IMPACT OF LIPID-BASED NUTRIENT SUPPLEMENTS On PREVENTION AND TREATMENT OF CHILDHOOD MODERATE UNDERNUTRITION
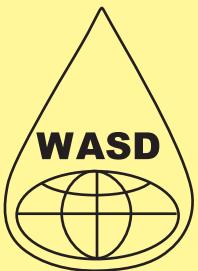
IMPACT OF LIP NUTRIENT SUPP PREVENTION AND OF CHILDHOOD UNDERNUT

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INTRODUCTION

Lipid-based nutrient supplements (LNS) have been successfully used in the treatment of severe acute malnutrition (SAM). However, their effect on moderate acute malnutrition (MAM) remains uncertain.

PURPOSE

This review aims at assessing the effectiveness of LNS interventions for prevention and/or treatment of moderate acute malnutrition (MAM), stunting and other anthropometric indicators for undernutrition in children younger than 5 years.

METHODOLOGY

Eighteen clinical trials on LNS (soy-based or milk-based) supplementation in children were compared with habitual diet/control or corn-soy blend (CSB). Mean changes in height for age (HAZ), weight for age (WAZ) and weight for height z-scores (WHZ) were assessed as primary outcomes. The secondary outcomes included: weight gain, height, mid upper arm circumference (MUAC), recovery from MAM, occurrence of fever, diarrhoea and cough.

FINDINGS

The pooled estimate revealed a statistically significant increase in WAZ (weighted mean difference [WMD] =0.09; 95%CI= 0.02, 0.15; p=0.01), WHZ (WMD=0.14; 95%CI= 0.01, 0.26; p=0.000) and improved recovery from MAM (Risk Ratio [RR] = 1.37; 95%CI= 1.14, 1.65; p=0.000) in children receiving LNS compared with control or CBS. No significant effect was observed in HAZ (WMD=0.00;95%-CI=-0.02,0.03: p=0.578). Children fed with milk-based LNS (RR=1.68; 95%CI=1.17, 2.39; p=0.005) were more likely to recover significantly from MAM when compared with CSB.

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CONCLUSION

Although there is evidence that LNS yield better nutritional outcomes than CSB and control, it is impossible to conclude that the milk-based LNS are superior to soy-based LNS and whether age and duration of intervention significantly affect the effectiveness of LNS on childhood undernutrition. Further research is required before these products can be recommended at scale.

KEYWORDS

Lipid-based nutrient supplements; undernutrition; CMAM; childhood

BIOGRAPHY

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Undernutrition occurs when the amount of micronutrients and macronutrients derived from food is inadequate to meet the body's daily nutritional requirement and to maintain optimum bodily functions (Manary and Sandige, 2008). Low- and middle-income countries have the highest prevalence rates of childhood undernutrition (Bhutta et al., 2013). More than 155 million children are stunted (<-2SD from median height for age of reference population) and 50 million suffer from wasting (<-2SD from median weight for height of reference population) in the world (UNICEF, WHO, Group WB, 2015). Wasting can be subdivided into Severe Acute Malnutrition (SAM; defined as <-3SD from median weight for height of reference population, or MUAC <115mm without presence of bilateral oedema), which accounts for 16 million cases of the total 50 million, and Moderate Acute Malnutrition (MAM; defined as <-2SD but >-3SD from median weight for height of reference population, or MUAC between 115mm and 125 mm without presence of bilateral oedema). Undernutrition is associated with around 45–50% of deaths in children younger than 5 years, which is approximately 2.5 million childhood deaths annually (Bhutta et al., 2013; UNICEF, WHO, Group WB, 2015). Malnutrition impairs cognitive function, reducing productivity and economic growth (Martins et al., 2011). It is estimated that undernutrition reduces economic development by 8% (Horton and Lo, 2013). Interventions prevent undernutrition, hence improving economic growth (Hoddinott et al., 2008).

Lipid-based nutrient supplements (LNS) are pre-packaged, in a semi-solid paste, containing essential macro- and micronutrients, including minerals, fatty acids, proteins, milk, sugar and peanuts (Chaparro and Dewey, 2010; Nutriset, n.d.; Arimond et al., 2015; Talley et al., 2012). Their low moisture content helps to ensure food safety, by discouraging bacterial growth. This reduces the risk of diarrhoea infections, a major cause of childhood morbidity and mortality (UNICEF, WHO, Group WB, 2015; Schoonees et al., 2013). There are numerous variants of LNS, such as fortified spreads (FS), ready-to-use supplementary foods (RUSF), ready-to-use foods (RUF), ready-to-use therapeutic food (RUTF), ready-to-use complementary food (RUCF) and energy-dense complementary food (Nutriset, n.d.; Arimond et al., 2015). These preparations have enabled more children to be treated at home, through the Community Management of Malnutrition (CMAM). The most commonly used variant of LNS, RUTF (PlumpyNut®), has been successfully used in the treatment of SAM in more than 50 countries, with more than 3 million cases being treated annually (UNICEF, WHO, Group WB, 2015). SAM children require a higher dose of plumpy nut (200–300g/day) to provide 200kcal of energy daily, compared with lower doses of other LNS products (20–50g/day), which supply about 100–250 kcal/day (Chaparro and Dewey, 2010). LNS should not be seen as a substitute for breast milk, which provides essential nutrients for infants (Bhutta et al., 2013; Briend and Collins, 2010; Owino et al., 2011).

Previous experimental studies showed that LNS are beneficial in improving anthropometric status in children (Talley et al., 2012; Lin et al., 2008; Isanaka et al., 2009; Isanaka et al., 2010; Mangani et al., 2013; Matilsky et al., 2009). However,

there were discrepancies in the results of certain outcomes, such as in Mangani et al. (2013). LNS did not improve linear growth and in Bismwa et al. 2012), LNS had no effect on stunting, or weight gain, amongst Congolese infants. Such disparities may be due to the varied duration of interventions (Simondon et al., 1996) and existing co-morbidities. Some nutrition stakeholders are unsure about the role of these products. Clear recommendations have not been issued for the utilisation of these products, to prevent undernutrition. The human and economic cost of malnutrition calls for an effective strategy to prevent the onset of undernutrition and halt the progression of MAM to SAM (Manary and Sandige, 2008; Chaparro and Dewey, 2010). The 2008 and 2013 Lancet nutrition series support the prioritisation of preventing undernutrition, as a key strategy in achieving global nutrition targets (Victoria et al., 2008). The United Kingdom's Department for International Development's (DFID) review of prevention activities highlighted the lack of robust evidence, supporting the continued use of ineffective interventions to prevent undernutrition. LNS products could help close the gap until underlying causes are addressed (Coffey, 2016).

To the best of the authors' knowledge, no systematic review, on the use of LNS for prevention and treatment of childhood malnutrition, has been conducted. There are two recent reviews, but both are focused on specific forms of LNS. A previous Cochrane review focused on RUTF for treating SAM (Schoonees et al., 2013) as well as a review by Lenters et al. (2013) focused on RUSF and RUTF for treating MAM and SAM. Previous reviews were limited, due to the inclusion of a few studies with the same variant of LNS. Included studies had high dropout rates, small sample sizes, and were conducted by the same authors in the same locations, affecting the generalisability of the results (Pope et al., 2007). This systematic review focuses on prevention and treatment of undernutrition, in particular, moderate undernutrition, with the use of all variants of LNS. This study can provide evidence to support resource allocation by countries and humanitarian organisations coping with the challenges of malnutrition. The systematic review includes a meta-analysis, to analyse the impact of LNS on prevention and treatment of undernutrition, in under -5s, by exploring changes in anthropometry, in those with wasting, underweight and stunting, as well as recovery from MAM. The meta-analysis also aims at assessing the effectiveness of LNS for prevention and/or treatment of MAM as compared with control (habitual diet) and/or corn soy blend (CSB). It further intends to compare whether milk-based LNS and soy-based LNS have different effectiveness as compared with each other or with CSB.

