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Lipid-based nutrient supplements for pregnant women and their impact on pregnancy, birth, and infant developmental outcomes in stable and emergency settings (Protocol)

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[Intervention Protocol]

Lipid-based nutrient supplements for pregnant women and their impact on pregnancy, birth, and infant developmental outcomes in stable and emergency settings

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

1. To review the effects of lipid-based nutrient supplements (LNS) when given to women during pregnancy, and their impact on maternal, birth and infant outcomes.

2. To explore the most appropriate composition, frequency and duration of LNS.

BACKGROUND

Description of the condition

The nutritional status of women prior to and during pregnancy plays a key role in fetal growth and development, and women's energy and protein requirements significantly increase during pregnancy (FAO/WHO/UNU 2004). Maternal undernutrition is still prevalent, especially in low- and middle- income countries (LMICs), with approximately 20% of women in Asia and 10% women in Africa having low body mass index (BMI) (less than (<) 18·5 kg/m² in adult women) (Black 2013). Apart from low BMI, deficiencies of micronutrients, including iron, folate, calcium, and vitamin A and D, are also prevalent in LMICs. The global prevalence of anaemia among pregnant women was estimated to be 38.2% in 2011 (WHO 2015). At least half of this anaemia burden is assumed to be due to iron deficiency, with the rest due to other conditions, including folate, vitamin B12 or vitamin A deficiencies, chronic inflammation, parasitic infections and inherited disorders (Black 2013). Calcium and vitamin D deficiency is also a major public health problem worldwide in all age groups; however, most countries are still lacking reliable data, particularly population representative data, with limited information on infants, children, adolescents and pregnant women (Palacios 2014). Globally, the prevalence of night blindness in pregnant women is estimated

to be around 8%, affecting around 10 million women, with an estimated 15.3% of pregnant women worldwide having low serum retinol levels (Black 2013). Estimates suggest that 28.5% of the world's population, or 1.9 billion individuals, are iodine deficient (Black 2013). Additionally, undernutrition and micronutrient deficiencies increase the risk of infections and, in turn, lead to further undernutrition (Black 2013).

Low birth weight (LBW) is complex and includes preterm neonates (born before 37 weeks of gestation), small for gestational age (SGA) neonates at term, and the overlap between these two situations - preterm SGA neonates, who typically have the worst outcomes. Maternal undernutrition causes maternal and child morbidity and mortality and also contributes to LBW and SGA births, which can lead to stunting, wasting, and micronutrient deficiencies in children (Black 2013). These nutritional deficiencies can impair child cognitive development (Shenkin 2004), and pose adverse health outcomes in adulthood (Harder 2007). Maternal iron deficiency anaemia has been strongly associated with adverse birth outcomes, including LBW and increased perinatal mortality, while maternal zinc and iodine deficiency has been suggested as a risk factor for adverse fetal and infant growth (Black 2013). LBW, defined by the World Health Organization (WHO) as weight-at-birth < 2500 g (5.5 lb), continues to be a significant public health problem globally. Overall, it is estimated that 15% to 20% of all births worldwide are LBW, representing more than 20 million births a year (WHO 2014). LBW is not only a major predictor of mortality and morbidity in infants and children, but recent studies have found that it also increases the risk for non-communicable diseases, such as diabetes and cardiovascular disease, in later life (Larroque 2011; Risnes 2011).

Addressing undernutrition is of utmost importance to improve maternal and child health outcomes. Early preventive measures could address general deprivation and inequity, and lead to substantial and long-term improved outcomes. Implementation of nutrition interventions and provision of delivery platforms to maximise scale-up to reach the unreached is also pivotal (Black 2013). Disruption and displacement of populations in emergency situations (including conflicts and natural disaster) pose an added threat to the existing situation of undernutrition. Statistics suggest that women and children represent over three-quarters of the estimated 80 million people in need of humanitarian assistance, and many countries with high maternal, newborn and child mortality rates are affected by humanitarian emergencies (UNICEF 2014).

