A modular systematic review of antenatal interventions to address undernutrition during pregnancy in the prevention of low birth weight

Patricia J Hunter[1]*, Yvonne Muthiani[2]*, Pieta K Näsänen-Gilmore[2,3], Annariina M Koivu[2], Pia Pörtfors[3], Kalpana Bastola[2], Raija Vimpeli[2], Juho Luoma[2], Ulla Ashorn[2], Per Ashorn[2, 4]

*These authors contributed equally to this work.

1. University College London Great Ormond Street Institute of Child Health, London, UK

2. Center for Child, Adolescent and Maternal Health Research, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

3. Finnish Institute for Health and Welfare, FI-00271, Helsinki, Finland

4. Department of Pediatrics, Tampere University Hospital, Tampere, Finland

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Juho Luoma - No conflicts of interest

Ulla Ashorn – No conflicts of interest

Per Ashorn – No conflicts of interest

Corresponding author: P. Hunter UCL Great Ormond Street Institute of Child Health, London, UK Tel +44 207 905 2679 Email patricia.hunter@ucl.ac.uk

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List of abbreviations

ANC - Antenatal care

BMI – Body mass index

BPE – Balanced protein and energy

CI - Confidence interval

ES - Effect size

FGR - Fetal growth restriction

GRADE - Grading of recommendations assessment, development and evaluation

HIC - High-income countries

LBW – Low birth weight

LIC – Low-income countries

LMIC – Low and middle-income countries

LNS – Lipid-based nutrient supplements

MIC – Middle-income countries

MMN – Multiple micronutrients

O3FA – Omega-3 fatty acids

PTB - Preterm birth

RCT – Randomized controlled trial

RDA – Recommended dietary allowance

RR - Relative risk

SA - South Asia

SB – Stillbirth

SRMA – Systematic review and meta-analysis

SSA – Sub-Saharan Africa

SGA - Small for gestational age

UNIMMAP – United Nations international multiple micronutrient antenatal preparation

WHO – World Health Organization

Abstract

Background: Poor nutrition during pregnancy can lead to adverse birth outcomes including low birth weight (LBW).

Objective: This modular systematic review aimed to provide evidence for the effects of seven antenatal nutritional interventions on the risks of LBW, preterm birth (PTB), small-for-gestational-age (SGA) and stillbirth (SB).

Methods: We searched MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and CINAHL Complete between April and June 2020, with a further update in September 2022 (Embase only). We included randomized controlled trials (RCTs) and reviews of RCTs to estimate the effect sizes of the selected interventions on the four birth outcomes.

Results: Evidence suggests that balanced protein and energy (BPE) supplementation for pregnant women with undernutrition can reduce the risk of LBW, SGA and SB. Evidence from low and lower middle-income countries (MIC) suggests that multiple micronutrient (MMN) supplementation can reduce the risk of LBW and SGA in comparison with iron or iron and folic acid supplementation and lipid-based nutrient supplements (LNS) with any quantity of energy can reduce the risk of LBW in comparison with MMN supplementation. Evidence from high and upper MIC suggests that supplementation with omega-3 fatty acids (O3FA) can reduce the risk and supplementation with high-dose calcium might possibly reduce the risk of LBW and PTB. Antenatal dietary education programs might possibly reduce the risk of LBW in comparison with standard-of-care. No RCTs were identified for monitoring weight gain followed by interventions to support weight gain in women who are underweight.

Conclusions: Provision of BPE, MMN and LNS to pregnant women in populations with undernutrition can reduce the risk of LBW and related outcomes. The benefits of O3FA and calcium supplementation to this population require further investigation. Targeting interventions to pregnant women who are not gaining weight has not been tested with RCTs.

Key words: nutrition, undernutrition, pregnancy, antenatal care, low birth weight, preterm birth, small-for-gestational age, stillbirth

Introduction

Infants born weighing less than 2500 grams are at increased risk of death and surviving infants face a lifelong struggle against a spectrum of health challenges. The vulnerability conferred by low birth weight (LBW) is further intensified in resource poor settings where access to care is limited. The prevalence of LBW ranges from 10 to 20% of births with the highest rates in Sub-Saharan Africa (SSA) and South Asia (SA) (1). LBW can result from preterm birth (PTB, birth before 37 completed weeks of gestation), fetal growth restriction (FGR, typically presenting as the newborn being small for gestational age (SGA, weight below the 10^{th} percentile for the gestation age and sex)), or both (2,3).

There is a direct, observable relationship between maternal undernutrition and poor fetal growth (4). Additionally, inadequate nutrition reduces immunity to infections, exacerbates chronic illnesses and contributes to poor mental health in pregnant women, all of which, in turn contribute to the prevalence of LBW (5). Being born too small is one of the largest contributors to childhood stunting, wasting and underweight (6). Long-term consequences of LBW include physical and neurological developmental delays, disability and chronic health conditions in adulthood (7, 8).

The World Health Organization (WHO) recommends education to increase intake of protein and energy and the use of balanced protein and energy supplements for pregnant women who are members of undernourished populations (9). Daily or weekly supplementation with iron and folic acid and supplementation with calcium and vitamin A is recommended for populations where deficiencies in these micronutrients contribute to adverse maternal and fetal outcomes (9). In these recommendations, undernutrition is an attribute of a population and there is no requirement for monitoring of individual weight gain or body mass index (BMI) or detection of individual micronutrient deficiencies. However, since WHO recommends antenatal care comprising at least eight antenatal contacts, and most gestational weight gain occurs after 20 weeks, it should be possible to monitor weight gain and respond with interventions designed to support individuals. It is therefore important to review the evidence base provided by RCT supporting what is currently recommended and what is under consideration. This will help to understand what might constitute best practice in terms of universal supplementation, dietary education and support for individuals who are failing to gain adequate weight during pregnancy.

This work is a systematic literature search and review of the evidence underpinning seven interventions aimed at reducing negative impacts of maternal undernutrition on infant birthweight. Specifically, we aim to bring together and synthesize the global evidence for what works to improve the weight gain and nutritional status of pregnant women and comment on the implications of the evidence in countries and regions with a moderate to high prevalence of undernutrition.

