09 (–0.22; 0.03)	0.15
Fat-free mass index, kg/m^2	11.9	11.5	0.35 (0.10; 0.61)	0.007
Fat mass index, kg/m^2	3.5	3.5	–0.15 (–0.40; 0.10)	0.24

All values are means and mean difference (95% CI) when using linear mixed models with study site and team as random effects and when adjusting for sex, age and outcome measure at admission.

3.5. Sensitivity analysis

In addition to the initial 3 data cleaning steps, further cleaning approaches were tested excluding measurements where no duplicate was available and measurements with poor precision defined as large difference between repeated measurements (R/height difference > 25, Xc/height difference > 7, PA difference > 0.51). However, further cleaning neither increased precision nor changed the findings. Furthermore, unadjusted analysis of the difference between dose arms gave similar results to the models adjusted for sex, age and outcome measure at admission (S1 Table).

4. Discussion

In this study we have shown that approximately half of the weight gained by children with SAM during home-based treatment with RUTF is FFM. We also showed that the FFM of treated children at recovery was similar to community controls when adjusting for height while their FM remained lower. This indicates incomplete FM recovery during SAM treatment.

We also observed that reducing the RUTF dose during treatment resulted in similar FFM, FM and FMI but a significantly lower Z ($p = 0.003$) and higher FFMI ($p = 0.007$) at recovery. Z is a composite marker of body water and cell mass and is inversely correlated with FFM. A lower Z thus reflects a higher FFM. From a clinical perspective the observed 0.11 kg difference in FFM ($p = 0.078$) in favour of the reduced dose seems small,

representing <2% of total weight. The higher FFMI in the reduced dose at recovery is explained by the combination of the small height difference (0.22 cm) in favour of the standard dose and the higher FFM in the reduced dose. Indexing the slightly higher FFM by the slightly lower height results in higher FFMI. Therefore, we conclude that the differences in the body composition parameters are trivial and do not provide evidence for worse body composition outcomes when providing less RUTF.

Previous studies on acutely malnourished children have reported diverse FFM proportions of the total weight gained during treatment: 94% [19] during treatment of moderate acute malnutrition (MAM) in Burkina Faso and approximately 60% in inpatient treatment of SAM in Peru and India [10,20]. These are higher than the 45% observed in the current trial. The proportion of different tissue accretion depends on nutritional status at admission [20,21] and on the type of diet used [22–24]. Depending on the initial weight deficit, in quantity and type of tissue, different weight gain patterns can be expected [21]. Compared to children with MAM, children with SAM have a greater WHZ deficit at start of treatment and can be expected to have lost relatively more FM prior to SAM diagnosis. Subsequently, more FM would be gained during treatment [21]. Also, compared to the previously mentioned studies, we only looked at recovered children (55% of all discharges) who potentially have a different weight gain pattern to non-recovered; in a study in Mali, children who recovered from MAM gained proportionally more FM than non-recovered [25]. Indeed, the weight gain pattern observed in the current study can likely be considered the “best case” while non-recovered children would present with a less adequate tissue accretion. Also, to gain a gram of FFM there is a comprehensive need for many supporting nutrients but relatively little (~2 kcal/g) energy, in contrast to FM gain which has a substantial energy cost (~8 kcal/g) but very low demand for other nutrients [26,27]. Thus, a different diet during rehabilitation can have an impact on the type of tissue deposited [22–24].

We observed a similar FFMI among children recovered from SAM when compared to community controls, similar to that reported in DRC by Bahwere et al. [14]. However, Bahwere et al. (2016) also reported a similar FM among children at discharge from SAM treatment when compared to community controls, unlike our observation of a deficient endline FM and FMI. This discrepancy might be due to the differences in the study protocols where Bahwere et al. included and discharged children only based on MUAC and oedema resulting in a higher endline WHZ in DRC than reported here: -0.6 vs. -1.3 z-scores, respectively. With a WHZ approaching that of community controls, FFMI and FMI, composing the WHZ, can also be expected to approach that of community controls.

The observation that the FFMI of children recovered from SAM is similar to community controls is reassuring and provides much needed evidence on the potential of RUTFs in promoting functional tissue accumulation during SAM treatment. There has been concern about potential excess fat deposition during SAM treatment, related to the high fat content of RUTF and the quick weight gain pattern [28]. The current findings point to the contrary: FM has not been caught up by the end of treatment and remains below that of community controls and British reference data [29]. Which tissue type gain, FFM or FM, provides the greatest short-term benefit is an outstanding question. Two recent studies suggest that low adiposity as evidenced by low leptin levels predicted mortality among children with SAM and medical complications [30,31]. The post-discharge growth trajectories should be investigated to study the relationship between body composition outcomes and relapse and observe if weight and FMI are caught up in the longer term. A recent follow-up study of survivors of SAM in Malawi found that 7

years post discharge from inpatient treatment children presented a lower FFMI but a similar FMI to community and sibling controls [32]. Whether there is a need for a longer treatment time, or specific post-discharge interventions to accompany treated children to recover fully, remains to be tested. There is also a need and increasing demand for body composition data from malnourished children to help reveal the relationship between early life exposure and later disease [33].

In this trial, and in the absence of internationally applicable standards, we used a convenience sample of age and sex matched non-malnourished community controls to act as reference in terms of body composition parameters. While the inclusion criteria to this community control group included a MUAC >125 mm and a WHZ >-2 and absence of oedema and illness, these children cannot be considered a perfect reference in terms of optimal health and nutrition status. Indeed, further research is warranted to develop body composition standards that reflect the normal variability to be able to compare malnourished children's growth trajectories against a real standard. This would also help determine what part of the tissue gains can simply be expected based on normal growth of children and what part is the additional catch-up growth accompanying recovery from SAM. In the current study, the community controls were only measured once and thus normal tissue growth patterns during the 2 month mean treatment duration are unknown in this context.

