Malian children with moderate acute malnutrition who are treated with lipid-based dietary supplements have greater weight gains and recovery rates than those treated with locally produced cereal-legume products: a community-based, cluster-randomized trial[1–5]

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ABSTRACT

Background: Moderate acute malnutrition (MAM), defined as weight-for-length *z* score between −3 and −2 or midupper arm circumference between 11.5 and 12.5 cm, affects ~33 million children aged <5 y worldwide.

Objective: The objective was to compare the effects of 4 dietary supplements for the treatment of MAM.

Design: Twelve community health centers in rural Mali were randomly assigned to provide to 1264 MAM children aged 6–35 mo one of 4 dietary supplements containing ~500 kcal/d for 12 wk: *1*) ready-to-use, lipid-based supplementary food (RUSF); *2*) special corn-soy blend (CSB++); *3*) locally processed, fortified flour (Misola); or *4*) locally milled flours plus oil, sugar, and micronutrient powder (LMF).

Results: In total, 1178 children (93.2%) completed the study. The adjusted mean (95% CI) change in weight (kg) from baseline was greater with RUSF than with the locally processed blends and was intermediate with CSB++ [1.16 (1.08, 1.24) for RUSF, 1.04 (0.96, 1.13) for CSB++, 0.91 (0.82, 0.99) for Misola, and 0.83 (0.74, 0.92) for LMF; $P < 0.001$]. For length change, RUSF and CSB++ differed significantly from LMF. Sustained recovery rates were higher with RUSF (73%) than with Misola (61%) and LMF (58%), $P < 0.0001$; CSB++ recovery rates (68%) did not differ from any of the other groups.

Conclusions: RUSF was more effective, but more costly, than other dietary supplements for the treatment of MAM; CSB++ yielded intermediate results. The benefits of treatment should be considered in relation to product costs and availability. This trial was registered at clinicaltrials.gov as NCT01015950. *Am J Clin Nutr* 2015; 101:632–45.

Keywords CSB++, locally milled flours, Misola, moderate acute malnutrition, Supplementary Plumpy

INTRODUCTION

Acute malnutrition, defined as low weight-for-height *z* score (WHZ)[6] and/or low midupper arm circumference (MUAC), is a leading cause of death and disability in young children worldwide. Severe acute malnutrition (WHZ <−3) is associated with a 9-fold increased mortality risk, and moderate acute malnutrition (MAM, defined as WHZ <−2 and ≥−3) is associated with a 3-fold increased mortality risk (1, 2). The 2013 *Lancet* series on maternal and child undernutrition (1) reported that in 2011, 52 million children aged <5 y had a WHZ <−2; of these, 33 million had MAM (1), making this the single most important risk factor associated with preventable deaths. A recent UNICEF Humanitarian Action for Children report estimated

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[6]Abbreviations used: AGP, α_1-acid glycoprotein; BIS, body iron stores; CRP, C-reactive protein; CSB, corn-soy blend; CSB++, corn-soy blend "plus-plus"; CSCom, community health center; CMAM, community-based management of acute malnutrition; HFIAS, Household Food Insecurity Access Scale; ID, iron deficiency; IDA, iron deficiency anemia; LAZ, length-for-age *z* score; LMF, locally milled flours; MAM, moderate acute malnutrition; MOH, Malian Ministry of Health; MUAC, mid-upper arm circumference; NCHS, National Center for Health Statistics; pTfR, plasma transferrin receptor; RBP, retinol binding protein; RUSF, ready-to-use supplementary food; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; TfR, transferrin receptor; VAD, vitamin A deficiency; WHZ, weight-for-height *z* score; WLZ, weight-for-length *z* score.

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that 450,000 Malian children aged <5 y had MAM in 2013, and this number was likely to increase in 2014 (3).

Community-based management of acute malnutrition (CMAM) is a comprehensive system for the screening, triage, and treatment of children with different degrees of acute malnutrition in the community setting (4). According to existing national CMAM protocols in several Sahelian countries, including Mali (5), children with acute malnutrition should be treated with special milk-based formulas, ready-to-use lipid-based supplements, or other food blends, along with dietary counseling and appropriate medicines, either as inpatients or outpatients, depending on the severity of acute malnutrition and whether clinical complications are present (6, 7). In Mali, children with MAM are generally treated as outpatients, using appropriate medicines and either processed food blends, such as a fortified corn-soy blend (CSB), when these products are available, or dietary counseling on the use of enhanced, home-available, cereal-legume mixtures (*farines enrichies*) and a complex of minerals and vitamins.

Recently developed approaches using processed food mixtures, such as lipid-based nutrient supplements and improved formulations of cereal-legume blends, are being advocated for several reasons (4, 8). First, the lipid-based products are recommended because of the success achieved with lipid-based, ready-to-use therapeutic food (RUTF) for the treatment of acutely malnourished children compared with milk-based formulas (9) and cereal-legume blends (10, 11). Second, improved cereal-legume blends are being promoted because newer formulations with enhanced nutrient density and reduced contents of anti-nutritional factors, such as phytates, antitrypsins, lectins, and hemagglutinins, are now available (12). Finally, because families with severe food insecurity may not be able to provide a sufficient quantity of food to meet current recommendations for home-prepared dietary regimens, especially during the food-scarce, preharvest season (13), it may be necessary for CMAM programs to provide food supplements rather than rely on home preparation of therapeutic diets.

To assist with decision making on these dietary treatment options, we conducted a cluster-randomized, community-based effectiveness trial to compare the impact of 4 different forms of dietary supplements among children with MAM. The major objectives of the study were to assess the impact of these dietary supplements on *1*) continued participation in the nutritional rehabilitation program and *2*) the children's physical growth, recovery from MAM, and change in micronutrient status.

METHODS

Study design

The study was designed as a cluster-randomized, community-based effectiveness trial, with partial crossover of treatment assignments midway through the study, as explained below. Because of the different physical nature of the dietary supplements and product-specific counseling on their preparation and serving methods, the study was not masked.

Study setting and trial participants

The study was conducted in the Dioila Health District, which is located 170 km southeast of Bamako, the capital of Mali, and covers an area of 12,794 km^2 (4940 square miles). The estimated total population of the district in 2009 was 488,937, of whom ~10% were children 6–35 mo of age (14). According to the Malian national protocol, children up to 5 y of age are eligible to receive treatment of acute malnutrition, but a more restricted age range was used for this study, both to limit the variability in expected growth responses and to focus on the younger children who might be more sensitive to different dietary regimens. Moreover, in Mali, the prevalence of wasting is greatest within the 6- to 35-mo age bracket.

The Dioila Health District has one district hospital, 20 community health centers or Centres de Santé Communautaire (CSComs), and 214 villages. The study was based in 12 of these CSComs and their surrounding communities, which were selected based on their accessibility, population size, and history of collaboration with external projects. In particular, the closest communities located within 15 km of the respective CSComs and containing a total population size >4000 individuals (~400 children 6–35 mo of age) were selected for censusing and inclusion in bimonthly screening for acute malnutrition.

Children in the selected communities who were potentially eligible to participate in the study were identified during a baseline census, which was updated bimonthly. The children's ages were ascertained from the date of birth on their health cards or by using a standardized local events calendar when the health card was not available. Children were then referred for possible enrollment into the treatment study if they met the study enrollment criteria, as described below.

Sample size

The sample size estimate was based on an assumed rate of recovery from MAM and the difference in recovery rate that was deemed sufficiently important to motivate a change in current treatment policies. Because we did not have reliable information on current rates of recovery from MAM in Mali, we conservatively assumed a 50% recovery rate. We also assumed that an important detectable difference to motivate policy change would be 20 percentage points (i.e., a recovery rate of >70% or <30% compared with the assumed current rate of 50%). On this basis, the necessary sample size was 138 per group, with a possibility of type I error of 0.05 and type II error of 1–0.80. To account for the cluster sampling design, this number was multiplied by 1.5, assuming a minimal degree of intracluster correlation of major outcomes. The final sample size estimate of 207 per group was rounded up to 210 per group for a total sample size of 840. Because we enrolled children by using 2 different sets of enrollment criteria, as described below, we further inflated the sample size by 50% to allow for separate analyses of children admitted to the study by using each of the 2 sets of entry criteria, resulting in a final sample size of 1260.

A subset of the children were selected for biochemical analyses. To detect a difference in effect size of 0.5 SD units in biochemical outcomes by treatment group, we estimated a sample size of 89 per group for the biochemistry subgroup. We inflated this by 15% to account for possible attrition or failure to obtain an adequate blood sample, resulting in a final sample size of 102 per group and a total sample size of 408 for the biochemical outcomes.