Methods

This article reports a part of an evidence synthesis on 46 antenatal interventions that could be used to reduce the incidence of LBW, PTB, SGA and stillbirth (SB) globally. Out of the 46, the current review focuses on seven interventions that aim to address deficits in nutrients and energy as well as dietary education during pregnancy. The other articles in this supplement cover interventions related to psychosocial support, infection control and environmental exposures (10-12).

For the search, study selection, and evidence synthesis, we used a recently described novel systematic search and review method, the modular review, that allows concomitant review of multiple interventions (13). For the modular review method, the population, outcomes and study design components of every search were identical; the search terms for each of the seven interventions were "modulated". For each intervention, we sought to identify a recent systematic review from the search to provide a summative estimate of the effect size (ES) of the intervention. If no review could be identified, we calculated the combined ES from RCTs retrieved in the search. Each intervention was then given a color code to categorize and enable comparisons for the amount and quality of evidence, the size of the effects and the likelihood that the intervention improves birth outcomes at least in some contexts. While the design of the method, particularly its ability to review multiple interventions simultaneously, precluded the registration of the study in prospective registers of systematic reviews of single interventions, an *a priori* protocol was used, and the method was published in detail (13).

Full details of the method are provided in the Supplementary methods. In brief, we designed and tested the population, outcome and study type modules to be used for all 46 interventions in the project. The intervention components of the searches were made broad to favor sensitivity over specificity in order to avoid excluding unusual or unconventional intervention designs. We performed five systematic searches in MEDLINE (OvidSP), Embase (OvidSP), Cochrane Database of Systematic Reviews (Wiley Cochrane Library), Cochrane Central Register of Controlled Trials (Wiley Cochrane Library), CINAHL Complete (EbscoHOST) between April 8 and June 9, 2020. Titles and abstracts were screened together by a single researcher with quality control measures as previously described (13).

Population: The population of interest was pregnant females at any stage of pregnancy as determined by the protocols of the RCTs. We required the interventions to be commenced prior to the perinatal period, the onset of labour or membrane rupture.

Interventions: There were five interventions involving supplementation: (1) balanced protein and energy (BPE), (2) lipid-based nutrient supplements (LNS), (3) multiple micronutrients (MMN), (4) calcium and (5) omega-3 fatty acids (O3FA). We also looked at (6) dietary education without supplementation and (7) screening for adequate weight gain followed by intervention if indicated (search terms are listed in Supplementary data 1-7). These interventions address risk factors of increased prevalence in low-income countries (LIC) and lower middle-income countries (MIC), both in sub-Saharan Africa (SSA) and South Asia (SA), due to their higher prevalence of undernutrition (**Table 1**). Dietary supplementation with iron and folic acid for the duration of pregnancy is currently recommended by WHO to reduce anaemia. Supplementation with a larger repertoire of micronutrients, such as the United Nations international multiple micronutrient antenatal preparation (UNIMMAP), is recommended in the context of rigorous research and, if effective, will likely replace individual micronutrient supplementation (such as vitamin A to reduce night blindness) in most contexts. Combining multiple micronutrients with protein and energy in the form of LNS may afford improvements toward the reduction in the prevalence of LBW. We compared LNS with MMN in order to focus on the theoretical benefits of receiving MMS that are dispersed in a paste rather than concentrated in a tablet and the effect of providing energy primarily as lipids; both of these aspects being independent of the amount of energy in the supplement. Dietary education and fetal growth monitoring are currently recommended but without evidence-based guidance or context-specific frameworks for best practice.

Outcomes: The included studies had to report at least one of LBW, PTB, SGA or SB. While LBW was the starting point of our project, PTB and SGA indicate the two main pathways that lead to it and SB is an extreme outcome that often results from the same processes that limit fetal growth or shorten the duration of pregnancy. Thus, all four outcomes can be partially attributed to the same antecedents (14).

Study types: As study designs, we included RCTs and reviews of RCTs. Case/control studies and observational studies were excluded, as were blanket food distribution programs, which are relevant to conflict and humanitarian contexts where it would be unethical to have a control group. RCTs of cash transfer programs are reported in another article in this series (10).

Language: We included only English language records.

For each intervention, we sought the best estimate of effect size (ES) from the included studies. ES documents consisted of the most recent quantitative evidence and were selected according to the following hierarchy. Reviews of reviews (umbrella reviews, meta-reviews, reviews of (systematic) reviews) constituted the highest level of evidence. The next level consisted of reviews from the Cochrane collaboration followed by high quality systematic reviews with or without meta-analyses. If there were no reviews available, we used peer-reviewed, published RCTs that met the inclusion criteria to calculate the combined effect size. The calculations were conducted using Meta-essentials (15) and R version 3.4.4. The graphs in the supplementary information were created with “forestplot” package (16). In addition to identifying the latest reviews as ES documents, we also identified RCTs published after the review as ES documents. In such case, results from the more recent RCTs were reported separately. In reporting of effect size, we used adjusted relative risk (RR) or odds ratio with 95% or 90% confidence intervals (CI) in order to conform with standard practice for systematic reviews and to have agreement with the way the numbers are presented in forest plots. Sub-populations that showed enhanced ability to benefit from interventions as revealed in subgroup analysis were reported in the Supplementary data for each intervention.

In assessing the quality of evidence, we primarily accepted the assessment given in the Summary of Findings tables of the ES documents that were reviews. Typically, the tables are produced according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) process and they provide the quality of evidence rating for each outcome (17). In the older ES documents, the assessment was typically described to indicate the "quality" of evidence, whereas in the newer documents it was marked as the "certainty" of evidence. When the ES documents were RCT, we assessed the risk of bias for individual studies. This was converted into assessment of quality of evidence (detailed in Supplementary methods). We used precision of the effect size for each outcome in our categorization of the evidence. Other attributes of the body of evidence for a single outcome, such as consistency and publication bias, were not considered.

