REVIEW ARTICLE

NUTRITIONAL SUPPLEMENTS AND THEIR USE IN THE TREATMENT OF MALNUTRITION IN DEVELOPING COUNTRIES

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Background: Despite the high global prevalence of malnutrition, it remains under-treated, or undetected. The high energy nutritional supplements are usually prescribed to promote rapid weight gain. However, there is no consensus on the most effective way to treat mild to moderate malnutrition. **Methods:** For identification of articles search engines of the databases OVID, MEDLINE, EMBASE and Pub med were used for papers published from 2003 to 2014 in English language. **Results:** The total energy intake including the supplements is significantly improved. However, the rate of weight gain by the high energy nutritional supplements in moderately malnourished children is less than the expected weight gain. **Conclusion:** While assessing the impact of the supplementation on child nutritional status, other factors should also be taken into account, including appetite suppression, replacement of habitual food intake and compliance to the intervention.

Keywords: Severe acute malnutrition, moderate acute malnutrition, child malnutrition, ready to use foods, therapeutic nutritional products, specially formulated foods, corn-soy blend.

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Malnutrition:
Prevalence, causes and consequences

Malnutrition is a condition in which nutrients such as proteins, vitamins, minerals and energy are deficient or in excess (imbalance). This causes severe measurable adverse effects on body composition, function and clinical outcomes.[1,2] There are the controversies and confusion regarding the definition of malnutrition and its recognition. There is no universally accepted definition of malnutrition.[3]

It is suggested that for defining malnutrition, deficiencies of energy, protein, fat free mass, and function should be included, and for the operational definition BMI, involuntary weight loss and nutritional intake should be incorporated. Malnutrition can be explained as either over or under-nutrition with inflammation.[4] In this context, we are using under-nutrition. The WHO cites malnutrition as the single greatest threat to the world's public health.[2] One out of twelve people is malnourished worldwide. According to estimates, 148 million children in the world are underweight, out of which 78 million are from South Asia and 36 million are from Sub-Saharan Africa. Approximately 19 million are severely malnourished.[5] Undernutrition is a direct cause of about 300,000 deaths per year and is indirectly responsible for about half of all the deaths in young children.[6–8]

Malnutrition is a highly pervasive and damaging condition in low and middle income countries, and is prevalent in community settings.[9] According to UNICEF 129 million children (25%) under 5 years of age in these countries are underweight and approximately 195 million children (28%) are stunted.[10] According to the UN, malnutrition kills 10 children every minute.[11] WHO estimates, that by 2015, the worldwide prevalence of malnutrition will be 17.6%, and 29% of the population will have stunted growth due to under nutrition. Not surprisingly in the low income countries 112 million (20%) out of 556 million children under 5 years of age are underweight and 36 million (6.4%) are suffering from moderate wasting.[12,13] The data from 139 countries showed that about 10.2 % of the deaths are attributable to wasting, and wasted children have a three times higher risk of death compared to well-nourished children.[9,14] South Central Asia has the highest estimated point prevalence (19%) of moderate acute malnutrition, and the highest absolute number of affected children (30 million).[15] In South Asian countries, the most prevalent public health issue is malnutrition among children under five years of age. It is documented that more than 50 percent of the world's malnourished children are residing in Pakistan, India and Bangladesh.[16,17]

The major underlying cause of malnutrition and its determinants is poverty.[10,18] In a given population the degree and distribution of malnutrition depends upon many factors, such as socio-economic, political, seasonal, climatic, sanitation conditions, educational level, food production, prevalence of infectious diseases, breast feeding habits, and non-availability of health services.[10,18–21] Poor dietary intake along with repeated infections especially in the underprivileged population is the main contributor to malnutrition. Inadequate calorie intake due to less dietary intake or decreased diet assimilation, stress due to critical acute illness, or chronic inflammation extensive burns or postoperative sepsis, gastrointestinal disease, mixed metabolic abnormalities like AIDS, cancer or chronic liver diseases are considered to be important etiological factors for malnutrition.[3,10]

Despite the high global prevalence of malnutrition, it remains under-treated, or undetected. This causes an enormous detrimental effect on the health of each individual and imposes a financial burden on both the individual and the health care system.[22] Malnourished children are at increased risk of mortality and morbidity as compared to well-nourished children. There is an increased risk of death with increasing severity of malnutrition.[10] Malnutrition predisposes the body to the risk of different diseases, and also causes severe adverse outcomes of disease in a variety of ways.[22] Disease related malnutrition is very harmful physiologically and clinically, by delaying recovery from illnesses and impairing the quality of life.[23] If malnutrition is not treated or inefficiently treated, it will lead to poor quality of life of the patients, increase complications, delay recovery from diseases, result into more use of healthcare facilities, more health care expenses and more rehabilitation needs.[2,3,22,24] Malnutrition leads to severe adverse metabolic events which compromise the body's immunity, impairs body function, composition and its ability to acclimatize, recover and to survive.[3,22] Malnutrition also has severe adverse effects on the cognitive development of children, decreased productivity, reduced ability to work and small adult physique.[10] Taking into consideration the enormous costs of malnutrition, a condition that is largely preventable and treatable, a timely identification followed by the most suitable, effective, efficient, evidence-based treatment is recommended.[24]

Nutritional supplements and their use in the treatment of malnutrition in developing countries

Interventions to prevent protein energy malnutrition include food supplementation, dietary diversification and fortification of salt with iodine.[18] Other preventive measures include maternal nutritional education, reduction in the price of food items, high immunization coverage and correct management of infectious diseases.[18] In the majority of cases of malnutrition, energy intake is low therefore supplements may be given to provide extra energy and macronutrients which in turn increases the body weight.[25]