Description of the intervention

Various interventions are recommended (or have been implemented) to improve maternal nutrition, including education, food provision, micronutrient supplements (iron, folic acid, multiple micronutrients), and other indirect interventions, such as agricultural and financial interventions (Bhutta 2013). One of the nutritional interventions advocated to improve undernutrition in pregnant women is **l**ipid-based **n**utrient **s**upplements (LNS), which could be provided to pregnant women to improve their nutritional status, and thereby enhance their infants' nutritional status. Adequate consumption of long-chain, omega-3 polyunsaturated fatty acids in the diet of pregnant women is essential, particularly the most biologically active forms (docosahexaenoic acid and eicosapentaenoic acid) (Coletta 2010), as these fatty acids support fetal growth, especially brain and eyes, and deficiency may be associated with visual deficit and suboptimal behavioural development. However, there is not enough evidence to support the routine use of marine oil or other prostaglandin precursor supplements during pregnancy to reduce the risk of pre-eclampsia, preterm birth, LBW or SGA (Makrides 2006).

LNS are a family of products designed to deliver nutrients to vulnerable people. There is no standard composition of LNS, however, the majority of the energy is supplied from fats. Three main LNS products are currently used in maternal and child nutrition: ready to-use therapeutic foods (RUTF); ready-to-use supplementary foods (RUSF), or medium-quantity LNS; and LNS for home fortification, or small-quantity LNS (Arimond 2015). Ready-to-use therapeutic foods are designed for treatment of severe acute malnutrition, provide almost all energy requirements and are given in large daily doses (Diop 2003); RUSF or medium-quantity LNS are designed for treatment of moderate acute malnutrition and they provide 50% to 100% of energy needed; while small-quantity LNS products are designed to prevent undernutrition and promote growth and development through home fortification of local diet, and provide less than 50% of the energy needed (Arimond 2015).

LNS provide a range of vitamins and minerals, but unlike most other micronutrient supplements they also provide energy, protein and essential fatty acids (Chaparro 2010). They are considered 'lipid-based' because most of the energy provided by these products is from lipids (fats). There is no recommended composition for LNS and hence various existing projects have used various compositions. LNS recipes can include a variety of ingredients, but typically include vegetable fat, peanut or groundnut paste, milk powder and sugar; other ingredients include whey, soy protein isolate, and sesame, cashew and chickpea paste (iLiNS Project 2016). Various commercial and locally available products are being used as LNS, however alternative recipes and formulations are currently being explored in efforts to develop affordable and culturally acceptable products for a range of settings. Similar products combining vegetable oil, groundnut paste, milk, sugar and micronutrients are being used as RUTF in the management of both severe acute malnutrition (WHO 2013) and moderate acute malnutrition in infants and children (WHO 2012). Some studies have evaluated the feasibility and acceptability of LNS, suggesting that it is acceptable to infants and pregnant and lactating women (Adu-Afarwuah 2011). Corn soy blends are different from LNS as these are fortified blended foods (FBF) used as complementary foods or as supplementary foods for pregnant women.

LNS can be used as point-of-use fortification of foods or can be consumed directly during pregnancy as a source of energy, as protein and micronutrients in public health programmes, and as an intervention to improve birth weight and other pregnancy outcomes in areas where maternal undernutrition is prevalent (Arimond 2015; iLiNS Project 2016). These are usually given at a daily dose of < 120 kcal/day. The doses and formulations of LNS can be modified according to the needs of the specific target group and, to date, there is no standard formulation widely accepted for women during pregnancy. Some of the advantages of LNS include the readiness to be consumed with no cooking required before use, and that it can be stored for up to six months even in hot climates (Phuka 2008). This makes LNS especially useful in emergency settings where safe water and hygiene are common issues.

