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Comparative Cost-Effectiveness of Four Supplementary Foods in Treating Moderate Acute Malnutrition in Children 6-59 Months In Sierra Leone

Section 2: Body Composition Sub-Study

A Report from the Food Aid Quality Review

Prepared by:

Devika Suri
Akriti Singh
Isabel Potani
Breanne Langlois
Stacy Griswold
Ye Shen
Ilana Cliffer
Kenneth Chui
Shelley Walton
Lindsey Green Ellis
Irwin Rosenberg
Patrick Webb
Beatrice Lorge Rogers

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For correspondence, contact:

Beatrice Lorge Rogers, PhD
Friedman School of Nutrition Science and Policy
Tufts University
150 Harrison Avenue
Boston, MA 02111
beatrice.rogers@tufts.edu
http://www.foodaidquality.org

ABBREVIATIONS AND ACRONYMS

BIA	Bioelectrical Impedance
C	Centigrade
Cm	Centimeter
CSB+	Corn-Soy Blend Plus
CWSB	Corn-Soy-Whey Blend
DD	Deuterium Dilution
D_2O	Deuterium Oxide
FBFs	Fortified Blended Foods
FFM	Fat-Free Mass
FM	Fat Mass
G	Gram
HAZ	Height-for-Age-Z-Score
IDRL	University Makeni Infectious Disease Research Laboratory
Kg	Kilogram
MAM	Moderate Acute Malnutrition
Ml	Mililiter
MUAC	Mid-Upper Arm Circumference
PHUs	Peripheral Health Units
RUSF	Ready-to-Use Foods
SAM	Severe Acute Malnutrition
SC+A	Super Cereal Plus Amylase
SNFs	Specialized Nutritious Foods
TBW	Total Body Water
W	Weight
WHZ	Weight-for-Height Z-score

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ABSTRACT

Introduction: Anthropometric indicators such as mid-upper arm circumference (MUAC) and weight-for-height z-score (WHZ) are currently used to determine recovery from moderate acute malnutrition (MAM). Body composition measures of fat mass (FM) and fat-free mass (FFM), however, give more detail to the quality of weight gained and may be important for understanding longer term maintenance of recovery and risk of chronic disease later in life.

Objectives: To determine differential changes in children's body composition—fat-free mass (FFM) and fat mass (FM)—after 4 weeks of treatment for moderate acute malnutrition (MAM) with one of 4 four specialized nutritious foods (SNFs).

Methods: Body composition was assessed using the deuterium dilution technique at program enrollment and after 4 weeks of treatment among a subset of children enrolled in the cost-effectiveness study. Children were enrolled in 8 of the 29 peripheral health units in which the cost-effectiveness study was conducted. Total sample size was fixed at 200/arm for logistical and budgetary reasons. Changes in weight, FM, FFM and %FFM overall and by study arm were calculated; statistical significance was determined using t-tests and ANOVA (unadjusted).

Results: Among 312 subjects at enrollment, mean ± SD age was 12.9 ± 7.2 mos, weight was 6.5 ± 0.96 kg, FM was 1.3 ± 0.5 kg, FFM was 5.2 ± 0.95 kg, and %FFM was 80.1 ± 7.03. After 4 weeks of treatment, mean ± SD change in weight was 0.45 ± 0.39 kg ($P < 0.001$), change in FM was 0.07 ± 0.60 kg ($P = 0.005$), change in FFM was 0.37 ± 0.57 ($P < 0.001$), and change in %FFM was 0.26 ± 8.44(NS). Overall, weight gain consisted on average of 20.9% FM and 79.8% FFM, thus the %FFM was unchanged from enrollment to four weeks. Changes in FM and FFM were not significantly different across study arms. By study arm, mean ± SD changes in FM and FFM respectively, were: 0.05 ± 0.59 kg and 0.38 ± 0.54 kg in CSB+ w/oil; 0.15 ± 0.66 kg and 0.33 ± 0.64 kg in SC+A; 0.07 ± 0.63 kg and 0.37 ± 0.57 kg in CSWB w/oil; -0.01 ± 0.49 kg and 0.42 ± 0.49 kg in RUSF.

Conclusions: Over 4 weeks of treatment for MAM, children gained roughly 80% lean mass and 20% fat mass. This body composition is consistent with association between sustainability of recovery from MAM and healthier long-term recovery. Differential effects on body composition by type of SNF were not detected after 4 weeks of treatment.

1. Background and Objective

A number of different specialized nutritious foods (SNFs) have been used to treat children with moderate acute malnutrition (MAM), but it is recognized that supplementary feeding programs (SFPs) need to assess outcomes other than anthropometric indicators such as mid-upper arm circumference (MUAC) and weight-for-height Z-score (WHZ) as indicators of recovery (1,2). One such outcome is lean body mass or fat-free mass (FFM). While fat mass (FM) represents energy stores, fat-free mass (FFM) represents functional organs and tissues. Their proportion indicates how the body is prioritizing these needs (2).

Body composition, and not just body weight, has been shown to be important for survival in both healthy and sick children (3), and inadequate accumulation of either FM or FFM has been shown to be detrimental to health (4). Body composition in infancy can have lasting influence on adult noncommunicable disease risk (5). In particular, rapid and/or catch-up weight gain in early childhood has been associated with adiposity, obesity and non-communicable diseases later in life (5,6). Overall, however, there is limited understanding of the changes in body composition that occur during MAM and MAM treatment (7). At present, body composition reference data in young children is limited, and targets for absolute or proportional gain of FFM and FM in children while recovering from MAM are unclear (6,8).

In recognition of the possible implications of body composition for health at different stages of the life cycle, studies investigating body composition in MAM could help build evidence on the management of MAM and its impact on the global burden of disease. Studies on body composition and its relationship to anthropometric measures could also improve the understanding of how MUAC and WHZ capture changes in body composition during MAM treatment. The objectives of this sub-study were to investigate the effects of four SNFs on changes in FM and FFM among children during four weeks of treatment for MAM, and to compare these changes with anthropometric measures in order to expand understanding of factors influencing recovery and sustainability of recovery from MAM.