According to the WHO, recommendations for the treatment of malnutrition, during the nutritional rehabilitation phase the children should receive an energy and protein dense diet fortified with vitamins and minerals, to promote rapid weight gain. For this purpose, a solid, ready-to-use-food (RTUF), has been developed which is made up of peanut butter.[26] RTUF was developed as an alternative to the F-100 formula or milk oil formula to be used in the hospitals and nutritional rehabilitation centres after initiation of cure.[27] In RTUF, the skimmed milk was replaced by groundnut paste and lacto-serum. RTUF is an energy dense paste which does not require cooking and can be stored for several months (24 months shelf life) without spoiling.[28,29] These RTUF have low osmolarity and can be eaten directly from the silver foil package by the child without the addition of water or milk which reduces risk of bacterial contamination.[15,26] In hospital settings the major limitation of RTUF is that it cannot be administered easily through a naso-gastric tube.[27] RTUF have the following salient features: good nutritional characteristics, low cost, resistant to bacterial contamination, long shelf life, does not need refrigeration, highly palatable, does not require any further processing, prior feeding and its consistency is suitable for feeding infants and children.[27,30]

Children with MAM are at three times greater risk of deaths as compared to the well-nourished children and are prone to morbidity from infectious diseases and suffer from delayed cognitive and physical development.[9,31,] Worldwide 11% of the children under 5 years of age are suffering from MAM.[9] It is estimated that in developing countries 32% (178 million) of children had weight-for-age Z score (WAZ) of less than -2.[32] A mildly underweight child with (WAZ) between -1.0 and -2.0 have twice the risk of death as compared with WAZ >-1.0, and the relative risk increases to five times and eight times for the moderately underweight (WAZ between -2.0 and -3.0) and severely underweight children (WAZ <-3.0), respectively.[32,33]

As major cause of malnutrition is reduced dietary intake, in 2006 the National Institute for Health and strategies including oral nutritional supplements, artificial nutritional support and dietary counselling. All these strategies are aimed to reverse inadequate food intake by increasing energy intake and to improve awareness, knowledge, practices and attitudes related to healthy diet.[15,21] Inadequate energy, protein and micronutrient intake mostly occurs in disease related malnutrition as appetite is poor due to diseases and patients ingest less food with less proteins and less nutrients, and in some cases protein requirements are also higher and there is the need for more protein to encourage damaged tissues repair and to facilitate body repletion.[22]Clinical Excellence (NICE) recommended an increase in dietary intake using a variety of nutrition support

The current evidence suggests that the nutritional supplements have several beneficial effects summarised in (Table-1).

Table-Error! No text of specified style in document.**: Summary of studies, assessing the beneficial clinical and functional outcomes of the oral tional supplement**

Systemic Review	Study design	Patient group	Settings	Interventions	No. of trials No. of Patients	Significant benefits to clinical and functional outcomes with supplements
(34)	Systemic review and meta-analysis	Adults of any nutritional characteristics (mostly elderly patients)	Community settings	All ONS types, energy density 1.00–2.48 kcal/ml, (475 to 1200 kcal/day) for 6wks - 1 yr,	Systematic review (9 RCT, n=1190) Meta-analysis (6 RCT, n=852)	**Hospital (re)admission:** Significant reductions with ONS vs. routine care (OR 0.59, 95% CI 0.43–0.80, $P = 0.001$)
(35)	Systemic review and meta-analysis	Stable patients with a diagnosis of COPD	All settings	ONS and ETF	12 RCT (n=448)	**Respiratory muscle strength:** Significantly improved with ONS (pressure +3.86 standard error (SE) 1.89 cm H2O,p=0.041; maximal expiratory mouth pressure +11.85 SE 5.54 cm H2O, p=0.032) **Handgrip strength:** Significantly improved (+1.35 SE 0.69 kg, $p = 0.05$) with ONS and ETF **Weight gains**: Weight gain of ≥2 kg with ONS. **QoL**: Improved with supplementation
(22)	Systemic review and meta-analysis	Elderly with hip fractures, pressure ulcers, COPD, cancer, gastro-intestinal disease, and a range of critical and acute illnesses	Hospital and community settings	ONS energy densities (0.75–3.85 kcal/ml) and the percentage energy from protein ranged from 20–54% (149 to 995 kcal/day)	36 RCT (n=3790)	**Complications:** ONS significantly reduced the incidence of complications **(**pressure ulcers, wounds, non-healing fracture, infections, or a combination of complications) compared to control (OR 0.68 (95% CI 0.55–0.83). **Functional:** ONS improved grip strength (1.76 kg (95%CI 0.36–3.17) **Energy Intake**: ONS increased intake of protein (p< 0.001) and energy (p < 0.001) **Improvements in weight**: ONS significantly improve weight **Readmissions:** ONS, significantly reduce hospital readmissions compared to control (OR 0.59 (95% CI 0.41–0.84).
(36)	RCT	Malnourished with benign Gl disease	Hospital	ONS (~200ml/day) for 3 months	n=114	**QoL:** Improved with ONS **Cost effective**: Treatment is cost effective according to international benchmarks
(37)	RCT	Patients with benign GI disease	Hospital setting	ONS (200 ml) per day (nutritionally complete, 150 kcal and 10 g protein/ 100 ml, 27% energy from protein) for three months compared with DC	n=80	The following outcome measures significantly improved with ONS as compared to DC **Energy intake:** Total energy and protein intake (p<0.0001) **Hand-grip Strength:** 26.1±11.3–31.5±10.1 kg, (p<0.0001) **Peak flow:** 329.2±124.0–388.9±108.4 l/min (p=0.004 **QoL:** Improved **Hospital readmissions:** Significantly less ($p = 0.041$).
(38)	RCT	Patients with femoral neck fracture aged ≥ 70 years	Hospital Settings	Nutritional and protein drinks (400 ml/day) and protein-enriched meals for at least 4 days postoperatively during hospitalization.	n=157	**Post-operative complications:** a) Fewer patients in the intervention group developed **post-operative delirium** (46 patients in the intervention group vs. 54 patients in the control group, p=0.022). b)The number of days with delirium was significantly fewer (p<0.001) in intervention group c) Significantly less number of patients developed decubitus ulcers in intervention group d) Hospitalization period was shorter in intervention group (p=0.019)
(39)	RCT	Geriatric patients aged ≥65 years submitted to surgery for hip fracture	Hospital settings	2 types of ONS: a) 37.6 g of protein (500 kcal/ day) b) 36 g of protein (152 kcal/day)	n=90	Small effect of ONS on serum albumin was detected in patients with post-surgical complications.
(40)	Review of reviews	Gastrointestinal surgical patients	All settings – mostly hospitalized patients	ONS (single nutrient and multi-nutrient) 250-600 kcal/day for 7 days-10 weeks	18 RCT (n=907) of ONS and ETF 6RCT (n=418) of ONS	**Mortality**: Significantly lower in supplemented group with OR 0.61 (95% CI 0.48-0.78). **Morbidity:** Supplements significantly reduced postoperative complications including wound and lung infections, postoperative ileus, unresolved peritonitis and wound dehiscence with OR 0.37 (95% CI 0.26-0.53).
(41)	Prospective, double-blind, placebo-controlled trial	Acutely ill elderly patients aged ≥65 years	Hospital setting	ONS (995 kcal/day) (carbohydrate 45%, fat 35% and protein 20%) and 100% of the Reference Nutrient Intakes for 6 weeks	n=225	**Nutritional status:** Serum Albumin concentration, red-cell folate and plasma vitamin B12 concentrations significantly improved in the supplement group as compared to placebo group. **Symptoms of depression:** In the supplement group there was a significant increase in the

