Gates Open Research 2019, 3:1657 Last updated: 24 SEP 2020

Check for updates

SYSTEMATIC REVIEW

Interventions to improve birth outcomes of pregnant women living in low- and middle-income countries: a systematic review and network meta-analysis [version 1; peer review: 3 approved with reservations]

Jay J. H. Park[1,2], Ofir Harari[1], Ellie Siden[1,2], Michael Zoratti[3], Louis Dron[1], Noor-E Zannat[1], Richard T. Lester[2], Kristian Thorlund[1,3], Edward J. Mills[1,3]

[1]MTEK Sciences, Vancouver, BC, V5Z 1J5, Canada
[2]Experimental Medicine, Department of Medicine, University of British Columbia, Vancouver, BC, V5Z 1M9, Canada
[3]Department of Health Research Methodology, Evidence, and Impact, McMaster University, Hamilton, Ontario, L8S 4L8, Canada

v1 **First published:** 08 Nov 2019, **3**:1657 https://doi.org/10.12688/gatesopenres.13081.1
Latest published: 24 Sep 2020, **3**:1657 https://doi.org/10.12688/gatesopenres.13081.2

Abstract

Background: Improving the health of pregnant women is important to prevent adverse birth outcomes, such as preterm birth and low birthweight. We evaluated the comparative effectiveness of interventions under the domains of micronutrient, balanced energy protein, deworming, maternal education, and water sanitation and hygiene (WASH) for their effects on these adverse birth outcomes.
Methods: For this network meta-analysis, we searched for randomized clinical trials (RCTs) of interventions provided to pregnant women in low- and middle-income countries (LMICs). We searched for reports published until September 17, 2019 and hand-searched bibliographies of existing reviews. We extracted data from eligible studies for study characteristics, interventions, participants' characteristics at baseline, and birth outcomes. We compared effects on preterm birth (<37 gestational week), low birthweight (LBW; <2500 g), and birthweight (continuous) using studies conducted in LMICs.
Results: Our network meta-analyses were based on 101 RCTs (132 papers) pertaining to 206,531 participants. Several micronutrients and balanced energy food supplement interventions demonstrated effectiveness over standard-of-care. For instance, versus standard-of-care, micronutrient supplements for pregnant women, such as iron and calcium, decreased risks of preterm birth (iron: RR=0.70, 95% credible interval [CrI] 0.47, 1.01; calcium: RR=0.76, 95%CrI 0.56, 0.99). Daily intake of 1500kcal of local food decreased the risks of preterm birth (RR=0.36, 95%CrI 0.16, 0.77) and LBW (RR=0.17, 95%CrI 0.09, 0.29), respectively when compared to standard-of-care. Educational and deworming interventions did not show improvements in birth

Open Peer Review

Reviewer Status ? ? ?

	Invited Reviewers		
	1	**2**	**3**
version 2 (revision) 24 Sep 2020			
version 1 08 Nov 2019	? report	? report	? report

1. **R Rima Jolivet**, Harvard T.H. Chan School, Boston, USA
2. **Elizabeth M. McClure**, RTI International, Durham, USA
3. **Sonali Kochhar**, University of Washington, Seattle, USA
Global Healthcare Consulting, New Delhi, India

Any reports and responses or comments on the article can be found at the end of the article.

outcomes, and no WASH intervention trials reported on these adverse birth outcomes.
Conclusion: We found several pregnancy interventions that improve birth outcomes. However, most clinical trials have only evaluated interventions under a single domain (e.g. micronutrients) even though the causes of adverse birth outcomes are multi-faceted. There is a need to combine interventions that of different domains as packages and test for their effectiveness.
Registration: PROSPERO CRD42018110446; registered on 17 October 2018.

