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Short malnourished children do not gain excessive fat with food supplementation

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Short malnourished children do not gain excessive fat with food supplementation

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Abbreviations: The Alliance for International Medical Action (ALIMA); (CHW); corn-soy blend (CSB); children recruited by MUAC and ≥67 cm (LONG); children recruited by MUAC and <67 cm (SHORT); lipid-based nutrient supplements (LNS); Mid-upper arm circumference (MUAC); moderate acute malnutrition (MAM);ready-to-use therapeutic food (RUTF); severe acute malnutrition (SAM); weight-for-height z-score (WHZ)

Table of Contents Summary
We assess if it is justified to exclude shorter children with moderate acute malnutrition from treatment out of fear they will accumulate too much fat

What's Known on This Subject
It is policy for national malnutrition programs in many African countries to exclude shorter children with moderate acute malnutrition (MAM) from treatment due to concerns they will accumulate too much fat thereby putting them at later risk of non-communicable diseases

What This Study Adds
Our study shows that shorter children with low MUAC do not gain excessive fat during supplementation and thus should be offered treatment. The WHO should integrate this evidence into its recently updated Integrated Management of childhood Illness (IMCI) recommendations

Contributors' Statement Page

Dr Fabiansen conceptualized the research, conducted the research, acquired the data, performed statistical analysis and wrote the first draft of the manuscript. Mr Phelan, Drs Kurpard, Wells, Filteau, Briend, Christensen and Drs Cichon, Iuel-Brockdorff and Mr Yaméogo conducted the research and acquired the data. Dr Ritz conceptualized the research and design and performed statistical analysis and interpretation of data. Dr Shepherd conceptualized the research and contributed to data interpretation. Drs Michaelsen and Friis conceptualized the research and design and contributed to the interpretation of data. All authors critically revised the article for important intellectual content, and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Background: In moderate acute malnutrition (MAM) programs, it is common practice not to measure mid-upper arm circumference (MUAC) of children whose length is<67 cm. This is based on expert opinion that supplementation of shorter children with low MUAC and weight-for-height z-score (WHZ)≥-2 may increase risk of excessive fat accumulation. Our aim was to assess if shorter children gain more fat than taller children when treated for MAM diagnosed by low MUAC alone.

Methods: This observational study included children aged 6-23 months with MUAC between 115-125 mm and WHZ ≥-2. Based on length at admission, children were categorized as SHORT if<67 cm and LONG if≥67 cm. Linear mixed-effects models were used to assess body composition based on deuterium dilution and skinfold-thickness.

Results: Following 12 weeks of supplementation, there was no difference in change in fat mass index (-0.038kg/m^2, 95%CI -0.257;0.181, p=0.74) or fat-free mass index (0.061kg/m^2, 95%CI -0.150;0.271; p=0.57) in SHORT vs LONG. In absolute terms, the SHORT children gained both less fat-free mass (-230g, 95%CI: -355;-106, P<0.001) and fat mass (-97g, 95%CI -205;10, p=0.076). There were no difference in changes in absolute subscapular and triceps skinfold-thickness and z-scores (p>0.5).

Conclusions: SHORT children with low MUAC do not gain excessive fat during supplementation. These data support a recommendation for policy change to include all children ≥6 months with low MUAC in supplementary feeding programs, regardless of length. The use of length as a criterion for measuring MUAC to determine treatment eligibility should be discontinued in policy and practice.

INTRODUCTION

Childhood malnutrition contributes to almost half the mortality in children under five years [1]. Moderate acute malnutrition (MAM) is currently defined as weight-for-height z-score (WHZ) between –3 and –2 (i.e. moderate wasting), and/or mid-upper arm circumference (MUAC) between 115 and 125 mm [2]. While the prevalence of MAM is unknown, moderate wasting alone affects 33 million children at any time [3] and is associated with a three-fold increased risk of death [4].

Protocols for management of acute malnutrition in many African countries (including Cameroon, Central African Republic, Chad, Guinea, Ivory Coast, Mali, Mauritania, Senegal, and Togo) instruct health personnel to measure MUAC only of children with length ≥67 cm when assessing eligibility for MAM or severe acute malnutrition (SAM) treatment programs [5–13]. In Ethiopia, admission by MUAC alone for SAM treatment is restricted to children with lengths >65 cm [14]. These shorter children are enrolled in treatment only if they meet WHZ criterion, which is less closely linked to the risk of death and misses high-risk children who would have been identified by MUAC. Hence, current practice excludes short children who would benefit from nutritional support.