						number of patients with no symptoms of depression and a decrease in those with symptoms of mild or severe depression as compared to placebo group.
(42)	Meta-analysis	Older people aged ≥65 years (excluding critically ill patients and patients recovering from cancer treatment)	All settings	Commercial ready-made ONS and other milk-based supplements 175-1000 kcal/day Duration of Supplementation: 10 days –18 months	55 trails (n=9187)	**Mortality:** Improved survival with supplementation in : a) Undernourished people (17 trials; 2093 participants) (Peto OR, 0.73 [CI, 0.56 -0.94]) b) People aged ≥75 years (18 trials; 1611 participants) (Peto OR, 0.64 [CI, 0.49 - 0.85]), c) Ill people (22 trials; 6630 participants) (Peto OR, 0.86 [CI, 0.74 - 1.00]). **Morbidity and Complications:** In hospitalized patients supplements significantly decrease complications (Peto OR, 0.72 [CI, 0.53 to 0.97]) like infective complications, incomplete wound healing etc.
(43)	RCT	Patients aged 65–92 years.	Hospital setting	ONS (995 kcal/day) and 100% of the Reference Nutrient for 6 weeks	n=445	**Readmission:** 29% patients in the supplements group were readmitted to the hospital compared with 40% in the placebo group (adjusted hazard ratio 0.68 [95% CI 0.49-0.94]). **Mean Length of hospital stay:** was 9.4 days in supplement group compared with 10.1 days in placebo group. **Nutritional Outcomes:** Serum albumin concentration increased significantly in the supplement group
(44)	Systemic review and meta-analysis	Patients with chronic kidney disease receiving maintenance dialysis	Any setting (hospital, outpatient or home)	ONS and enteral tube feeding	18 studies: RCT (n=5), non-RCTs[13]	**Biochemical outcomes:** Enteral nutritional support increased serum albumin concentration by 0.23g/dl. **Energy Intake:** Increased total energy intake **Clinical outcome:** May improve clinical outcomes
(45)	Systemic review and meta-analysis	Patients with, or at risk of developing, pressure ulcers	All settings – mostly hospitalized elderly, post-surgical patients.	ONS (250–500 kcal/day) Duration of supplementation: 2–26 weeks	15 studies: RCT (n=8),CCTs (n=1),CTs (n=1) and cohort studies (n=5)	**Prevention of pressure ulcers:** ONS were associated with significantly lower incidence of development of pressure ulcers compared to routine care with OR 0.75(95% CI 0.62-0.89, n=1224) **Healing of existing pressure ulcers**: A tendency of improved wound healing
(46) **(47)**	Systemic review	Patients with specific diseases	Community settings	ONS (were used in 80% of the studies) with energy density (3·25–16·0 kJ/ml), ranged from < 0·42 MJ/d to > 10·5 MJ/d. Duration of supplementation: 1 week -over 2 years.	84 trials; 45 RCT (n=1728) and non-39 RCT (n=842). Studies grouped according to disease: COPD (n=14), Crohn's disease (n=9), cystic fibrosis (n=11), elderly (n=12), HIV and AIDS (n=15); liver disease (n=2), malignancy (n=15); other conditions (n=6).	**Weight change**: The mean percentage weight change of patients receiving ONS (2·93 %) was greater than that of the control patients (1·15 %). Patients with a mean BMI < 20 kg/m2 had a greater percentage weight change (4·7 % of the body weight) than patients with a mean BMI > 20 kg/m2 (2·4 % of the body weight). **Total energy intake:** Mean increase in energy intake = 67 % of the energy of the ONS consumed), which varied considerably according to the disease state and the BMI of patients. **Functional benefits:** **COPD patients**: Improved muscle strength, walking distance and well-being. **Children with cystic fibrosis**: Improved growth performance. **Elderly**: reduced falls and increased activities of daily living
(48)	RCT	Elderly people aged ≥ 65 years	Community setting (private nursing home)	ONS (300-500 kcal/day) for 60 days	n=88	ONS improved: a) **Mini-nutritional assessment score:** in subjects at risk of malnutrition and in malnourished subjects (from 13.9± 2.6 to 17.1±.9). b) **Weight gain:** (1.4±0.5kg) in subjects at risk of malnutrition and (1.5±0.4kg) in malnourished subjects.