2. Methods

2.1 Study Design

This Body Composition Sub-Study was nested within the *Four Foods MAM Treatment Study,* a prospective, cluster-randomized, controlled clinical and cost-effectiveness trial assessing four SNFs to treat children 6-59 months with MAM, defined as MUAC ≥11.5 cm and <12.5 cm without bipedal edema. The sub-study was conducted in eight of the 29 peripheral health units (PHUs) in the *Four Foods MAM Treatment Study,* two per arm. Selection was purposively based on logistical needs and on the number of MAM cases to ensure that the target sample size was met within the allocated data collection time. The research team also considered the availability of sheltered and adequate space for study procedures to minimize the risk of sample contamination. Lastly, proximity of the data collection sites to the study office was a necessary logistical consideration. This was important because the study office was the only location in Pujehun, Sierra Leone that was accessible to the team and had consistent electrical power for a freezer to store the urine samples.

The PHUs selected from each study arm were:

- Corn-Soy Blend Plus (CSB+) w/oil: Blama Massaquoi and Makorma
- Super Cereal Plus with Amylase (SC+A): Sahn Malen and Taninahun
- Corn-Soy Whey Blend (CSWB) w/oil: Bandajuma and Kowama
- Ready-to-Use Supplementary Food (RUSF): Konia and Funyehun

2.2 Ethical Approvals

The sub-study was approved by the Tufts University Health Sciences Institutional Review Board and Sierra Leone Ethics and Scientific Review Committee. Written informed consent was obtained for all participants.

2.3 Participants and Sample Size

All subjects (beneficiary children and caregivers) at the selected PHUs were eligible to participate in the sub-study. A sample size of 200 per arm was determined, based on logistical/budgetary feasibility and the expected number of children to be recruited from the PHUs in the Sub-Study. The original primary outcome was change in the percentage of FFM after four weeks of treatment. (The main outcome on which results were compared was changes to absolute FM and FFM gain. See the "Limitations" section for further detail.) At the time of developing the study protocol, there were few studies of body composition in MAM using any of the food formulations under investigation that also used this outcome, so the researchers determined an estimated detectable effect using this maximum sample size.

To adjust for the cluster-randomized design, a conservative design effect of 1.115 was applied. This was because the outcome variable was continuous, with an expected low intra-class correlation, and therefore little variance between the clusters (i.e. PHUs) was expected. Furthermore, stratified analyses were planned based on age groups (6-23.9 months, and 24-36 months), thereby doubling the required sample size. As arms were capped at 200, power calculations were based on sample sizes of 89 per group: (i.e. 100/1.115). Using simple random sampling and a two-sided paired t-test, a sample size of 89 per group achieves 80% power to detect a mean of paired differences of 0.2 percentage points with an estimated standard deviation of differences of 0.5 and with a 0.05 significance level. This is consistent with a previous study (9) that examined similar foods, where change in percentage FFM after 12 weeks of treatment within each group ranged from -1.5 to 0.4 percentage points for fortified blended foods (FBFs), and -0.2 for RUSF.

2.4 Deuterium Dilution Method, Sample Collection and Analysis

To assess body composition, the research team used the deuterium dilution (DD) technique, which has been validated for assessing body composition in children with MAM (10) and is based on a two-component model of body composition (11). This technique requires the subject to ingest an oral dose of deuterium oxide (D_2O); their urine is collected approximately four hours later. Participants in the Body Composition Sub-Study were asked to return to the

clinic the *day after* collecting a ration from the PHU in order to have sufficient time for the body composition protocol (i.e. consuming the DD, waiting, and urine collection). This occurred at enrollment (baseline) and Week 4 (endline). This four-week time period was chosen so that all enrolled children would have the same exposure to the intervention, since children who graduated would not continue to receive the treatment food (those who graduated at two weeks would receive one more food ration which would bring them to a total of four weeks on the study food).

The body composition data collection team consisted of a research assistant (technical lead), two research assistant aides (in charge of recruiting participants, preparing and administering D_2O doses, and collecting urine samples), a driver (responsible for taking caregivers to and from the study site and their villages, as well as observing the caregiver's adherence to instructions), and a community health worker when one was available (assisted in locating caregiver villages, communicating instructions to caregivers and serving caregivers food).

Diluted D_2O was prepared using a 1:10 dilution of a 99% D_2O (Sigma Aldrich, US) with locally-purchased bottled water. Each dilution was approximately 1000 ml and was made of approximately 905 g of bottled drinking water and 90 g of D_2O. The dose was stored in a 1000-ml Nalgene bottle that was sealed with parafilm and stored in a freezer at the study office. Each stock solution lasted for approximately four weeks. Portions of the diluted dose and water used in the dilution were shipped for lab analysis. Since samples containing deuterium are susceptible to contamination—which can result in over or underestimation of body composition values—the first two weeks of the study were considered a pilot test of the DD technique under the field conditions in Pujehun. Additional samples of the dose, water, and urine for 16 study subjects from seven sites were sent for lab analysis and plausibility of the findings was confirmed.

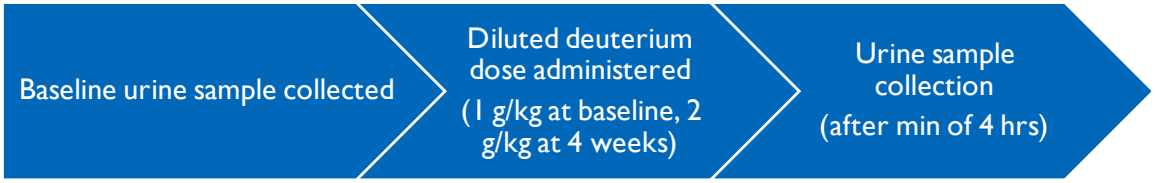
At baseline, participants were given a dose of diluted D_2O at 1 g/kg body weight. At endline (four weeks), the dose given was doubled to: 1) minimize natural variation in isotope enrichment in the post-dose urine sample; and 2) offset the effect of residual deuterium from the first dose on the deuterium enrichment at the four-week assessment. The doses were given orally using locally-purchased syringes, and subjects were not required to fast at any time before dose administration. The prescribed doses were weighed in grams to two decimal places at the study office and placed in syringes in sealed Ziploc bags.