Screening for acute malnutrition

A total of 5 bimonthly community-based screening sessions were conducted from May 2010 through May 2011 to identify

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potentially eligible children with MAM. All children who were screened received an identification card, whereas children identified as having MAM during screening were given a referral card and asked to report to the nearest CSCom the following day for reassessment and possible enrollment into the treatment study. Children were identified as having MAM by using 2 sets of criteria (15). The first set of criteria was based on the 2006 WHO Growth Standards (16) [weight-for-length z score (WLZ) <-2 and ≥-3 or MUAC <12.5 cm and ≥11.5 cm]. The second set of entry criteria was based on the national norms that were being used in Mali at the time of the study [WLZ $<80\%$ and $\geq70\%$ of the National Center for Health Statistics (NCHS) median or MUAC <12.0 and ≥11.0 cm] (5). All children meeting one of these sets of criteria and without edema were referred to the CSCom for possible study enrollment. Children who were confirmed as fulfilling one of the entry criteria during this second clinic-based assessment were invited to participate in the treatment study if a parent provided written, informed consent. Children were excluded if they had severe anemia (hemoglobin <50 g/L); severe acute malnutrition (WLZ <-3 or MUAC <11.5 or $<70\%$ NCHS median); other acute illnesses requiring inpatient treatment; congenital abnormalities or underlying chronic diseases, including known HIV infection that might interfere with nutritional recovery; or a history of allergy to peanuts or previous serious allergic reactions to any substance and requiring emergency medical care. The children with severe malnutrition and hemoglobin <50 g/L were referred immediately for treatment at the local district hospital.

Informed consent

Caretakers of all potential participants received information about the study during their enrollment visit, and those who were willing to let their child participate provided signed consent. The trial was approved by the Nutrition Division of the Malian Ministry of Health (MOH) and the Ethical Review Committees of the Faculty of Medicine of the University of Bamako; the University of California, Davis; and Boston University. The trial was registered at www.clinicaltrials.gov as NCT01015950.

Randomization

Children were assigned to a treatment group according to the CSCom of their catchment area. The 12 CSComs included in the study were first stratified according to their distance from the main village of Dioila and the number of communities within 15 km that were needed to reach >800 households (a proxy for population density). CSComs were then randomly assigned to one of 4 dietary interventions within each stratum at the beginning of the study, and they were randomly reassigned, within stratum, to a different dietary group after the first 3 rounds of screening. Thus, a total of 6 CSComs were assigned to each of the 4 treatment groups over the course of the study. All study children reporting to a particular CSCom during a given round received the same dietary supplement.

Treatment protocol

Children were treated according to the current Malian national CMAM protocol (5), which was based on international treatment guidelines (17, 18). In particular, all children received a high-dose vitamin A capsule (100,000 IU for children 6–11 mo of age and 200,000 IU for children 12–35 mo of age) if they had not received one in the previous 3 mo; antihelminthic treatment (200 mg albendazole for children 12–23 mo of age and 400 mg albendazole for children 24–35 mo of age); specific ambulatory treatment, as required, for malaria or other acute infections; and one of the 4 randomly assigned dietary supplements. The dietary supplements were distributed during scheduled weekly or biweekly clinic visits over a period of 12 wk. Each supplement was supplied in an amount to provide 500 kcal/d, which was to be consumed in addition to the usual home diet.

The specific food supplements provided were: *1*) ready-to-use supplementary food (RUSF; supplied by Nutriset): a lipid-based RUSF (Supplementary Plumpy) containing peanut paste, sugar, vegetable oil, whey and soy protein isolates, maltodextrin and cocoa flavoring, and a vitamin-mineral complex; 2) corn-soy blend "plus plus" (CSB++; supplied by the World Food Program), a specially formulated refined cereal-legume-milk blend for children with MAM, which contains dehulled soybean flour, maize flour, dried skimmed milk, soy, sugar, soya oil, and a micronutrient premix designed for the treatment of moderate acutely malnourished children; *3*) Misola (supplied by Misola, Mali), a less-refined micronutrient-fortified cereal-legume blend, containing 60% millet or maize flour, 20% soy flour, 10% peanut flour, micronutrient premix, and amylase powder (19); or *4*) a less-refined cereal-legume milled flour mix (LMF), a mixture of home-available foods, including millet (605 g/kg food mixture), beans (273 g/kg), sugar (32 g/kg), and oil (90 g), as is currently recommended by the Malian national CMAM protocol when specially processed foods are not available. The last 2 products, Misola and LMF, are produced locally in Mali. The millet and beans were toasted, dehulled, ground, and mixed with sugar at a local production facility under project supervision to facilitate distribution to the families. On the day of distribution, 910 g LMF was mixed with 90 g vitamin A–fortified oil and repackaged in the same bag. In addition, multiple micronutrient powder sachets (Mixme, supplied by DSM) were given to the LMF group in accordance with the Malian national treatment protocol.

The RUSF was supplied in 92-g sachets for daily use; 7 sachets/wk were provided. The CSB++, Misola, and LMF were packaged in 1-kg bags; one bag of supplement/wk was given. The Mixme was packaged in 1-g sachets, and 5 sachets/wk were provided.

The composition of the supplements is presented in **Table 1**. Based on figures provided by the respective assistance agencies, the estimated local costs (in US dollars) of daily rations of the respective products, including any international shipping and local transport costs in Mali, are approximately \$0.38 for 92 g RUSF, \$0.22 for 127 g CSB++, \$0.21 for 125 g Misola, and \$0.18 for 129 g LMF. The daily cost of the multiple micronutrient powder alone (if home foods were provided by the family instead of the study) would be \$0.035.

Measurements

At enrollment, information was collected on selected indicators of household socioeconomic and demographic background (parental education, religion, language, housing type, water source, type of cooking fuel, and material possessions).

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TABLE 1
Nutrient contents per daily ration of supplements provided to children with moderate acute malnutrition[1]

	Supplement					WHO recommendation
Nutrient	RUSF	CSB++	MI	LMF	MNP	2008
Dry mass, g	92.0	127.0	125.0	129.0	1	NA
Energy, kcal	500	501	500	500	0	500
Protein, g	12.5	18.4	18.5	15.5	0	13.0
Fat, g	32.9	11.6	14.2	14.1	0	NA
Carbohydrate, g	38.5	83.8	74.6	77.8	0	NA
Calcium, mg	276	948	480	49	0	420
Iron,[2] mg	10.6[a]	13.5[b]	20.0[c]	7.0	10[d]	9.0
Magnesium, mg	85	169	125	72	0	150
Phosphorus, mg	276	660	400	383	0	450
Potassium, mg	1022	1270	530	507	0	800
Zinc, mg	12.9	9.5	12.6	2.5	4.1	10.0
Copper, μg	160	579	700	NA	560	445
Selenium, μg	27.6	19.0	33.0	NA	0	27.5
Iodine, μg	92	51	NA	90	90	100
Vitamin A, μgRAE	840	800	576	115	400	950
Riboflavin, mg	1.7	1.1	0.9	0.2	0.5	0.9
Niacin, mg	4.9	9.5	7.9	1.8	6	9.0
Vitamin B-6, mg	0.6	2.8	0.9	0.3	0.5	0.9
Folate, total, μgDFE	193	152	60	216	150	175
Vitamin B-12, μg	1.7	2.9	0.6	NA	0.9	15.0
Vitamin C, mg	49	129	50	NA	30	50
Vitamin D, IU	600	287	NA	NA	200	220
Vitamin E, mg	18.4	11.0	NA	NA	5	11.0
Vitamin K, μg	19.3	143.0	NA	NA	0	20.0

[1]CSB++, corn-soy blend "plus plus" (for malnourished children); DFE, dietary folate equivalent; LMF, locally milled flours; MI, Misola; MNP, micronutrient powder; NA, not available; RAE, retinol activity equivalent; RUSF, ready-to-use supplementary food. Nutrient composition for RUSF and CSB++ supplied from manufacturers; MI and LMF calculated from USDA and Malian food databases.

[2]Iron type: a) ferrous sulfate, b) ferrous fumarate, c) electrolytic iron, and d) sodium iron ethylenediaminetetraacetate.