The practice of restricting treatment admission by MUAC alone to children of length ≥67 cm is not supported by data and has never been formally endorsed by the World Health Organization (WHO). Two reasons can be identified to explain this exclusion. First, the inclusion of a length restriction for MUAC is likely a holdover from older versions of emergency nutrition guidelines that used length as a proxy for age (<6 months) because it can sometimes be difficult to ascertain age in a fast moving emergency. The WHO, for example, used length of 60 cm as a proxy for age of 6 months in publications from 1995 and 2000 [15,16] while length of 65 cm was used in older versions of guidelines from non-governmental humanitarian organizations like Médecins Sans Frontières (MSF) in 1995 and Valid International in 2006 [17,18]. It is important to identify children <6 months

of age as they should be exclusively breastfed, and treated as in-patients if in need of treatment. However, length is a poor proxy for age, and most often a caretaker can recall the month of birth for an infant.

Second, WHO now recommends against routine food supplementation of children with MAM due to a concern it may promote obesity and increase the risk of non-communicable diseases later in life [19]. Some experts worry that shorter children above 6 months of age who only meet the low-MUAC criteria for MAM are at most at risk of excessive fat accumulation during treatment [2]. Although only based on expert opinion, this seems to be the reason why many national malnutrition protocols exclude shorter children from having their MUAC measured, thereby making children ineligible for treatment, unless they meet WHZ criteria. This concern led WHO to call for research to identify appropriate MUAC admission and discharge criteria for children <67 cm and ≥6 months to supplementary feeding programs [2].

We have previously shown, that when supplemented, ponderal growth rates are similar in short and long children ≥6 months with a low MUAC [20]. Niger dropped this length restriction in 2016, and its revised protocols now call for measuring MUAC in all children ≥6 months, regardless of length [21].

To what extent there is a difference in fat accumulation during treatment has not been assessed. The objective of this paper is to assess if short children (<67 cm) gain more fat than long children (≥67 cm) when treated for MAM diagnosed by low MUAC (115-125 mm).

SUBJECTS AND METHODS

As previously reported [20], a prospective cohort study was nested in a randomized nutrition trial (Treatfood) [22] investigating the effectiveness of 500 kcal/day supplement either as corn-soy blend

(CSB) porridge or ready-to-use lipid-based nutrient supplements (LNS). The LNS supplements provided almost three times more energy as fat than the CSB supplements (~57% vs ~21%). Assignment to one of the 12 supplements (6 CSB and 6 LNS) followed randomisation stratified by site.

Participants

Data were collected in the Province du Passoré in the Northern region of Burkina Faso at 5 research sites located at different governmental health centers and staffed by the non-governmental organization Alliance for International Medical Action (ALIMA, Dakar, Senegal).
Children were screened in villages either by community health workers using MUAC tapes or by designated screening teams with the use of both MUAC and WHZ. Moreover, children could be referred from a health centre or could present at site on caretaker´s initiative. At the sites, the final assessment of eligibility for inclusion was performed.

For the main Treatfood trial, children aged 6–23 months with MAM (defined as MUAC between 115-124 and/or a WHZ between –3 and –2), resident in the catchment area and whose caretaker consented to participate, were included. Children were not included if treated for severe acute malnutrition (SAM) or hospitalized within the past two months, if already in a nutritional program or if they presented medical complications requiring hospitalization. Likewise, children with a severe disability limiting the possibility of investigations and children with suspected allergy to milk, peanuts, corn or soy were not included.

Of the 1609 children included in the trial 468 had MUAC between 115-125mm and WHZ ≥-2, and were included in the current study. In many settings these children are excluded from treatment if they are also short (i.e. <65 or 67 cm). Accordingly, children in this study were categorized, based

on baseline length, as SHORT (<67 cm) or LONG (≥67 cm) to assess if SHORT children gain more fat than LONG children when treated for MAM diagnosed by low MUAC.

Procedures and study visits

We previously described clinic visits, standard anthropometric measurements and age determination [20]. In the present paper we additionally report on indices of body composition and skinfolds assessed at baseline and at end-intervention at 12 weeks. Total body water (TBW) was assessed using the deuterium dilution technique (D2O) to enable calculation of fat-free mass (FFM) and fat mass (FM). The method involved giving an oral dose of 5 g deuterium oxide (D2O) (99.8%, Cambridge Isotope Laboratories Inc., Andover, USA). The isotope was diluted in 5 g of bottled water (LAFI, Burkina Faso), with the dosing bottle weighed with 0.01 g precision (Adam equipment: model CQT 202, United Kingdom) before and after administration of the dose. Pre-dose saliva samples were obtained to assess background isotope levels in body fluids, and post-dose saliva samples were collected after a three-hour equilibration period as established during the pilot study [23]. For each assessment, D2O enrichment was measured in duplicate in the pre- and post-dose saliva samples and in a diluted sample of the dose, using Fourier Transform Infrared Spectrometry (FTIR; Agilent Technologies, CA, USA) [24] at St. John's Research Centre, Bangalore, India. Saliva samples required at least 60 µl saliva for analysis. Deuterium dilution space was calculated as described previously [25], and converted to total body water (TBW) using a factor of 1·044 to adjust for proton exchange [26]. FFM was calculated as TBW/hydration, using age- and sex-specific hydration coefficients [27]. FM was calculated as weight minus FFM. Data were cleaned for typographical errors and implausible TBW values, based on the association of TBW with length and a cut-off for FM of <-0·1 and >2·4 kg.