Prepared doses were then transported in a cold box with gel ice packs. At the time of administration, the dose was weighed before and after administration, the difference between the two weights was the dose received by the participant. In cases when there were spills, the spills were recovered with pre,-weighed cotton balls. Losses were estimated from the difference in weights of the cotton balls before and after collecting the spill. When spills could not be successfully collected, this was noted in the participant's record. Other events that required noting on the day of D_2O dosing were vomiting, diarrhea, and any other occurrence that the study personnel thought might affect the outcome of the study. Subjects with greater than 10% spit-up or spilled deuterium solution were excluded from analysis.

After D_2O administration was complete, the participants were not allowed to take any food or drink for two hours, after which they were permitted to eat and drink water and breast milk under the watch of study personnel. While free intake of water was permitted, the amount of breast milk taken was estimated by weighing children before and after breast feeding. Older children were also served lunch, usually rice, local vegetables and meat. Younger children were served a rice porridge. Body water calculated from the DD method was adjusted for water coming from breast milk consumed during the four-hour protocol assuming breast milk has a water content of 87%. Metabolic water generated from non-aqueous food consumption during the four-hour period was considered to be negligible and was not adjusted.

Urine samples were collected before dosing with D_2O and after a minimum of four hours following D_2O administration (12), allowing the isotope to reach isotopic equilibrium (i.e. plateau value) in the body. The concentration of the excess deuterium, which is the difference between the pre-dose and post-dose samples, is then calculated. Urine was collected using PDC Healthcare-Assure Urine Collectors urine bags (ThermoFisher Scientific, US). Aliquots of approximately 1.5 ml of baseline and post-dose urine samples were transferred to airtight cryovials from the urine collection bags and then placed in cryoboxes. This was done at a urine collection station. The cryoboxes were stored and transported in an ice box to the study office for storage in a freezer at -20°C for at least four weeks, after which they were transferred to the University Makeni Infectious Disease Research Laboratory (IDRL) which was eight hours away. They were kept in -20°C freezer until shipment to the United States Department of Agriculture/Agricultural Research Service Children's Nutrition Research Center at Baylor College of Medicine in Houston, Texas for isotope ratio analyses. Refrigeration and freezing is not required but recommended for samples using the DD technique, due to potential mold and bacteria growth which would result in dilution of the isotopes in the urine samples (13).

Body Composition Data Collection Procedure



The deuterium content of the urine samples, the diluted dose and water used to prepare it were analyzed in duplicate at the Baylor lab using continuous-flow isotope ratio mass spectrometry (14). The lab reported the deuterium content of the diluted D_2O dose, the water used to prepare the diluted dose and the pre- and post-dose urine samples. The deuterium dilution space, as well as FFM, FM, and percent FM with adjustment, if necessary, of missing dose and/or milk intake during the four-hour equilibration period were calculated as shown in **Appendix I.**

2.5 Data Management

The body composition study used a data collection form at enrollment and at four weeks, which was then uploaded to a KoboCollect[1] data collection tool kit using a laptop computer at each study site. All demographic and anthropometric data were collected for the *Four Foods MAM Treatment Study*. However, for some children who graduated at two weeks (or did not show up at the fourth week visit), MUAC, weight and length were collected as per study protocol at the four-week time point by the Body Composition sub-study team. Prior to sending samples to the lab, relevant participant information was exported from the KoBoCollect online database to minimize typographical errors. A clean data file in Excel format along with the samples was sent to the analyzing lab for deuterium measurements.

Unphysiological total body water (TBW) values due to errors in dose weight and dose spillage (>10%) were excluded from the dataset (n = 92). Since the quality control of the mass spectrometric measurements is well established (13), errors at various steps of the study most likely are the primary causes of implausible TBW values. Data management and cleaning were conducted with Stata 15 and Microsoft Excel 2017.

2.6 Research Questions and Hypotheses

After four weeks of treatment:

1. What are the changes in body composition (specifically FM and FFM) of 6-59 month-old children with MAM after four weeks of treatment? (Exploratory, no *a priori* hypothesis)
2. What is the relation of FM and FFM to MUAC, WHZ and recovery?
   Hypothesis: Changes in body composition will be correlated with changes in MUAC, WHZ and recovery.
3. Are there differences in body composition changes among the four SNFs?
   Hypothesis: The four food supplements will have different effects on the body composition of the 6-59 month-old children with MAM.

Body Composition Measures:

- TBW, kg
- FFM, kg
- FM, kg
- FFM percent (FFM/body weight x 100)
- FFM index (FFM kg/height^2)

Anthropometric Measures and Covariates (from study clinic data):

- Weight, kg
- MUAC, cm (*Four Foods MAM Treatment Study* main outcome, used to determine recovery from MAM)
- Weight-for-height z-score
- Age of child at enrollment, in months

[1] Kobotoolbox: https://www.kobotoolbox.org/

- Sex of child
- Wealth quintile
- Whether the child graduated into the MAM program from severe acute malnutrition (SAM) treatment (0=Not SAM start; 1=SAM start)
- Whether the child recovered from MAM within 12 weeks (0=Did not recover; 1= Recovered in 12 weeks)

2.7 Statistical Analysis

The dataset used for the Body Composition Sub-Study analysis consisted of body composition measures (listed below) plus anthropometric and demographic variables from the *Four Foods MAM Treatment Study* clinic cards.

To answer the first research question, descriptive statistics for baseline and outcome values of body composition and anthropometry for the included subjects were tabulated. The average changes in these variables were calculated, as well as the average percent of weight gain that was from FM and FFM.

To address the second research question and hypothesis, the research team calculated Pearson correlations among the changes in FM, FFM, MUAC and WHZ. The research team further estimated mean changes in FFM, FM and weight by whether a child recovered by 12 weeks and whether that recovery was sustained at the 4-week follow-up visit, using margins from logistic regressions of recovery or sustained recovery (binary) on each outcome, adjusted for baseline FFM, age, sex, baseline WHZ and wealth quintile.