To interpret the impact of the interventions on each outcome, we sorted our findings into five categories based on the calculated effect size, the precision given by the 95% or 90% CI, the number of studies and the quality of evidence. Each intervention was given standardized statement in relation to its effect on each outcome, accompanied by a color code (**Table 2**). If the CI of the effect size was entirely below 1, we considered that the effect might be likely or possibly positive. It was likely (green) if there were two or more good quality studies and possibly (yellow) if there was only one study or problems with quality. If the CI was narrow and included 1, we considered effect unlikely (red), if the CI was broad (grey), there were no studies (white) or there was one study where the CI included 1 (white), we considered the result inconclusive. We wanted to separate situations where there was insufficient evidence from situations where there was evidence of no or minimal effect.

For reporting the results, we applied a modified preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 checklist (18). For each intervention, we report quantitative estimates on the size of effect of the intervention on the prevalence of LBW, PTB, SGA and SB with an assessment of the quality of evidence. Finally, we provide a description of the geographical context of the evidence base.

To make our evidence synthesis results timely despite the relatively long period of data processing, we repeated each of the five searches between August 30th and September 11th 2022. The search strategies in the update were identical to the original search strategies, but the update was limited to the Embase database and covered the time elapsed since the original searches (April 2020). As with the original searches, the title/abstract screen was conducted by one researcher with some dual screening and the fulltexts were assessed against the inclusion criteria by two researchers (PH and YM). Since the updated searches were only conducted in a single database, we reported the results separately from the original searches except in cases where the new evidence led to a change in categorization. In such cases, we conducted a new meta-analysis and quality assessment or reported the combined ES from the more up-to-date review.

Results

We found 13,398 records across five searches. After electronic removal of duplicate records, we screened 7280 records for eligibility and reviewed 1795 full texts of which 101 records met the inclusion criteria. Out of 101 records, 12 documents contributed data that could be used to estimate the effect size (ES) of the interventions (**Figure 1**).

Provision of nutrients and energy

Six ES documents (two systematic reviews and four RCTs) published between 2009 and 2017 covered interventions that provided combinations of nutrients and energy to pregnant women (**Table 3**). The ES documents reported results from 13 RCTs published between 1973 and 2017.

Two reviews published in 2012 and 2015 reviewed nine RCTs published between 1973 and 2009 assessing the *provision of proteins and energy to pregnant women with undernutrition*. Three of the RCT were conducted in SSA (Burkina Faso and two in the Gambia) and one in SA (India). The others were conducted in Chile, Columbia, USA, UK and Taiwan. The target group included pregnant women who were undernourished due to poverty or membership of a vulnerable sub-population, including those living in high-income countries (HIC). The number of studies (participants) reporting specific outcome data was 5 (N=4196) for LBW, 5 (N=3384) for PTB, 7 (N=4408) for SGA and 5 (N=3408) for SB. The relative risks (RR) for women who received the intervention were: LBW (RR: 0.68 [95% CI 0.51, 0.92]), PTB (RR: 0.96 [95% CI 0.8, 1.16]), SGA (RR: 0.79 [95% CI 0.69, 0.9]) and SB (RR: 0.6 [95% CI 0.39, 0.94]). The quality of evidence for the effect of the intervention on all outcomes was considered moderate. A detailed summary of the impact of BPE is provided in Supplementary data 1.

Four individual RCTs published between 2009 and 2017 and conducted in Burkina Faso, the Gambia, Ghana and Malawi were used to estimate the effect of the *provision of lipid-based nutrient supplements instead of multiple micronutrients to pregnant women with undernutrition.* In these trials, both groups received 1-2 times the recommended dietary allowance of a standard set of MMN but the LNS group received them as part of a pre-portioned lipid-soluble preparation of protein and fat including essential fatty acids and additional minerals. For all four RCTs, the intervention was commenced before mid-gestation. All four trials were in SSA in rural populations with a moderate level of undernutrition. The Ghana and Malawi studies used LNS with small quantity of energy (118 kcal, SQ-LNS) designed to supplement meals cooked at home. The Gambia study used LNS with a medium quantity of energy (373 kcal, MQ-LNS), designed to have a sustained impact on overall energy intake. The LNS intervention used in the Burkina Faso study contained a large quantity of lipid-based energy (746 kcal, LQ-LNS) which could replace meals or significantly boost the overall energy intake. The number of studies (participants) reporting specific outcome data was 4 (N=2727) for LBW, 4 (N=2953) for PTB, 4 (N=2719) for SGA and 3 (N=2771) for SB. The risks for the women who received LNS compared with MMN were: LBW (RR: 0.92 [95% CI 0.86, 0.98]), PTB (RR: 1.16 [95% CI 0.87, 1.54]), SGA (RR: 0.95 [95% CI 0.84, 1.07]) and SB (RR: 1.08 [95% CI 0.19, 5.50]). The overall quality of the studies was rated moderate. A detailed summary of the impact of LNS is available in Supplementary data 2.

In summary, for the interventions that combine nutrients and energy, there is evidence that provision of BPE to pregnant women with undernutrition can lower the risk of LBW, SGA and SB but not the risk of PTB. There is also evidence that provision of LNS instead of MMN to pregnant women with undernutrition can lower the risk of LBW but not likely the risk of PTB or SGA. The impact on SB is inconclusive due to the large confidence interval (**Table 4**).

Provision of nutrients without energy

Three ES documents (three Cochrane reviews) published between 2018 and 2019 covered the effect of providing essential micronutrients as tablets, capsules or food additives without additional macronutrients or energy. Most of the pregnant women participating in these trials had micronutrient deficiencies and/or some level of risk, such as first pregnancy (**Table 5**).