METHODS

This systematic review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009), and the research protocol was registered on the University of York's PROSPERO database (CRD42015025019) for systematic reviews and meta-analysis.

BIOGRAPHY

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Types of studies

All randomised control trials (RCT), quasi-randomised trials (trials that lacked adequacy of randomisation, such as alternation of study participants) and cluster-randomised trials (trials randomised by villages and health care centres) for treating and/or preventing MAM (Moderate Acute Malnutrition) as well as chronic malnutrition (stunting) were included.

Types of participants

Trials with children aged between 6 months and 5 years identified as normal, underweight, stunted, wasted or with MAM were included, irrespective of the country and study setting. MAM, also known as moderate wasting, is defined by a weight for height indicator between -3 and -2 z-scores (standard deviations) of the international standard or by a mid-upper arm circumference (MUAC) between 11 cm and 12.5 cm with no oedema. Stunting and underweight are defined by height for age and weight for age indicators below -2z-scores from median of reference population, respectively (UNICEF, WHO, Group WB, 2015).

Types of interventions

For the experimental group, we included data from studies with lipid-based nutrient supplements (LNS) regardless of type and source (soy-based or milk-based, locally or commercially produced). The control group included data from children not receiving LNS supplements or who were on habitual diet. Interventions such as corn soybean (CSB), also known as improved dry ration (IDR) or Likuli Phala, were classified as the non-LNS supplementation group to form another comparison arm. Likuli Phala is a mixture of corn and soya bean fortified with micronutrients (Matilsky et al., 2009). Trials that made comparisons only between variants of LNS or combined another form of management with LNS such as sprinkles, zinc, iron, micronutrient powder and those solely on acceptability of LNS were not included in this review. Studies on the management of SAM and MAM with use of products other than LNS were excluded.

Data was classified into five comparison groups: 1) LNS (milk- or soy-based) versus Control (habitual diet); 2) LNS (milk-based) versus CSB; 3) LNS (soy-based) versus CSB; 4) LNS (milk-based) versus LNS (soy-based); and 5) LNS versus Control and/or CSB. For comparison group 1, due to missing information on whether LNS (in the included studies) was milk- or soy-based, we could not split comparison 1 into milk-based and soy-based groups. Comparison group 5 drew data from comparisons 1, 2 and 3 to provide a summarised effect of LNS on undernutrition, and this was performed only for the primary outcomes.

Types of outcomes

To be eligible, studies must include data from at least one primary outcome of interest, which included: mean change in height/length for age z-scores (HAZ), mean change in weight for age z-scores (WAZ), mean change in weight for height/length z-scores (WHZ) and recovery from MAM. The secondary outcomes were as follows: mean change in mid-upper arm circumference (MUAC), mean weight gain in kg and mean height/length gain in cm. Occurrence of diarrhoea, fever and cough during the intervention were also included as secondary outcomes. Cases of allergies to peanut were considered as adverse effects of the intervention.

Methods of search for identification of studies

The following electronic databases were searched from inception (up to 2017) to identify relevant studies for this review:

- The Cochrane central register of clinical trials (CENTRAL)
- The Medline - 1946
- EMBASE – from 1980

- Clinicaltrials.Gov
- CINAHL - 1947
- WHO international clinical trials registry platform

In addition, references of selected trials were hand searched. Similarly, grey literature and relevant websites such as those of CMAM Forum, Emergency Nutrition Network, Epicentre and World Bank were searched. All international organisations using LNS as well as authors of trials in the trial register were contacted through standard emails requesting information about ongoing research and unpublished trials. Only one organisation responded to having an ongoing trial. There was no reply from other organisations or authors, despite establishing contact through reminder emails at 2-week intervals (total of 6 weeks). Hence, this review was solely based on primarily published studies.

Relevant studies were included, regardless of the language and status of publication (published, unpublished or ongoing) and the date of publication or the date when the study was conducted. Two independent reviewers selected the papers for inclusion. The title and abstract of each study identified through the search strategy were carefully screened by OTR and ARAA while being guided by the pre-specified eligibility criteria, to select relevant papers. The full text of any study considered to be eligible after reading the abstract was obtained.

Data extraction

Data were extracted systematically by using a specially designed and pre-piloted data extraction form. For every relevant study, the following information was extracted: source (e.g. study identification, citation and contact details), eligibility criteria, methods (e.g. study design, total duration, blinding), characteristics of participants (e.g. sample size, age, setting and sex), interventions (e.g. type, dose and duration), outcome (e.g. outcome description, unit and time points), results for each outcome, safety issues, funding and conclusions. The extracted data

were enlisted into either characteristics of included studies or characteristics of excluded studies or characteristics of ongoing studies.

To identify instances of multiple publications from the study, information about characteristics of the participants, type of intervention, period and place of study from all the papers were extracted. In addition, the primary reviewer (OTR) tried to contact the trial authors to confirm whether the articles reported results of the same study. In the case of multiple publications, the most complete articles were considered, such as those including a greater number of outcomes and more methodological information, as primary references.

Quality appraisal

Each study included in this review was assessed for the risk of bias by using the Cochrane risk of bias tool (Higgins, 2011). The potential sources of biases assessed in the studies were: random sequence generation, allocation concealment, blinding, attrition, selective reporting and other bias such as the source of funding and compliance. Each of these domains were rated as high risk of bias, low risk of bias or unclear risk of bias when information was not clearly provided in the text. For attrition bias, each study was represented: as high risk if more than 20% were lost to follow-up or if loss to follow-up was more than allowed for the study, as low risk if less than 20% or less than the rate allowed for that particular study and unclear when information was not clearly stated. Cluster-randomised trials were further assessed for recruitment bias, missing clusters and discrepancies in baseline characteristics.

Data analysis

Where insufficient or incomplete data were reported in a paper, the corresponding author was contacted. The extracted data were entered into both Revman and STATA (version 12.0, StataCorp, College Station, Texas, USA) for the analysis. Meta-analyses were

conducted when a group of studies was sufficiently homogeneous in terms of participants, interventions and outcomes to provide a meaningful summary. However, it is acknowledged "a priori" due to the diverse nature of intervention type, in terms of duration, intensity, settings and type of participants. Therefore, statistical heterogeneity seemed inevitable and random-effects models were applied when appropriate. The summary estimates for continuous data were calculated by using weighted mean difference (WMD) based on changes from baseline to post-intervention using the generic inversevariance and expressed with the random-effects model. Dichotomous data were calculated by risk ratio (RR) and expressed with random effect (DerSimonian and Laird, 1986). All results were presented with 95% confidence interval (CI) and represented on a forest plot, and the null hypothesis of no effect was rejected at $P \leq 0.05$.

For cluster-randomised trials, we followed the method of adjusting for clustering as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011). The data were adjusted by the design effect using the following formulae: $1 + (M$ [average cluster size] $-1)$ ICC [intra-cluster correlation coefficient]. Whenever the ICC was not reported in the study, a low ICC of 0.001 (based on previous literature [Schoonees et al., 2013; Huybregts et al., 2012]) was imputed because we did not anticipate large between-cluster variability. For dichotomous outcomes, both the number of participants and the number who experienced the event were divided by the same design effect; however, for continuous outcomes, only the sample size was reduced (means and SDs were left unchanged).