ONS, Oral nutritional supplements; RCT, Randomized controlled trial; ETF, Enteral tube feeding; OR; Odds ratio; CI, Confidence interval; CCTs, Controlled clinical trials; CTs, Clinical trials; GI disease, Gastrointestinal disease; COPD, Chronic obstructive pulmonary disease; QoL, Quality of life; DC, dietary counselling.

The evidence suggests that there was slight suppression of normal food intake with the oral nutritional supplements but they effectively increased the total energy and nutritional intake.[22,23,42,49–51] In one prospective randomized trial based on interviews with patients about their dietary habits and appetite, no significant difference was found in appetite between the two groups; one on the nutritional supplement, and another without the supplement, in older non-demented females with hip-fracture.[52] Studies have also found that there was significantly more protein and energy intake with the supplements[53], and there was no significant reduction in food intake[37]. A multi-centre trial to look at the effects of nutritional supplements in critically-ill elderly patients found that, whilst oral nutritional supplements increased energy and protein intake of elderly patients, the actual intake was low compared to what was expected.[54] Another study found that there was suppression of voluntary intake of food in the supplement group compared to controls but the total energy intake including the supplement was significantly higher in the supplement group.[55]

A recent meta-analysis suggested that the consumption of oral nutritional supplements could increase the daily energy intake by a mean of 375 kcal/d.[49] However; another systematic review suggested that this translated into an average total weight gain of only 1.7 kg, with wide variability (Cawood *et al*). A rare longer term trial in children and adolescents with cystic fibrosis showed no net gain in BMI (Poustie *et al*). The difference between the intake and the net weight gain thus must reflect some degree of energy compensation.[55]

Specially formulated therapeutic foods for treatment of moderate acute malnutrition in children from low- and middle-income countries

Moderate acute malnutrition (MAM) affects approximately 10% of the children under five years of age in low and middle income countries. Different approaches have been used for the nutritional recovery of the children in these settings such as lipid based nutrient supplements (food with high energy density and high lipid content) or blended foods (dry food mixtures without high lipid content), which can be provided in a low dose or full dose as a supplement to their habitual diet.[15,18] The provision of these supplements to MAM children increased the recovery rate by 29% and significantly improved weight-for-height as compared to standard care.[15]

An early study by Walker *et al* performed on stunted children (<-2 SD of the National Centre for Health Statistics (NCHS) reference) aged 9–24 months, were randomly assigned to four groups: a nutritional supplement group (milk based supplement providing 750 kcal per day), psychosocial stimulation group, both the supplement and stimulation group and a control group for 12 months. Supplementation significantly increased weight, head circumference, mid upper arm circumference and triceps skinfold in the first 6 months, but no significant increase was reported in the subsequent six months. In this study dietary intake was measured by two 24 hour dietary recalls before the intervention and then after 6 months of the intervention. The baseline dietary intakes were similar in the stunted and non-stunted children, while at 6 months, dietary intake was significantly reduced in the supplement group.[56] Lack of further improvement in weight, head circumference, mid upper arm circumference and triceps skinfold in the last six months of the study might be due to decreased food intake or/and to a decline in the intake of the supplement.

On the other hand, a study by Gershoff *et al*, observed no demonstrable changes in anthropometric indices as a result of high caloric supplementation (300 kcal) provided to pre-school children, in Thailand, from December 1981 to October 1983. No impact of supplementation on the anthropometric indices of the children in the intervention group was thought to be due to increased physical activity and reduced intake of habitual food, although neither were not measured in that study.[57] The disparity of the results in these studies may be due to differences in the energy density of the supplements provided and duration of the intervention.

Ready to use foods in the treatment and prevention of moderate malnutrition

RTUF have also been used to supplement the dietary intake of the moderately malnourished[58–62] as shown in table-2 RTUF was found to be effective in preventing malnutrition in non-wasted children in areas of food insecurity.[14,63–65] It has been recommended that the nutritional intervention to prevent malnutrition might be more effective than the curative treatment of malnutrition.[66] A cluster-randomized trial of children aged 6–60 months, found that 3 months of supplementation with 1 packet of RTUF per day (500 kcal/day) reduced the incidence of wasting and severe wasting over a period of 8 months of follow-up. Although, a significant reduction in the incidence of wasting was observed in the intervention group, no difference in mortality was found between the intervention and control group.[64] Here it is worth mentioning that two different growth standards were used in that study. For inclusion, NCHS growth standards were used while for the analysis outcomes WHO growth standards were used. In the WHO growth reference the estimates of wasting tend to decrease[67] and the use of WHO growth reference for analysis of outcomes may have showed exaggerated improvements in weight for height.

Similarly, Defourny *et al* evaluated a large scale distribution of ready-to-use food (RUF 1000kcal/day), during the 2007 hunger gap in Maradi region, Niger and reported that the incidence of severe acute malnutrition remained extremely low. Recovery rates were higher in approximately 60,000 moderately malnourished children who received a blanket supplementation.[63] Although it is important to mention here that, the moderate malnourished children consisted of a group with severe malnutrition without complications.