Information on household food security was obtained by using the standardized Household Food Insecurity Access Scale (HFIAS) questionnaire (20); households with HFIAS scores <4 were considered food insecure. At each scheduled follow-up visit (1, 2, 3, 4, 6, 8, 10, and 12 wk later), adherence to the treatment protocol was assessed, children were reexamined, and their weight, length, and MUAC were remeasured. To assess adherence, the child caregivers were requested to return the unused food supplements and/or any empty packages during each scheduled clinic visit. Returned packages were weighed to 1 g as an indirect assessment of compliance to the dietary protocol, but it was not possible to determine what proportion of the ration the index child actually consumed. Home visits were also scheduled among a subset of children (n = 167) to observe inconspicuously how the food supplements were being used. For these home observations, the families were told that a fieldworker would spend 8 h in the home to assess the children's physical activity in response to treatment. During these activity assessments, all episodes of consumption of the study products were observed, and the amounts that were prepared, served, and consumed were estimated by the data collector, who also noted which person(s) in the household actually consumed the food.

During each follow-up clinic visit, the child's weight was measured to the nearest 20 g with the Seca 383 electronic baby and child scale (Seca), length was measured to the nearest 0.1 cm with a Shorr Board (Shorr Productions), and MUAC was measured to the nearest 0.1 cm with a Shakir Strip (UNICEF Supply Division). All children identified as having severe acute malnutrition (SAM; based on MOH criteria) with complications were referred immediately for treatment at the district hospital. If children missed the scheduled clinic appointments at 4, 8, or 12 wk, a fieldworker visited the home to determine the reason for this absence and to encourage continued participation; however, no treatments were provided at the home. All anthropometrists were trained and standardized at the beginning of the study and on 3 more occasions during the study. During standardization exercises completed every 3 mo, the mean intra- and interindividual technical errors of measurement for length were 0.62 cm and 0.22 cm, respectively (CV: 0.28% and 0.80% respectively). For MUAC, mean intra- and interindividual technical errors of measurement were 0.19 cm and 0.13 cm, respectively (CV: 0.93% and 1.41%, respectively).

Capillary blood hemoglobin concentration was measured in all children at baseline and after 12 wk of treatment. Malaria was assessed at baseline by using a rapid diagnostic test; those children who tested positive were managed according to national treatment guidelines with artemether-lumefantrine (Co-Artem; Novartis). Plasma ferritin, soluble transferrin receptor (TfR), retinol binding protein (RBP), C-reactive protein (CRP), α_1-acid glycoprotein (AGP), and zinc concentrations were measured in venous blood obtained from a subset of children at baseline and at the end of 12 wk of treatment. Blood samples were collected

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by trained phlebotomists by using trace element–free S-Monovette Li-Heparin syringes (Sarstedt Monovette) and were stored at 4°C until plasma was separated later in the day at the study laboratory in Dioila. Plasma was separated into aliquots into sterile microtubes (Sarstedt Monovette) and stored at −30°C before shipping to external collaborating laboratories for analysis.

Hemoglobin was analyzed by using HemoCue portable photometers calibrated daily (HemoCue Inc.). Anemia was defined as whole-blood hemoglobin concentration <110 g/L (21). Plasma ferritin, TfR, RBP, CRP, and AGP were analyzed by sandwich ELISA (22). Plasma zinc concentrations were analyzed by inductively coupled plasma–optical emission spectrophotometry (Vista; Varian Inc.) at the Children's Hospital of Oakland Research Institute (Oakland, CA) (23). All samples were coded and analyzed in the laboratory without knowledge of the subjects' study group. Each analysis was completed in duplicate, and mean values were used. The CVs of each of these biomarkers were <5% during repeated analyses of a pooled plasma sample.

Adjusted plasma ferritin concentration <12 ng/L was considered to reflect depleted iron stores (24), and plasma TfR (pTfR) >8.3 mg/L was defined as tissue iron deficiency (ID) (25). Iron deficiency anemia (IDA) was defined as the presence of low adjusted plasma ferritin concentration (<12 μg/L) and anemia (25). Body iron stores (BIS) were calculated by using the formula of Cook and colleagues (26): BIS (mg/kg) = $-[\log_{10}(\text{transferrin receptor} \times 1000 \div \text{ferritin}) - 2.8229] \div 0.1207$. Low BIS was defined as <0 mg/kg. Adjusted plasma RBP concentration <0.83 mmol/L was considered to reflect vitamin A deficiency (VAD) (27, 28). Adjusted plasma zinc concentration <65 μg/dL was considered to reflect zinc deficiency (29). Thresholds for elevated acute phase proteins were CRP >5 mg/L and AGP >1 g/L (30, 31). Plasma ferritin, pTfR, RBP, and zinc concentrations were adjusted for the presence of inflammation and stage of infection, as recommended by Thurnham (32) and described in detail in Statistical analysis.

Statistical analysis

All data collection forms were reviewed by the field supervisors for accuracy and completeness and then transferred to the field office in Dioila for double data entry into a Microsoft Access database. Range and consistency checks were used to assess data quality before final analysis by using STATA 12 (StataCorp LP) and SAS 9.3 (SAS Institute). Continuous outcome variables were examined for conformance to the normal (Gaussian) distribution, and variables were transformed as appropriate. Anthropometric indexes were calculated based on the 2006 WHO Child Growth Standards (15). Sustained recovery from MAM was defined as WLZ >−2.0 and MUAC >12.5 cm during at least 2 consecutive follow-up visits. Recovery rates were compared by treatment group by using the Kaplan-Meier (log rank) test. Adjusted plasma ferritin, pTfR, and RBP are reported as geometric means (95% CIs). To adjust for the effect of inflammation on iron, vitamin A, and zinc biomarkers, the results were divided into 4 groups based on "stage of infection" categories, according to the presence of one or more elevated acute phase proteins: *1*) noninfected reference group (CRP <5 mg/L and AGP <1 g/L), *2*) incubation (CRP >5 mg/L and AGP <1 g/L), *3*) early convalescence (CRP >5 mg/L and AGP >1 g/L), and *4*) late convalescence (CRP <5 mg/L and AGP >1 g/L). For biomarkers in which concentrations are increased in the presence of elevated acute phase proteins (i.e., ferritin, serum TfR), correction factors for stage of infection were calculated by using the ratios of geometric means of the micronutrient status indicators for each stage of infection category divided by the noninfected reference category. Conversely, for biomarkers in which concentrations are decreased in the presence of elevated acute phase proteins (i.e., zinc, RBP), correction factors for stage of infection were calculated by using the ratios of geometric means of the noninfected reference category divided by the micronutrient status indicator for each stage of infection category. Adjusted biomarker concentrations were then calculated by multiplying each individual value by its biomarker-specific and category-specific correction factor (31, 32). The same-pooled correction factors were used at baseline and endline. Continuous variables were compared among intervention groups by using mixed models (PROC GLM), with treatment group as a fixed main effect and CSCom as a random effect. Baseline variables were used as covariates in the models to improve the power of the test and to reduce possible intracluster correlations. Categorical variables were analyzed by using generalized linear models procedures. Statistical significance was set at 0.05 for main effects and 0.10 for interactions. Because of the logistical challenges in implementing the study over a widely dispersed geographic area, we adopted a rolling enrollment scheme, which resulted in unequal enrollment numbers among groups in some months. Therefore, we developed 2 sets of statistical models, with and without adjustments for month of enrollment. The possible modifying effect of household food security status on treatment response was tested by including the food security category as a fixed effect in all statistical models.

RESULTS

A total of 1264 children 6–35 mo of age (mean ± SD: 14.9 ± 6.2 mo) were enrolled (**Figure 1**). Of these, 969 satisfied enrollment criteria according to the current WHO recommendations for diagnosis of MAM, 701 fulfilled the criteria used by the MOH national CMAM program, and 465 children fulfilled both criteria. Of the children admitted to the study as having MAM according to the MOH definition, 236 fulfilled WHO criteria for SAM but were treated as having MAM in the current study. A total of 59 children who were originally screened as having MAM in the community no longer met the diagnostic criteria at the time of the clinic-based examination, but these children were nevertheless enrolled in the study, treated as having MAM, and included in the analysis. Removing these children from the analysis did not change any of the study outcomes. Among all children meeting WHO enrollment criteria, 35% were identified on the basis of MUAC only, 11% were identified based on weight-for-length only, and 54% were identified based on both MUAC and weight-for-length. Among children meeting the Malian MOH CMAM criteria, the respective percentages were 41%, 27%, and 32%.