When studies with continuous outcomes did not report required standard deviations to allow for meta-analysis, other reported measures of dispersion (e.g. confidence intervals, standard errors, P values) were used to approximate the missing values (standard deviation) by using the formulas described in Higgins (2011). This was also used to derive the changes in outcome variables for studies that only provided the baseline and end-of-intervention measures.

Three studies (Mangani et al., 2013; Matilsky et al., 2009; LaGrone et al., 2011) had two treatment groups of LNS compared with CSB data: One experimental arm had milk-based LNS, and the other had soy-based LNS. However, as these two experimental arms can form three kinds of research questions, they were analysed separately (Higgins and Green, 2011): LNS (milk-based) versus CSB; LNS (soy-based) versus CSB; and LNS (milk-based) versus LNS (soy-based). Similarly, this strategy was applied to Thakwalakwa et al. (2010), Thakwalakwa et al. (2012) (29) and Mangani et al. (2013) (17), which included a control group (habitual diet), apart from CSB and LNS experimental arms. Since there were no substantial distinctions of the types of fortified spreads (FS50, FS25 and others) used in some studies (Lin et al., 2008; Phuka et al., 2009a), data from studies that used two or more types of fortified spreads (Phuka et al., 2008; Kuusipalo et al., 2006) were merged together and compared with the CSB.

For the comparison group 5 (LNS versus Control and/or CSB), data were drawn from comparison groups 1, 2 and 3 (LNS versus control/habitual diet, LNS milk-based versus CSB, LNS soy-based versus CSB respectively). We collated the data from each study and analysed them with Revman to generate a single forest plot. For dichotomous outcomes, both the number of events and the total number of participants were divided. For continuous outcomes, only the total number of participants were divided and the means and standard deviations were left unchanged. This analysis was performed only for the primary outcome of the review. This was done to provide an overall effect of LNS (regardless of type) over undernutrition compared with control or CSB.

The heterogeneity among studies was initially assessed by a visual inspection of forest plots to evaluate whether confidence intervals overlapped. Statistically, heterogeneity in each meta-analysis was

assessed by using the Tau2, I2 and Q statistics. The null hypothesis of homogeneity was rejected if P < 0.1, as the power of this test is low (Higgins and Green, 2011). I2 values of 30% to 50% were considered as moderate to high heterogeneity. Analysis with I2 ≥ 50% signified a great deal of heterogeneity, which was explored by using pre-specified subgroup analysis and sensitivity analysis.

A subgroup analysis was intended to be performed to compare the effects of LNS across the following subgroups:

- LNS for < 6 months versus for ≥ 6 months—to determine whether a longer duration of intervention was more effective than a shorter duration.
- Children aged 6 months to 24 months (this time is when weaning takes place) versus children aged 25 months to 60 months (time when the diet is more diverse).

Further, sensitivity analysis was performed while omitting every single study, one by one, in successive steps, to evaluate the influence of each study on the pooled effect size, in the context of significant heterogeneity, by applying the "metainf" command in STATA. In addition, a sensitivity analysis was performed with the exclusion of studies with small sample size and with allocation concealment bias to explore the influence of quality of the studies on results. The study design was also used as a marker for the source of heterogeneity (cluster-randomised trials versus single randomised trials versus quasi-experimental trials).

For primary outcomes and for each intervention with 10 or more included studies in the meta-analysis, putative publication bias was planned to be assessed by funnel plot charts of pooled effect size standard error (SE). The funnel plot was visually assessed for sources of asymmetry, such as small study effects, publication bias or other. If it was likely that the asymmetry was caused by small study effects, sensitivity analysis was conducted to explore how this affected the results and the conclusion of the meta-analysis. Analysis of publication

bias was assessed by the funnel plot and Egger´s test (p-value <0.1 indicated significant asymmetry) (Egger et al., 1997).

RESULTS

The summary of the result of the search is provided in the PRISMA flow chart (Figure 1 in online supplementary material). In total, 2061 papers were screened, and 18 studies were included in this review with 15,876 children.

The characteristics of included studies are presented in Table 1. Eleven studies were performed in Malawi (Lin et al., 2008; Mangani et al., 2013; Matilsky et al., 2009; LaGrone et al., 2011; Thakwalakwa et al., 2010; Phuka et al., 2009; Phuka et al., 2008; Phuka et al., 2012; Phuka et al., 2009; Thakwalakwa et al., 2012; Maleta et al., 2004), two in the Democratic Republic of Congo (Bisimwa et al., 2012; van der Kam et al., 2012) and one each in Niger Republic (Isanaka et al., 2009); Sudan (Talley et al., 2012), Chad (Huybregts et al., 2012), Ethiopia (Karakochuk et al., 2012) and Haiti (Iannotti et al., 2014). Seventeen were RCT (including three cluster RCT [Isanaka et al., 2009; Huybregts et al., 2012; Karakochuk et al., 2012]), and one was a quasi-experimental trial (Talley et al., 2012). The staple foods used in the studies were made from blended corn or maize and are also known as Likuni Phala or Improved Dry Ration. The characteristics of excluded studies and ongoing studies are presented in Tables 1 and 2, respectively, in supplementary online material.

Risk of bias of included studies.

Randomisation was applied in 16 out of 18 studies, of which 11 studies had adequate randomisation of study participants with a low risk of bias, 6 had an unclear randomisation sequence and only one study had inadequate randomisation sequence. Blind assessment of outcomes by investigators was done in 11 studies (Figure 2 supplementary online material). The three studies with cluster RCT (Isanaka et al., 2009; Huybregts et al., 2012; Karakochuk

FIGURE 1
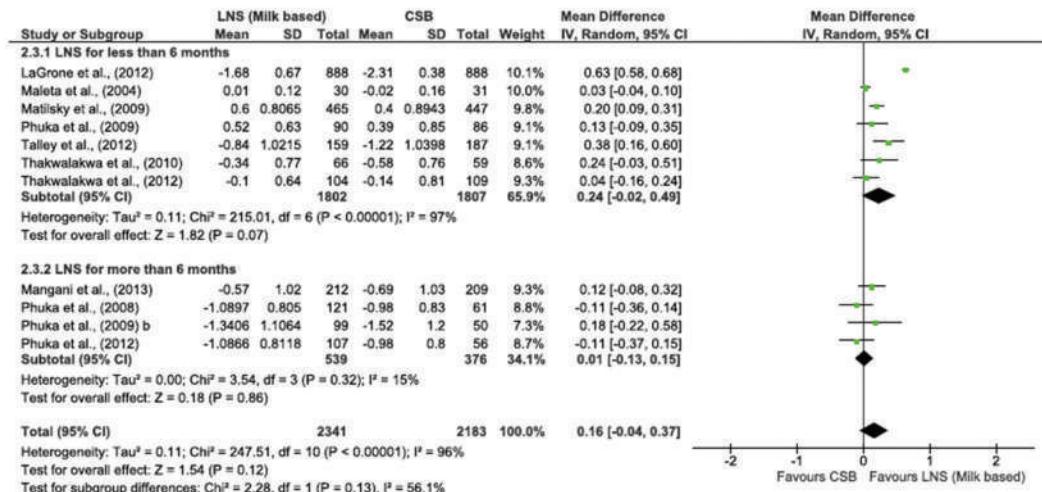
Forest plot for the comparison of LNS (milk-based) versus CSB for the mean change in WHZ outcome according to study duration.

The shaded squares represent the sample size, and solid horizontal lines represent the 95% confidence interval (CI).
The diamond represents the pooled WHZ difference, and the solid vertical line represents the null hypothesis of no
effect of LNS. Subgroup analysis according to the study duration (short-term < 6 months vs long-term ≥ 6 months).