The main strength of this study is that we obtained measurements both at admission and at recovery from SAM, which enables the evaluation of change in body composition parameters. This circumvents the difficulty of estimating absolute values of FFM and FM but gives a more reliable estimation of the average composition of weight change. We also measured a sample of non-malnourished children from the same communities, which allowed us to estimate which tissue has the greatest deficit in children starting SAM treatment, and what deficits remain at the end of the treatment. The study was nested in an RCT and implemented by well-trained research staff measuring body composition with a BIA device that is easy to operate. The measures were quality-assessed to improve precision and reduce error. We did not include oedematous cases which reduces error as fluid disturbances are known to influence both BIA deuterium results [34].

The study also has limitations. Firstly, for reasons related to ease of implementation and cost, we opted for measuring body composition via BIA instead of the current gold standard of deuterium dilution technique. Obtaining additional deuterium dilution data would have enabled us to cross-validate the FFM equations and this way refine and confirm the absolute FFM values. Different BIA equations provide slightly different FFM and FM estimates, with both ethnicity and nutritional status potentially relevant [35,36]. With no equation calibrated for malnourished nor Burkinabé children, the absolute FFM values obtained from any specific BIA equation should therefore be treated with caution. However, the equation we used was calibrated among Gambian children of similar age, thus limiting bias from this source. To estimate the robustness of our estimations derived from the Gambian equation, we compared them with those obtained from applying other equations calibrated among children [37–42]: the % of FFM from the total weight gain during treatment varied between 44% and 69%. Our estimation of 45% of weight gain during treatment being FFM obtained with the Gambian equation falls towards the lower end of the spectrum, and this might be an accurate result as none of the other equations were calibrated in African populations. Importantly however, analyses of crude HT2/Z and FFM, or 1/Z and FFMI, demonstrate near-identical results in statistical models as they differ only in terms of constants. Therefore, we do not expect a

more accurate FFM estimation to have changed the main conclusions of there being no difference in the body composition of children at recovery from SAM after treatment with different doses of RUTF, and FMI but not FFMI remaining lower among children recovered from SAM compared to non-malnourished community controls. Nonetheless, we recommend future studies to use several body composition techniques to increase accuracy of tissue mass assessment.

Secondly, because we staggered the sub-study to start 5 months into the main study and due to a proportion of BIA measurements being unsuccessful, we only obtained body composition from a sub-sample of trial participants and were underpowered to conclude on the non-inferiority of the reduced dose on body composition outcomes. Thirdly, we only managed to obtain representative data from children that were discharged recovered from SAM treatment. Recovered and non-recovered children probably display different body composition changes during treatment and the current results can only be considered as the best response to treatment. Having data on non-recovered children would have enabled us to investigate how the body composition change differs from recovered children and observe if the reduced dose impacted their body composition differently. Lastly, and as discussed in the previous paragraph, community controls were only measured once and thus we ignore the normal tissue deposition patterns among them and cannot conclude whether the catch-up growth tissue gain pattern among children with SAM is considerably different from normal tissue gain patterns.

The study findings are generalizable to contexts with similar SAM profile consisting of children primary <24 months of age and with access to similar complementary foods. Body composition changes are strongly related to age and thus a reduced dose of RUTF among older children might result in different tissue gain patterns. Additionally, the weight gain and tissue accretion patterns could possibly be different in a context with different complementary foods being offered to children. Depending on the nutrient density of the complementary foods used, a reduced RUTF dose could result in different tissue gain patterns.

In conclusion, we observed that half of the weight gained by children treated for SAM with RUTF was of FFM and that by recovery their FFMI was similar to community controls. However, the FMI remained lower at recovery. Additionally, we found no evidence of a sub-optimal effect of a reduced RUTF dose on the body composition of children by recovery. This indicates that in a relatively food secure context a reduction in the RUTF dose can result in similar body composition by recovery.

Funding sources

This trial was funded by Action Against Hunger France, European Commission's Civil Protection and Humanitarian aid Operations, Children's Investment Fund Foundation, European Commission's Civil Protection and Humanitarian aid Operations Enhanced Response Capacity and Humanitarian Innovation Fund, a programme managed by Enhancing Learning and Research for Humanitarian Assistance. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability

The dataset used and analysed during the current study is available from the Zenodo data repository: <http://doi.org/10.5281/zenodo.3522237>.

Conflict of interest

HF has received research grants from ARLA Food for Health Centre, Danish Dairy Research Foundation and also has research collaboration with Nutriset. JW has received BIA devices from BodyStat used in other research projects but not in the current one. Other authors declare no conflicts of interest.

CRediT authorship contribution statement

Suvi T. Kangas: Writing - original draft, Supervision, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing - original draft, Writing - review & editing. **Pernille Kaestel:** Writing - review & editing, Conceptualization, Investigation, Methodology, Supervision, Validation. **Cécile Salpéteur:** Writing - review & editing, Conceptualization, Funding acquisition, Project administration, Resources. **Victor Nikièma:** Writing - review & editing, Supervision, Data curation, Investigation. **Leisel Talley:** Writing - review & editing, Conceptualization, Investigation, Methodology, Supervision, Validation. **André Briend:** Writing - review & editing, Conceptualization, Investigation, Methodology, Supervision, Validation. **Christian Ritz:** Methodology, Supervision, Validation, Writing - review & editing. **Henrik Friis:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing - review & editing. **Jonathan C. Wells:** Writing - review & editing, Conceptualization, Investigation, Methodology, Supervision, Validation.

Acknowledgements

We thank the research teams for their everyday efforts in implementing the trial and the study participants and caregivers for participating in the trial.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2020.02.038>.

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