One Cochrane review published in 2019 reviewed 19 RCTs published between 2003 and 2014 assessing the *replacement of iron-folic acid supplementation with MMN supplementation.* Sixteen of the reviewed RCTs took place in LIC and lower MIC. Eight were in SSA and five were in SA. The number of studies (participants) reporting specific outcome data was 18 (N=68801) for LBW, 18 (N=91425) for PTB, 17 (N=57348) for SGA and 17 (N=97927) for SB. The risks for the women who received MMN compared with IFA or iron alone were: LBW (RR: 0.88 [95% CI 0.85, 0.91]), PTB (RR: 0.95 [95% CI 0.90, 1.01]), SGA (RR: 0.92 [95% CI 0.88, 0.97]) and SB (RR: 0.95 [95% CI 0.86, 1.04]). The quality of evidence was high for LBW and SB but moderate for the PTB and SGA. A detailed summary of the impact of MMN supplementation is provided in Supplementary data 3.

One Cochrane review published in 2018 reviewed 17 RCTs published between 1987 and 2016 pertaining to *dietary supplementation with high-dose calcium* and *dietary supplementation with low-dose calcium* compared with placebo or no supplementation. Nine out of the 21 countries covered by RCTs in the review were in lower-MIC with one from SSA and four from SA. Eleven RCTs of daily high-dose (>1g) calcium supplementation versus placebo or no supplementation published between 1987 and 2009 were used to determine the ES; four of which the population was enriched for first pregnancies and other risk factors for pregnancy-related hypertension. Additionally, there was a mixture of adequate and low baseline dietary calcium levels in the participants across the reviewed studies. The number of studies (participants) reporting specific outcome data for the effect high dose calcium was 9 (N=14883) for LBW, 11 (N=15275) for PTB, 4 (N=13615) for SGA and 11 (N=15665) for SB. The risks for women who received high-dose calcium compared with placebo or no supplementation were: LBW (RR: 0.85 [95% CI 0.72, 1.01]), PTB (RR: 0.76 [95% CI 0.60, 0.97]]), SGA (RR: 1.05 [95% CI 0.86, 1.29]) and SB (RR: 0.9 [95% CI 0.74, 1.09]). The 90% CI for LBW ([90% CI 0.74, 0.97]) excluded the possibility of no effect. The quality of the evidence on the effect of high-dose calcium on PTB was considered low.

Six RCTs published between 1998 and 2016 contributed to the effect size estimate for the provision of daily low-dose (<1g) calcium compared with placebo or no calcium during pregnancy on PTB, all of which included lower MIC. Five out of six of these RCTs combined the calcium with other supplements including vitamin D (3 RCTs), linoleic acid (1 RCT) and 10 additional micronutrients with antioxidative capacity (1 RCT). The ES for supplementation with low dose calcium on the risk of PTB from 6 RCTs (N=1290) was 0.83 [95% CI 0.34, 2.03]. A detailed summary of the impact of calcium supplementation is provided in Supplementary data 4.

One Cochrane review published in 2018 reviewed 30 RCTs of *supplementation with omega-3 fatty acids* published between 1992 and 2018. None of the RCTs were conducted in LIC and only eight took place in MIC. Only one took place in SSA (Angola) and one took place in SA (Bangladesh). The RCTs compared supplementation or enrichment of the diet with O3FA versus placebo, no supplementation or no enrichment. The number of RCT (participants) reporting specific outcome data was 15 (N=8449) for LBW, 26 (N=10304) for PTB, 8 (N=6907) for SGA and 16 (N=7880) for SB. The risks for women who received O3FA compared with no O3FA were: LBW (RR: 0.90 [95% CI 0.82, 0.99]), PTB (RR: 0.89 [95% CI 0.81, 0.97]), SGA (RR: 1.01 [95% CI 0.9, 1.13]) and SB (RR: 0.94 [95% CI 0.62, 1.42]). The quality of the evidence for the effects of O3FA on LBW and PTB was high and for SGA and SB, the quality was moderate. A detailed summary of the impact of O3FA supplementation is provided in Supplementary data 5.

To summarize the interventions consisting of nutrients without energy, there is evidence from RCT conducted mainly in LIC and lower MIC that blanket supplementation with MMN likely reduces the risks of LBW and SGA but not likely the risks of PTB or SB compared with IFA or iron alone. There is evidence that blanket supplementation with high-dose calcium may possibly lower the risks of LBW and PTB. The effect of low dose calcium on the risk of PTB is inconclusive. The evidence regarding blanket supplementation with O3FA suggests that it likely lowers the risk of LBW and PTB but not the risks SGA or SB. The majority of RCT of calcium and O3FA have been conducted in upper MIC and HIC (**Table 6**).

Nutritional interventions without dietary supplementation

Three ES documents (individual RCTs) published in 2014, 2017 and 2019 reported interventions that addressed inadequate nutrition during pregnancy but did not involve blanket dietary supplementation (**Table 7**).

Three RCTs conducted in Bangladesh, Burkina Faso and Kenya examined *dietary education of pregnant women with undernutrition* compared with standard of care. The Bangladesh and Burkina Faso trials delivered classes on how to achieve good nutrition in pregnancy including how to prepare nutritious staples for frequent consumption. The Kenya trial delivered the intervention during antenatal home visits in the form of counselling and advice. The Bangladesh trial used individual randomization to select participants for the intervention. The

Burkina Faso and Kenya trials used cluster randomization; the former randomizing health centers to provide the intervention or standard-of-care and the latter randomizing villages to receive dietary counselling in addition to the usual procedures followed at antenatal home visits. All three RCTs (N=3440) reported data for LBW. Only the Kenya trial (N=1001) reported outcomes for PTB. The risks for women who received dietary education compared with standard-of-care were: LBW (RR: 0.46 [95% CI 0.27, 0.79]) and PTB (RR: 0.84 [95% CI 0.68, 1.04]). A detailed summary of the impact of dietary education is shown in Supplementary data 6.

We did not find any RCT of *regular screening for maternal weight gain followed, if indicated, by dietary supplementation or other intervention.* A summary of the search for RCT of this intervention is in Supplementary data 7.