To address the third research question and hypothesis, the research team ran linear regression models by study arm on change in FFM and FM, controlling for baseline body composition (FFM or FM), age, sex, baseline WHZ and wealth quintile. Statistical differences among the study arms was assessed using a Wald test. Mixed models were used to adjust for clustering at the PHU levels, but these results showed a negligible design effect, and thus, the final models did not adjust for clustering. Models were assessed for goodness-of-fit, collinearity, and potentially-influential outliers. Adjusted outcome values for change over four weeks were obtained using predicted margins. Data analysis procedures were conducted with Stata 15 and Microsoft Excel 2017.

3. Results

3.1 Study Population and Characteristics

A total of 578 children were recruited and their caregivers consented to participation in the body composition study. Of these, 516 children completed the baseline body composition procedure and 407 completed the four-week follow-up procedure. Reasons for not completing the four-week measure included loss to follow up (38), progression to SAM (50), unsuccessful or missing samples (11) and death (4). Six subjects were dropped from the *Four Foods MAM Treatment Study* dataset due to data collection issues. Once the urine samples were

analyzed and the body composition measures had been calculated, 92 subjects were removed from the analysis dataset due to methodology issues (see "2.5 Data Management" and "2.7 Statistical Analysis" sections above). Two values were identified as influential outliers and removed from analysis. A total of 312 subjects were included in the final analysis dataset.

Baseline descriptive statistics for the 312 subjects included in the Body Composition Sub-Study analysis can be found in **Table 1**. Although the age range for the program spanned 6-59 months, children were on average about 12 months of age, and there were slightly more females than males. A quarter of subjects had graduated into the MAM treatment program from SAM treatment. The wealth quintiles were significantly different among the four study arms.

Table 1: **Baseline Descriptive Statistics of Subjects Included in Body Composition Analysis, *n*=312**

	Total	CSB+ w/ oil	SC+A	CSWB w/ oil	RUSF	*P*-value[3]
n	312	84	94	68	66	
Age, months	12.19±7.18[1]	11.98±6.64	12.69±7.80	12.45±7.20	11.46±6.97	0.733
Females	173 (55%)[2]	49 (58%)	55 (59%)	35 (51%)	34 (52%)	0.685
Previous SAM	78 (25%)	23 (28%)	23 (24%)	15 (22%)	17 (26%)	0.880
HAZ	-2.72±1.15	-2.73±1.13	-2.73±1.04	-2.84±1.26	-2.58±1.19	0.634
WHZ	-1.70±0.74	-1.63±0.69	-1.76±0.74	-1.85±0.76	-1.57±0.75	0.105
Wealth quintile						<0.001
Lowest	69 (22%)	22 (26%)	11 (12%)	17 (25%)	19 (29%)	
Low	52 (17%)	9 (11%)	13 (14%)	9 (13%)	21 (32%)	
Middle	62 (20%)	16 (19%)	23 (25%)	10 (15%)	13 (20%)	
High	71 (23%)	20 (24%)	21 (23%)	18 (26%)	12 (18%)	
Highest	56 (18%)	17 (20%)	24 (26%)	14 (21%)	1 (2%)	
Recovered within 12 weeks	229 (73%)	61 (73%)	70 (74%)	51 (75%)	47 (71%)	0.954

[1] Mean ± SD, all such values
[2] Frequency (percent), all such values
[3] ANOVA tests were used for continuous variables; chi-square tests were used for categorical variables
Abbreviations: CSB+, Corn-Soy Blend Plus; CSWB, Corn-Soy-Whey Blend; HAZ, height-for-age z-score; RUSF, ready-to-use supplementary food; SAM, severe acute malnutrition; SC+A, Super Cereal plus Amylase; WHZ, weight-for-height z-score

Research Question 1: What are the changes in body composition in children with MAM after four weeks of treatment?

Baseline anthropometric and body composition measures are shown in **Table 2**. There were no significant differences in baseline measures among the study arms. Overall, changes in anthropometric and body composition measures over four weeks of treatment were highly variable among study subjects. Weight gain ranged from -0.65 kg to 2.1 kg, change in FFM ranged from -1.5 kg to 2.2 kg, and change in FM ranged from -1.8 kg to 1.6 kg (**Figure 1**).

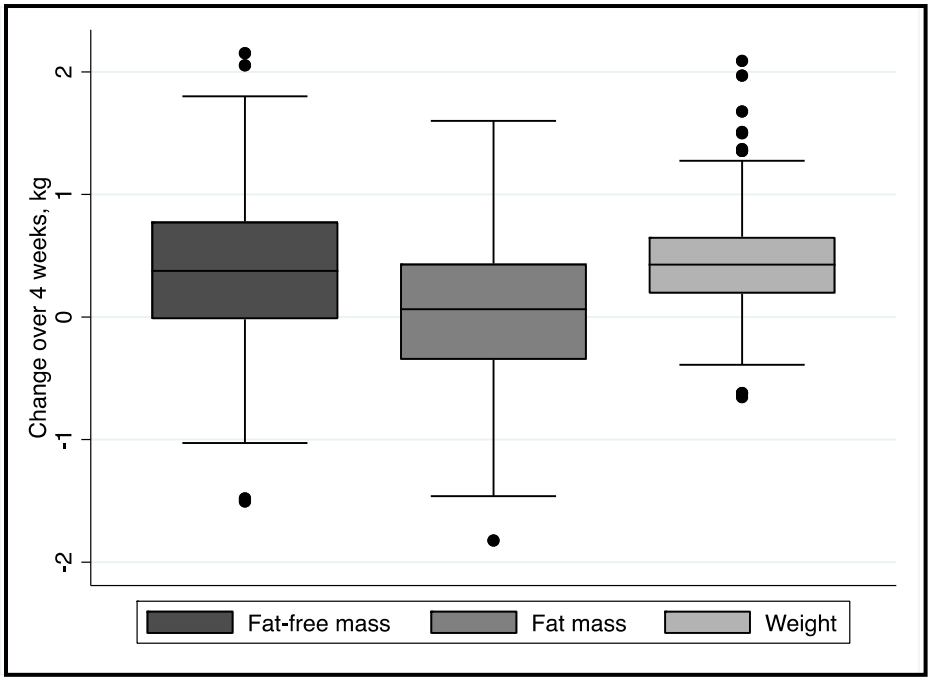
Percent FFM was even more varied, with changes over four weeks ranging from -21.1 to 22.6 percentage points. Unadjusted mean changes in anthropometric and body composition measures over four weeks of treatment are also shown in **Table 2**. On average, children gained weight over the four weeks of treatment; approximately 82% of the weight gained during this period was FFM (a slightly higher proportion of FFM compared to average baseline FFM of 80.1%).