Keywords
Pregnancy, low- and middle-income countries, network meta-analysis, evidence synthesis, preterm, birthweight, birth outcomes

Corresponding author: Edward J. Mills (emills@mteksciences.com)

Author roles: Park JJH: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Supervision, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Harari O**: Formal Analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Siden E**: Data Curation, Methodology, Project Administration, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Zoratti M**: Data Curation, Investigation, Methodology, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Dron L**: Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Zannat NE**: Data Curation, Investigation, Project Administration, Visualization, Writing – Review & Editing; **Lester RT**: Investigation, Methodology, Project Administration, Supervision, Validation, Writing – Review & Editing; **Thorlund K**: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Mills EJ**: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This study was supported by the Bill & Melinda Gates Foundation (Contract Number: 52565).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Park JJH, Harari O, Siden E *et al.* **Interventions to improve birth outcomes of pregnant women living in low- and middle-income countries: a systematic review and network meta-analysis [version 1; peer review: 3 approved with reservations]** Gates Open Research 2019, **3**:1657 https://doi.org/10.12688/gatesopenres.13081.1

First published: 08 Nov 2019, **3**:1657 https://doi.org/10.12688/gatesopenres.13081.1

Introduction

Despite global substantial progresses that have been made towards improving maternal, newborn, and child health (MNCH) in the last two decades, adverse birth outcomes such as preterm birth and low birthweight still remain as an important global health challenge, particularly in low- and middle-income countries (LMIC)[1–3]. Determinants of these challenges are multifaceted[4–7]. Pregnant women in LMICs have a higher risk of nutritional deficiencies, stemming from physiological changes that involve fetal development and growth resulting in an increased demand for nutrients[4,5]. Poor water, sanitation, and hygiene (WASH) control can also increase likelihood for infectious diseases, including intestinal worm infections that may contribute to conditions, such as anemia, which negatively affects fetal survival and growth[6,8,9]. Poor maternal health during pregnancy is associated with preterm birth (<37 gestation weeks) and low birthweight (<2500 g), and these adverse birth outcomes are associated with adverse neonatal events, such as respiratory distress syndrome, neurocognitive impairment, poor linear growth (stunting), and overall mortality[1,2,10,11].

Several reviews have aimed to assess the effectiveness of various promising interventions for pregnant women (Table 1). Despite the extensive research conducted to date, the comparative effectiveness of interventions remains unclear across different domains, such as micronutrients, balanced energy protein supplements, maternal education, deworming, and WASH. Few clinical trials have directly compared interventions across domains. Rather, the majority of clinical trials has only compared interventions within a domain. Similarly, most summaries of the evidence for pregnancy interventions have used traditional pairwise meta-analysis, allowing only for the quantitative assessment of a single intervention versus a comparator. Thus far, no attempts have been made to synthesize the evidence indirectly in order to make quantitative comparison of interventions that have not been directly compared in studies.

Recognizing the paucity of direct head-to-head randomized clinical trials (RCTs) between existing interventions, a network meta-analysis can be used to summarize the entirety of evidence for pregnancy interventions. A network of interventions connected via the comparisons that have been made in head-to-head trials can be constructed, and where there is a path from one intervention to another, these interventions can be compared indirectly via some common comparators[12–16]. In addition, where both direct and indirect evidence exists, the indirect evidence can be used to strengthen the inferences for the particular comparison. This is particularly important for pregnancy interventions because many head-to-head trials of active interventions have limited sample sizes. Furthermore, network meta-analysis allows us to simultaneously analyze all potential treatment options and make full use of the available evidence within a single analysis.

The purpose of this study was to assess the comparative effectiveness across intervention domains in micronutrient supplements, balanced energy protein supplements, deworming, maternal education, and WASH interventions using network meta-analysis. Effectiveness of interventions are determined by the following outcome indicators: preterm birth, low birthweight, and birthweight for LMIC-based pregnant women.

Methods

Our analysis and report was designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension to network meta-analysis[17]. The protocol for this study is registered on PROSPERO (CRD42018110446).