In summary, screening for weight gain followed by intervention if indicated does not appear to have been tested as a stand-alone intervention in the context of an RCT. There is evidence that dietary education in various forms might possibly be able to reduce the risk of LBW. The corresponding impact on the risks of PTB, SGA and SB is not known (**Table 8**).

Search update to identify recent evidence

We found 1166 records across five searches in Embase covering the period from April 2020 until September 2022. Of these, seven publications, covering provision of nutrients and energy (one publication), provision of nutrients without energy (five publications) and nutritional interventions without dietary supplementation (one publication) met our original inclusion criteria (flow chart, Supplementary data 8).

The new publication on nutrients and energy described an RCT from Pakistan comparing provision of protein, energy and multiple micronutrients against standard of care. The authors reported a significant reduction in the risk of SB in the intervention group. The prevalence of LBW was identical in both groups, but the validity of this finding might have been compromised because less than half of the newborns were weighed immediately after birth (37).

The new publications on the provision of nutrients without energy included one umbrella review, three systematic reviews with meta-analyses (SRMA), and one RCT on the effect of maternal *supplementation with omega-3 fatty acids* on birth outcomes. One of the SRMA was excluded because it combined data that used differing definitions of PTB and some of the data was used twice in the meta-analysis (39). The umbrella review was excluded as it used this SRMA to estimate the effect of O3FA on the prevalence of PTB (38). The other two SRMA reported the same positive effect on the risk of PTB (40, 41). The newly published RCT compared supplementation with omega-3 fatty acids with placebo in India and reported no differences in the risks of LBW, PTB, SGA or SB (42).

The new publication on nutritional interventions without dietary supplementation described a cluster RCT in Ethiopia comparing the effect of guided nutritional counselling during pregnancy with standard of care. The authors reported a positive effect of the intervention on LBW (43).

The results from the newly identified RCTs on provision of proteins and energy and provision of dietary education were consistent with our original findings. The new reviews on the impact of omega-3 fatty acids were in agreement with our ES document result of a positive effect on PTB. However, the new umbrella review and the systematic review that it used to derive the effect size for PTB were excluded from our analyses because they combined different definitions of PTB for their effect size estimates. Hence, the search update did not change our categorized interpretation of the data and color codes given in tables 2, 4, and 6.

Discussion

The aim of this review was to synthesize evidence from RCTs conducted anywhere in the world to improve the nutritional status of women during pregnancy toward the reduction of the prevalence of LBW and related birth outcomes of PTB, SGA and SB. From the English-language literature from five databases, there was evidence that blanket supplementation with BPE, MMN, LNS or O3FA is likely to reduce the prevalence of LBW and related adverse birth outcomes. The evidence suggests that blanket supplementation with BPE was the only intervention able to reduce the prevalence of SB. The evidence points to the possibility that high-dose calcium supplementation and dietary education may reduce the prevalence of LBW. Evidence for the efficacy of low-dose calcium supplementation to reduce the risk of LBW is inconclusive at present. There is insufficient published evidence from RCT of efforts to target weight gain-promoting interventions to women with inadequate weight gain.

The methodology of the modular review used a broad approach to the search phase favoring sensitivity over specificity. As a result, the electronic searches were unlikely to have missed relevant records, but due to the large number of records that were selected, relevant records may have been missed at the abstract screening stage due to human error. Furthermore, we might have missed records where our specified outcomes were not the primary outcomes or were not reported in abstracts. To address both sources of error, we consulted the reference lists of documents that met the inclusion criteria as a parallel route to the identification of relevant articles. We also performed simplified versions of the searches in databases not included in the five used for the systematic searches (for example, a Google search using only terms “pregnancy”, “zinc”, “low birth weight”). No other relevant articles were identified using the simplified searches and all articles identified through reference lists had been missed on account of our specified outcomes not appearing in abstracts (13).

The validity of our finding could also be compromised by reviews and RCT published since the search dates in April 2020. To address the time gap, we performed identical searches in Embase covering the period from April 2020 to August 2022. None of the documents identified in the updated searches provided more comprehensive estimates of the effect sizes of the interventions when compared with the selected ES documents from the original searches. Therefore, we consider that our review covers the relevant published literature. The prevalence of LBW can be reduced by interventions that involve dietary supplementation with BPE, MMN, LNS or O3FA.

There is impetus for replacing IFA with MMN supplementation in the WHO recommendations for antenatal care of undernourished pregnant women (44, 45, 50). Between 2005 and 2012, there was concern about an observed association between MMN supplementation and peri- and neonatal mortality (46-49). However, RCT published since 2012, particularly the JiVitA-3 trial in Bangladesh with over 28000 participants (50), have provided new data suggesting that MMN supplementation is unlikely to increase the risk of these outcomes, which may have been associated with commencement before mid gestation (31, 45, 51). It is possible that the positive and negative effects of MMN on peri/neonatal mortality resulted in no net effect. Interestingly, from the meta-analyses of RCTs of individual components of the UNIMMAP formulation of MMN, such as vitamin A (52), vitamin D (53) and zinc (54), there does not appear to be any single micronutrient supplementation regimen that consistently reduces the risk of LBW on its own. Thus, it is likely more advantageous to address multiple deficiencies simultaneously in a single supplement than to address the documented deficiencies of a specific population.

A finding of this review is that supplementation with either BPE or MMN can impact the risk of LBW and SGA. Thus, it is somewhat surprising that when micronutrients and energy are combined in the form of LNS, the effect on the prevalence of LBW was small in comparison with MMN alone, with no significant effect on the risk of SGA or PTB. We found that changing from MMN to LNS supplementation resulted in a small increase in birth size, consistent across all four of the included RCT, regardless of energy quantities. This consistency could be interpreted as an indication that the differences in the amount of energy may not be playing a significant role in the small increase in infant size. Others have made the case that the amount of energy in the supplement is crucial to the effect (55). A potential confounder is the degree to which trial participants consumed the entire quantity of LNS, particularly when the portion was large. The benefits of added energy may be offset by the failure to receive the full RDA of micronutrients if the entire portion is not consumed. It is biologically plausible that the energy and macronutrient content is able to modify the effect, however, and our results should be interpreted with caution.