Similarly, Grellety *et al*, performed a non-randomized 4- months cohort study on 2238 children, aged 6–23 months, and found a positive effect on anthropometric status as presented in table-2 and prevention of wasting by RUSF (250 kcal/day) supplementation. However, no difference in length gain was observed between the two groups. In the intervention group, fewer initially non-wasted children also developed moderate wasting compared to the group (without supplementation).[68] Although the baseline anthropometry of the children was not significantly different between the two groups, the children in the intervention group had slightly lower mean weight-for-length (Table-2). They were younger, and came from larger families, which might have increased the chances of sharing the supplement and could have an impact on the findings of this study. Likewise, Huybregts *et al* performed a cluster-randomized controlled pragmatic intervention study on 6–36 months, non-wasted children (WHZ ≥80% of NCHS reference median and absence of bilateral pitting oedema) from city Abache. The intervention group was provided with 46 grams of ready–to-use supplementary food (RUSF=247 kcal) daily for 4 months. It was found that the intervention group had significantly higher gain in height-for-age Z score, haemoglobin concentration accompanied by reduction in fever episodes, and lower risk of diarrhoea, compared to control group, at the end of the study. However, no significant differences were detected in weight increase, mean change in WHZ, between the two groups. The provision of RUSF packets in the intervention group did not result in a reduction in cumulative incidence of wasting. Compared to baseline mean WHZ increased slightly in both arms while mean HAZ was slightly lower in both arms. This study could not establish clear evidence that addition of RUSF to the household food ration was effective in the prevention of acute malnutrition.[14] In this study, a general food ration was also provided to both groups, which might dilute the effects of the intervention, and may be a possible reason for not finding the effect of the supplementation on nutritional status of the children in the intervention group.

For treating children with MAM, besides RTUF, other supplements, such as fortified blended flours, like corn-soy blend and corn-soy blend plus oil, and milk (CSB++) are also used.[31] The evidence regarding the comparison of the efficacy of RTUF with the corn-soy blend in children with MAM has conflicting results. The majority of the studies reported higher recovery rates with RTUF compared to the corn-soy blend.[33,58–60,69] However, other studies demonstrated that CSB++ and RTUF are equally effective.[70]

A randomized clinical effectiveness trial in rural Malawi, on moderately wasted children (WHZ <-2 but ≥-3), found that 8-week intervention with milk/peanut fortified spread, soy peanut fortified spread, or corn soy blend, each providing 314 kJ/kg/day, had higher and faster recovery rates with the fortified spread groups compared to CSB group. However, no difference was detected in the rates of the length gain among three groups, and 8% of children in each group developed severe malnutrition.[58] Karakochuk *et al* performed a cluster randomized effectiveness trial on 1125 Ethiopian children aged 6–60 months with moderate acute malnutrition (MAM) (WHZ between -2 and -3). They reported that after 16 weeks of supplementation with Ready-to-use supplementary food (RUSF) 92 g (500 kcal) and corn-soy blend (CSB) 300g (1413 kcal) daily resulted in the higher recovery rate with RUSF, however this difference was not statistically significant.[69]

Likewise, Patel *et al* found greater rates of weight gain 3.1g/kg/day, higher recovery rates and lower relapse rates with RTUF than corn/soy blend (1.4g/kg/day), after 8 weeks of supplementation. Nackers *et al* performed a field randomized trial in Niger. Four hundred and fifty one children aged between 6 to ≥36 months measuring 65 to <110 cm, with moderate acute malnutrition (WHM% between 70% and <80% of the NCHS median) were randomized to receive either RUTF (Plumpy' Nut 1000 kcal/day) or CSB premix (1231 kcal/day). Two hundred and fifteen children were recruited in RTUF group and 236 in the corn/soy-blend (CSB-based-premix). Children were assessed weekly until their recovery (discharge criteria: WHM %≥85% for 2 consecutive weeks). Children who recovered after the intervention were additionally followed up for 6 months.

Although RUTF group resulted in higher weight gain, higher recovery rates (79% versus 64% in the CSB group) and shorter length of stay as compared to the CSB group, during follow up, height and height-for-age gains were similar in both groups. Also, and one fifth of the cured children relapsed.[60] On the other hand, a study by Lagrone *et al* reported that 12 weeks of supplementation with 75 kcal of either soy whey RUSF, soy RUSF and CSB++ are equally effective and there were no significant differences in the recovery rate of the children in each group.[69]

During the 12-months following period, this study demonstrated that only 63% of children who recovered from the MAM remained well-nourished, 17% relapsed to MAM and 10% developed severe acute malnutrition.[31]

Table-1: Studies assessing the comparison of effectiveness of specially formulated therapeutic foods for the treatment malnutrition in children