How the intervention might work

Ready-to-use lipid-based nutrients could be a good source of macro- and micronutrients in a highly nutrient-dense supplement, and could supplement the nutrient requirements as part of the diet in undernourished populations of pregnant women. It has been hypothesised that LNS works through changes in hormone concentrations in pregnancy. Some trials have shown that LNS increase birth size, possibly through a change in the endocrine regulation of foetal development, and are associated with higher cord blood leptin in primigravidae and women from the highest tertile of BMI (Huybregts 2013). The supplement composition can be tailored to meet the nutritional requirements of the target population. Cost is an important consideration, however, it should be weighed against the effectiveness in maintaining and improving nutritional outcomes (Chaparro 2010).

Multiple studies have evaluated the impact of LNS when given to pregnant women and children in LMICs. The use of LNS has been associated with improved nutritional status among pregnant women and thereby improved growth and development outcomes among infants and children (Arimond 2015; Iannotti 2014; Thakwalakwa 2010); however, one study suggests that these initial effects are not sustained during infancy (Lanou 2014). One study from Malawi suggested that LNS did not influence the occurrence of maternal *Plasmodium falciparum* parasitaemia, trichomoniasis, vaginal candidiasis or urinary tract infection (Nkhoma 2017). Studies have also suggested that LNS are palatable and acceptable to women in LMIC settings (Adu-Afarwuah 2011; Mridha 2012; Mridha 2016), although there are variances to adherence within the population (Harding 2014), as beneficiaries tend to make their own adaptations in terms of how much and how often to consume (Harding 2014). A study evaluating home delivery of LNS products in rural Malawi suggests that the cost of procurement, storage and weekly home delivery of LNS is largely comparable to other product delivery mechanisms currently undertaken in the public sector; however, the study suggests that the expected health and other benefits associated with each proposed intervention strategy should be compared to the costs to set priorities (Vosti 2015).

Why it is important to do this review

LNS are currently being used in programmes targeting pregnant women in LMICs with the expectation of improving birth outcomes and reducing LBW (Schofield 2009; WHO 2007), and current studies have shown mixed effects of this intervention using varying composition, dose, frequency and comparison groups between studies. This review will assess the effects and safety of LNS for women during pregnancy on maternal, birth and infant outcomes, as currently there is no systematic evaluation in this domain, and will attempt to assess the appropriate composition, frequency and duration of this intervention through various subgroup analyses. In addition, we will carry out a subgroup analysis on whether the pregnant women were identified and the LNS were distributed through a facility or in a community. We are also developing a companion review to assess the effectiveness of preventive lipid-based nutrient supplements (LNS) given with complementary foods on health, nutrition and developmental outcomes of non-hospitalised infants and children 6 to 23 months of age (Das in press). Together these reviews will guide policy makers to make informed decisions on the effectiveness and safety of LNS compared to other interventions and to assess which delivery platforms are effective.

Micronutrient supplements and powders are not recommended for pregnant women, based on the lack of evidence for their impact on maternal anaemia (WHO 2016), but they will be compared to the provision of LNS, given the assumption that other micronutrients contained in the micronutrient powders could have an impact on pregnancy, birth and infant developmental outcomes; for example, zinc on preterm births (Ota 2015a). We will also compare LNS to antenatal nutrition education, since nutrition education conducted during the antenatal period with the aim of increasing energy and protein intake appears to be effective in reducing the risk of preterm birth and LBW, increasing head circumference at birth, increasing birth weight among undernourished women, and increasing protein intake (Ota 2015b).

OBJECTIVES

1. To review the effects of lipid-based nutrient supplements (LNS) when given to women during pregnancy, and their impact on maternal, birth and infant outcomes.

2. To explore the most appropriate composition, frequency and duration of LNS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs (i.e. trials that use methods of assignment such as alternation, or assignment based on date of birth or case record number) (Lefebvre 2011). We will include randomised cross-over trials if the authors include the measurements before crossing the study arms.

Types of participants

Women with singleton pregnancy of any age and parity, living in stable or emergency settings.

Types of interventions

Interventions involving the provision of LNS at any point-of-use fortification of foods or direct consumption, irrespective of dose, frequency and duration. We will include any LNS disregarding its content. Specifically, we will assess the evidence on the following comparisons.