Compliance with consumption of the full portion of the supplement is an important consideration for blanket RCTs, particularly those intended to increase macronutrient consumption. Women may resist efforts to promote weight gain due to fear of obstructed labour associated with giving birth to a larger infant. A 2018 systematic review identified studies consisting of interviews of women around food intake and taboos during pregnancy (56). Nine studies, including the Burkina Faso LNS trial, identified the practice of ”eating down” during pregnancy to limit weight gain among those interviewed although most women reported no change in their eating habits on becoming pregnant. For the LNS RCTs, it is difficult to compare compliance between studies as it was encouraged and measured in different ways. The Malawi SQ-LNS trial reported the highest compliance with an average of 85% of the intervention consumed (29). For the LQ-LNS trial in the Gambia, compliance was lower, but sensitivity analysis suggested that this was not a factor in the infant biometry outcomes (30). Most of the RCTs of BPE did not report on compliance, even if it was monitored (26).

Whilst O3FA supplementation appeared to reduce the prevalence of LBW by about 10%, there are several reasons why more research is needed before it can be considered a useful tool in the global effort to reduce undernutrition during pregnancy. First, the evidence for the efficacy of O3FA comes largely from HIC and it has not been tested in undernourished populations. Secondly, the evidence points to a mechanism in wherein O3FA delays the onset of natural labor. This could occur through the competitive inhibition of prostaglandins E2 and F2α production from omega-6 fatty acids, which is dependent on the same enzyme that converts O3FA to E3 prostaglandins (57). Support for the predominance of this mode of action comes from the 60% increase in the risk of post term birth in the O3FA supplemented groups (33) suggesting that O3FA can inhibit the onset of labor at any point during the pregnancy. Gestation beyond 42 weeks is the highest directly attributable risk factor for SB (58). Furthermore, in LIC and lower MIC where the infectious disease burden is high, preterm labor and delivery may serve to avert SB if the fetus is threatened with infection (59). There is also some evidence that supplementation with O3FA could potentially increase SB. After 16 trials reporting 77 SB, the confidence interval remained wide with the possibility that O3FA consumption could increase the prevalence of SB by up to 42% (33). Indeed, an overview of Cochrane systematic reviews on interventions to reduce the prevalence of SB rated the evidence for the impact of O3FA supplementation on the risk of SB to be very low certainty on account of the wide confidence interval (60). More research is therefore required to establish which populations can benefit from O3FA and avoid the associated risks.

High-dose calcium supplementation is currently recommended by WHO for populations with low calcium intake in order to reduce the risk of preeclampsia (9). Since iatrogenic PTB is a common treatment for severe preeclampsia and eclampsia, it is not clear the extent to which the observed reduction in the prevalence of PTB in the supplemented groups was mediated through the reduction in preeclampsia or whether high-dose calcium has independent effects on the risk of spontaneous PTB although some attempts have been made to disaggregate this effect (22). Historically, calcium has been notable by its exclusion from MMN formulations. When RCT of calcium supplementation in pregnancy began 35 years ago, clinical and epidemiological studies pointed to a requirement for a high dose (>1g) to achieve impact in the reduction of hypertension and preeclampsia (61, 62), which precluded combining it with any other supplement. By 2009, trialing high doses had ended and low doses with and without other micronutrients, most notably vitamin D, were tested. However, not enough evidence has been published to be able to make conclusions about the effects of low-dose supplementation on birth outcomes or how it interacts with other supplements.

This review used meta-analyses to make judgements regarding the effectiveness of interventions to reduce the prevalence of LBW. It is well recognized that there are limitations to extent to which such aggregates of data may be relevant when the data is derived from RCTs conducted in a variety of settings and contexts (63). A single RCT conducted in any given context may be more relevant to that context than a global estimate produced by a meta-analysis. For instance, baseline population characteristics such as age, body mass index and parity as well as cultural aspects of food consumption may affect the uptake and acceptability of supplements and the supplemented group's ability to respond to or benefit from the supplement in one context but not another (64). Therefore, we caution against taking any of the relative risks provided in this article as a sign of a fixed and universal effect size. Rather, the modular review, with multiple concomitant meta-analyses, provides a summary of available quantity and quality of evidence of multiple alternative interventions in different settings. This will hopefully help program planners and managers make decisions on the interventions and approaches they want to use in improving birth outcomes in their own settings.

A strength of this review is the juxtaposition of the body of evidence for universal nutrient supplementation, which is reaching maturity, against the lack of evidence for targeting support to pregnant women who are not gaining adequate weight. Further work is required to demonstrate the efficacy and cost effectiveness of targeted interventions in comparison with universal supplementation. The implementation of eight antenatal contacts provides the framework for more extensive monitoring of pregnancy BMI and weight gain and the opportunities to support women with identified nutritional inadequacies through supplementation.

In summary, there is sound evidence that improving the nutritional status of pregnant women by addressing caloric and nutrient deficiencies at the population level will reduce the prevalence of LBW and related adverse outcomes. Future research should seek to delineate what form of education and supplementation should be offered to all women and what should be targeted to those with the greatest ability to benefit. The path to the birth of the thriving newborn involves holistic approaches to nutrition and its seamless integration in a complete program of social, environmental and medical support.

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Figure legends

Figure 1. Summary flow diagram for the selection of publications for the analysis of nutritional interventions to reduce adverse birth outcomes. Adapted from PRISMA 2020 (18). [1]Some records occur more than once due to being relevant to more than one intervention.