Table 2: Unadjusted Anthropometric and Body Composition Measures at Baseline and Changes After Four Weeks of Treatment for MAM, *n* = 312

	Total	CSB+ w/ oil	SC+A	CSWB w/ oil	RUSF	*P*-value[2]
n	312	84	94	68	66	
Baseline						
Weight, kg	6.53±0.961	6.55±1.09	6.57±0.98	6.52±0.78	6.47±0.95	0.915
WHZ	-1.70±0.74	-1.63±0.69	-1.76±0.74	-1.85±0.76	-1.57±0.75	0.105
MUAC, cm	11.97±0.27	12.01±0.27	11.98±0.26	11.94±0.27	11.93±0.28	0.264
Total body water, kg	4.16±0.71	4.15±0.64	4.19±0.81	4.16±0.65	4.11±0.72	0.914
FFM, kg	5.24±0.95	5.23±0.86	5.29±1.07	5.25±0.87	5.18±0.96	0.901
FM, kg	1.29±0.48	1.33±0.52	1.28±0.49	1.27±0.49	1.29±0.43	0.871
FFM %	80.11±7.03	80.00±6.39	80.17±7.48	80.42±7.57	79.84±6.71	0.968
FFM index	11.62±1.15	11.64±1.18	11.57±1.20	11.62±1.16	11.66±1.04	0.968
Change after 4 weeks[4]						
Weight, kg	0.45±0.39	0.43±0.39	0.48±0.41	0.44±0.38	0.41±0.38	0.696
WHZ[3]	0.30±0.61	0.24±0.57	0.35±0.57	0.42±0.65	0.16±0.64	0.154
MUAC, cm [4]	0.32±0.46	0.29±0.49	0.32±0.41	0.37±0.49	0.30±0.48	0.827
Total body water, kg	0.29±0.45	0.29±0.43	0.26±0.51	0.28±0.45	0.33±0.39	0.791
FFM, kg	0.37±0.57	0.38±0.54	0.33±0.64	0.37±0.57	0.42±0.49	0.807
FM, kg	0.07±0.60	0.05±0.59	0.15±0.66	0.07±0.63	-0.01±0.49	0.415
FFM %	0.26±8.44	0.34±8.14	-0.65±9.03	0.28±8.81	1.46±7.54	0.492
FFM index[5]	0.49±1.28	0.57±1.21	0.43±1.49	0.42±1.19	0.54±1.18	0.899

[1] Mean ± SD, all such values
[2] ANOVA tests used to determine differences among the 4 study arms
[3] *n*=257 due to missing values at 4 weeks
[4] *n*=250 due to missing values at 4 weeks
[5] *n*=234 due to missing values at 4 weeks
Abbreviations: CSB+, Corn-Soy Blend Plus; SC+A, Super Cereal plus Amylase; CSWB, Corn-Soy-Whey Blend; RUSF, ready-to-use supplementary food; WHZ, weight-for-height z-score; MUAC, mid-upper arm circumference; FFM, fat-free mass; FM, fat mass

Figure 1: Changes in FFM, FM and Weight Over Four Weeks, *n* = 312



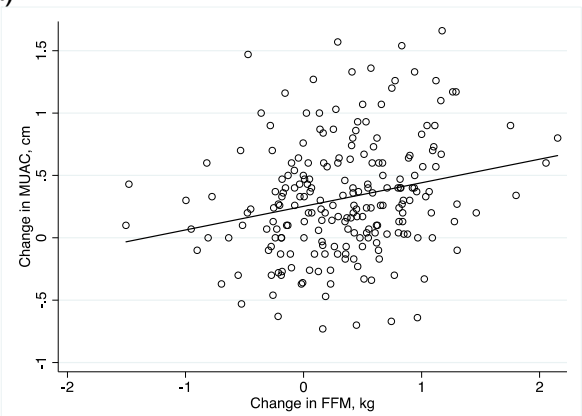
Research Question 2: What is the relation of FM and FFM to MUAC, WHZ and recovery?

The results of this study supported the hypothesis that changes in body composition and changes in anthropometric indicators were correlated. While the correlations were statistically significant, however, they were fairly weak. Scatterplots of changes in MUAC versus changes in FFM or FM are shown in **Figure 2a** and changes in WHZ versus changes in FFM or FM are shown in **Figure 2b**. Pearson correlations and adjusted R-squared values were similar.

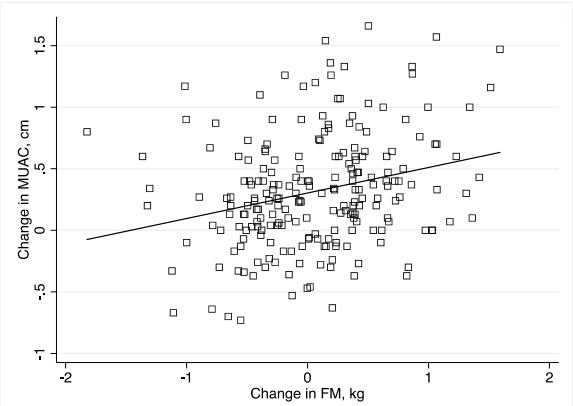
Gains in FFM, FM and weight in the first four weeks of treatment for MAM were significantly higher among children who recovered within the full 12 weeks of treatment (**Figure 3**). Children who recovered within 12 weeks gained an average of 0.43 kg FFM during the first 4 weeks of treatment, while those who did not recover by 12 weeks gained an average of 0.22 kg FFM ($P = 0.002$). Similarly, children who recovered within 12 weeks gained an average of 0.14 kg FM during the first four weeks of treatment, while those who did not recover by 12 weeks *lost* an average of 0.13 kg FM ($P < 0.001$). In terms of proportions of FFM and FM, children who recovered gained in a similar proportion to their starting body composition, on average, while children who did not recover gained proportionately more FFM than FM, on average, resulting in a higher percent FFM at endline. The pattern was similar for children who recovered and whether or not they sustained that recovery at their one-month follow-up or relapsed to MAM (**Figure 4**). Children who sustained recovery tended to have gained more FFM, FM and weight over the first four weeks of treatment, though only weight gain was significantly different between the groups ($P<0.001$).