Skinfold thickness was measured in duplicate by a Harpenden caliper. The mean of the duplicate measurements were taken for analysis. Weight was measured in duplicate to the nearest 100 g using electronic scales (Seca model 881 1021659) with double weighing function. Length was measured in duplicate with a wooden length board to the nearest 1 mm. WHZ was determined at sites using WHO field tables, and this value was used for recruitment. MUAC was measured in duplicate to the nearest 1 mm, at the midpoint between the olecranon and the acromion process using a standard measuring tape. Anthropometric measurements were undertaken by trained staff, after standardization sessions.

In later analyses, WHZ, length-for-age z-score (LAZ) and weight-for-age z-score were calculated using the package "zscore06" in STATA 12 (College Station, Texas, USA). Skinfold-for-age z-scores were calculated using WHO's Anthro Plus software (version 3.2.2, 2011, World Health Organization, Geneva, Switzerland). All z-scores were calculated using the 2006 WHO child growth standards.

Outcomes

Changes were evaluated in FM, FFM, weight, length, and skinfold thickness (both raw values and skinfold thickness-for-age z-scores). By dividing FFM and FM by length squared the indices are expressed as (kg/m^2) independent of length, i.e. FFM index (FFMI) and FM index (FMI). In addition, fat was calculated as a percentage of total body weight.

Statistical analysis

Data were double entered in Epidata 3.1 (Epidata Association, Odense, Denmark) and double entry checks were performed on a daily basis. All statistical analyses were carried out using the statistical software package Stata version 12 (StataCorp, College station, Texas, USA). Baseline and endline

characteristics of children were summarized as mean (SD) or percentages, and categories were compared at baseline using two-sample t-tests for continuous variables and chi-square tests for categorical variables.

To evaluate differences in outcomes between groups during the 12-week supplementation intervention, a linear mixed analysis of covariance model was considered as the main analysis, resulting in an estimated mean difference at the end of the study adjusted for differences at baseline. Specifically, the analyses included adjustment for food intervention as well as a number of baseline characteristics: baseline measure of the outcome, age, sex, and month of admission (as fixed effects). Random intercepts were included in the model to adjust for variation between sites. In the adjusted analysis, weight was derived by adding FFM and FM. Additionally, for direct outcomes of fat (FM and FMI) we evaluated the two-way interaction between length group and product group (CSB compared with LNS) in order to assess effect modification by type of product. Moreover, possible effect modification was also evaluated for stunting at admission in a) two categories: above and below LAZ of <-2, or b) or three categories: severe stunting (LAZ <-3), moderate stunting (LAZ ≥-3 to <-2) or absence of stunting (LAZ ≥-2). The same adjustments were applied in these additional analyses as in the main analysis. Model checking was based on residuals and normal probability plots. A significance level of 0.05 was applied.

RESULTS

A total of 1609 children, of which 55% were girls, were randomized to 12 weeks of supplementary feeding in the Treatfood trial [22]. Of these, 50% (804) were included by both WHZ and MUAC, 21% (337) by WHZ alone and 29% (468) by MUAC alone. Among the 468 children recruited by MUAC

only, on whom this this paper is based, 230 (49%) were <67 cm (SHORT) and 238 (51%) ≥67 cm (LONG) [20]. During the intervention, 3 SHORT and 11 LONG children dropped out prior to completion of supplementation at week 12. Body composition based on D2O dilution both at baseline and after 12 weeks were successfully determined in 195 (85%) of SHORT children and 195 (82 %) of LONG children **(Figure 1).** At baseline, there were substantial differences in age and sex distributions, as well as in standard anthropometry between SHORT and LONG, whereas there were no differences in allocation to the different experimental diets and season of inclusion **(Table 1).** Mean values of body composition variables determined at baseline and after supplementation are presented in **Table 2.** At baseline, the weight of SHORT children was 1.474 (95%CI: 1.355; 1.593) kg less than that of LONG children, which reflected a 0.120 (0.047; 0.193) kg lower FM and a 1.354 (1.219; 1.489) kg lower FFM. Adjusted for length squared this corresponded to a 0.325 (0.163; 0.487) kg/m^2 higher FMI in SHORT compared to LONG children, but no difference (-0.056 kg/m^2, -0.230; 0.118) in FFMI. Body fat was 1.9 (0.8; 3.0) percentage points higher in SHORT compared to LONG children.