FIGURE 2
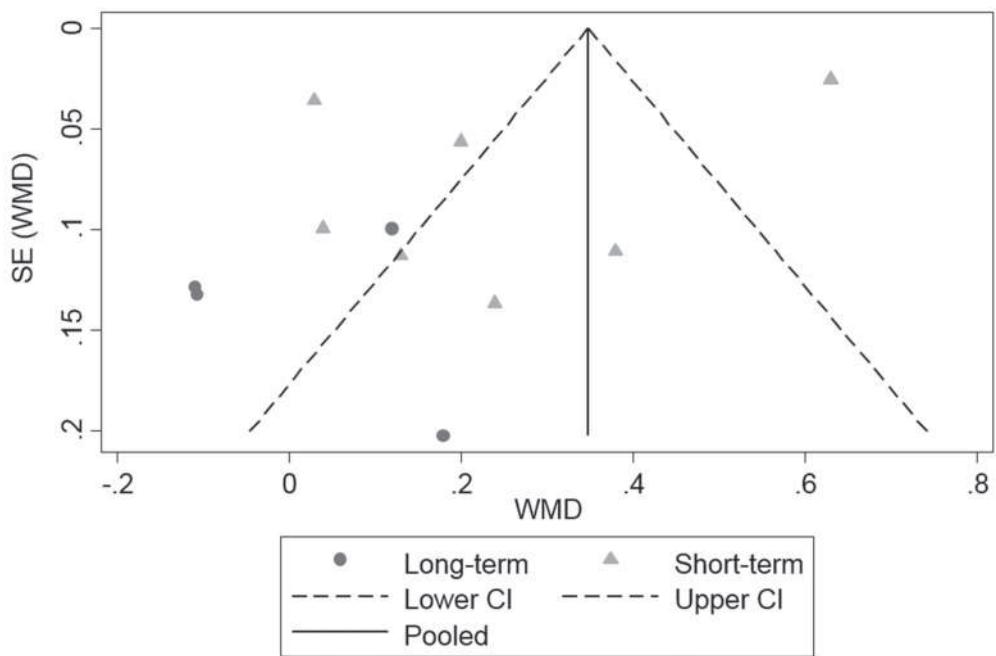
Funnel for WHZ outcome for milk-based LNS versus CSB.

SMD, standardized mean difference; SE, standard error

The vertical solid line represents the pooled estimate (WMD), and the diagonal dashed lines represent the pseudo 95%CI around the
pooled estimate. The WMD of zero indicates no effect. Each circle represents a long-term study, and each triangle is a short-term study.

TABLE 1

Characteristics of included studies

Author/year	Country	Design	Population	Recruitment	Intervention	Description
Bisimwa et al., (2012)	Democratic Republic of Congo.	RCT	N = 1383 Age: 6 to 12 months	October 2009 to March 2010	1. RUCF (soy-based) 2. UNIMIX (CSB)	RUCF: 50g/day for 6 months UNIMIX: 50g/day for 6 months Follow-up visits weekly (in the 6 months intervention period)
Huybregts et al., (2012)	Chad	Cluster RCT	N = 1038 Age: 6 to 36 months	June 2010 to July 2010	1. RUSF(unspecified) 2. Control (habitual diet)	RUSF: 46g/day for four months. 7 villages (RUSF) and 7 had no supplementation Monthly visits by field nurses and assistants
Iannotti et al., (2014)	Haiti	RCT	N = 589 Age: 6 to 11 months	May to December 2011	1. LNS (unspecified) 2. Control (habitual diet)	LNS: (Nutributter) half sachet given twice daily for 6 months (108 kcal/day) Monthly visits during intervention period to up to a month afterwards (7 months)
Isanaka et al., (2009)	Niger republic	Cluster RCT	N = 3533 Age: 6 to 60 months		1. RUTF(unspecified) 2. Control (habitual diet)	RUTF: 1 sachet daily (500 kcal/day) for 3 months Monthly visits during intervention and up to 5 months post-intervention (8 months)
Karakochuk et al., (2012)	Ethiopia	RCT	N = 1125 Age: 6 to 60 months	April 2009 to October 2009	1. RUSF(milk-based) 2. CSB	RUSF: 500kcal/day for 16 weeks CSB: 300g/day for 16 weeks. Biweekly follow-up done by trained nurses during intervention period
LaGrone et al., (2012)	Malawi	RCT	N = 2890 Age: 6 to 59 months	Not mentioned	1. RUSF (soy-based) 2. Whey RUSF (milk-based) 3. CSB	Supplements were given daily for 12 weeks. 2 weekly follow-up visits for up to 6 follow up visits. Caretaker reported on child's clinical symptoms and trained officers measured anthropometry.

TABLE 1

Characteristics of included studies (*Cont.*)

Author/year	Country	Design	Population	Recruitment	Intervention	Description
Lin et al., (2008)	Malawi	RCT	N = 240 Age: 6 to 18 months	Study conducted between July 2005 and September 2006	1. Fortified spread (soy-based) 2. Fortified porridge made from corn flour (CSB)	Supplements were given for 6 months, and children were followed up to 12 months through monthly visits by health aides.
Maleta et al., (2004)	Malawi	RCT	N = 61 Age: 42 to 60 months	Participants were recruited between 1995 and 1996 as live neonates.	1. RUF (milk) 2. Maize soy flour (CSB)	RUF: 92g/day for 12 weeks CSB: 140g/day for 12 weeks 4 weekly follow-ups during the intervention period and for up to 12 weeks after intervention were done by field workers.
Mangani et al., (2013)	Malawi	RCT	N = 840 Age: 6 to 18 months	28 January 2008 to 25 May 2009	1. LNS (milk-based) 2. LNS (soy-based) 3. CSB 4. Control (habitual diet)	Both LNS had 54g/day each. CSB: 71g/day for 12 months 2 weekly follow-ups for 12 months by field workers
Matilsky et al., (2009)	Malawi	RCT	N = 1362 Age: 6 to 60 months	July 2007 to February 2008	1. FS (milk-based) 2. FS (soy-based) 3. CSB	Milk FS: 314kJ/kg/day Soy FS: 314kJ/ kg/day CSB: 314kJ/ kg/day Duration of intervention = 8 weeks Biweekly follow-up of participants
Phuka et al., (2008)	Malawi	RCT	N = 182 Age: 6 to 18 months	Study conducted from October 2004 to December 2005. Recruitment date not mentioned.	1. FS 50 (milk-based) 2. FS 25 (milk-based) 3. CSB (Likuli Phala)	FS: 50g/day for 12 months CSB:71g/day for 12 months Follow-ups were done every 17 weeks for one year during the intervention.