Study	Study Design	Study participant	Intervention duration	Results				
(14) City of Abache Central Africa	Cluster RCT	n=1,038, non-wasted children (≥ 80 % of NCHS reference) between 6-36 mths.	RTUF (Plumpy' Doz) = 247 kcal/day for 4 mths		**Intervention** (n= 598)	**Control** (n=440)		***p*-value**
				WHZ (SD)	-1.05 (0.93)	-1.09 (0.95)		
				Intervention effect (95%CI) WHZ	-0.002 (-0.03,0.03)			0.89
				HAZ (SD)	-1.79 (1.46)	-2.06 (1.39)		
				Intervention effect(95% CI) HAZ	0.03 (0.01,0.04)			<0.001
				Prevalence of stunting (%)(n)	46.2 (276)	52.3 (230)		
				MUAC (cm)(SD)	14.3 (1.1)	14.1 (1.2)		
				Intervention effect(95% CI) MUAC	0.01(-0.02,0.04)			0.49
(71) Malawi	RCT	Underweight (WAZ<-2) age 6-15 mths	12 wks an average daily 71 g CSB= 1188kJ or 43g LNS =920kJ and no supplement (control) group.		**LNS** (n=99)	**CSB** (n=106)	**Control** (n=77)	***p*-value**
				↑Weight(kg) (SD)	0.75 (0.41)	0.68(0.50)	0.63(0.40)	0.21
				↑ Length (cm) (SD)	3.6 (1.3)	3.3(1.3)	3.4(1.2)	0.29
				↑ MUAC (cm) (SD)	0.4 (0.7)	0.3(0.9)	0.3(0.8)	0.74
				△ WAZ(SD)	-0.12 (0.60)	-0.13 (0.71)	-0.13(0.61)	0.40
				△ WHZ(SD)	-0.10(0.64)	-0.14 (0.81)	-0.25(0.71)	0.40
				△ HAZ(SD)	0.02 (0.47)	-0.02 (0.47)	0.06 (0.44)	0.45
(72) Malawi	RCT	n=600 age 6 -59 mths SAM (MUAC <11.0 cm or pitting edema +1 or +2).	P-RTUF and WPC-RTUF =175kcal/kg. till recovery (weight gain of at least 15%, MUAC >11.0cm)		**WPC-RUTF** (n=308)	**P-RUTF** (n=292)		
				average weight gain (g/kg/d)	3.1	2.9		
				recovery rate	84.8%	84.2%		
				defaulter rate	12.2%	12.2%		
				Mortality rate	1.6%	0.7%		
				In both groups recovery rate exceeds the SPHERE minimum standards of > 70%.				
(73) Demographic republic of Congo	Prospective, non blinded, RCT	n=1331full term born infants (gestational age >37 weeks) when became 4–5 mths.	RUCF 280 kcal or UNIMIX 275 kcal daily for six mths.		**RUCF** (n= 656)	**UNIMIX** (n=675)	***p*- value**	
				Weight gain (kg)	1.2 (1.2,1.3)	1.3 (1.3, 1.4)	0.08	
				Underweight	20%	18%	0.42	
				Stunting	48%	46%	0.31	
				Length gain (cm)	5.2 (5.0, 5.3)	5.4 (5.3, 5.6)	0.039	
				MUAC gain (mm)	5.3 (4.6, 6.1)	5.2 (4.5, 6.0)	NS	
				Diff HAZ	-1.1 (-1.2, -1.0)	1.0 (-1.1, -0.9)	NS	
				Diff WAZ	-0.3 (-0.4, -0.2)	0.3 (-0.3, -0.2)	NS	
				Diff WHZ	0.1 (0.0, 0.2)	1 (0.0, 0.2)	NS	
(70) Malawi	Prospective, RCT	n= 2712 MAM (WHZ <-2 and ≥ -3) children aged 6-59 mths	75 kcal/ kg/day of CSB ++, locally produced soy RUSF or an imported soy/whey RUSF for ≤ 12 wks		**CSB++** (n=888)	**Soy RUSF** (n= 906)	**Soy/whey RUSF** (n=918)	
				Weight gain (g/kg/d)	3.1±2.4[1]	3.4±2.6	3.6±2.8	
				Length gain (mm/d)	0.13±0.46	0.13±0.44	0.15±0.47	
				MUAC gain(mm/d)	0.13±0.40[1]	0.13±0.43	0.21±0.44	
				WHZ	-1.68±0.67	-1.61±0.63	-1.59±0.60	
				Recovered %(n)	85.9 (763)	87.7 (795)	87.9 (807)	
				Develop SAM % (n)	6.6 (59)[1]	5.2 (47)	4.2 (39)	
				Continue MAM % (n)	0.9 (8)	0.6 (5)	0.9 (8)	
				[1] SG from soy/whey RUSF.				
(69) Ethiopia	Cluster randomized effectiveness trial.	n=1125 age 6–60 mths with MAM (WHZ between -2 and -3)	92 g RUSF =500 kcal 300g CSB =1413 kcal daily for 16 wks		**RUSF** (n= 351)	**CSB** (n=698)	***p*-value**	
				Recovery rate % (n)	73 (265)	67 (482)	0.056	
				Defaulted % (n)	2 (7)	2 (12)	NS	
				Non responsive % (n)	24 (86)	30 (216)	NS	
				Met sphere target	No	No		
(74) India	RCT	n=128, 18-59 mths children with WAZ of ≤-2SD.	RTUF 50g/ child /day (550 cal/ 100 g) HCCM (187 calories/ 100ml)		**RTUF** (n=51)	**HCCM** (n=45)	***p*-value**	
				Weight gain (kg)	0.54 (0.44-0.65)	0.38 (0.25-0.51)	0.047	