Adjusted differences from baseline to endline are presented in **Table 3.** Following the 12 weeks of supplementation, there was no difference of change in FMI (-0.038 kg/m^2, 95%CI -0.257; 0.181, p=0.74) or FFMI (0.061 kg/m^2, 95%CI -0.150; 0.271; p=0.57) in SHORT vs LONG children. The SHORT children actually gained both less FFM (-230 g, 95%CI: -355; -106, p<0.001) as well as FM (-97 g, 95%CI -205; 10) although the latter was not significant (p=0.076). The differences in FM and FFM summed up to a 328 g (95%CI: 199; 456, p <0.001) lower weight gain in SHORT compared to LONG children. There were no differences in subscapular and triceps skinfold thickness and z-scores (all p>0.5).

For FM and FMI there was no effect modification of product type, (CSB or LNS) (p>0.30). Likewise, there was no effect modification by stunting at admission (present or non-present)

(p>0.50) or stunting at admission stratified by severity (severe stunting, moderate stunting or non-present) (p>0.45).

DISCUSSION

In response to WHO´s call for research to identify appropriate MUAC admission and discharge criteria for children <67 cm and ≥6 months to supplementary foods [2], we show here that short children with MUAC 115-125 mm but WHZ >-2 do not gain excessive fat during supplementation. Our results therefore challenge current policy and practice in several African countries of measuring MUAC only in children more than 6 months of age above a certain length threshold, thus excluding shorter children with only low MUAC from eligibility for MAM or SAM treatment programs [5–14].

The exclusion of short children is based solely on expert opinion, and reflects a concern that these children are just stunted rather than wasted, have slow catch-up growth, and may accumulate excessive fat mass following supplementation, thereby putting them at risk of non-communicable diseases later in life. We previously reported that ponderal growth rates were similar in short and long children who received supplementation for MAM determined only by low MUAC [20], and a similar finding was reported in children with SAM [28].

The current study is the first to report direct evidence on fat accumulation following treatment for such children, and our data show there is no excessive fat gain in the SHORT children compared to LONG children. In fact, weight gain in both groups overwhelmingly came in the form of FFM. These findings were independent of children having received LNS or CSB supplement. Because LNS contains a high level of fat, some experts were concerned that this food could lead to higher fat deposition in the malnourished child. Earlier we showed that LNS did not lead to high fat accumulation in treatment of children for MAM [22]. We now show that this concern is unwarranted even in shorter children enrolled in treatment solely by MUAC and, furthermore, is not modified by stunting at admission.

By using the state-of-the-art deuterium dilution technique seconded by skinfold thickness measurements, we present comprehensive data on body fat following supplementation in MAM. Since the gold standard for body composition is cadaver dissection, all *in vivo* techniques are necessarily imperfect. Here, we used two different techniques in which their error is uncorrelated, but their results are similar, making our findings more robust.

At baseline, the SHORT compared to the LONG children were younger, contained more girls, had lower MUAC, and had higher prevalence of stunting and underweight, but were less wasted [20]. More than 90% of the 1.5 kg higher weight in LONG children at baseline was FFM, while SHORT children had higher baseline FMI and fat%, and this was supported by higher baseline skinfold thicknesses.

One possible explanation for this baseline difference is that, in the process of growing poorly, SHORT children invested relatively more in fat reserves than LONG children, at a cost to their functional fat-free tissue. However, a simpler alternative explanation is that even in children with optimal growth conditions, such as those used to establish WHO 2006 growth standards, both triceps and subscapular skinfold thicknesses tend to decrease in thickness between 6 months and 2 years, and more so in boys than girls. Hence, the fact that the SHORT children were also ~6 months younger at baseline might explain the higher FMI at baseline. Supporting this, baseline skinfold thicknesses were thicker in SHORT children, but when expressed as z-scores relative to WHO reference data, SHORT children actually had lower triceps values than LONG children, while their subscapular skinfold thickness was only 0.2 z-score greater than in LONG children.

At the end of the intervention, the average skinfolds thickness in this study were below -1 z-score in both groups suggesting no excessive fat gain in either group.

At the end of the supplementation relative measures of FMI, FFMI and percentage fat were similar between the two groups and likewise there was no difference between groups in skinfold thickness changes, whether expressed in absolute terms or as z-scores. The SHORT children gained less weight and FFM and also showed a trend towards less FM gain.