Search strategy and selection criteria

Our search strategy was developed after first reviewing the papers published in the Lancet's 2013 Maternal and Child Nutrition series[1,18], including the umbrella review on evidence-based interventions by Bhutta and colleagues[2], for an overview of the literature. Specifically, we reviewed the bibliography of Bhutta *et al.* 2013[2] for relevant systematic reviews, global health guidelines, and LMIC-based trials. We also performed hand searches on PubMed and the Cochrane Database of Systematic Reviews for reviews that have been published after 2013. The list of published reviews relevant to this study is provided in Table 1.

For our systematic literature search, the following databases were searched from inception to September 17, 2019: the Cochrane Central Register of Controlled Trials, Embase, and MEDLINE (*Extended data*, Supplementary Tables 1–3)[45]. In addition to database searches, we included the relevant trials identified from bibliographies of prior reviews (Table 1). Table 2 describes the PICOS criteria used to guide the study selection. We included LMIC-based RCTs on interventions related to the domains of micronutrient supplements, balanced energy protein (i.e. food supplementation) supplements, deworming, maternal education, and WASH; the outcomes of interest were preterm birth (<37 weeks of gestational age), low birthweight (<2500 grams), and birthweight (continuous). We excluded non-English language studies.

A paired group of four reviewers (JJHP, ES, MZ, and LD) independently reviewed all abstracts and proceedings identified in the literature searches. JJHP and ES worked in one pair, while MZ and LD worked in another pair. The same paired team independently reviewed abstracts potentially relevant in full-text. If any discrepancies occurred between the studies selected by the two investigators, a third investigator (KT) provided arbitration.

Using a standardized data sheet, a paired group of four reviewers (JJHP, ES, MZ, and NEZ) independently extracted data for study characteristics, interventions used, patient characteristics at baseline, and outcomes from the final list of selected eligible studies. Any discrepancies observed between the data extracted by the four extractors were resolved by consensus through discussion. Primary outcomes were dichotomous, consisting of preterm birth and low birthweight. Our secondary endpoint was the continuous outcome of birthweight. We preferentially extracted intention-to-treat outcomes.

Table 1. Existing reviews on interventions for pregnant women.

Review ID	Title	Interventions	No of studies	Types of studies included
Imdad 2011[20]	Effect of balanced protein energy supplementation during pregnancy on birth outcomes	Balanced protein energy supplements	11	RCTs and quasi-RCTs
Imdad 2012[21]	Maternal Nutrition and Birth Outcomes: Effect of Balanced Protein-Energy Supplementation	Balanced protein energy supplements	16	RCTs and quasi-RCTs
Liberato 2013[22]	Effects of protein energy supplementation during pregnancy on fetal growth: a review of the literature focusing on contextual factors	Balanced protein energy supplements	20	RCTs, quasi-RCTs, and observational study
Stevens 2015[23]	The effect of balanced protein energy supplementation in undernourished pregnant women and child physical growth in low- and middle-income countries: a systematic review and meta-analysis	Balanced protein energy supplements	7	RCTs, quasi-RCTs, and observational study
Buppasiri 2015[24]	Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes	Calcium	25	RCTs and cluster-RCTs
Hofmeyr 2014[25]	Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems	Calcium	13	RCTs
Bassani 2013[26]	Financial incentives and coverage of child health interventions: a systematic review and meta-analysis	Conditional cash transfer	25	Non peer-reviewed institutional reports, RCTs, and observational studies
Glassman 2013[27] *	Impact of Conditional Cash Transfers on Maternal and Newborn Health	Conditional cash transfer	24	Cochrane reviews, systematic reviews, and other papers
Salam 2015[28]	Effect of administration of antihelminthics for soil-transmitted helminths during pregnancy	Deworming	4	RCTs
Lassi 2013[29]	Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes	Folic acid	31	RCTs and cluster-RCTs
Yang 2011[30] *	Review of fortified food and beverage products for pregnant and lactating women and their impact on nutritional status	Fortified products	14	RCT, quasi-RCT
Bratton 2015[31]	Maternal Influenza Immunization and Birth Outcomes of Stillbirth and Spontaneous Abortion: A Systematic Review and Meta-analysis	Influenza vaccine	7	Observational and cross-sectional studies
Nunes 2016[32]	The Effects of Influenza Vaccination during Pregnancy on Birth Outcomes: A Systematic Review and Meta-Analysis	Influenza vaccine	18	RCTs and observational studies
Pena-Rosas 2009[33]	Effects and safety of preventive oral iron or iron+folic acid supplementation for women during pregnancy	Iron; Iron + folic acid	49	RCTs and quasi-RCTs
Suchdev 2015[34]	Multiple micronutrient powders for home (point-of-use) fortification of foods in pregnant women (Review)	Multiple micronutrient powders	2	RCTs
Haider 2017[35]	Multiple-micronutrient supplementation for women during pregnancy	Multiple micronutrient supplements	19	RCTs
Imhoff-Kunsch 2012[36]	Effect of n-3 Long-chain Polyunsaturated Fatty Acid Intake during Pregnancy on Maternal, Infant, and Child Health Outcomes: A Systematic Review	N-3 long chain polyunsaturated fatty acid	15	RCT
Thorne-Lyman 2012A[37]	Vitamin A and carotenoids during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis	Vitamin A	17	RCTs