(59) South Niger	Field Randomized trial	MAM (WHM% between 70% and <80% of the NCHS median) age 6 to ≥ 36 mths.	RTUF =1000 kcal/d or CSB =1231 kcal/day. until recovery (WHM% ≥ 85% for 2 wks).	**RTUF** **CSB** ***p*-value** (n= 215) (n=236) Weight gain(g/kg/d) 5.67±3.02 4.59±2.59 <0.001 MUAC gain (mm/d) 0.37±0.29 0.32±0.24 0.11 LOS (weeks) 4 (2-16) 6 (2-16) <0.001 Recovered % (n) 79.1 (170) 64.4 (152) <0.001 Non responder % (n) 6.0 (13) 8.9 (21) 0.25
(33) Malawi	Clinical randomized trial	n=182 underweight children (WAZ <-2) between 6-15 mths	43g/day LNS =1189 kJ, 71 g/day CSB =921kJ control group= No supplement.	**LNS** **CSB** **Control** ***p*-value** (n=99) (n=106) (n=77) ↑Weight(kg) 0.62±0.47 0.51±0.35 0.47±0.35 0.11 ↑ Length (cm) 3.4±1.1 3.5±1.1 3.3±1.2 0.60 ↑ MUAC (cm) 0.2±0.8 -0.1±0.6 0.0±0.6 0.06 Δ WAZ .02±1.11[1] -0.31±0.59 -0.32±0.54 0.03 Δ WHZ -0.34±0.77 -0.58±0.76 -0.55±0.73 0.16 Δ HAZ 0.29±1.07 0.14±0.37 0.11±0.42 0.29 [1] LNS vs Control SG
(75) Malawi	RCT	6 -18 mths with low (WAZ < -2.0)	50g/d FS or 71 g/day LP for 12 wks.	**LP** **FS** ***p*-value** (n=86) (n=90) Δ Weight(kg) 0.84±0.46 0.89±0.38 NS Δ Length (cm) 2.65±1.1 2.50±1.3 NS Δ MUAC (cm) 0.3±0.8 0.4±0.8 NS Δ WAZ 0.22±0.69 0.29±0.51 NS Δ WHZ 0.39±0.85 0.52±0.63 NS Δ HAZ -0.08±0.41 -0.13±0.42 NS
(60) Malawi	Controlled clinical effectiveness trial	Weight for height <85% but>80% of the international standard.	7 kg of RTUF/mth and 50 kg of CSB/mth for 8 wks	**RTUF** **CSB** ***p*-value** (n= 331) (n=41) Rate of weight gain (g/kg/d) 3.1±2.7 1.4±2.5 <0.001 Rate of height gain (mm/d) 0.28±0.27 0.17±0.21 0.003 Rate of MUAC gain (mm/d) 0.30±0.31 0.18±0.29 0.02
(63) Maradi	Evaluation of large scale distribution of nutritional supplement on prevention of wasting.	n= 60,000 age between 6-36 mths with a height between 60 and 85 cm	Six monthly distribution of RTUF) 1000kcal/day for children < 8kg and 1500 kcal/day for children> 8kg	**RTUF** **No RTUF** ***p*-value** (n= 3,362) (n=2,949) Weight gain (g/kg/d) 5.1±4.6 5.5±4.7 0.005 LOS (days) 44.4±29.8 44.4±29.6 0.951 Cured % (n) 92.3 (3054) 90.1 (2621) 0.003 Died % (n) 1.8 (60) 2.2 (65) 0.23 Non respondent % (n) 1.1 (37) 1.4 (41) 0.30
(64) Niger	Cluster randomized trial	n= 3533 children aged 6-60 months with weight for height 80% or more of the NCHS reference.	RTUF (92g(500kcal/day) for three months	**RTUF** **No RTUF** ***p*-value** (n= 1671) (n=1862) ΔRate of WHZ <0.001 WHZ differences between groups at baseline= -0.10 z (-0.23-0.03) WHZ differences between groups at end = 0.12 z (0.02-0.21) HAZ differences between groups at baseline = -0.06z (-0.18-0.06) HAZ differences between groups at end = 0.08 (-0.18-0.06) ↓ incidence of wasting with RTUF =36% (17-50%) ↓incidence of severe wasting with RTUF =58% (53-68%)
(58) Malawi	Randomized clinical effectiveness trial	1362 moderately wasted children WHZ <-2 but ≥ -3	Milk/ peanut FS=314kj/kg/day, Soy/peanut FS =314kj/kg/day or CSB for 8 wks.	**Milk /Peanut FS** **Soy/Peanut FS** **CSB** (n=465) (n=450) (n=447) Recovered % (n) 79 (369) 80 (360) 72 (323) Remained wasted % (n) 8 (35) 7 (29) 15 (67) WHZ at discharge ~1.6±0.7 ~1.7±0.7 ~1.8±0.8 HAZ at discharge ~2.7±1.3 ~2.6±1.5 ~2.8±1.9 Duration of Supplementation (days) 14 (14,42) 14 (14,42) 28 (14,56)
(76) Malawi	RCT	n=182 age between 5.5-6.69 mths	One year of daily supplementation with 50 g (FS50) =256 kcal, 25g FS (FS25)=127kcal or 71 g LP=282 kcal	**LP** **FS50** **FS25** ***p*-value** (n=61) (n=61) (n=60) Δ Weight(kg) 2.37±0.60 2.47±0.77 2.37±0.61 0.66 Δ Length (cm) 12.7±1.7 13.5± 2.9 13.2±2.9 0.23 Δ MUAC (cm) 1.1±0.9 1.0±1.1 1.0±0.8 0.64 Δ WAZ -1.29±0.63 -1.18±0.90 -1.32±0.65 0.53 Δ WHZ -0.98±0.83 -1.05±0.86 -1.13±0.75 0.62 Δ HAZ -0.74±0.95 -0.59±1.22 -0.64±0.8 0.71