Table 1. Reviewed interventions, risk factors, prevalence, and mechanism to address the risk

Intervention	Addressed risk factor	Prevalence of the risk factor	Assumed mechanism of action for the intervention
Provision of nutrients and energy			
Blanket balanced proteins and energy supplementation (<25% of calories from proteins)	Caloric and nutrient intake deficits	BMI < 18.5 kg/m^2 10% in SSA, 17% in SA (19)	Corrects maternal deficiency and increases nutrient availability to support fetal growth
Blanket lipid-based nutrient supplements	Micronutrient and caloric intake deficits		Addresses both caloric and micronutrient deficiencies
Provision of nutrients without energy			
Blanket administration of multiple micronutrient tablets or capsules	Multiple micronutrient deficiencies	Anaemia 3.21% (20, 21)	Addresses multiple micronutrient deficiencies simultaneously
Blanket administration of calcium tablets	Calcium deficiency	1.23% (20, 22)	Addresses calcium deficiency. May also reduce iatrogenic preterm birth due to high blood pressure and growth restriction due to poor placentation
Blanket administration of omega 3 LCPUFA	Essential fatty acid deficiency	Total omega 3 < 2% of total LCPUFA, 10% of a Danish birth cohort (23)	Addresses essential fatty acid deficiencies. Supports fetal growth and brain development. Lengthens gestation by delaying the onset of labour.
Nutritional interventions without dietary supplementation			
Screening for adequate growth followed by intervention where indicated.	Inadequate weight gain during pregnancy	23% in HIC (24)	Targets nutritional intervention to women who can benefit the most
Dietary education in groups or individual counselling	Lack of knowledge about nutrition to support pregnancy	Not known	Increases knowledge about how to optimize diet to support pregnancy

HIC - high-income countries, LCPUFA – long chain poly unsaturated fatty acid, SA – South Asia, SSA – sub-Saharan Africa

Table 2. Evidence categories, definitions and criteria

Colour	Interpretation	Criteria
Green	The intervention likely reduces the risk of the adverse outcome.	• At least two moderate-to-high quality RCT in a meta-analysis / IPD analysis, with 95% CI of the point estimate of the RR entirely below 1.
Yellow	The intervention may reduce the risk of the adverse outcome.	• At least two RCT in a meta-analysis / IPD analysis, where either the 95% CI of the point estimate of the RR is entirely below 1 but the quality of the evidence is low or the quality is moderate-to-high and the 90% CI of the point estimate of the RR entirely below 1. • One moderate-to-high quality RCT, with 95% CI of the point estimate of the RR entirely below 1.
Red	The intervention is not likely to reduce the risk of the adverse outcome.	• Situations that do not be meet the requirements for other categories, including meta-analysis results suggestive of harm. In other words, there is sufficient evidence to conclude that the intervention is unlikely to have a positive effect on the outcome.
Grey	Inconclusive published research on the intervention's effect on the outcome.	• At least two RCT, 95% CI of the point estimate of the RR ranges from < 0.5 to > 2.
White	Insufficient published research on the intervention's effect on the outcome.	• No RCT or one low quality RCT (any result) • One moderate-to-high quality RCT where 95% CI of the RR includes 1. • Narrative reporting.

CI= confidence interval, IPD = individual participant data, RCT = randomized controlled trial, RR=relative risk.

Table 3 Summary of effect size (ES) documents for the provision of nutrients and energy

Intervention	First Author	Year	Study design	Country (number of studies)	Population	Description of Intervention	Description of Control	Outcomes reported	Risk of bias
Balanced proteins and energy	Imdad (25)	2012	SRMA	Burkina Faso (1), Chile (1), The Gambia (2), Taiwan (1)	Pregnant women with undernutrition	Balanced protein and energy dietary supplements	Placebo or equivalent supplementation without proteins or energy.	LBW	
	Ota (26)	2015	Cochrane review	Burkina Faso (1), Columbia (1), The Gambia (1), India (1), UK (1), USA (1), Taiwan (1)	Under-nourished Pregnant women	Balanced protein and energy dietary supplements	Placebo or equivalent supplementation without proteins or energy.	PTB, SGA, SB	
Lipid-based nutrients	Huybregts (27)	2009	RCT	Burkina Faso	Under-nourished Pregnant women	Daily lipid-based preparation containing essential fatty acids, proteins, multiple micronutrients	Multiple micronutrients taken daily as a tablet.	LBW, PTB, SGA, SB	Moderate

						and 373 kcal of energy (MQ-LNS)			
	Adu-Afarwuah (28)	2015	RCT	Ghana	Under-nourished pregnant women	Daily lipid-based preparation containing essential fatty acids, protein, multiple micronutrients and 118 kcal of energy (SQ-LNS)	Multiple micronutrients taken daily as a tablet.	LBW, PTB, SGA, SB	Low
	Ashorn (29)	2015	RCT	Malawi	Under-nourished Pregnant women	Daily lipid-based preparation containing essential fatty acids, protein, multiple micronutrients and 118 kcal of energy (SQ-LNS)	Multiple micronutrients taken daily as a tablet.	LBW, PTB, SGA, SB	Low
	Johnson (30)	2017	RCT	The Gambia	Pregnant women with undernutrition	Daily lipid-based preparation containing essential fatty acids, proteins, multiple micronutrients and 746 kcal of	Multiple micronutrients taken daily as a tablet.	LBW, PTB, SGA	Low

						energy (LQ-LNS)			

LNS – lipid-based nutrient supplements, SQ – small qualitiy, MQ – moderate quantity, LQ – large quantity, RCT = randomized controlled trial, SRMA – systematic review and meta-analysis

Table 4. Evidence of efficacy of the provision of nutrients and energy to reduce LBW, PTB, SGA and SB.