The baseline characteristics of the children's households are presented by study group in **Table 2**. In general, the children originated from agricultural households, with a low rate of literacy, meager household possessions, and poor housing quality and sanitary infrastructure. More than a third of the households

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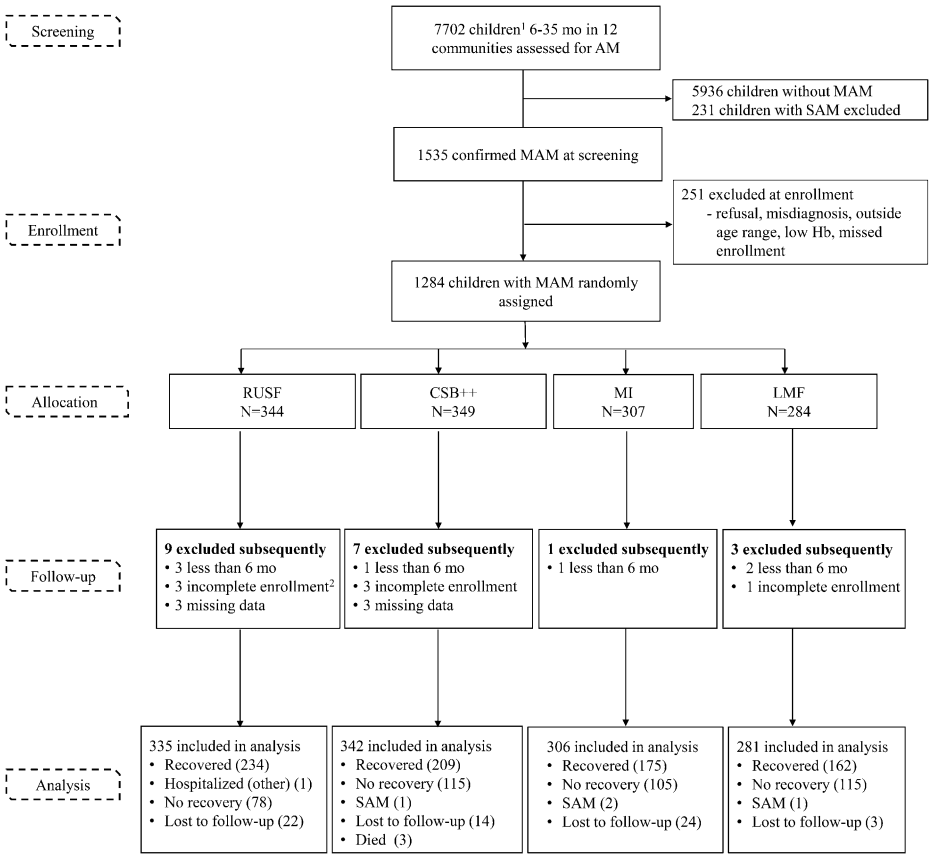

FIGURE 1 Study profile. [1]This number includes children who were screened in subsequent rounds if they were not identified as having MAM in the previous screening. [2]Incomplete enrollment: attended only one of 2 enrollment days. AM, acute malnutrition; CSB++, corn-soy blend "plus plus"; Hb, hemoglobin; LMF, locally milled flours + micronutrient powder; MAM, moderate acute malnutrition; MI, Misola; RUSF, ready-to-use supplementary food; SAM, severe acute malnutrition.

were reportedly food insecure (HFIAS category <4) at the time of the children's enrollment. Because the community-based screening sessions were staggered during each round of enrollment, and the prevalence of MAM varied across communities, the number of children enrolled in each treatment group differed by month of study ($P < 0.001$; **Supplemental Table 1**).

At the time of enrollment, the children's overall mean WLZ was -2.24 ± 0.72, mean MUAC was 12.0 ± 0.5 cm, and mean length-for-age *z* score (LAZ) was -2.34 ± 1.35 (**Table 3**); these measurements did not differ by study group except for MUAC, which was slightly lower among children in the RUSF group compared with those in the other 3 groups. Of the 1264 children originally enrolled, 1175 (93.3%) completed the full 12 wk of treatment and scheduled observations. The overall decline in participation did not differ by study group ($P > 0.05$; **Supplemental Figure 1**), but children in the LMF group were more likely to attend the scheduled visits at weeks 10 and 12 than those in the other groups ($P < 0.05$). The children's caregivers returned the unused food supplements or empty packages, as requested, on 92% of the follow-up clinic visits; the percentage of caregivers who returned the supplements did not differ by study group. Among those who returned the unused supplements or empty packages, 93.2% ± 16.2% of the allocated amount of supplement disappeared among those in the RUSF group, 83.1% ± 18.1% in the CSB++ group, 84.9% ± 17.5% in the Misola group, and 83.0% ± 18.4% in the LMF group ($P < 0.001$). The supplement disappearance rate was significantly greater for the RUSF group than for the other 3 groups ($P < 0.001$) (**Figure 2**).

Home observations were scheduled within 1–4 d of the last weekly clinic visit or within 6–9 d of the last biweekly clinic visit. Because of logistical constraints related to availability of transportation and seasonally inaccessible roads, there were different numbers of home observations in the 4 treatment groups. Therefore, the results have been used only for qualitative assessment of supplement use rather than for statistical comparisons of treatment groups (**Table 4**). During the 8 h of in-home observation (n = 164), >70% of mothers in all groups breastfed the study child at least once, and the study supplement was prepared and/or served at least once on 66% of observation days. The person who prepared the cereal-based supplements spent an average of 11–15 min to prepare the products. Most of these cereal-based supplements were mixed with water before preparation (>92%), but a few children (8%) were fed the CSB++ as a dry powder. The supplements were usually prepared once a day, but most children consumed them in 2 separate feeding sessions. The supplements were served alone most of the time (~82% of servings) or occasionally mixed with another food item. The supplement was served mainly by the mother (>60%) or self-fed by the child (25%). Notably, the supplement was almost always consumed by the study child (>94% of observation days) and was shared with other children during fewer than 4% of home visits. Home visits were completed in RUSF

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TABLE 2
Household SES and food security at baseline by treatment group[1]

Characteristic	Treatment group			
	RUSF (n = 335)	CSB++ (n = 342)	MI (n = 306)	LMF (n = 281)
No. of children for whom complete baseline characteristic data were available	332	338	301	280
Profession of household head				
Farming	256 (77.1)	304 (89.9)	223 (74.8)	231 (82.5)
Unskilled labor	44 (13.3)	16 (4.7)	34 (11.3)	21 (7.)
Business owner	9 (2.7)	6 (1.8)	10 (3.3)	7 (2.5)
Technical/skilled labor	18 (5.4)	6 (1.8)	24 (7.9)	13 (4.6)
Government worker/teacher/student	5 (1.5)	6 (1.8)	10 (3.3)	8 (2.9)
Educational level of household head				
None	175 (52.7)	194 (57.4)	174 (57.8)	168 (60.0)
Completed primary school	41 (12.3)	52 (15.4)	39 (13.0)	41 (14.6)
Some secondary school	14 (4.2)	18 (5.3)	12 (4.)	16 (5.7)
Senior high complete/university	2 (0.6)	2 (0.6)	5 (1.7)	1 (0.4)
Islamic school	63 (19.0)	37 (10.9)	37 (12.3)	21 (7.5)
Don't know	37 (11.1)	35 (10.4)	34 (11.3)	33 (11.8)
Educational level of mother				
None	293 (88.3)	285 (84.3)	246 (81.7)	244 (87.1)
Completed primary school	26 (7.8)	40 (11.8)	35 (11.6)	30 (10.7)
Some secondary school	2 (0.6)	7 (2.1)	7 (2.3)	3 (1.1)
Senior high complete/university	0	0	2 (0.7)	0
Islamic school	11 (3.3)	6 (1.8)	11 (3.7)	3 (1.1)
Primary light source				
Electricity (national grid)	24 (7.2)	12 (3.6)	5 (1.7)	28 (10.0)
Kerosene	44 (13.3)	70 (20.7)	29 (9.6)	24 (8.6)
Torch light	190 (57.2)	201 (59.5)	212 (70.4)	208 (74.3)
Traditional oil lamp	12 (3.6)	11 (3.3)	7 (2.3)	4 (1.4)
Battery-operated power	45 (13.8)	36 (10.7)	40 (13.3)	12 (4.3)
Other	17 (5.1)	8 (2.4)	8 (2.7)	4 (1.4)
Type of toilet facility				
Pit latrine without slab/open	108 (32.5)	81 (24.0)	78 (25.9)	77 (27.5)
Bucket/pan	217 (65.3)	248 (73.4)	205 (68.1)	197 (70.4)
None	7 (2.1)	9 (2.7)	18 (6.0))	6 (2.2)
Food security status,[2] n	334	341	300	281
Food insecure	152 (45.5)	126 (37.0)	108 (36.0)	115 (40.9)

[1]Values are n (%) unless otherwise indicated. Incomplete SES data are not included. CSB++, corn-soy blend "plus plus"; LMF, locally milled flours + micronutrient powder; MI, Misola; RUSF, ready-to-use supplementary food; SES, socioeconomic status.
[2]Food security status based on Household Food Insecurity Access Score. See text for definitions.

households on just 18 occasions, and the RUSF was served during 16 (89%) of these home visits. Caregivers tended to serve a greater proportion of the recommended amount of RUSF compared with the other supplements.