A recent study found that children with MAM diagnosed solely on low MUAC experienced high rates of deterioration to SAM if left untreated [29]. We are not aware of data on mortality data specifically for short children with MAM based only on low MUAC. However, the low MUAC SHORT children in our cohort exhibited high prevalence of additional anthropometric deficits. Half of the SHORT children were stunted and SHORT children were more underweight compared to LONG children. Stunted and underweight children have a higher mortality risk and may therefore benefit most from nutritional interventions [30]. MUAC is a simple way to target them for treatment.

The WHO recently updated its Integrated Management of Childhood Illness (IMCI), and now recommends against routinely supplementing children with MAM due to a concern for obesity. We previously showed that there was no excess fat accumulation in children with MAM supplemented with LNS or CSB [22]. Our findings here show that even the shorter children with MAM determined solely by MUAC, who were considered by some experts to be at the greatest risk for obesity from food supplementation, do not become obese. Such children should no longer be excluded from treatment eligibility.

We are not aware of any data on fat accumulation following treatment in short children with SAM by MUAC alone. Indeed, currently only data on skinfolds could be generated in large field studies in children with SAM, as current techniques available for body composition assessment are not suitable for use in SAM. However, we see no rationale in maintaining a length restriction for MUAC assessment in SAM.

In conclusion, SHORT children with low MUAC do not gain excessive fat during supplementation. Admission by the same MUAC criteria (i.e. <115 mm for SAM and 115-125 mm for MAM) should apply to any child 6-59 months of age, regardless of their length, and irrespective of their WHZ. The use of length as criterion for measuring MUAC should be discontinued in policy and practice wherever such restrictions exist. It will also be important for the WHO to integrate this evidence showing that children with MAM are not put at risk for obesity following food supplementation into its recently updated IMCI recommendations.

DECLARATIONS

Ethics approval and consent to participate

The trial was approved by the Ethics Committee for Health Research in Burkina Faso (2012-8-059) and consultative approval was obtained from the Danish National Committee on Biomedical Research Ethics (1208204). Consent was obtained from caregivers, prior to inclusion, verbally and in writing (signature or fingerprints). All children were treated free of charge at the study sites, irrespective of study participation. The trial is registered at www.controlled-trials.com (ISRCTN42569496).

Consent for publication

Not applicable

Availability of data and material

The dataset used during the current study is available from the corresponding author on reasonable request.

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Not applicable

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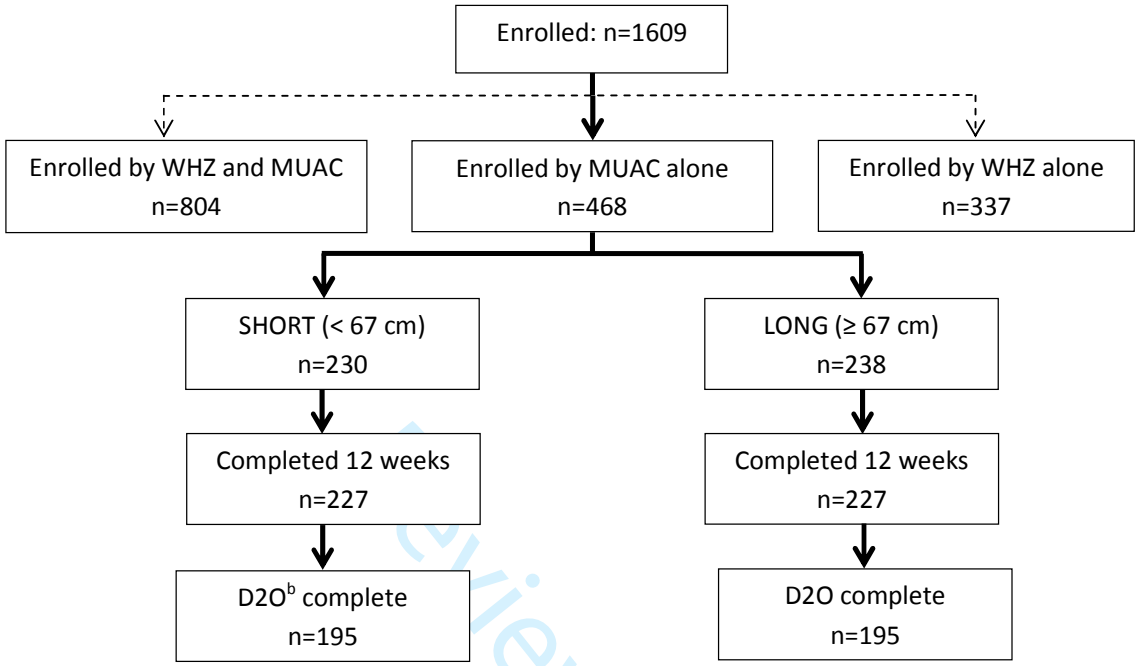
Figure 1 participant flow chart[a]