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Provision of proteins and energy to pregnant women with undernutrition	Yes	No	Yes	Yes
	RR: 0.68 [0.51, 0.92] (N=4196)	RR:0.96 [0.8, 1.16] (N=3384)	RR: 0.79 [0.69, 0.9] (N=4408)	RR: 0.6 [0.39, 0.94] (N=3408)
	MODERATE	MODERATE	MODERATE	MODERATE
Provision of lipid-based nutrient supplements instead of multiple micronutrients to pregnant women with undernutrition	Yes	No	No	Inconclusive
	RR: 0.92 [0.86, 0.98] (N=2727)[1]	RR: 1.16 [0.87, 1.54] (N=2953)[1]	RR: 0.95 [0.84 , 1.07] (N=2719)[1]	RR: 1.08 [0.19, 5.50] (N=2771)[1]
	MODERATE	MODERATE	MODERATE	MODERATE

1.The proportion of studies coming from sub-Saharan Africa or South Asia is 50% or higher. RR – relative risk [95% confidence interval]

Table 5 Summary of effect size (ES) documents for the provision of nutrients without energy

Intervention	First Author	Year	Study design	Countries (number of studies)	Population	Description of Intervention	Description of Control	Outcomes reported
Multiple micro-nutrients	Keats (31)	2019	Cochrane review	Bangladesh (2), Burkina Faso (1), China (1), The Gambia (1), Ghana (1), Guinea-Bissau (1), Indonesia (2), Malawi (1), Mexico (1), Nepal (2), Niger (1), Pakistan (1), Tanzania (1), UK (1), Vietnam (1), Zimbabwe (1)	Pregnant women with undernutrition/ mixed levels of micronutrient deficiency	Daily capsules. Various formulations of 15 - 18 micronutrients equivalent to 1 -2 RDA.	Daily iron (60 mg) +/- folic acid (0.25 - 0.4 mg)	LBW, PTB, SGA, SB
Calcium	Hofmeyr (32)	2018	Cochrane review	(Argentina, Egypt, India, Peru, South Africa, Vietnam (1)), (Argentina, USA (1)), Argentina (1), Australia (1), Bangladesh (1), Columbia (1), Ecuador (2), India (2), Indonesia (1), Iran (3), Philippines (1), USA (2)	Primiparous and other groups at risk of gestational hypertension/ various levels of baseline calcium deficiency	High dose > 1 g or low dose < 1 g calcium tablets	Placebo or no calcium	High dose: LBW, PTB, SGA, SB Low dose: PTB
Omega-3 fatty acids and fish oils	Middleton (33)	2018	Cochrane review	Angola (1), Australia (1), Belgium (1), Canada (1), Chile (2), Croatia (1), Denmark (3), Egypt (1), Germany (2), India (1), Iran (3), Italy (1),	Pregnant women	Daily omega-3 fatty acids or fish oils in capsules or as food additive and/or advice	Placebo, no omega-3 fatty acids or generic dietary advice	LBW, PTB, SGA, SB

				Mexico (1), Netherlands (3), Norway (1), Russia (1), Sweden (1), Turkey (1), UK (4), USA (8)		to increase fish in diet		

RDA – recommended daily allowance

Table 6. Evidence of efficacy of nutrients without energy to reduce LBW, PTB, SGA and SB.

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Replacement of iron-folic acid supplementation with MMN supplementation	Yes	No	Yes	No
	RR: 0.88 [0.85, 0.91] (N=68801)[1]	RR: 0.95 [0.90,1.01] (N=91425[1]	RR: 0.92 [0.88, 0.97] (N=57348)[1]	RR: 0.95 [0.86, 1.04] (N=97927)[1]
	HIGH	MODERATE	MODERATE	HIGH
Dietary supplementation with high-dose calcium	Possibly	Possibly	No	No
	RR: 0.85 [0.72, 1.01] (N=14883)	RR: 0.76 [0.60, 0.97] (N=15275)	RR: 1.05 [0.86, 1.29] (N=13615)	RR: 0.9 [0.74, 1.09] (N=15665)
	LOW	LOW	LOW	LOW
Dietary supplementation with low-dose calcium	Insufficient data	Inconclusive	Insufficient data	Insufficient data
	N/A	RR: 0.83 [0.34, 2.03] (N=1290)	N/A	N/A
	N/A	Not assessed	N/A	N/A
Supplementation with omega-3 fatty acids	Yes	Yes	No	No
	RR: 0.90 [0.82, 0.99] (N=8449)	RR: 0.89 [0.81,0.97] (N=10304)	RR: 1.01 [0.9, 1.13] (N=6907)	RR: 0.94 [0.62, 1.42] (N=7880)
	HIGH	HIGH	MODERATE	MODERATE

1.The proportion of studies coming from Sub-Saharan Africa or South Asia is 50% or higher. RR – relative risk [95% confidence interval], N/A – not applicable

Table 7 Summary of effect size (ES) documents for nutritional interventions without supplementation

Intervention	First Author	Year	Study design	Country	Population	Description of Intervention	Description of Control	Outcomes reported	Risk of bias
Dietary education	Jahan (34)	2014	RCT	Bangladesh	Pregnant women with undernutrition	3x1-hour group education sessions spaced 1 month apart held at the clinic. Topics included how to make nutritious food from local ingredients	Routine antenatal care	LBW	High
	Nikièma (35)	2017	cluster RCT	Burkina Faso	Pregnant women with undernutrition	Health centres (cluster) randomised to deliver dietary counselling	Routine antenatal care	LBW	High
	Nyamasege (36)	2019	cluster RCT	Kenya	Pregnant women with undernutrition	Monthly individual nutritional counselling in the home	Routine antenatal care	LBW, PTB	Moderate

RCT = randomized controlled trial

Table 8. Evidence of efficacy of nutritional interventions without dietary supplementation to reduce LBW, PTB, SGA and SB.

Intervention	Does the indicated intervention reduce the prevalence of the following adverse birth outcomes?			
	Low Birth Weight (LBW)	Preterm birth (PTB)	Small for Gestational Age (SGA)	Stillbirth (SB)
Dietary education of pregnant women with undernutrition	Possibly	Insufficient data	Insufficient data	Insufficient data
	RR: 0.46 [0.27, 0.79] (N=3440)[1]	RR: 0.84 [0.68, 1.04] (N=1001)[1]	N/A	N/A
	LOW	MODERATE	N/A	N/A
Regular screening for maternal weight gain followed, if indicated, by dietary supplementation or other intervention	Insufficient data	Insufficient data	Insufficient data	Insufficient data
	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

1.The proportion of studies coming from Sub-Saharan Africa or South Asia is 50% or higher. RR – relative risk [95% confidence interval], N/A – not applicable