The children's mean weight, MUAC, length, WLZ, and LAZ, adjusted for baseline values, are shown by week of treatment in **Figures 3–5**. All groups showed increases in mean weight and length and adequate recovery of WLZ and MUAC, but not LAZ, over the 12-wk treatment period. The mean changes in anthropometric data were compared by treatment group after adjusting for cluster, household food security status, and initial anthropometric value, or for these same variables and month of enrollment. According to the first model (**Supplemental Table 2**), the adjusted mean change in weight from baseline to week 12 was greater with RUSF than with the other 3 regimens ($P < 0.001$), which did not differ from each other. When enrollment month was also included in the model (**Table 5**), the adjusted mean change in weight remained greater for the RUSF group than for the Misola and LMF groups. However, RUSF was no longer significantly different from CSB++, which did not differ from Misola but did differ from LMF ($P = 0.017$). For MUAC and WLZ changes, the groups followed similar patterns as described for weight, although CSB++ did not differ significantly from RUSF, Misola, or LMF in the models that adjusted for month of enrollment along with the other variables.

The overall mean length gain was 2.8 ± 1.3 cm, and there were no significant groupwise differences in linear growth when just cluster, food security status, and initial length were included in the model. However, when month of enrollment was also considered, children in the RUSF and CSB++ groups had greater linear growth than did those in the LMF group. Household food security status was unrelated to the children's growth outcomes and did not modify the growth responses to treatment.

Four children developed SAM with complications (edema or systemic infection) and were hospitalized during the study. Of these, 2 were in the Misola group and one each in the CSB++ and LMF groups ($P = 0.87$, Fisher exact test). An additional 103 developed SAM without complications and were continued in the study protocol. There were no significant groupwise differences in the number of children who developed SAM ($P = 0.80$).

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TABLE 3
Baseline characteristics of enrolled subjects, by treatment group[1]

Characteristic	Treatment group			
	RUSF (n = 335)	CSB++ (n = 342)	MI (n = 306)	LMF (n = 281)
Female sex, % (95% CI)	50.2 (44.8, 55.5)	51.2 (45.9, 56.5)	56.6 (51.0, 56.5)	52.0 (46.1, 57.8)
Age, mo	15.0 ± 6.9[2]	14.7 ± 7.2	15.4 ± 6.9	14.5 ± 6.6
MUAC, cm	11.9 ± 0.5[a]	12.0 ± 0.6[b]	12.0 ± 0.6[b]	12.0 ± 0.5[b]
Weight, kg	7.00 ± 1.07	6.99 ± 1.09	7.08 ± 1.09	7.05 ± 1.04
Length, cm	70.8 ± 5.7	70.8 ± 6.0	71.4 ± 5.7	71.0 ± 5.6
WLZ	−2.22 ± 0.69	−2.26 ± 0.74	−2.26 ± 0.72	−2.33 ± 0.72
LAZ	−2.49 ± 1.31	−2.30 ± 1.47	−2.34 ± 1.30	−2.21 ± 1.28
Malaria, % (95% CI) positive	62.3 (57.5, 69.0)	48.3 (42.9, 53.8)	49.2 (49.2, 55.5)	58.1 (51.4, 62.8)

[1]Values with the same superscript letter are not significantly different from each other (Scheffé test, $P > 0.05$). CSB++, corn-soy blend "plus plus"; LAZ, length-for-age z score; LMF, locally milled flours + micronutrient powder; MI, Misola; MUAC, mid-upper arm circumference; RUSF, ready-to-use supplementary food; WLZ, weight-for-length z score.
[2]Mean ± SD (all such values).

Of those who developed SAM, 11 still had SAM at the time of the week 12 visit.

Sustained recovery from MAM, defined as WLZ >-2.0 and MUAC >12.5 cm for ≥ 2 follow-up visits, was highest among children in the RUSF group compared with the 3 other regimens (73.1% for RUSF, 61.2% for CSB++, 61.1% for MI, and 57.9% for LMF, $P < 0.0001$; **Figure 6**). A total of 487 observations were treated as censored in the survival analysis of time to recovery; of these, 413 had not recovered by week 12, and 63 left the study earlier without recovery and are reported as lost to follow-up. The median (95% CI) time required for sustained recovery was 5.9 (4.9, 7.0), 6.5 (5.6, 8.9), 8.7 (7.0, 10.4), and 9.7 (8.1, 11.8) wk for RUSF, CSB++, Misola, and LMF, respectively, with RUSF significantly different from the Misola and LMF groups ($P < 0.001$) but not different from the CSB++ group ($P = 0.06$). Children who were enrolled in the study by using entry criteria based only on NCHS reference data were more undernourished and younger than those who were enrolled using the WHO standards, and the former required a longer period of time to achieve sustained recovery (**Supplemental Table 3**). Applying less stringent criteria for recovery—namely, surpassing both the W/L and MUAC criteria on one occasion only—the recovery rates followed the same pattern as described above, and the median (95% CI) time to recovery was 3.8 (3.2, 4.6), 4.3 (3.7, 5.5), 5.7 (4.3, 7.1), and 5.0 (3.6, 6.4) for the respective treatment groups ($P < 0.001$).

We also explored the effect of excluding from analysis children who fulfilled WHO criteria for SAM but were treated for MAM in the current trial to explore whether the inclusion of these children affected the responses to dietary supplementation. There were no significant interactions between the severity of acute malnutrition (MAM or SAM) and treatment group for any of the growth or recovery outcomes. The overall magnitude of effects and rank order of effects remained unchanged, and all treatment outcomes remained statistically significant.

Among children included in the biochemistry subset, 84% had evidence of systemic inflammation (elevated CRP or AGP) at the beginning and 88% at the end of treatment, so it was necessary to adjust the micronutrient biomarkers for the presence of inflammation. The percentage of children with evidence of inflammation did not differ by treatment group at either stage of the study. Mean initial and final concentrations of blood hemoglobin and biomarkers of iron, vitamin A, and zinc status, adjusted for cluster, initial values, and month of enrollment, are shown in **Table 6**, along with the related prevalence of anemia, ID, IDA, VAD, and zinc deficiency. Approximately 90% of the children were anemic at enrollment, and there were no differences in anemia prevalence by study group. Children in all groups except the Misola group had increased mean final hemoglobin concentration compared with their respective baseline values, and the change in hemoglobin from baseline was significantly greater in the RUSF group than in the Misola group ($P = 0.015$). The final prevalence of anemia decreased slightly in the RUSF group but not in the other groups; the final prevalence of anemia remained high (>81%) in all groups.

The prevalence of low baseline plasma ferritin concentration (<12 μg/L after adjusting for inflammation) ranged from 31% to 39% initially and did not differ significantly by study group; 25–33% of the children had IDA, based on the presence of anemia and low adjusted plasma ferritin concentration. The geometric mean inflammation-adjusted plasma ferritin concentration decreased significantly during the study in the Misola group ($P < 0.001$) but did not change from baseline in the other groups. The final prevalence of ID (based on low adjusted

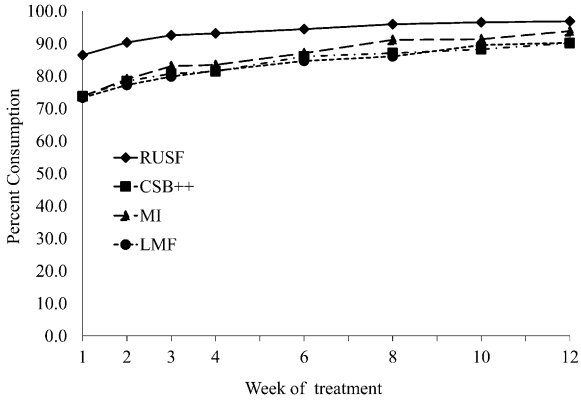

FIGURE 2 Mean consumption of study foods (based on returned packages), by week of treatment and treatment group. ANCOVA, $P < 0.001$. CSB++, corn-soy blend "plus plus"; LMF, locally milled flours + micronutrient powder; MI, Misola; RUSF, ready-to-use supplementary food.