[a] Treatfood participants included in the cohort study [22]. [b] D2O = Body composition assessment by deuterium dilution technique

Table 1. Baseline characteristics of children with moderate acute malnutrition included by MUAC only with complete D2O data (n=390), by length category[a]

	[b]SHORT (n=195)	[c]LONG (n=195)	P-value
Girls, % (n)	84% (163)	72% (140)	**0.005**
Age, months	7.7 (1.6)	14.0 (4.3)	**<0.001**
Weight, kg	6.012 (0.4)	7.487 (0.7)	**<0.001**
Length, cm	63.9 (2.1)	72.0 (3.9)	**<0.001**
Mid upper arm circumference, mm	121.0 (2.6)	122.2 (1.9)	**<0.001**
Weight for height z-score	-1.5 (0.4)	-1.7 (0.3)	**<0.001**
Weight for age z	-2.4 (0.6)	-2.1 (0.6)	**<0.001**
Length for age z	-2.0 (1.0)	-1.7 (1.0)	**0.002**
Length for age z, <-2 % (n)	49% (95)	35% (68)	**0.006**
Season at time of inclusion, % (n)			0.17
Dry season	61% (118)	67% (131)	
Rainy season	40% (77)	33% (64)	
Food supplement, % (n)			0.84
CSB	48% (94)	47% (92)	
LNS	52% (101)	53% (103)	
Site, % (n)			**0.009**
0	12% (24)	27% (52)	
1	15% (30)	11% (21)	
2	21% (41)	18% (35)	
3	31% (60)	26% (50)	
4	21% (40)	19% (37)	
Breastfeeding, % (n)	100% (194)	91% (178)	**<0.001**

[a]Data are mean (±SD) unless otherwise indicated. [b]SHORT <67 cm, [c]LONG ≥67 cm.

Table 2. Body composition among short and long children with moderate acute malnutrition at baseline and endline, without adjustments[a]

	Baseline			Endline		
	[b]**SHORT (n=195)**	[c]**LONG (n=195)**	[d]**P Δ**	**SHORT (n=195)**	**LONG (n=195)**	[e]**P Δ**
Fat mass, kg	1.098 (0.4)	1.218 (0.4)	**0.001**	1.123 (0.4)	1.246 (0.4)	**0.003**
Fat-free mass, kg	4.914 (0.5)	6.268 (0.8)	**<0.001**	5.673 (0.5)	7.096 (0.9)	**<0.001**
%Fat, (Fat-mass/weight*100)	18.3 (5.8)	16.4 (5.3)	**<0.001**	16.3 (5.7)	15.0 (4.9)	**0.015**
Fat mass index, kg/m^2	2.689 (0.9)	2.364 (0.8)	**<0.001**	2.499 (0.9)	2.259 (0.8)	**0.006**
Fat-free mass index, kg/m^2	12.000 (0.9)	12.056 (0.9)	0.53	12.640 (0.8)	12.723 (0.9)	0.36
Triceps skinfold, mm	6.6 (1.1)	6.3 (1.0)	**0.001**	6.8 (1.1)	6.8 (1.2)	0.85
Triceps skinfold-for-age z	-1.5 (0.8)	-1.3 (0.8)	**0.04**	-1.1 (0.8)	- 0.8 (0.9)	**0.007**
Subscapular skinfold, mm	5.6 (0.9)	5.1 (0.8)	**<0.001**	5.8 (1.0)	5.4 (0.8)	**<0.001**
Subscapular skinfold-for-age z	-1.3 (0.9)	-1.5 (0.9)	**0.03**	-0.9 (1.0)	-0.9 (0.9)	0.96

[a]Data are mean (±SD) unless otherwise indicated. [b]SHORT <67 cm, [c]LONG ≥67 cm. [d]P value for difference at baseline between SHORT and LONG children. [e]P value for difference at endline between SHORT and LONG children.

Table 3. Changes in outcomes during supplementation[a]

	[b]SHORT (n=195)	[c]LONG (n=195)	[d]Difference in change	[e]P Δ
Fat mass, kg	-0.022 (-0.088; 0.043)	0.075 (0.010; 0.140)	-0.097 (-0.205: 0.010)	0.076
Fat-free mass, kg	0.678 (0.604; 0.752)	0.908 (0.834; 0.982)	-0.230 (-0.355; -0.106)	**<0.001**
%Fat (Fat-mass/weight*100)	-1.8 (-2.6; -1.0)	-1.5 (-2.3; -0.7)	-0.3 (-1.6; 1.1)	0.70
Fat mass index, kg /m^2	-0.166 (-0.309; -0.234)	-0.128 (-0.271; 0.015)	-0.038 (-0.257; 0.181)	0.74
Fat-free mass index, kg/m^2	0.684 (0.556; 0.813)	0.624 (0.495; 0.752)	0.061 (-0.150; 0.271)	0.57
Triceps skinfold, mm	0.39 (0.04; 0.73)	0.35 (-0.002: 0.70)	0.04 (-0.24; 0.32)	0.77
Triceps skinfold-for-age z	0.48 (0.25; 0.71)	0.50 0.26; 0.73)	-0.02 (-0.22; 1.85)	0.88
Subscapular skinfold, mm	0.32 (0.17; 0.47)	0.24 (0.09; 0.40)	0.08 (-0.15; 0.30)	0.52
Subscapular skinfold-for-age z	0.52 (0.36; 0.67)	0.49 (0.34; 0.65)	0.02 (-0.21; 0.26)	0.84