1. Provision of a LNS compared to no intervention or placebo.
2. Provision of a LNS compared to oral multiple micronutrient (MMN) supplements. We will include studies comparing LNS with MMN and report the differences in the micronutrients between the groups as mentioned by the study authors.
3. Provision of a LNS compared to multiple micronutrient powders (MNPs). We will include studies comparing LNS with MMP and report the differences in the micronutrients between the groups as described by the study authors.
4. Provision of a LNS compared to nutrition counselling.

Iron and folic acid is a recommendation for pregnancy and hence would be given to both the intervention and the comparison groups. We will only include studies that combine provision of LNS with other cointerventions, or other approaches, if the same cointerventions are provided in both the intervention and comparison groups.

This review will exclude comparisons to FBF; these foods are given in larger quantities (more calories and nutrients) and so are difficult to compare with LNS, which are given in much smaller quantities.

Types of outcome measures

Primary outcomes

Maternal

1. Maternal anthropometric status (weight, BMI, gestational weight gain)
2. Maternal anaemia at term or near term (haemoglobin (Hb) < 110 g/L)
3. Adverse effects (any), for example, allergic reactions as diagnosed by clinical assessment (atopic dermatitis, urticaria, oedema (oral), ophthalmic pruritus, allergic rhinitis, asthma, anaphylaxis)

Newborn and infant

1. Low birth weight (birth weight < 2500 g)
2. Weight at birth (in g)
3. Length at birth (in cm)
4. Small-for-gestational age (as defined by authors of the trials)
5. Preterm births (births before 37 weeks of gestation)
6. Development outcomes (milestones, as defined by authors)

Secondary outcomes

Maternal/newborn

1. Maternal Hb at term or near term (in g/L at 34 weeks' gestation or more)
2. Miscarriage and stillbirths (as defined by trial authors)
3. Maternal satisfaction with LNS (as defined by trial authors)
4. Maternal adherence or compliance with LNS (as defined by study authors)

Infant

1. Head circumference (in cm)
2. Mid upper arm circumference (MUAC) (in cm)
3. Stunting at any time within the first six months (-2 Z-score or lower)
4. Wasting at any time within the first six months (-2 Z-score or lower)
5. Underweight at any time within the first six months (-2 Z-score or lower)
6. Neonatal death (death occurring between 0 and 28 days of life)
7. Infant mortality (death occurring in the first year of life)

Search methods for identification of studies

Electronic searches

We will search the sources listed below.

International databases

1. Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library, and which includes the Cochrane Developmental, Psychosocial and Learning Problems Specialised Register.
2. MEDLINE Ovid (1946 onwards).
3. MEDLINE In-Process and Other Non-Indexed Citations Ovid (current issue).
4. MEDLINE E-pub ahead of print Ovid (current issue).
5. Embase Ovid (1980 onwards).
6. CINAHL Plus EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1937 onwards).
7. Social Sciences Citation Index Web of Science (SSCI; 1970 onwards).
8. Science Citation Index Web of Science (SCI; 1970 onwards).
9. Conference Proceedings Citation Index - Science Web of Science (CPCI-S; 1990 onwards).
10. Conference Proceedings Citation Index - Social Science & Humanities Web of Science (CPCI-SS&H; 1990 onwards).
11. *Cochrane Database of Systematic Reviews* (CDSR; current issue) part of the Cochrane Library.
12. Epistemonikos (epistemonikos.org; current issue).
13. POPLINE (www.popline.org; current issue).
14. ClinicalTrials.gov (clinicaltrials.gov).
15. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; who.int/trialsearch).