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TABLE 4
Eight-hour home observation of the preparation and serving of study supplements[1]

Observation	Intervention group			
	RUSF	CSB++	MI	LMF
No. of observation days[2]	18	77	32	37
Supplement prepared during observation	—	52 (67.5)	22 (68.8)	19 (51.4)
Amount of supplement prepared (% of recommended amount)				
Recommended amount[3]	—	49 (94.1)	20 (91.4)	15 (78.9)
75% of recommended	—	3 (5.7)	2 (9.0)	1 (5.2)
50% of recommended	—	—	—	2 (10.5)
25% of recommended	—	—	—	1 (5.2)
Time spent preparing supplement, min	—	14.8 ± 8.7[4]	12.8 ± 7.4	10.8 ± 4.4
Supplement consumed during observation[5]	16 (88.9)	61 (79.2)	30 (93.8)	28 (75.7)
No. of supplement feeding episodes (among children fed at least once)	2.6 ± 1.2	1.8 ± 0.8	2.0 ± 0.8	1.9 ± 1.1
Person who consumed the prepared supplement[6]				
No one	1 (6.3)	—	—	—
Study child	15 (93.8)	61 (100)	30 (93.8)	27 (96.4)
Study child + other child	—	—	2 (6.2)	1 (3.6)

[1]Values are *n* (%) unless otherwise indicated. CSB++, corn-soy blend "plus plus"; LMF, locally milled flours + micronutrient powder; MI, Misola; RUSF, ready-to-use supplementary food.
[2]Each home was visited only once on observation days.
[3]Recommended daily amounts were 92 g for RUSF, 127 g for CSB++, 125 g for MI, and 129 g for LMF.
[4]Mean ± SD (all such values).
[5]Includes children for whom food preparation was not seen but prepared food was served.
[6]Does not include sessions where the observer was unable to estimate the amount of food consumed.

plasma ferritin concentration) was significantly lower among children in the RUSF and CSB++ groups than among those in the Misola group. The prevalence of IDA increased significantly in the Misola and LMF groups, both of which had a final prevalence approaching 50%, but the final prevalence of IDA did not change from baseline levels in the other 2 groups. The final prevalence of IDA was significantly less in the RUSF and CSB++ groups than in the Misola group.

The prevalence of elevated pTfR concentrations ranged from 68% to 80% initially, and 42–51% of the children had BIS <0. The mean adjusted final pTfR concentrations decreased significantly from baseline in the RUSF and LMF groups but not in the CSB++ and Misola groups, and the final adjusted mean pTfR concentration was significantly less in the RUSF group than in the other groups. The prevalence of elevated pTfR decreased during treatment in the RUSF group but not in the other groups, resulting in a lower final prevalence of elevated pTfR in the RUSF group compared with the CSB++ and Misola groups. The final adjusted mean BIS increased significantly compared with baseline in the RUSF group but decreased in the Misola group and did not change in the other groups; the percentage of children with BIS <0 at the end of the study was significantly less in the RUSF and CSB++ groups than in the Misola group. In summary, the RUSF group consistently performed better than the other groups with regard to final iron status indicators, the Misola group consistently performed worse, and the other groups were intermediate.

Slightly more than one-third of the children had low inflammation-adjusted plasma RBP concentrations initially, and the prevalence of VAD did not differ significantly by treatment group. Mean adjusted plasma RBP concentrations increased significantly and the proportion of low values decreased significantly in the Misola and LMF groups but not in the other groups. However, the adjusted final mean values and prevalence of VAD did not differ by treatment group.

More than one-third of the children had low plasma zinc concentrations initially (<65 μg/dL after adjusting for inflammation), but there were no groupwise differences in the mean values or prevalence of low values. The mean plasma zinc concentrations declined slightly in the Misola group following treatment, and the prevalence of low values increased slightly, but there were no time-related changes in the other groups and

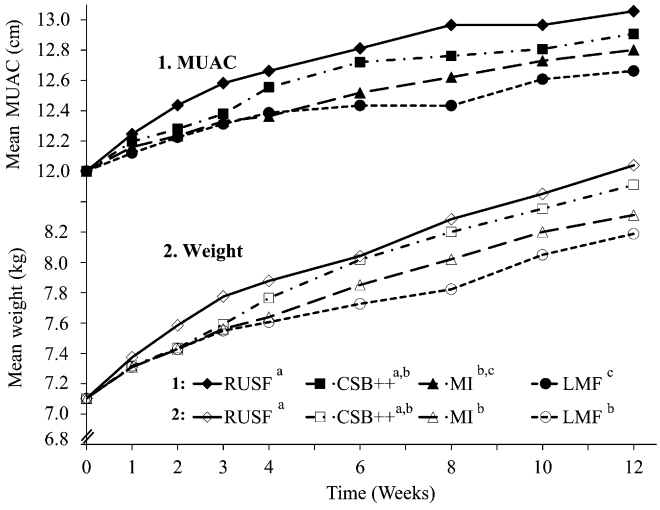

FIGURE 3 Mean MUAC and body weight by week of treatment and treatment group, adjusted for baseline values. ANCOVA, $P < 0.001$. Variability reported in tables. Supplements with the same letter are not significantly different from each other (repeated-measures ANOVA). Variability reported in tables. CSB++, corn-soy blend "plus plus"; LMF, locally milled flours + micronutrient powder; MI, Misola; MUAC, midupper are circumference; RUSF, ready-to-use supplementary food.

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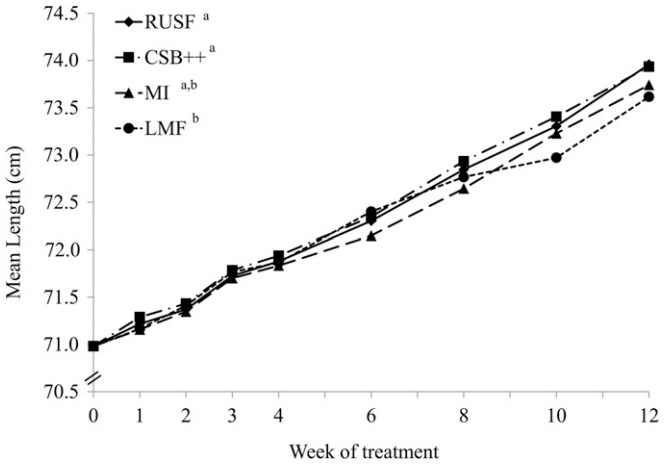

FIGURE 4 Mean length by week of treatment and treatment group adjusted for baseline values. ANCOVA, $P < 0.001$. Variability reported in tables. Supplements with the same letter are not significantly different from each other; repeated-measures ANOVA. Variability reported in tables. CSB++, corn-soy blend "plus plus"; LMF, locally milled flours + micronutrient powder; MI, Misola; RUSF, ready-to-use supplementary food.

no significant groupwise differences in either of these variables at either time point.

DISCUSSION

The results of this community-based intervention trial indicate that most caregivers of children with MAM voluntarily attended the scheduled weekly or biweekly follow-up clinic visits and fed their children the recommended dietary supplements. On average, children in all treatment groups increased their body weight, MUAC, and length during the 12-wk observation period, but children in the RUSF group gained more in terms of weight, MUAC, and WLZ than those in the Misola and LMF groups, which did not differ from each other. Results for children in the CSB++ group were generally intermediate between those for children who received RUSF and those for children who were given one of the 2 locally prepared cereal-legume mixtures. The term *locally prepared* is used to differentiate imported specialized products from those locally available in country. Children who received RUSF were more likely to achieve sustained recovery than those in the LMF group, and those in the RUSF group recovered sooner. Unlike the results for body mass accrual relative to reference standards, the children did not increase in LAZ during the course of treatment, possibly because a longer period of supplementation is needed or because stunted children are resistant to compensatory increases in linear growth, even with targeted treatment. The fidelity of our study results is supported by the randomized clinical trial research design, indirect assessments of adherence to the treatment protocol, and frequent standardization of the anthropometric measurements.

The reported period of greatest household food insecurity corresponded with the "hunger season" (April–October 2010) predicted by the Famine Early Warning System for Mali (33–35). However, reported household food security assessment did not modify the effect of dietary supplement group on recovery, possibly because children in all groups were provided with food supplements. On the other hand, younger children and those who were more wasted initially required more time to recover, as has been observed previously (36), and the groupwise differences seemed more pronounced in the younger and more undernourished children.

Although we were not able to achieve the desired number of home visits to complete quantitative comparisons of supplement consumption by treatment group, these visits confirmed that the supplements were consumed frequently, regardless of treatment group, and almost always by the study child. It is possible that children in the RUSF group received and used the supplement more frequently and consumed a greater proportion of the prescribed amount than did those in the other groups, but the limited amount of available information does not permit a definitive conclusion. The observation results imply, however, that RUSF is more convenient to administer, given that no further preparation is required, whereas caregivers spent an average of 11–15 min to prepare the daily servings of the cereal-based products.