Figure 2: Changes in FFM and FM Over Four Weeks Versus Change in MUAC (a) and WHZ (b), *n*=218 and *n*=225, Respectively.

a)

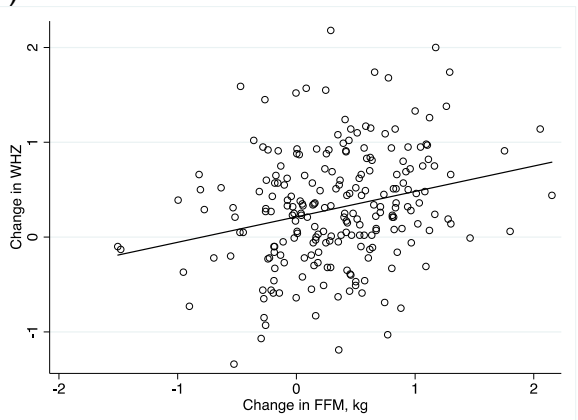


Adjusted R-squared: 0.05
Pearson correlation: 0.23 (P<0.001)

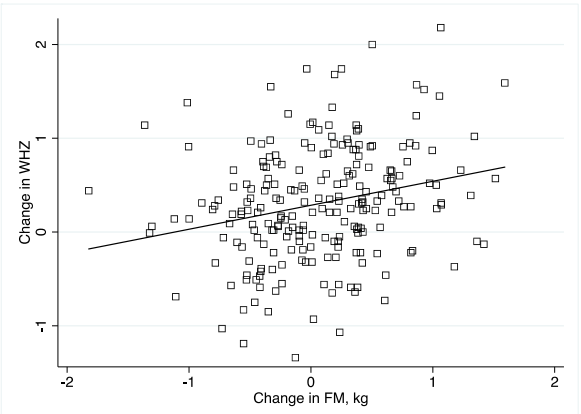


Adjusted R-squared: 0.06
Pearson correlation: 0.26 (P<0.001)

b)



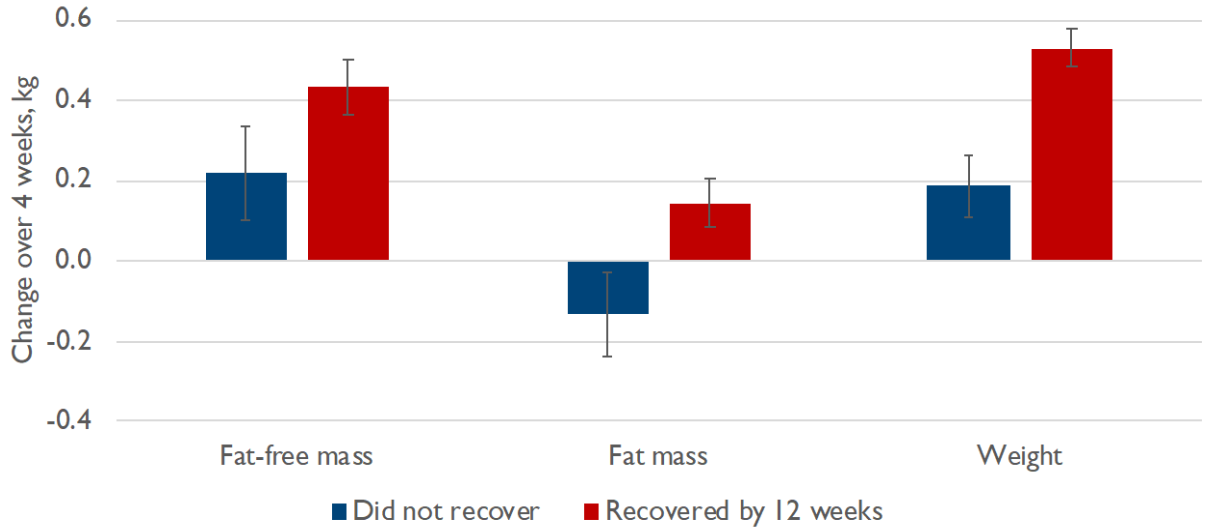
Adjusted R-squared: 0.06
Pearson correlation: 0.25 (P<0.001)



Adjusted R-squared: 0.06
Pearson correlation: 0.24 (P<0.001)

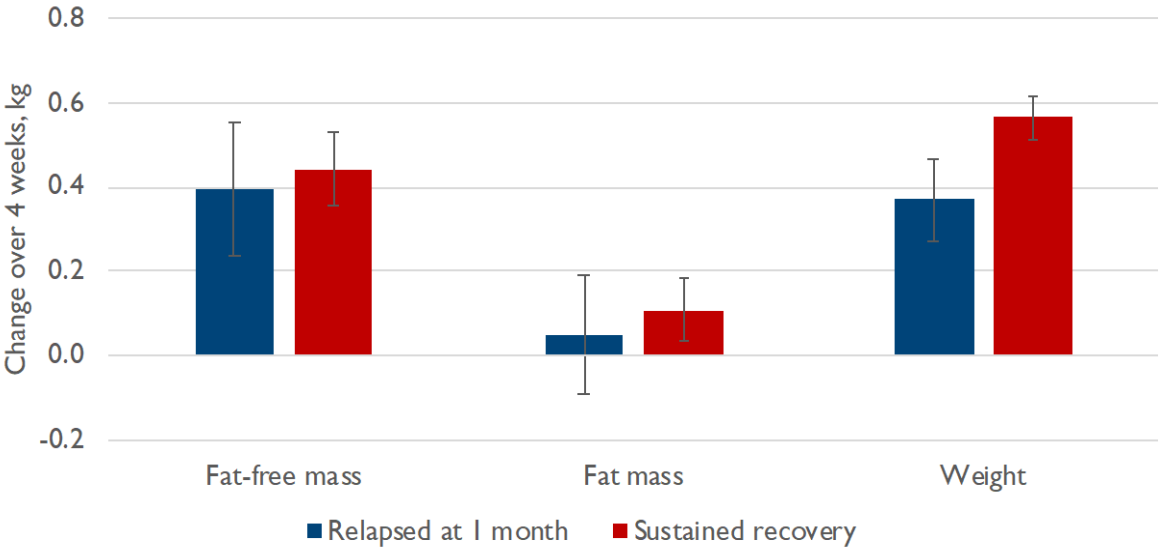
Abbreviations: FFM, fat-free mass; FM, fat mass; MUAC, mid-upper arm circumference; WHZ, weight-for-height z-score