Regional databases

1. IBECS (Índice Bibliográfico Español en Ciencias de la Salud; ibecs.isciii.es; current issue).
2. Scieclo (Scientific Electronic Library Online; www.scielo.br; current issue).
3. AIM Africa Global Index Medicus (Africa Index Medicus; search.bvsalud.org/ghl/?lang=en&submit=Search&where=REGIONAL; current issue).
4. IMEMR Global Index Medicus (Index Medicus for the Eastern Mediterranean Region; search.bvsalud.org/ghl/?lang=en&submit=Search&where=REGIONAL; current issue).
5. LILACS (Latin American and Caribbean Health Sciences Literature; lilacs.bvsalud.org/en; current issue).
6. PAHO/WHO Institutional Repository for Information Sharing (iris.paho.org/xmlui; current issue).
7. WHOLIS Global Index Medicus (WHO Library Database; search.bvsalud.org/ghl/?lang=en&submit=Search&where=REGIONAL; current issue).
8. WPRIM Global Index Medicus (Western Pacific Index Medicus; search.bvsalud.org/ghl/?lang=en&submit=Search&where=REGIONAL; current issue).
9. IMSEAR Global Index Medicus (Index Medicus for the South-East Asian Region; search.bvsalud.org/ghl/?lang=en&submit=Search&where=REGIONAL; current issue).
10. IndMED (indmed.nic.in/indmed.html; current issue).
11. Native Health Research Database (hscssl.unm.edu/nhd; current issue).

We will adapt the MEDLINE search strategy for use in the other databases using the appropriate controlled vocabulary, if available (Appendix 1). We will not apply language or date restrictions for any database. If we identify studies written in a language other than English, we will commission their translation into English. We will record any such studies as 'Studies awaiting classification' until a translation becomes available.

Searching other resources

We will check the reference lists of included studies and relevant reviews for further studies. We will contact authors of eligible studies for information about ongoing or unpublished studies we may have missed or, where necessary, to provide missing data.

Data collection and analysis

Selection of studies

Two review authors (ZH and RAS) will independently assess for inclusion all records generated by the search strategy. First, they will screen titles and abstracts of all records retrieved and shortlist those deemed relevant. Next, they will obtain and assess the full texts of all potentially relevant records, assessing each one against the inclusion criteria (see Criteria for considering studies for this review), before deciding on the final list of studies to be included. Any disagreements will be resolved through discussion or, if required, in consultation with a third author (JKD). We will record our decisions in a PRISMA diagram (Moher 2009).

Data extraction and management

For eligible trials, two review authors (ZH and RAS) will independently extract data using a form designed for this review. We will resolve any discrepancies through discussion with the entire group and will document these in the review. We will complete a data collection form electronically and will extract and record the following information.

Trial methods

- Study design
- Unit and method of allocation
- Method of sequence generation
- Masking of participants, personnel and outcome assessors

Participants

- Location of the study
- Sample size
- Age
- Sex
- Socioeconomic status (as defined by trialists and where such information is available)
- Baseline prevalence of anaemia
- Baseline BMI status
- Inclusion and exclusion criteria

Intervention

1. Dose (< 120 kcal/day; 250 to 500 kcal/day)
2. Formulation of LNS
3. Frequency of distribution of LNS to the participants
4. Duration of the intervention
5. Cointervention

Comparison group

- No intervention or placebo
- Multiple micronutrient supplements
- Micronutrient powders
- Nutrition counselling

Outcomes

- Primary and secondary outcomes, as outlined in the Types of outcome measures section
- Exclusion of participants after randomisation and proportion of losses at follow-up

We will record both prespecified and non-prespecified outcomes, although the latter will not be used to underpin the conclusions of the review.
When information regarding any of the trials is unclear, we will attempt to contact authors of the original reports to provide further details.
We will enter the data into Review Manager (RevMan) software, version 5 (RevMan 2014).

Assessment of risk of bias in included studies

Two review authors (ZWP and JKD) will independently assess the risk of bias of each study using the criteria below, and as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions,* hereafter referred to as *Cochrane Handbook* (Higgins 2011a). We will resolve any disagreement by discussion or by involving a third assessor (ZH).

(1) Random sequence generation (checking for possible selection bias)

We will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it produces comparable groups.

- Low risk of bias (any truly random process, for example, random number table; computer random number generator).
- High risk of bias (any non-random process, for example, odd or even date of birth; hospital or clinic record number).
- Unclear risk of bias (where there is insufficient information provided to permit judgement of high or low risk of bias).