Study	Country	Design	Sample	Date	Groups	Intervention
Phuka et al., (2009)	Malawi	RCT	N=176, Age: 6 to 18 months	March 2005	1. FS (milk-based) 2. CSB (Likuli Phala)	FS: 350g/week for 12 weeks; CSB: 500g/week for 12 weeks; Follow-up was done for 6 weeks during intervention by trained field officers.
Phuka et al., (2009)b	Malawi	RCT	N=182, Age: 6 months	Conducted between October 2004 and January 2008. Recruitment date not mentioned.	1. FS 50 (milk-based) 2. FS25 (milk-based) 3. CSB (Likuli Phala)	FS: 50g daily for 12 months; CSB:71g/day for 12 months; Follow-up was done for 4 weeks during the intervention to 2 years post-intervention.
Phuka et al., (2012)	Malawi	RCT	N=163, Age: 6 months	Conducted between October 2004 and December 2005 (recruitment date not mentioned)	1. FS 50 (milk-based) 2. FS 25 (milk-based) 3. CSB (Likuli Phala)	FS: 50g/day for one year; LP: 71g/day for one year; Follow-up visits done during intervention on a weekly basis
Talley et al., (2012)	Sudan	Quasi experimental	N=1451, Age: 6 to 36 months	Conducted between May and August 2009 (recruitment date not mentioned)	1. LNS (milk-based) 2. CSB (IDR)	LNS: 247kcal, 5.9g protein, 16g fat/day for 4 months; IDR:785kcal, 28.2g protein, 27.4g fat/day for 4 months; Monthly follow-up by field officers during intervention
Thakwalakwa et al., (2010)	Malawi	RCT	N=182, Age: 6 to 18 months	December to February 2007	1. LNS (milk-based) 2. CSB 3. Control (habitual diet)	LNS: 43g/day for 12 weeks; CSB:71g/day for 12 weeks; Weekly monitoring of participants by trained field assistants
Thakwalakwa et al., (2012)	Malawi	RCT	N=299, Age: 6 to 18 months	November 2007 to January 2008	1. LNS (milk-based) 2. CSB 3. Control (habitual diet)	LNS: 43g/day for 12 weeks; CSB:71g/day for 12 weeks; Weekly monitoring of participants by trained field assistants
Van Der Kam et al., (2012)	Democratic republic of Congo.	RCT	N=180, Age: 6 to 59 months	Not mentioned	1. RUTF (unspecified) 2. Control (habitual diet)	RUTF: 500kcal/day for 14days; Monitoring of weight gain was done on days 14 and 28 by field staff.

Abbreviation: CSB, corn soy blend; FS, fortified spreads; IDR, improved dry ration; LNS, lipid-based supplement; MAM, moderate acute malnutrition; RCT, randomised controlled trial; RUCF, ready-to-use complementary food; RUSF, ready-to-use supplementary food; RUTF, ready-to-use therapeutic food

Summary of the pooled estimates for all comparison groups

TABLE 2

Outcome / subgroup	Studies	N	Method	Effect Estimate	P^I	I^2
LNS vs Control						
HAZ	6	3046	WMD (IV, Rand 95%CI)	-0.01 (-0.07, 0.05)	0.80	25%
Short-term trials	4	2121		-0.02 (-0.10, 0.06)	0.66	33%
Long-term trials	2	925		0.04 (-0.07, 0.15)	0.44	0%
WAZ**	4	1240	WMD (IV, Rand 95%CI)	0.29 (-0.03, 0.62)	0.08	89%
Short-term trials	2	315		0.55 (0.17, 0.93)	0.005	76%
Long-term trials	2	925		0.07 (-0.05, 0.18)	0.25	0%
WHZ*	5	2752	WMD (IV, Rand 95%CI)	0.13 (0.05, 0.22)	0.002	17%
Short-term trials	4	2121		0.09 (0.01, 0.18)	0.03	0%
Long-term trials	1	631		0.25 (0.09, 0.41)	0.002	10%
Recovery from MAM	0	0	NA	NA	NA	NA
Weight gain (kg)	4	1126	WMD (IV, Rand 95%CI)	0.12 (0.05, 0.18)	0.0004	0%
Short-term	3	495		0.13 (0.06, 0.20)	0.0005	0%
Long-term	1	631		0.08 (-0.06, 0.21)	0.26	NA
Height increase (cm)	3	946	WMD (IV, Rand 95%CI)	0.13 (-0.07, 0.34)	0.20	0%
Short-term	2	315		0.16 (-0.11, 0.42)	0.25	0%
Long-term	1	631		0.10 (-0.22, 0.42)	0.54	NA
MUAC (cm)	3	1259	WMD (IV, Rand 95%CI)	0.05 (-0.13, 0.23)	0.58	55%
Fever (% events)	4	2280	RR (M-H, Rand, 95%CI)	0.45 (0.31, 0.66)	<0.0001	0%
Short-term	3	1986		0.45 (0.29, 0.70)	<0.001	NA
Long-term	1	294		0.46 (0.22, 0.94)	0.03	0%
Cough (% events)	4	2280	RR (M-H, Rand, 95%CI)	0.81 (0.71, 0.92)	0.0009	0%
Short-term	3	1986		0.80 (0.79, 0.91)	0.0007	0%
Long-term	1	294		1.07 (0.45, 2.55)	0.88	NA

Outcome/subgroup	Studies	N	Method	Effect Estimate	P	I2
Diarrhoea (%events)	6	2595	RR (M-H, Rand, 95%CI)	0.74 (0.54,1.02)	0.07	4%
Short-term	5	2301		0.75 (0.47,1.19)	0.23	22%
Long-term	1	294		0.78 (0.46,1.31)	0.34	NA
LNS (milk-based) vs CSB						
HAZ*	9	2410	WMD (IV, Rand 95%CI)	0.02(-0.01,0.05)	0.24	0%
Short-term trials	5	1495		0.01(-0.002,0.04)	0.53	0%
Long-term trials	4	915		0.11(0.00,0.21)	0.04	0%
WAZ*	8	1498	WMD (IV, Rand 95%CI)	0.04(0.00,0.08)	0.06	0%
Short-term trials	4	583		0.05(-0.03,0.13)	0.26	28%
Long-term trials	4	915		0.09(-0.01,0.19)	0.08	0%
WHZ	11	4524	WMD (IV, Rand 95%CI)	0.16(-0.04,0.37)	0.12	96%
Short-term trials	7	3609		0.24(-0.02,0.04)	0.07	97%
Long-term trials	4	915	WMD(IV, Rand 95%CI)	0.01(-0.13,0.15)	0.86	15%
Recovery from MAM b,d	4	3701		1.68(1.17,2.39)	0.005	98%
Weight gain (kg)	7	1335	WMD (IV, Rand 95%CI)	0.09(0.04,0.13)	0.0001	0%
Short-term	4	583		0.08(0.03,0.12)	0.001	0%
Long-term	3	752		0.15(0.03,0.27)	0.01	0%
Height increase cm*	7	1327	WMD (IV, Rand 95%CI)	0.07(-0.09,0.24)	0.17	34%
Short-term	4	575		0.01(-0.13,0.15)	0.89	20%
Long-term	3	752		0.33(0.00,0.66)	0.05	0%
MUAC (cm)	5	845	WMD (IV, Rand 95%CI)	0.14(0.02,0.25)	0.02	0%
Short-term	3	515		0.16(-0.03,0.29)	0.56	0%
Long-term	2	331		0.07(0.16,0.30)	0.02	0%
Outcome/subgroup	*Studies*	*N*	*Method*	*Effect Estimate*	*P*	*I2*
Fever (% events)	1	240	RR (M-H, Rand, 95%CI)	0.61(0.26,1.45)	0.26	NA
Cough (% events)	1	170	RR (M-H, Rand, 95%CI)	0.84(0.32,2.21)	0.72	NA
Diarrhoea (%events)	4	2328	RR (M-H, Rand, 95%CI)	1.09(0.95,1.24)	0.21	0%