[a]Data are mean and 95% CI calculated using linear mixed models adjusted for food intervention, baseline measure of the outcome, age, sex, month of admission and site (random effects).[b]SHORT <67 cm, [c]LONG ≥67 cm. [d]Difference in change of SHORT vs LONG**.** [e]P value for difference in change from baseline to endline for SHORT and LONG children.

List word counts below (do not paste the text here). Please see the Decision Letter Attachment for allowances as they pertain to your manuscript type.

# of words in Abstract: **247** (250 words allowed)
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# of characters in Main Title: **79** characters (97 characters allowed, including spaces)
# of characters in Short Title: **55** (55 characters allowed, including spaces)
# of words in "Table of Contents Summary": **25** (25 words allowed; this section appears in all articles with abstracts)
# of words in "What's Known on this Subject": **40** (40 words allowed; this section appears in Regular Articles only)
# of words in "What this Study Adds": **39** (40 words allowed; this section appears in Regular Articles only)

2016-XXXX.RX – Short malnourished children do not gain excessive fat with food supplementation **-- by Fabiansen et al.**

EDITOR/REVIEWER COMMENTS *Paste each of the editor and reviewer queries here.*	**AUTHOR'S RESPONSE** *Paste your answer to the editor and reviewer queries here.* *If you alter your manuscript to address this query, you MUST paste the relevant altered text here – verbatim as it appears in the manuscript.*	**REFERENCE PAGE** *State where* the change now appears in your newly revised manuscript.*	**CHANGE APPROVED ? FOR EDITORIAL USE ONLY**
Editors Comments	We thank you for provisionally accepting our manuscript. Our current title is: Short malnourished children with a low MUAC do not gain excessive fat with food supplementation You suggest we change it into: Short malnourished children and fat accumulation with food supplementation We fully acknowledge that our original title was rather long. However, we would like the title to give an idea of the main message of the paper, and your suggestion may indicate fat accumulation. We therefore kindly ask to change the title into: "Short malnourished children do not gain excessive fat with food supplementation" Likewise, we hope it is acceptable that your suggested short title Short malnourished children and fat accumulation		

	Is changed into: "Short malnourished children do not gain excessive fat"		
Reviewer 1's comment 1. If possible avoid the use of an abbreviation in the title. 2. Could you please clarify the criteria for sample size calculation? 3. Please adjust superscript 2 in Figure 1. 4. In Table 1 and 2 homogenize the use of MAM (moderate acute malnutrition).	We thank reviewer 1 for the very positive review. 1. Yes thanks, this is now avoided in the new title. 2. Thanks for pointing this out. Sample size calculation was made for the main trial. We now made it clearer which children were included in current study. The text now reads: "Of the 1609 children included in the trial 468 had MUAC between 115-125mm and WHZ ≥-2, and were included in the current study. In many settings these children are excluded from treatment if they are also short (i.e. <65 or 67 cm). Accordingly, children in this study were categorized, based on baseline length, as SHORT (<67 cm) or LONG (≥67 cm) to assess if SHORT children gain more fat than LONG children when treated for MAM diagnosed by low MUAC ." 3. Thanks for pointing this out. The problem is that "[22]" is a reference in "Pediatrics" format. To improve readability we now changed table superscripts to letters. 4. Thanks. MAM is now written as moderate acute malnutrition.	1. Title 2. In *statistical analysis* 3. In *Participants* 4. Tab 1 +2	
Reviewer 2´ comment	We thank reviewer 2 for the kind comments on our study and for us testing BOGSAT opinion		
Reviewer 3´s comment	We thank reviewer 3 for the very positive review	**1** In *statistical*	