(2) Allocation concealment (checking for possible selection bias)

We will describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.

- Low risk of bias (for example, telephone or central randomisation; consecutively numbered, sealed, opaque envelopes).
- High risk of bias (open random allocation; unsealed or non-opaque envelopes).
- Unclear risk of bias (where there is insufficient information provided to permit judgement of high or low risk of bias).

(3) Blinding of participants and personnel (checking for possible performance bias)

We will describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received.
We will assess the risk of performance bias associated with blinding as follows.

- Low risk of bias (blinding of participants and personnel and unlikely that the blinding could have been broken, or no blinding or incomplete blinding but outcome unlikely to be influenced).
- High risk of bias (participants and personnel not blinded, incomplete or broken blinding, and outcome likely to be influenced).
- Unclear risk of bias for participants and personnel (where there is insufficient information provided to permit judgement of high or low risk of bias).

Whilst assessed separately, we will combine the results into a single evaluation of risk of bias associated with blinding.

(4) Blinding of outcome assessment (checking for possible detection bias)

We will describe all measures used, if any, to blind outcome assessors from knowledge as to which intervention a participant received.

- Low risk of bias (blinding of outcome assessment and unlikely that the blinding could have been broken, or no blinding but measurement unlikely to have been influenced).
- High risk of bias (for example, no blinding of outcome assessment, where measurement is likely to be influenced by lack of blinding, or where blinding could have been broken).
- Unclear risk of bias (where there is insufficient information provided to permit judgement of high or low risk of bias).

(5) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We will assess outcomes in each included study as follows.

- Low risk of bias (either there are no missing outcome data or the missing outcome data are unlikely to bias the results based on the following considerations: study authors provide transparent documentation of participant flow throughout the study, the proportion of missing data is similar in the intervention and control groups, the reasons for missing data are provided and balanced across intervention and control groups, the reasons for missing data are not likely to bias the results (for example, moving house)).
- High risk of bias (if missing outcome data are likely to bias the results: reasons related to outcome when proportion missing or plausible effect size enough to have a clinically relevant effect; 'as-treated' analysis with substantial departure from allocation and inappropriate use of imputation. Trials will also receive this rating if an 'as-treated (per protocol)' analysis is performed with substantial differences between the intervention received and that assigned at randomisation, or if potentially inappropriate methods for imputation have been used).
- Unclear risk of bias (where there is insufficient information provided to permit judgement of high or low risk of bias).

(6) Reporting bias (checking for possible reporting bias)

Selective reporting can lead to reporting bias. We will compare methods to results and look for outcomes measured (or likely to have been measured) but not reported.

- Low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review are reported).
- High risk of bias (where not all of the study's prespecified outcomes have been reported; one or more reported primary outcomes are not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported).
- Unclear risk of bias (where there is insufficient information provided to permit judgement of high or low risk of bias).

(7) Other sources of bias (checking for other possible sources of bias)

We will assess if the study was free of other potential bias as follows.

- Low risk of bias (where there is similarity between outcome measures at baseline, similarity between potential confounding variables at baseline, or adequate protection of study arms against contamination).
- High risk of bias (where there is no similarity between outcome measures at baseline, similarity between potential confounding variables at baseline, or adequate protection of study arms against contamination).
- Unclear risk of bias (where there is insufficient information provided to permit judgement of high or low risk of bias).

(8) Overall risk of bias

We will summarise the risk of bias within trials (across domains). We will assess the likely magnitude and direction of the bias in each of the above-mentioned domains and whether we consider they are likely to impact on the findings. We will consider trials at high risk of bias if they have poor or unclear allocation concealment and either inadequate blinding or high/imbalanced losses to follow-up. We will explore the impact of the level of bias through a Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as risk ratios (RR) with 95% confidence intervals (CI).

Continuous data

For continuous data, we will use the mean difference (MD) with 95% CI if outcomes are measured in the same way between trials. We will use the standardised mean difference (SMD) with 95% CI to combine trials that measure the same outcome but use different measurement methods.