TABLE 2

Summary of the pooled estimates for all comparison groups *(cont.)*

Outcome / subgroup	Studies	N	Method	Effect Estimate	P^a	I^2
			LNS (soy-based) vs CSB			
HAZ	4	2887	WMD (IV, Rand 95%CI)	0.04 (-0.04, 0.11)	0.33	0%
Short-term	1	897		0.10 (-0.18, 0.38)	0.48	NA
Long-term	3	1990		0.03 (-0.05, 0.11)	0.42	0%
WAZ[b, c]	3	1989	WMD (IV, Rand 95%CI)	0.03 (-0.05, 0.11)	0.52	0%
WHZ	4	4441	WMD (IV, Rand 95%CI)	0.07 (0.02, 0.11)	0.007	0%
Short-term	2	2691		0.08 (0.02, 0.13)	0.004	0%
Long-term	2	1750		0.02 (-0.09, 0.12)	0.72	0%
Recovery from MAM[b, d]	2	2691	RR (M-H, Rand, 95%CI)	1.06 (0.97, 1.15)	0.18	75%
Weight gain (kg)	3	1989	WMD (IV, Rand 95%CI)	0.000 (-0.12, 0.13)	0.96	60%
Height increase(cm) [b, c]	3	1989	WMD (IV, Rand 95%CI)	-0.11 (-0.31, 0.09)	0.28	0%
MUAC (cm) [b]	1	1331	WMD (IV, Rand 95%CI)	0.01 (-0.09, 0.11)	0.84	NA
Fever (% events) [b]	1	240	RR (M-H, Rand, 95%CI)	0.96 (0.36, 2.37)	0.86	NA
Cough (% events) [b]	1	240	RR (M-H, Rand, 95%CI)	0.71 (0.32, 1.55)	0.39	NA
Diarrhoea (% events)	2	2034	RR (M-H, Rand, 95%CI)	1.09 (0.95, 1.24)	0.22	0%
Short-term	1	1794		1.10 (0.96, 1.25)	0.18	NA
Long-term	1	240		0.66 (0.21, 2.01)	0.46	NA
Outcome/subgroup	Studies	N	Method	Effect Estimate	Pa	I2
			LNS (milk-based) vs LNS (soy-based)			
HAZ	3	3131	WMD (IV, Rand 95%CI)	-0.04 (-0.12, 0.03)	0.26	23%
Short-term	2	2709		-0.07(-0.13, -0.01)	0.02	0%
Long-term	1	422		0.05(-0.09, 0.19)	0.48	NA
WAZb	1	422	WMD (IV, Rand 95%CI)	0.04 (-0.12, 0.20)	0.63	NA

WHZ	3	3131	WMD (IV, Rand 95%CI)	0.02 (-0.11, 0.15)	0.79	76%
Short-term	2	2709		0.01 (-0.16, 0.18)	0.91	87%
Long-term	1	422		0.05 (-0.15, 0.25)	0.62	NA
Weight gain (kg) b	1	422	WMD (IV, Rand 95%CI)	0.07 (-0.09, 0.23)	0.39	NA
Height increase (cm) b	1	422	WMD (IV, Rand 95%CI)	0.20 (-0.15, 0.55)	0.27	NA
Recovery from MAMb, d	2	2739	RR (M-H, Rand, 95%CI)	1.00 (0.97, 1.03)	0.98	0%
Diarrhoea (% events) b	1	1824	RR (M-H, Rand, 95%CI)	1.01 (0.88, 1.15)	0.92	NA
LNS (milk-based/ soy-based) vs Control and/ or CSB						
HAZ	14	10601	WMD(IV, Rand,95%CI)	0.00(-0.02,0.03)	0.578	0%
Short-term	7	6771		0.00(-0.04,0.04)	0.93	30%
Long-term	7	3830		0.06(0.00,0.11)	0.73	0%
WAZ	11	4727	WMD(IV, Rand,95%CI)	0.09(0.02,0.15)	0.01	52%
Short-term	4	898		0.23(0.03,0.43)	0.93	30%
Long-term	7	3829		0.05(-0.001,0.11)	0.04	0%
WHZ	14	12199	WMD(IV, Rand,95%CI)	0.14(0.01,0.26)	<0.00001	93%
Short-term	9	8903		0.11(0.06,016)	<0.00001	38%
Long-term	5	3259		0.06(-0.04,0.16)	0.22	43%
Recovery from MAMb ,d	4	6710	RR(M-H,Rand,95%CI)	1.37 (1.14,1.65)	0.000	97%

Abbreviation: CSB, corn soy blend; HAZ, height for age z-scores; IV, inverse of variance; LNS, lipid-based supplement; MAM, moderate acute malnutrition; M-H, Mantel Hanzel; MUAC, mid-upper arm circumference; NA, not applicable; RR, relative risk; WAZ, weight for age; WHZ, weight for height z-scores; WMD, weighted mean difference; I2 refers to the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance).

Short-term trials: Intervention was administered for less than six months.

Long-term trials: Intervention was administered for more than six months.

* P-value for the test for subgroup difference borderline (p <0.09)

** P-values for the test for subgroup difference <0.05

*** P-values for the test for subgroup difference <0.01

a P-value for the pooled effect, b Subgroup analysis not applicable

c All trials were long-term, d All trials were short-term.

Effects of interventions

The summary of pooled estimates of all outcomes for all 5 comparison groups is presented in Table 2. We were unable to analyse results by different age groups for all outcomes. There was no explicit measuring of allergic reactions as an adverse outcome.

Comparison group 1: LNS versus control

Seven trials contributed data for this group. The majority (n=4) of the trials did not specify whether LNS was milk- or soy-based. Two trials (Thakawalakwa et al., 2010; Thakwalakwa et al., 2012) applied milk-based LNS. One trial (Mangani et al., 2013) applied both LNS milk- and soy-based versus control. In this situation, we combined data from both milk- and soy-based arms and compared with control.

Primary outcomes

There was no effect of LNS on HAZ (WMD= -0.01; 95% CI= -0.07, 0.05; n=3046; I2= 25%) compared with those in the control group. Subgroup analysis by study duration presented similar results. Long-term studies (≥ 6 months) were quite homogeneous (I2= 0%; P = 0.62) compared with short-term studies (I2= 63%; P = 0.04). Heterogeneity seemed to be driven by one cluster-randomised study (Huybregts et al., 2012).

The pooled estimate showed that there was a tendency to a higher increase in WAZ in the LNS group (WMD= 0.29; 95% CI = -0.03, 0.62; n=1240) compared with the control group, but the result was not statistically significant (P= 0.08) and presented high heterogeneity (Chi2=26.71, df =3, P< 0.00001, I2= 89%). Exclusion of a small study (Thakwalakwa et al., 2010) as well as cluster RCT (Iannotti et al., 2014) did not reduce heterogeneity. Heterogeneity was partially explained by subgroup analysis, as long-term studies were homogeneous (I2= 0%). Results with shorter administration of LNS were statistically significant (WMD= 0.55; 95% CI= 0.17, 0.93; n=315; I2= 76%). It was not possible to perform subgroup analysis based on the age of participants as all the children in the trials were younger than 2 years.

There was a significant increase in WHZ in the LNS group compared with the control group (WMD = 0.13; 95% CI= 0.05, 0.22; n= 2752; P= 0.002) with no significant heterogeneity (Chi2=5.02; df= 4; P=0.29; I2=17%). Subgroup analysis showed no significant difference between long-term and short-term studies (WMD = 0.09 versus WMD = 0.25; P= 0.09 [for subgroup difference]). None of the studies considered recovery from MAM, and, therefore, no analysis was performed.

Secondary outcomes

There was a significant higher weight gain (WDM = 0.12 kg, 95%CI= 0.05, 0.18; P= 0.0004) among those in the LNS group compared with those in the control group. Children in the LNS group were significantly less likely to have fever and cough compared with those in the control group (p<0.05). There was a tendency toward less events of diarrhoea among the LNS group compared with the control group, but the p-value was borderline (P= 0.07). There was no significant effect on increase in height and MUAC. All subgroup analyses showed no significant differences on effect sizes between long-term and short-term studies. No significant heterogeneity was found in all outcomes, except for MUAC (I2 = 55%). However, it was not possible to conduct a subgroup analysis based on the duration of intervention as all the trials were short-term and all the children in the 3 included studies were between 6 months and 24 months.