Information is available from several previous randomized trials of the dietary treatment of children with MAM. Nackers et al. (10) examined the effects of 2 randomly assigned food supplements on weight gain and recovery of 451 children with MAM in Niger. One group of children received RUTF (Plumpy'Nut; Nutriset) to provide 1000 kcal/d, and the other group received conventional CSB to provide 1231 kcal/d. Children who received RUTF had higher rates of sustained recovery (79% compared with 64%; $P < 0.001$), and fewer of these children had to be referred for inpatient care (9% compared with 19%; $P < 0.003$).

Investigators in southern Ethiopia enrolled 1125 nonedematous children 6–60 mo of age with MUAC >110 and <135 mm and weight-for-height ≥70% and <80% of the NCHS median. Feeding centers in one district were assigned to receive an RUSF, to provide 500 kcal/d, and those in another district were assigned to receive conventional CSB and vegetable oil (1413 kcal/d, to include a household food-sharing ration). The recovery rate was slightly higher in RUSF centers than in CSB centers (73% compared with 67%; $P = 0.056$) (37).

Matilsky et al. (38) compared recovery rates among 1362 Malawian children 6–60 mo of age with moderate wasting. The

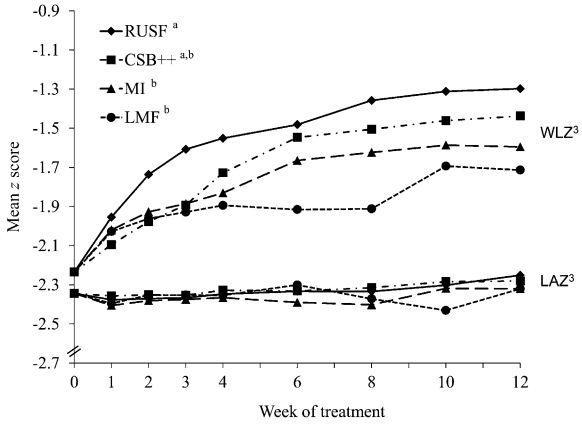

FIGURE 5 Mean WLZ and LAZ by week of treatment and treatment group adjusted for baseline values. ANCOVA, $P < 0.001$. Variability reported in tables. Supplements with the same letter are not significantly different from each other (only for LAZ); repeated-measures ANOVA. CSB++, corn-soy blend "plus plus"; LAZ, length-for-age z score; LMF, locally milled flours + micronutrient powder; MI, Misola; RUSF, ready-to-use supplementary food; WLZ, weight-for-length z score.

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TABLE 5
Changes in anthropometric measurements during 12 wk of treatment, by treatment group[1]

	Treatment group				
Characteristic	RUSF (n = 335)	CSB++ (n = 342)	MI (n = 306)	LMF (n = 281)	P value
Adjusted weight gain, kg	1.16 (1.08, 1.24)[a]	1.04 (0.96, 1.13)[a,b]	0.91 (0.82, 0.99)[b,c]	0.83 (0.74, 0.92)[c]	0.001
Adjusted length gain, cm	2.9 (2.8, 3.1)[a]	2.9 (2.8, 3.1)[a]	2.7 (2.5, 2.9)[a,b]	2.6 (2.4, 2.7)[b]	0.003
Adjusted WLZ gain	0.94 (0.82, 1.05)[a]	0.76 (0.64, 0.88)[a,b]	0.65 (0.53, 0.76)[b]	0.54 (0.43, 0.67)[b]	0.001
Adjusted MUAC gain, cm	1.1 (1.0, 1.2)[a]	0.9 (0.8, 1.0)[a,b]	0.8 (0.7, 0.9)[b]	0.7 (0.6, 0.8)[b]	0.001

[1]Values are adjusted means (95% CIs). Adjusted means with the same superscript letter are not significantly different from each other (Tukey-Kramer test, $P > 0.05$). Groups were compared by using ANCOVA models. Model adjusts for cluster site (community health clinic), baseline anthropometric characteristic (weight, length, MUAC, and WHZ), age, sex, food security status, and month of enrollment. CSB++, corn-soy blend "plus plus"; LMF, locally milled flours + micronutrient powder; MI, Misola; MUAC, midupper arm circumference; RUSF, ready-to-use supplementary food; WHZ, weight-for-height z score; WLZ, weight-for-length z score.

children received one of 3 different food supplements providing 75 kcal/kg body weight per day in addition to the usual home diet for as long as 8 wk until recovery. One group received a lipid-based RUSF containing a milk/peanut-fortified spread, the second group received a soy/peanut-fortified spread, and the third group received conventional CSB. Children who received either of the 2 lipid-based RUSFs gained more weight during the early phase of treatment and were more likely to recover within 8 wk than were those in the CSB group (80% compared with 72%, respectively; $P < 0.01$). There were no groupwise differences in linear growth during the period of observation.

In another, more recent study from Malawi, 2712 children with MAM received one of 2 different types of RUSF (locally produced soy RUSF or imported soy/whey RUSF) or the same specially formulated CSB++ that was used in the current study (39). All products were distributed in amounts to provide 75 kcal/kg body weight per day for up to 12 wk. The overall recovery rate of ~87% did not differ significantly by study group, but children who received soy/whey RUSF had slightly greater gains in weight and MUAC and were less likely to develop severe wasting (WLZ <-3) than those who received CSB++. The authors concluded that these minor differences in favor of soy/whey RUSF were not sufficient to justify the greater cost of the imported product.

In summary, 3 previous studies that compared a lipid-based RUTF or RUSF with conventional CSB found a slight advantage of RUSF with regard to weight gain and rate of recovery. By contrast, one study of RUSF compared with specially formulated CSB++ found no differences in recovery rates, although children who received RUSF had slightly greater weight gains. Although our study reported slightly lower recovery rates overall compared with the second Malawian study (using slightly different definitions of recovery), the findings of both studies are consistent, in that RUSF performed better than CSB++ in both cases, although the differences between RUSF and CSB++ were of small magnitude. The results of the current study suggest that this small advantage of RUSF may be amplified among younger and more undernourished children.

The present study provides additional information on micronutrient status outcomes in relation to the different supplementation regimens. Among the subgroup of children included in the biochemical assessments of micronutrient status, those in the RUSF group had greater increases in hemoglobin and improvement in iron status indicators than those in the Misola group. Although the Misola supplement contained nearly twice as much iron as RUSF, the electrolytic iron incorporated in Misola was presumably less well absorbed than the ferrous sulfate in RUSF. Despite receiving micronutrient-fortified food or supplements, 31–56% of children, depending on treatment group, were still iron deficient at the end of the treatment period, and 29–51% still had IDA. This may be because of inadequate iron intake from the study supplements and home diets, poor iron absorption because of absorption inhibitors in the supplements or underlying intestinal dysfunction (40, 41), and/or the high observed rate of subclinical infection, which can impair iron uptake (42, 43). The 3 indicators of iron status used in the present study (ferritin, sTfR, and BIS) gave widely varying estimates of the prevalence of ID and IDA, possibly due in part to the differential effects of underlying infections, such as malaria, on these indicators (41–44). Our estimates of ID and IDA, which are based on adjusted plasma ferritin concentration, provide the lowest prevalence estimates of the 3 indicators considered. It is also important to recognize that less than half of the anemia was associated with ID, so other causes of anemia in this population remain unexplained. Unlike the results for iron status indicators, the mean plasma RBP concentrations increased from baseline only in the Misola and LMF groups. However, the baseline concentrations were slightly lower

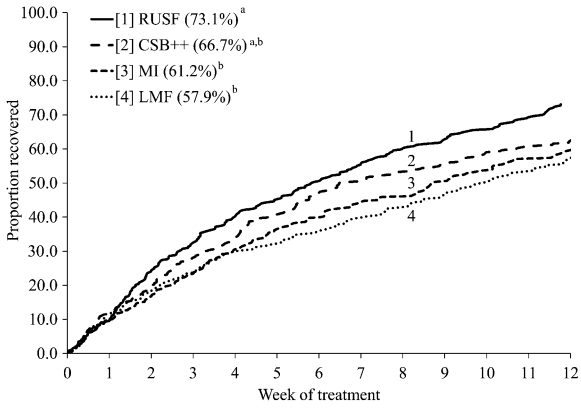

FIGURE 6 Sustained recovery of children with moderate acute malnutrition (MUAC >12.5 and WLZ >-2 for ≥2 visits) by week of treatment and treatment group. Log-rank test, $P < 0.001$. Supplements with the same letter are not significantly different from each other; repeated-measures ANOVA. Variability reported in tables. CSB++, corn-soy blend "plus plus"; LMF, locally milled flours + micronutrient powder; MI, Misola; RUSF, ready-to-use supplementary food.