When some trials report endpoint data and others report change from baseline data (with errors), we will combine these in the meta-analysis, if the outcomes are reported using the same scale.

Rates

If rates represent events that could have occurred more than once per participant, we will report the rate difference using the methodologies described in Deeks 2011.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. Cluster-randomised trials will be labelled with a 'C'. Where possible, we will estimate the intra-cluster correlation co-efficient (ICC) from trials' original data sets and will report the design effect. We will use the methods set out in the *Cochrane Handbook* to calculate the adjusted sample sizes (Higgins 2011b). We will use an estimate of the ICC derived from the study (if possible), from a similar study or from a study of a similar population. If we use ICCs from other sources, we shall report this and conduct sensitivity analyses to investigate the effect of variation in the ICC (see Sensitivity analysis). If we identify both cluster-RCTs and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit (see Sensitivity analysis).

Trials with more than two treatment groups

For trials with more than two intervention groups (multi-arm trials) and a single control group, we will include the directly relevant arms only. If we identify trials with various relevant arms, we will combine the groups into a single pair-wise comparison (if possible), according to the *Cochrane Handbook* (Higgins 2011b). If the control group is shared by two or more intervention groups, we will divide the control group (events and total population) over the number of relevant subgroup categories, to avoid double counting the participants in the control group. We will note the details in the 'Characteristics of included studies' tables.

Dealing with missing data

We will attempt to obtain missing data from the investigators. If this is not possible we will report the data as missing and will not attempt to impute values. We will describe missing data, including dropouts, in the 'Risk of bias' tables. Differential dropout rates can lead to biased estimates of the effect size, and bias may arise if the reasons for dropping out differ across groups. We shall report the reasons for dropout. If data are missing for some cases, or if the reasons for dropping out are not reported, we will try to contact the study authors and we will document if the authors could not be contacted or did not respond. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis (see Sensitivity analysis). For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis (i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention). The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess methodological heterogeneity by examining the methodological characteristics and risk of bias of the trials, and will assess clinical heterogeneity by examining the similarity between the types of participants, the interventions and the outcomes.
For statistical heterogeneity, we will examine the forest plots from meta-analyses to look for heterogeneity among trials and use the I^2 statistic, Tau^2 statistic and Chi^2 test to quantify the level of heterogeneity among the trials in each analysis. If we identify moderate or substantial heterogeneity, we will explore it by prespecified subgroup analysis (see Subgroup analysis and investigation of heterogeneity). We will regard heterogeneity as substantial if the value of the I^2 statistic is greater than 50%, and either Tau^2 is greater than zero or there is a low P value (< 0.10) in the Chi^2 test for heterogeneity. In case of absence of heterogeneity, we will perform prespecified subgroup analysis (see Subgroup analysis and investigation of heterogeneity).
We will advise caution in the interpretation of analyses with high degrees of heterogeneity.

Assessment of reporting biases

If 10 or more studies are included in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes, we will use the test proposed by Egger 1997. For dichotomous outcomes, we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using RevMan 2014. We will use a random-effects model as our primary analysis for combining data, considering the differences in the intervention. We will only use a fixed-effect model as a sensitivity analysis (if it is likely to be plausible); see Sensitivity analysis. We will conduct a meta-analysis where it is reasonable to assume that studies are estimating the same underlying treatment effect (i.e. where trials are examining the same intervention, and the trials' populations and methods are judged to be sufficiently similar). We will use the generic inverse variance for the analysis of properly analysed cross-over trials and

cluster-randomised trials, as well as outcome data that are ordinal, time-to-event or rates.

We will present the results as the average treatment effect with 95% CIs and the estimates of Tau^2 and I^2 (Deeks 2011).

Where it is not appropriate to conduct a meta-analysis, we will describe the results as reported by the study authors.

Summary of findings

For the assessment across trials, we will set out the main findings of the review in 'Summary of findings' tables, prepared using GRADE profiler software (GRADEpro 2014). We will list the primary outcomes for each comparison with estimates of relative effects along with the number of participants and trials contributing data for those outcomes. For each individual outcome, we will assess the quality of the evidence using the GRADE approach (Balshem 2010), which involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias, and results in one out of four levels of quality (high, moderate, low or very low). We will limit this assessment to the trials included in the review only.