1. Methodology: Were the mixed models "random intercept" or "random intercept" and "random slope" models? 2. Results: How were the results (mean difference, 95% CI and P-value) for weight gain obtained? For me is not clear: why as the weight difference between end of intervention and baseline not used? 3. Discussion: Are there potential bias that could limit the generalization of the results? 4. Are other studies needed to validate the results from this study? 5. Is it possible that these supplemented children develop obesity later in childhood or adolescence?	1. We've now clarified that the linear mixed models only included random intercepts corresponding to the sites. The text now reads: "To evaluate differences in outcomes between groups during the 12-week supplementation intervention, a linear mixed analysis of covariance model was considered as the main analysis, resulting in an estimated mean difference at the end of the study adjusted for differences at baseline. Specifically, the analyses included adjustment for food intervention as well as a number of baseline characteristics: baseline measure of the outcome, age, sex, and month of admission (as fixed effects). Random intercepts were included in the model to adjust for variation between sites. In the adjusted analysis, weight was derived by adding FFM and FM. Additionally, for direct outcomes of fat (FM and FMI) we evaluated the two-way interaction between length group and product group (CSB compared with LNS) in order to assess effect modification by type of product. Moreover, possible effect modification was also evaluated for stunting at admission in a) two categories: above and below LAZ of <-2, or b) or three categories: severe stunting (LAZ <-3), moderate stunting (LAZ ≥-3 to <-2) or absence of stunting (LAZ ≥-2). The same adjustments were applied in these additional analyses as in the main analysis. Model checking was based on residuals and normal probability plots. A significance level of 0.05 was applied." 2. Thanks for the question. Weight gain was estimated using the weight measurements at the end of the study but adjusted for baseline weight (analysis of covariance). We've now spelled out that we used an analysis of covariance type of linear mixed model. In this way, confidence intervals and p-values were obtained directly from the model fits (This is included in text in the paper as seen in the answer to your first question) 3. We don't consider bias to be a problem in this study. First, selection bias is unlikely, since we included a large proportion of	*analysis*	

	those with MAM, based on MUAC, in the study, and the follow-up rate was very high, and not different between the two groups being compared. Hence, it is unlikely that selection could have led to a bias because of, say, lower probability of inclusion/higher attrition of children more prone to accumulate fat in the short compared to the long children. Second, information bias is unlikely since the outcome was assessed in the lab by staff who were unaware of the exposure of interest. Theoretically, a source of information bias could be that short children were more or less likely to spit when given the deuterium. For example, if short (younger) children were more likely to spit, then the concentration of deuterium would be underestimated, and the total body water overestimated, and therefore, the fat mass would be underestimated. However, since this would then happen base at baseline and endline, it is not likely to affect the change in fat mass, which is our outcome of interest. In general, generalizability is likely to be lower in nutrition compared to other intervention trials, since the effect of an intervention depends on the background nutritional intake and status. However, in this substudy, we are not testing the effect of a nutrition intervention, but if short stature affects changes in body composition. Certainly, since we used strict inclusion criteria we think that our findings can be generalized to other West African populations of young children with MAM, diagnosed using MUAC, at least. Yet, we cannot exclude the possibility that different fetal and early life trajectories in growth and body composition, as well as differences in background diets, may modify the difference in change in body composition during supplementation. This paper specifically asks for a policy change in the remaining African countries where length restriction is applied to MUAC measurements, these countries are located in West and Central Africa where morbidity/mortality and malnutrition patterns (very high incidence of acute malnutrition accompanied by high levels of stunting) are similar to that seen in Burkina. We would welcome further studies. It is probably worthwhile to repeat such body		

	composition studies in other malnutrition contexts such as high prevalence of kwashiorkor in DRC/East Africa and in South Asia. However, we feel that policy must be changed now as no evidence support fat accumulation in this group of children. Given the fact that we are already at the full word limit we hope it is acceptable that we make no further changes in the manuscript text. 4. This is a very good question. Malnutrition in itself might dispose to later non-communicable diseases (NCD) including increased susceptibility to fat accumulation, but firm evidence is lacking. However, if children with MAM are not treated, they are at a 3 times higher risk of dying here and now. The fact that they do not accumulate excess fat directly following 12 weeks treatment indicates, we believe, that the risk of later obesity following modern supplementation is, if at all present, low. The longer term implications of nutritional supplementation on NCD risk would be more likely to emerge in studies of young children supplemented over longer periods, e.g. the 9-18 month. However, the only way to find out would be doing long-term follow-up and compare our present cohort with another cohort who received different or no supplementation. Also, while getting fat later increases NCD risk, so does losing lean mass early, ie the thrifty phenotype. So, it makes sense to try to address the lean deficit when it is still amenable to nutritional therapy (early critical window). Given the fact that we are already at the full word limit we hope it is acceptable that we make no further changes in the manuscript text.		

Instructions:

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For clarity, use one row per question. Make sure to list the page and line reference where your change can be found. If no change was made, please make sure to note that in your response in addition to your reasoning. You may delete the sample row and insert rows to this table as needed.