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TABLE 6
Initial and final indicators of anemia and micronutrient status (adjusted for inflammation) by treatment group[1]

	Treatment groups				
Indicator	RUSF	CSB++	MI	LMF	*P* value
Hemoglobin, g/dL					
n	300	318	273	263	
Initial	8.6 ± 1.7[2,a]	9.3 ± 1.5[b]	9.2 ± 1.6[a,b]	8.7 ± 1.6[a]	0.001[3]
Final	9.6 ± 1.5[a,]*	9.6 ± 1.3[a,b,]*	9.1 ± 1.4[b]	9.3 ± 1.4[a,b,]*	0.015[4]
% Anemic[5]					
Initial	92.3 (89.3, 95.4)	86.5 (82.7, 90.3)	87.9 (84.0, 91.8)	91.6 (88.3, 95.0)	0.515[3]
Final	81.3 (76.9, 85.8)*	87.4 (83.8, 91.1)	91.9 (88.7, 95.2)	88.6 (84.7, 92.5)	0.092[4]
Plasma ferritin, μg/L[6,7]					
n	93	113	128	118	
Initial	17.7 (14.4, 22.0)	22.5 (18.6, 27.2)	17.6 (14.9, 20.9)	18.3 (15.0, 22.4)	0.827[3]
Final	20.0 (16.2, 24.6)[a]	19.6 (16.9, 22.9)[a]	10.7 (9.0, 12.6)[b,]*	14.4 (12.1, 17.2)[a,b]	0.001[4]
% Iron deficiency[5,7]					
Initial	38.7 (28.6, 48.8)	31.0 (22.3, 39.6)	35.2 (26.8, 43.5)	33.1 (24.4, 41.7)	0.190[3]
Final	32.3 (22.6, 41.9)[a]	31.0 (22.3, 39.6)[a]	55.5 (46.7, 64.2)[b,]*	48.3 (39.2, 57.5)[a,b,]*	0.001[4]
% Iron deficiency anemia[5,7]					
Initial	32.6 (22.5, 42.7)	25.2 (17.0, 33.4)	29.7 (21.7, 37.7)	29.8 (21.3, 38.4)	0.325[3]
Final	29.1 (19.3, 38.9)[a]	28.8 (20.3, 37.4)[a]	50.8 (42.0, 59.6)[b,]*	44.7 (35.5, 54.0)[a,b,]*	0.001[4]
Plasma TfR, mg/L[6,7]					
Initial	12.9 (11.7, 14.4)	11.8 (10.7, 13.0)	12.9 (11.7, 14.1)	13.5 (12.3, 14.8)	0.296[3]
Final	9.14 (8.3, 10.2)[a,]*	11.7 (10.6, 12.9)[b]	12.2 (11.2, 13.3)[b,c]	11.3 (10.4, 12.3)[c,]*	0.001[4]
% High plasma TfR[5,7]					
Initial	79.6 (71.2, 87.9)	68.1 (59.4, 76.9)	77.3 (70.0, 84.7)	78.8 (71.3, 86.3)	0.089[3]
Final	49.5 (39.1, 59.8)[a,]*	71.7 (63.2, 80.1)[b]	78.1 (70.9, 85.4)[b]	72.9 (64.7, 81.0)[a,b]	0.002[4]
BIS[6,7,8]					
Initial	−0.3 (−1.2, 0.6)	0.9 (0.1, 1.7)	0.3 (−1.1, 0.4)	−0.4 (−1.2, 0.5)	0.896[3]
Final	1.4 (0.5, 2.2)[a,]*	0.4 (−0.3, 1.0)[a,b]	−1.9 (−2.7, −1.2)[b,]*	0.6 (−1.4, 0.2)[b]	0.001[4]
% Low BIS, <0 mg/kg[5,7]					
Initial	47.3 (37.0, 57.7)	41.6 (32.4, 50.8)	49.2 (40.4,58.0)	50.8 (41.7, 60.0)	0.700[3]
Final	32.3 (22.6, 41.9)[a,]*	40.7 (31.5, 49.9)[a]	67.2 (58.9, 75.4)[b,]*	54.2 (45.1, 63.4)[a,b]	0.001[4]
RBP, μmol/L[6,7]					
Baseline	0.92 (0.85, 1.00)	0.92 (0.86, 1.00)	0.87 (0.83, 0.93)	0.87 (0.81, 0.93)	0.924[3]
Final	0.99 (0.92, 1.05)	0.95 (0.89, 1.02)	0.97 (0.90, 1.03)*	0.95 (0.89, 1.01)*	0.175[4]
% Low RBP, <0.83 μmol/L[5,7]					
Baseline	36.6 (26.6, 46.5)	38.9 (29.8, 48.1)	39.8 (31.2, 48.4)	36.4 (27.6, 45.3)	0.953[3]
Final	31.2 (21.6, 40.8)	31.0 (22.3, 39.6)	30.5 (22.4, 38.6)*	30.5 (22.1, 38.9)*	0.358[4]
Plasma zinc, μg/dL[6,7]					
n	71	93	95	86	
Baseline	67.7 (63.4, 72.3)	66.7 (62.5, 71.2)	65.8 (62.1, 69.8)	68.9 (64.2, 73.9)	0.877[2]
Final	66.9 (63.2, 70.9)	63.3 (59.9, 66.8)	62.8 (59.8, 66.0)*	66.6 (62.5, 70.8)	0.458[3]
% Low PZC, <65 μg/dL[5,7]					
Baseline	34.9 (20.2, 49.6)	42.2 (27.7, 56.8)	40.4 (28.1, 52.7)	37.1 (24.2, 50.1)	0.940[3]
Final	39.6 (23.4, 55.7)	53.6 (37.0, 70.2)	47.3 (33.5, 61.1)*	46.4 (28.7, 64.2)	0.765[4]

[1]Values with the same letter are not significantly different from each other (Tukey-Kramer test, $P > 0.05$). *Significant within-group changes from baseline (paired *t* test, $P < 0.05$). BIS, body iron stores; CSB++, corn-soy blend "plus plus"; LMF, locally milled flours + micronutrient powder; MI, Misola; PZC, plasma zinc concentration; RBP, retinol binding protein; RUSF, ready-to-use supplementary food; TfR, transferrin receptor.

[2]Mean ± SD (all such values).

[3]Groupwise comparison at baseline (ANOVA) adjusting for cluster.

[4]Groupwise comparison at endline, controlling for baseline variable of respective dependent variable (ANCOVA) adjusting for baseline and cluster.

[5]Values are percentages; 95% CIs in parentheses.

[6]Values are geometric means; 95% CIs in parentheses.

[7]Values were adjusted for inflammation by using inflammatory group-specific correction factors, as explained in the text.

[8]BIS (mg/kg) = $-[\log_{10}(\text{transferrin receptor} \times 1000 \div \text{ferritin}) - 2.8229] \div 0.1207$.

in these groups, and there were no significant groupwise differences in the final adjusted mean RBP values, so the within-group changes in the Misola and LMF groups may simply indicate that more children in these groups were deficient initially and therefore able to manifest a change with supplementation. Plasma zinc concentration did not change over the course of treatment, except for a slight decrease in the Misola group despite the relatively high zinc content of this supplement. Nevertheless, there were no significant differences in the final mean plasma zinc concentrations or prevalence of ZD by study group.

The implications of this constellation of findings for CMAM programs can still be debated. Whereas children who received RUSF were somewhat more likely to recover within the time frame of the current study, it is uncertain whether this difference

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merits the additional cost of the product compared with cereal-based preparations. In programs where treatment is provided only until the original diagnostic criteria are resolved (rather than for a fixed period of time, as with the current protocol), the RUSF would be needed for less time than the other products. The total costs (in US dollars) of the food supplements per treatment course, based on daily cost of supplements multiplied by the median time to recovery, were $15.69 for RUSF, $10.01 for CSB++, $12.79 for Misola, and $11.54 for LMF, including transportation costs. Thus, the total cost of treatment until recovery is still somewhat greater for RUSF than for the other products, even when the shorter duration of treatment is taken into consideration. CMAM program managers will need to decide on optimal treatment regimens in particular settings based on current clinical recovery data, local availability and cost of dietary treatment options, and local cultural and political acceptability of industrially produced or imported supplementary foods.

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