Subgroup analysis and investigation of heterogeneity

1. By anaemia status of the participants at baseline: anaemic versus non-anaemic versus mixed/unknown/unreported.
2. By baseline BMI of the participants: low BMI versus normal BMI.
3. By delivery strategy: facility versus provided in community versus mixed/unknown/unreported.
4. By duration of intervention: less than three months versus three to six months versus six months or more.
5. By energy density and formulation of product provided (as defined in the trials).
6. By setting: stable versus emergency versus mixed/unknown/unreported. We use the Inter-Agency Standing Committee's (IASC) definition of emergency (IASC 1994): a situation threatening the lives and well-being of a large number of people or a very large percentage of a population and often requiring substantial multi-sectoral assistance.

Sensitivity analysis

We will carry out sensitivity analysis to examine:

1. the effects of removing trials at high risk of bias (trials with poor or unclear allocation concealment and either blinding or high/imbalanced loss to follow-up) from the analysis;
2. the effects of different ICC values for cluster trials (if these are included);
3. trials with mixed populations in which marginal decisions are made; and
4. the robustness of the results when using a fixed-effect model.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Ovid MEDLINE search strategy

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1 exp Lipids/
2 fatty acid$.tw,kf.
3 Docosahexaenoic acid$.tw,kf.
4 Eicosapentaenoic Acid$.tw,kf.
5 PUFA$.tw,kf.
6 lipid$.tw,kf.
7 (omega 3$ or omega 6$).tw,kf.
8 (soy$ or peanut or groundnut or whey or sesame or cashew or chickpea or oil$).tw,kf.
9 or/1-8
10 Dietary Supplements/
11 Food, fortified/
12 ((diet$ or food$) adj3 (fortif$ or enrich$ or supplement$)).tw,kf.
13 (complement$ adj3 (food$ or feed$)).tw,kf.
14 "Ready to use".tw,kf.
15 (RUSF or RUTF).tw,kf.
16 "point of use".tw,kf.
17 (home$ adj2 fortif$).tw,kf.
18 or/10-17
19 9 and 18
20 lipid based.tw,kf.
21 (lipid$ adj3 supplement$).tw,kf.
22 (lipid$ adj3 nutrient$).tw,kf.
23 (lipid$ adj3 fortif$).tw,kf.
24 (lipid$ adj2 formulation$).tw,kf.
25 (lipid$ adj3 enrich$).tw,kf.
26 (lipid$ adj2 emuls$).tw,kf.

27 (lipid$ adj3 powder$).tw,kf.
28 (lipid adj3 spread$).tw,kf.
29 (lipid$ adj3 paste$).tw,kf.
30 (Nutributter$ or Plumpy$).tw,kf.
31 (LNS$1 or iLiNS).tw,kf.
32 or/20-31
33 19 or 32
34 Pregnancy/
35 Pregnant Women/
36 Prenatal care/
37 Perinatal care/
38 (perinatal$ or peri-natal$ or prenatal$ or pre-natal$ or antenatal$ or ante-natal$).tw,kf.
39 pregnan$.tw,kf.
40 trimester$.tw,kf.
41 Mothers/
42 (mother$ or maternal$).tw,kf.
43 or/34-42
44 randomized controlled trial.pt.
45 controlled clinical trial.pt.
46 randomi#ed.ab.
47 placebo$.ab.
48 drug therapy.fs.
49 randomly.ab.
50 trial.ab.
51 groups.ab.
52 or/44-51
53 exp animals/ not humans.sh.
54 52 not 53
55 33 and 43 and 54

CONTRIBUTIONS OF AUTHORS

All authors contributed to writing this protocol.

As the contact author, Jai K Das has overall responsibility.

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Jai K Das - none known.

Rehana A Salam - none known.

Zita Weise Prinzo - none known.

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