Figure 3: Changes in FFM, FM and Weight Within First Four Weeks of Treatment, Comparing Children Who Recovered Within 12 Weeks Of Treatment for MAM and Those Who Did Not[1], *n*=312



[1] Difference in change in FFM, FM and weight by recovery status: $P = 0.002$, $P < 0.001$ and $P < 0.001$, respectively; recovered $n = 229$, did not recover $n = 83$
Error bars represent 95% confidence intervals
Values are predicted margins estimates using linear models adjusted for baseline value of measure, study arm, sex, baseline WHZ and wealth quintile
Abbreviations: FFM, fat-free mass; FM, fat mass; MAM, moderate acute malnutrition

Figure 4: Changes in FFM, FM and Weight Within First Four Weeks of Treatment, Comparing Children Who Sustained Recovery for One Month After Program Exit With Those Who Relapsed to MAM, *n* = 217[1]

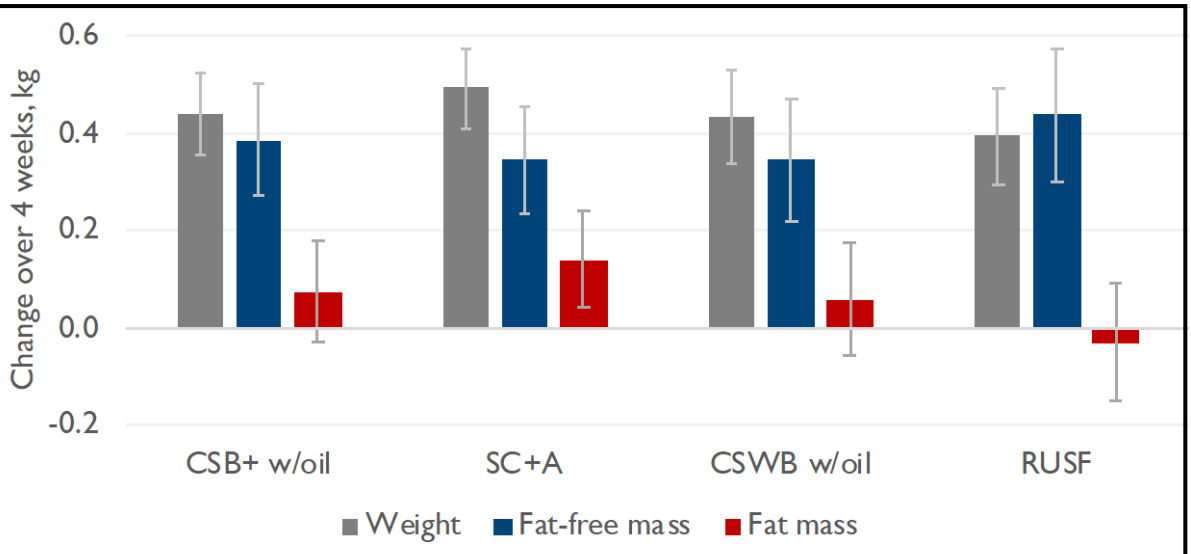


[1] Difference in change in FFM ($P = 0.605$), FM ($P = 0.479$) and weight ($P < 0.001$) by recovery status: relapsed at 1 month, $n = 50$; sustained recovery $n = 169$; and missing $n = 93$
Error bars represent 95% confidence intervals
Values are predicted margins estimates using linear models adjusted for baseline value of measure, study arm, sex, baseline WHZ and wealth quintile
Abbreviations: FFM, fat-free mass; FM, fat mass.

Research Question 3: Are there differences in body composition changes among the four SNFs?

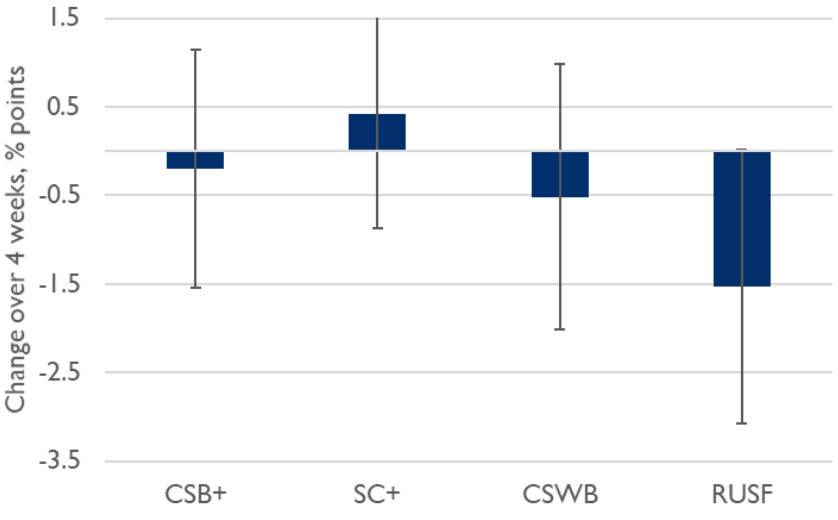
The results of this study did not find differential changes in body composition by study food. There were no differences in change in anthropometry or body composition across the groups (**Table 2**). An adjusted analysis of changes in weight, FM, FFM and %FM also showed no significant difference (**Figure 5** and **Figure 6**).

Figure 5: Changes in Weight, Fat-Free Mass and Fat Mass by Study Arm After Four Weeks of Treatment for MAM by Study Arm, *n* = 312.[1]



[1] Models adjusted for baseline outcome measure, age, sex, baseline WHZ and wealth quintile
Abbreviations: MAM, moderate acute malnutrition; CSB+, Corn-Soy Blend Plus; SC+A, Super Cereal plus Amylase; CSWB, Corn-Soy Whey Blend; RUSF, ready-to-use supplementary food.