Comparison group 2: LNS (milk-based) versus CSB

Primary outcomes

There was a non-significant increase in HAZ among children in the LNS group compared with those in

the CSB group (WMD=0.02; 95% CI= -0.01, 0.05; n=2410; P= 0.24). However, the magnitude of the intervention tended to be higher in long-term trials (WMD = 0.11; 95% CI = 0.0, 0.21; n = 915; P = 0.04) compared with short-term trials (WMD = 0.01; 95% CI = -0.002, 0.04; n = 1495; P = 0.53).

Children in the LNS group tended to have a higher increase in WAZ compared with those in the CSB group (WMD = 0.04; 95%CI = -0.001, 0.08; n = 1498), but the increase was borderline significant (P = 0.06). Included studies were homogeneous, and subgroup analysis showed no significant difference between long-term and short-term studies (P for subgroup difference = 0.51).

There was a non-significant increase in WHZ in children in the LNS group compared with those in the CSB group. Results showed significant heterogeneity among trials (Chi^2= 247.51, df 10; P<0.00001; I2 = 96%). Subgroup analysis according to intervention duration did not yield statistically significant results; however, short-term trials appeared to have a higher increase than longer term trials (WMD= 0.24; 95%CI = -0.02, 0.49 versus WMD =0.01; 95% CI = -0.13, 0.15), (Figure1) but the test for subgroup difference was not statistically significant (P = 0.13). Subgroup analysis based on children's ages (6 – 24 months versus > 24 months) did not reduce heterogeneity (I^2 = 96%). Similarly, sensitivity analysis excluding the smallest study (Maleta et al., 2004) and quasi-experimental study (Talley et al., 2012) did not reduce heterogeneity.

Children who received LNS (milk-based) were more likely to recover from MAM compared with those who received CSB (RR = 1.68; 95%CI = 1.17, 2.39; n= 3701, P= 0.005), and there was no significant heterogeneity detected among trials (Chi^2 = 196, df = 3; P<0.00001, I2 = 98%). Subgroup analysis was not performed as all trials were short-term and all trials included children up to 6 months of age or older.

Secondary outcomes

Children who received LNS (milk-based) had a significant higher weight gain (WMD = 0.09 kg;

95%CI = 0.04, 0.13; P = 0.0001) and higher gain in MUAC (WMD = 0.14 cm; 95%CI = 0.02, 0.25; P = 0.02) compared with those fed with CSB. There was a non-significant increase in height and improvement in fever and cough. There was no significant effect on diarrhoea events among participants. No significant heterogeneity was found for all outcomes, except for height (I2 = 34%; P = 0.08). Subgroup analysis showed that children who had LNS for a longer time tend to gain more weight and height compared with those who had LNS for less than 6 months; however, the subgroup differences were borderline significant.

Comparison group 3: LNS (soy-based) versus CSB

Primary outcomes

There was no significant increase in HAZ (WMD = 0.04; 95%CI = -0.04, 0.11; n = 2887; P = 0.33), WAZ (WMD = 0.03; 95%CI = -0.05, 0.11; n = 1989; P = 0.52) and WHZ (WMD = 0.07; 95% CI = 0.02, 0.11]; n = 4441; P = 0.007) among children in the LNS (soy-based) group compared with those in the CSB group. No significant heterogeneity was detected among trials.

For WAZ, it was not possible to conduct subgroup analyses regarding the duration of intervention and children's age as all trials were less than 6 months duration and included children between 6 and 24 months. The magnitude of the intervention tended to be higher in short-term trials for WHZ and HAZ compared with long-term trials, but the difference between groups was not statistically significant (P for subgroup difference > 0.05).

There was no significant improvement in recovery from MAM recovery (RR = 1.06; 95%CI = 0.97, 1.15; n = 2691; P = 0.18). A significant heterogeneity was found (Chi^2 = 4.02; df = 1; P = 0.05; I2 = 75%). Only two short-term studies contributed data for this outcome. Therefore, subgroup analysis was not performed.

Secondary outcomes

LNS (soy-based) had no significant effect on weight gain, gain in height and MUAC and it did not significantly decrease the risk of fever, cough and diarrhoea compared with CSB. Analysis showed no significant heterogeneity among all the outcomes apart from weight gain (I2= 60%). Subgroup analysis for weight gain was not performed as all 3 included trials were long-term. All studies included children between 6 and 24 months; hence, subgroup analysis was not performed based on age for none of the secondary outcomes.

Comparison group 4: LNS (milk-based) versus LNS (soy-based)

Primary outcomes

There was no significant difference in HAZ among children in the milk-based group compared with those in the soy-based group (WMD= -0.04; 95%CI= -0.12, 0.03; n= 3131). Although results for short-term trials tended to favour the soy-based group (P= 0.02), subgroup differences between short-term (WMD= -0.07; 95%CI= -0.13, -0.01; n =2709) and long-term trials (WMD= 0.05; 95%CI= -0.09, 0.19; n = 422) were not statistically significant.

A non-statistically significant increase in WAZ was found among children (Mangani et al., 2013) who had milk-based LNS compared with soy-based (WMD= 0.04; 95%CI=-0.12,0.20; n= 422, P=0.63).

There was no significant difference in WHZ among children in the milk-based group compared with those in the soy-based group (WMD= 0.02; 95%CI= -0.11, 0.15; n= 3131; P= 0.79), with significant heterogeneity (Chi2= 8.20; df= 2; P= 0.02; I2= 76%). Subgroup analysis by duration of the intervention did not explain the heterogeneity.

There was no difference between milk-based and soy-based groups regarding recovery from MAM (RR=1.00; 95%CI= 0.97, 1.03; n= 2739; P=0.98), with no heterogeneity among two included trials

(I2=0%). Both trials were short-term, and subgroup analysis was not applicable.

Secondary outcomes

There was no significant difference between milk-based and soy-based groups regarding all secondary outcomes. Subgroup analysis and test for heterogeneity were not applicable as only single studies considered the aforementioned as outcomes.

Comparison group 5: LNS (milk- or soy-based) versus Control and/or CSB

Analyses for this comparison group were performed for primary outcomes only.

Overall, children receiving LNS had a non-significant increase in HAZ (WMD=0.00; 95%CI= -0.02, 0.03; I2 = 0%) compared with control and/or CSB. Children receiving LNS had a significant increase in WAZ (WMD=0.09; 95%CI= 0.02, 0.15; I2 = 52%) and WHZ (WMD=0.14; 95%CI= 0.01, 0.26; I2 = 93%) and were more likely to recover from MAM (RR=1.37; 95%CI= 1.14,1.65; I2 = 97%) compared with those receiving control and/or CSB (See Supplementary online material Figure 4).

Publication bias

Publication bias was assessed in only one primary outcome (WHZ) in LNS (milk-based) versus the CSB comparison group, which had 11 included studies in the analysis. Figure 2 shows that the funnel plot was asymmetric, indicating the presence of publication bias. We further assessed publication bias by using Egger's test and found a significant p-value (0.019) for the presence of small study effect. Similar results were observed for the LNS (milk- or soy-based) versus Control and/or CSB comparison group (LAZ, n = 19 studies, P = 0.10; WHZ, n= 20 studies, P = 0.103; WAZ, n = 15 studies, P = 0.03). Since only six studies were included for recovery from MAM, analysis was not performed.