(77) Ghana	Community based randomized trial	All infants attending weight monitoring session were potentially eligible.	Complementary foods with SP=1sachet/d NT=1 tablet/d or NB=20g/d from 6–12 months of age.	NB group had a significantly higher WAZ (-0.49 ± 0.54) LAZ (-0.20±0.54) as compared to NT group (WAZ:-0.67±0.54; LAZ: -0.39±0.54) **SP** (n=96) / **NT** (n=101) / **NB** (n=97) / **NI** (n=81) WAZ: -0.53±1.1[a,b] / -0.88±1.1[a] / -0.40±1.1[b] / -0.74±1.1[a,b] HAZ: -0.40±1.0 / -0.44±1.0 / -0.14±1.0 / -0.40±1.0 WHZ: -0.45±1.1[a,b] / -0.89±1.1[a] / -0.43±1.1[b] / -0.74±1.1[a,b] Values in the same row with different superscripts are significantly different P<0.05
(62) Malawi	RCT	n=128 6-17 mths underweight infants (WAZ<-2, WHZ greater than -3).	12 wks supplementation 1 of 8 supplements, nothing, 5,25,50,or 75g/day milk based fortified spread (FS), or 25, 50, or 75 g/day soy-based fortified spread.	Change in WAZ score, HAZ, and WHZ score was not significantly different between the groups. Average gain in weight and height was higher among infants receiving FS (daily 25 to 75 g) than among those receiving only 0 to 5 g FS. The maximum weight gain was 0.83 kg with 50g of milk base fortified spread
(30) Malawi	Controlled, comparative clinical effectiveness trial	n=1178 children aged between 10-60 mths with wasting (WHZ < -2)	Home based therapy with RTUF (260g plastic jar/day) for 8 weeks. Standard therapy (F100).	**F100** (n=186) / **RTUF** (n=992) Rate of weight gain (g/kg/d) 4 wks: 2.0±6.9 / 3.5±3.7* Rate of height gain (mm/d) 8 wks: 0.12±0.29 / 0.19±0.59* Rate of MUAC gain (mm/d) 4wks: 0.23±0.33 / 0.32±0.41* Children died %(n): 5.4 (10) / 3.0 (30) Children relapsed % (n): 16.7 (31) / 8.7 (87)*
(78) Malawi	RCT	n=282 children > 1 year old discharged from nutrition unit were systematically allocated to treatment	RTUF, blended maize/soy flour =730kJ/kg/d, or RTUF supplement=2100 kJ/d Recovery WHZ >0. provided	**RTUF** (n=69) / **RTUF-S** (n=96) / **Maize/soy** (n=117) Average weight gain (g/kg/d): 5.2* / 3.1 / 3.1 Children likely to reach WHZ>0: 95% / 78% / 78% (1.1-1.3%)
(79) **Maawi**	RCT	n=260 with severe malnutrition	Imported RTUF or local RTUF=175 kcal/kg/d) till they reach WHZ> -0.5 or after 16 wks	**Local RTUF** (n=135) / **Imported RTUF** (n=125) Weight gain (g/kg/d): 5.2±4.6 / 4.8±4.0 Height gain (mm/d): 0.33±0.29 / 0.24±0.23 MUAC gain (mm/d): 0.35±0.30 / 0.36±0.31
(26) Senegal	Open-labeled randomized trial	n=70 severely malnourished (WFH Z score < -2) age 6-30 mths	The children received either 3 meals of F100 or 3 meals of RTUF daily *ad libitum*	**F100** (n= 30) / **RTUF** (n=30) Rate of weight gain (g/kg/d): 10.1 (8.7, 11.4) / 15.6 (13.4, 17.8)* Average duration of rehabilitation: 17.3 (15.6,19.0) / 13.4(12.1, 14.7)* Daily energy intake (kJ /kg body wt/d): 573201 / 808±280*
(80) Ethiopia	A retrospective cohort study	n= 628 age 6–59 mths treated for SAM (MUAC <110 cm or weight for height ratio <70%)	Plumpy'Nut sachets according to their body weight	Weight gain= 5.24 (4.98, 5.63) gm/kg/day. Recovery rate =61.78%, Defaulter rate=13.85% Mortality rate= 3.02% Weight increase=21.4% Mean length of stay under intervention = 6.48 weeks (95% CI=6.25, 6.72). The overall rate of weight gain and recovery rate < sphere standards
(68) Niger	Cohort study	n=2238 age 6 - 23 mths between 60 - 80 cm in length	RUSF (Plumpy'Doz) 4 x325 g pots (4 pots = 1 mth) for 4 mths.	**RUSF** (n= 1400) / **Control** (n=838) / ***p*-value** ∆ Weight (g): 395 (364-425) / 327 (281-372) / 0.05 ∆ Length (cm): 2.7 (2.6-2.8) / 2.8 (2.6-2.9) / 0.24 ∆ WHZ: -0.2 (-0.2-0.2) / -0.3 (-0.4-0.3) / 0.006 ∆ MUAC (mm): -2.8 (-3.2-2.3) / -4.0 (-4.7-3.3) / 0.002
(65) Niger	Cohort study	n=1645 age 6-36 mths	RUSF= 247 kcal / day for 6 mths, RTUF =500 kcal /day for 4 mths.	**RUSF** / **RTUF** Reduction in wasting: 46% (6-69%) / 59% (17-80%) Incidence of wasting: NS / NS Incidence of severe wasting: NS / NS Reduction in incidence of stunting: / ↓
(81)	Cross-sectional semi-structured questionnaire survey	Care givers and community health workers of malnourished children age 6-59 mths	149 care givers interviewed	Expressed problems with acceptability = 60% Perceived child dissatisfaction with taste = 43% Attributed side effects to PPN = 64% Children took PPN willingly = 48% Needed encouragement or had to be forced = 47% children completely rejected PPN after 3 weeks = 5%

RCT, randomized control trial; P-RTUF, Peanut based RTUF; WPC-RTUF, whey protein concentrate RTUF; RUCF, Lipid based ready to use complementary foods; UNIMIX, fortified corn soy blend porridge; LNS, lipid based nutrient supplement; SAM, severe acute malnutrition; MUAC, mid-upper arm circumference; RTUF, ready-to-use therapeutic food; WAZ, weight-for-height Z-score; HAZ, height-for-age Z-score; WHZ, weight-for-height Z- score; WLZ, weight-for-length Z- score; LAZ, length-for-age Z- score; CSB, corn-soy blend; CSB++, corn-soy blend "plus-plus"; LNS, A lipid-based nutrient supplement; RUSF, ready-to-use supplementary food; FS, fortified spread; LP, micronutrient- fortified maize-soy flour ; PPN, peanut-based ready-to-use therapeutic food; HCCM , High Calorie Cereal Milk; NB, Nutributter; NT, Nutritabs; SP, Sprinkle powder; NI, non-intervention; LOS, Length of stay; SG, significantly different; NS, Not statistically significant; Diff, Difference;, change; wks, weeks; months, mth.

CONCLUSION

The majority of the existing evidence on the use of community based management of uncomplicated, moderately acute malnutrition has emerged from the studies conducted in Africa in emergency settings. There is little evidence exploring the impact of RTUF with other commercially available milk-based proprietary supplement in settings where food is available, and nutritional habits, nutritional education and sanitation are the main determinants of malnutrition. There are no studies on MAM from Asia where MAM is mainly prevalent. Furthermore, while assessing the impact of the supplementation on child nutritional status, other factors should also be taken into account, including appetite suppression, replacement of habitual food intake and compliance to the intervention.

AUTHORS' CONTRIBUTION

SF, FF, SAK: contributed to concept development and drafted the manuscript; SF, SAK revised manuscript. None of the authors had a personal or financial conflict of interest to disclose.

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