Figure 6: Changes in Percent of Fat Mass by Study Arm After Four Weeks of Treatment for MAM by Study Arm, *n* = 312[1]



Models adjusted for baseline outcome measure, age, sex, baseline WHZ and wealth quintile
Abbreviations: MAM, moderate acute malnutrition; CSB+, Corn-Soy Blend Plus; SC+A, Super Cereal plus Amylase; CSWB, Corn-Soy-Whey Blend; RUSF, ready-to-use supplementary food.

4. Limitations and Challenges

4.1 Limitations

Due to the methodological challenges described above, the final analyzable sample size was reduced by almost a quarter. Because the proportion of dropped subjects was similar among the study arms, it is not likely that this biased the results. However, it did reduce the statistical power to detect any potential differences among the study arms in terms of body composition changes.

4.2 Challenges

The research team faced a number of challenges during the Body Composition Sub-Study. First, the oral diluted deuterium dose was poorly accepted by the partcipants possibly due to reduced appetite (common in malnourished children), and participants often refused, spit up or spilled the deuterium solution dose. This loss was estimated using cotton balls, which is a poor estimator of deuterium loss but the only practical method available at present. Second, urine sampling resulted in a high time burden on the participants and caregivers due to the long equilibration time. Frustration was observed as caregivers would attempt to force the participants to drink more water to facilitate the post-dose urine sample collection. Children with MAM are often dehydrated which reduces the urge to urinate.

5. Summary of Findings

This study found that body composition (FM and FFM) changes measured by deuterium dilution provided additional information to the outcomes of recovery and sustainability of recovery in children treated for MAM. In summary:

1. Over four weeks of treatment, children on average gained mostly FFM.
2. FM and FFM were weakly correlated with anthropometric measures MUAC and WHZ.
3. Children who recovered from MAM by 12 weeks were already showing a different pattern of weight gain at four weeks compared to children who did not recover by 12 weeks: on average, higher gains in FM and FFM, and no overall change to the proportion of FM and FFM (whereas children who did not recover had an increase in the proportion of FFM to FM, on average).
4. Similarly, children who sustained recovery for one month after graduation showed greater gains in both FM and FFM during the first four weeks of treatment than those who did not.
5. Changes in FM, FFM, %FFM, and weight gain were similar across the four SNFs.

The findings of this study are comparable to other studies that found children gained mainly FFM during treatment of MAM. A nine-month supplementary feeding study in Cambodia looked at changes in FM and FFM among 419 children starting at six months of age and found an average increase in weight of 1.73 kg, with a 1.96 kg increase in FFM and a 0.21 kg decrease in FM; unfortunately, the authors did not report % change in FFM (15). A study in Burkina Faso found that 93.5% (95% CI 89.6, 97.4) of the weight gain comprised of FFM (16), a bit higher than the finding of 82% FFM of the weight gain in this study. A study in Mali compared body composition changes in children 6-35 months with MAM treated for 12 weeks with one of four supplementary foods. Body weight increased on average 1.02 ± 0.54 kg, FFM 0.69 ± 0.53 kg (67.6% of weight gain), and FM 0.31 ± 0.54 kg (30.4% of weight gain). Stratifying by recovery, they saw a similar pattern to these results, with children who recovered gaining more in FFM and FM than those who did not recover (FFM 0.81 ± 0.50 kg, FM 0.44 ± 0.52 kg and FFM 0.50 ± 0.56 kg, FM 0.09 ± 0.51 kg, respectively) (17,18). These findings contribute to evidence that may alleviate concers that "unhealthy weight gain" may occur during treatment of wasting with lipid-based or other supplementary foods (19).

While there appeared to be slight differences in the trends for FFM and FM gain among study arms, these were not statistically significant. This could be due to the relatively short duration between measures (four weeks), combined with the variability in both measurement of body composition and children's responses to the intervention. This study was different from previous studies in that it was the shortest duration between baseline and endline body composition measures, i.e. four weeks compared with 12 weeks at the minimum in other studies. (The choice of four weeks was made for logistical reasons, to have comparable study food exposure; see the "2. Methods" section.)

Other studies also restricted their maximum age to two or three years or followed a cohort of children of the same age over time. Similar studies did find statistically significant differences between study foods: a supplementary food trial in Burkina Faso compared children 6-23 months of age with MAM (n = 1,609) treated for 12 weeks and found that children treated with a lipid-based nutrient supplement (similar to RUSF) had significantly more gains in FFM index (but not FFM g) compared with CSB (16). However, a study in Mali comparing body composition changes in children 6-35 months with MAM (n = 289) treated for 12 weeks with one of four supplementary foods, found a higher increase in FM in the RUSF group compared to CSB++, although there was no difference in FM gains as a percent of body weight among the groups (17,18). While this study found no differences among the study arms, future studies with higher sample size and longer duration (i.e. higher statistical power) are warranted.

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Appendix 1: Estimation of Body Composition

In order to calculate the deuterium dilution space (N) the following equation was used:

$$N = (T \cdot A/a) \cdot [(Ed–Et)/(Es–Ep)]$$

In the equation, T is the mass of water used to dilute the D_2O dose in grams, A is the mass in grams of the ingested dose in the field, a is the mass in grams of the dose that is diluted in the lab for mass spectrometry analysis, Ed is the isotopic abundance (ppm) in the diluted dose solution, and Et is the isotope abundance in ppm of the water used to dilute the dose, Es is the isotope abundance of the post-dose urine sample in ppm and Ep is the isotope abundance in ppm of the pre-dose urine sample. The dilution space (N) is then divided by a proton exchange factor of 1.040 to account for non-aqueous exchange of ^2H in order to convert it to total body water (TBW). FFM is calculated from TBW using age and gender specific appropriate hydration factors (H) (20): FFM = TBW / H

Below are the best fit equations to calculate the hydration factors:

Girls: $H = (-0.0003 \times Age^3 + 0.027 \times Age^2 – 0.704 \times Age + 84.064)/100$
Boys: $H = (-0.001 \times Age^3 + 0.037 \times Age^2 – 0.710 \times Age + 83.764)/100$

FM is then calculated as the difference between body weight (W) and FFM: FM = W - FFM