DISCUSSION

The aim of this review was to explore the impact of LNS in normal to moderately malnourished children on HAZ, WAZ, WHZ and recovery from MAM. Eighteen studies were found eligible, of which seventeen were RCTs (including three cluster RCTs) and one was a quasi-experimental study.

The main findings show that children receiving LNS tend to have better results for most primary and secondary outcomes compared with those having their habitual diet (Control) or receiving CSB, although not all the results were statistically significant. In addition, improved recovery from MAM was observed in LNS (milk-based) compared with CSB (P<0.05). However, no significant difference in recovery from MAM was seen in the soy-based LNS compared with CSB. It is important to consider that only two trials contributed data for this particular comparison (soy-based LNS versus CSB). The pooled estimate of effect of LNS compared with control or CSB (Table1) revealed a statistically significant increase in WAZ, WHZ and recovery from MAM. However, no effect was seen in HAZ. It is important to consider that the duration of some studies could have been too short for LNS to have a significant effect on HAZ.

Quality of evidence

Most of the trials had moderate quality, and only two studies required contact with trial authors to clarify unclear methodological aspects of which responses were not received. Seventeen out of 18 studies reviewed were RCTs, which have a higher quality than any other type of study design (Moher et al., 2009). However, three of these trials were cluster RCTs that were prone to selection bias. Overall, the risk of bias was found to be high for detection, attrition, performance and other biases, which could have led to overestimation of the effects of intervention.

Overall completeness and applicability of evidence

This systematic review researches the best evidence on the effectiveness of LNS to prevent undernutrition in childhood. We assessed whether LNS was more effective than having no supplements or a CSB meal. More importantly, it was paramount to know whether the milk-based LNS yielded a better outcome than the soy-based LNS when compared with CSB. The cost of these products can dictate which of them will be used consistently to tackle undernutrition since the price of milk-based LNS is twice that of soy-based LNS (Matilsky et al., 2009). Also, the target of the WHO to achieve a 40% reduction of less than 5 stunted children and to reduce childhood wasting to less than 5% by the year 2025 (WHO 2015) may not be met without completely exhausting the potential of LNS. Further, the first 1000 days of life and up to 5 years is a very crucial period where nutritional interventions have major contributions towards children's health (UNICEF, WHO, Group WB, 2015). This intervention can supply essential nutrients that are optimal for preventing undernutrition.

Despite many studies having been carried out on LNS, most of them focussed on the use of RUTF for treatment of SAM and, because of the elicited comparison groups, they were not eligible for this review. A previous Cochrane review on treatment of SAM with RUTF, including only four trials (three having a high risk of bias and one trial including children infected with human immunodeficiency virus [HIV]), all conducted in Malawi with the same contact author, did not reach any definitive conclusion on whether home-based RUTF (soy-based) was better than the standard type (Nutributter containing Milk) (Schoonees A et al., 2013). The result of our current review regarding the effect of LNS on recovery from MAM is, however, consistent with a meta-analysis by Lenters et al., 2013, in which RUSF yielded better recovery than CSB for treatment of MAM.

This review has several limitations. Eleven of the 18 included studies were conducted in Malawi, where the staple diet is corn, which makes it less possible to generalise our findings to other countries where staple food is different. External validity limitation is also prominent as the studies explored the effect of LNS on children in a similar age range (6–18 months), and a few studies included children from 6 months up 60 months. Only Maleta et al. (2004) conducted a trial among older children solely (42 to 60 months). Therefore, it was not possible to compare the effect of LNS between younger and older children. Further, only Maleta et al. (2004) had information on total daily dietary intake per group. There was no detailed information on probability of sharing the LNS supplement with other children in the household or family members and measures to prevent that from occurring. Compliance was measured through checking the level of paste in jars, sachet counting and caretaker interviews, which does not guarantee that the supplements were taken by the intended study participant.

As children were exposed to peanuts, soy and milk occurrence of allergy would be an important adverse effect of the intervention. However, only two studies (Thakwalakwa et al., 2010; Thakwalakwa et al., 2012) explored the possibilities of peanut allergies and no study tested for soy and milk allergies. LNS have low moisture content, which makes them less able to cause diarrhoea; however, very few studies explored diarrhoea as an outcome, even though diarrhoea is a main cause of childhood mortality (UNICEF, 2013). In addition, only one study (Phuka et al., 2009a) monitored post-intervention effects of LNS on growth for more than 12 months, limiting the possibility to draw conclusions for sustained effect of LNS on growth. Therefore, further prospective cohort studies may be needed to measure effects on growth through assessment of expected cognitive developments for age and anthropometric measures after a few years on supplementation with LNS.

We had limited response from authors and organisations, which could have affected the number of studies included in this review. There were limited data on recovery from MAM as well as secondary outcomes such as MUAC, events of fever, cough and diarrhoea. Though some studies are of good quality, some bias is commonly present, which may compromise results. Only published studies were added and, as such, unpublished articles may have been missed. Another limitation is that only trials published in English were included, with most of them being conducted in Africa (Malawi) by the same authors. Further, all identified studies conducted in Asia, a continent with a high rate of malnutrition (UNICEF, 2013) focussed on treatment of SAM. Hence, these Asian studies were not included in the review. Publication bias could not be fully assessed for all comparison groups and outcomes because of the limited number of included studies. For comparison 2 (WHZ), the funnel plot (Figure 2) shows evidence of asymmetry, indicating publication bias. However, the asymmetry of the funnel plot might also be due to heterogeneity, methodological quality and chance. When heterogeneity is presented, as observed in this particular outcome (I2= 96%), the funnel plot is considered inadequate and trim-and-fill analysis is usually poorly performed. When the analysis was performed by using all trials (comparison 5), the level of heterogeneity was slightly reduced (I2= 93%) and Egger test showed a borderline p-value for small study effect (p=0.103) (data not shown). Therefore, our findings need to be interpreted with caution.

Implications for practice & research

Given the evidence from the pooled estimates, LNS tend to have a slightly better clinical outcome on nutritional status compared with CSB and control. However, other studies on feasibility, acceptability, cost effectiveness and long-term effects are needed before LNS can be routinely administered in developing countries that are prone to malnutrition. The meta-analysis of the few studies with data on diarrhoea found that LNS did not significantly lower the risk of diarrhoea in children compared with CSB, but it tended to reduce the risk of diar-

rhoea when compared with control (P > 0.05). In addition, LNS significantly reduced the risk of fever and cough compared with control.

Adequately designed randomised controlled trials according to CONSORT guidelines (Consolidated standards of reporting trials) on LNS on nutritional outcomes are needed in Asia, with focus also on diarrhoea and allergies to peanut, milk and soybean. Since it is not possible to deduce conclusively that milk-based LNS are better than soy-based LNS, further research is needed to ascertain which product yield is more effective. To properly elicit whether outcome results are dependent on duration of intervention, studies that compare short and long durations of interventions are still needed. Future research should also compare interventions between younger and older children.

CONCLUSION

The overall results show that LNS showed significant improvement on wasting (WHZ), underweight (WAZ) and recovery from moderate acute malnutrition, although the effect on stunting (HAZ) was insignificant. Hence, these small differences in stunting found make it slightly difficult to recommend this intervention at scale. Results of this review might not be applicable to other regions of the world with a non-corn-based staple diet. Firm conclusions could not be drawn on whether milk-based LNS were more effective than soy-based LNS due to the limited number of included trials that used soy-based LNS. Similarly, it is not certain whether duration of the intervention and age at beginning of the intervention are factors that can determine the effect size of the LNS supplementation until more trials directly addressing these issues are carried out. Future research should also focus on other contexts and other outcomes (cost effectiveness, long-term, relapse, recovery rates and death rates) as well as make a comparison with other interventions.

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