Review ID	Title	Interventions	No of studies	Types of studies included
De-Regil 2016[38]	Vitamin D supplementation for women during pregnancy	Vitamin D	15	RCTs and quasi-RCTs
Perez-Lopez 2015[39]	Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials	Vitamin D	13	RCTs
Thorne-Lyman 2012B[40]	Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis	Vitamin D	5	RCTs
Ota 2015[41]	Zinc supplementation for improving pregnancy and infant outcome	Zinc	21	RCTs
Goudet 2019[42]	Nutritional interventions for preventing stunting in children (birth to 59 months) living in urban slums in low-and middle-income countries (lmic)	Nutrient supplementation and Education	15	RCTs, quasi-RCTs, non-RCTs, controlled before-and-after, and interrupted time series

*All reviews were systematic literature reviews with pairwise meta-analysis, except for Glassman 2013 and Yang 2011.

Table 2. Population, interventions, comparator, outcomes, and study design criteria for study inclusion.

Category	Inclusion criteria
Population	Pregnant women living in low- and middle-income countries
Intervention	• Micronutrient and calcium supplementation to mother • Balanced energy protein (i.e. food) supplementation to mother • Deworming • Maternal education • Any water, sanitation and hygiene intervention
Comparators	• Placebo • Standard-of-care (if applicable) • No intervention • Any of the interventions listed above as monotherapy or in combination that can be used for indirect comparison
Outcomes	At least one of the following outcomes: • Preterm birth (<37 weeks of gestational age) • Low birthweight (<2500 g) • Birthweight (continuous)
Study Design	Randomized clinical trials
Other	Published in the English language

Data analysis

We performed our analyses within the Bayesian framework in *R* using the R2WinBUGS v14 package[43,44]. Bayesian models were performed according to the National Institute for Health and Care Excellence (NICE) in their Technical Support Document 2 (TSD2)[45]. The network diagrams with respective to the analyzed outcome can be seen in *Extended data*, Supplementary Figures 1–6[19]. Estimates of comparative effectiveness are measured using risk ratios (RRs) with associated 95% credible intervals (95% CrI) for preterm birth and low birthweight, and mean differences and the associated 95% CrI for birthweight. We performed random-effects network meta-analysis models using an empirically informative priors for the heterogeneity variance, as suggested by Rhodes *et al.*[46] for mean birthweight and Turner *et al.*[47] for preterm birth and low birthweight. This was done to stabilize the estimation of heterogeneity in the face of low number of trials per comparison in the network. Our model selection was informed by the deviance information criterion (DIC) and the deviance-leverage plots that could help identify outliers or lack of model fit.

As our primary analysis, we included both cluster and individually randomized (non-cluster) clinical trials. To adjust for clustering effects of the cluster trials, we adjusted the sample sizes and number of cases for preterm birth and low birthweight and inflated variances for mean birthweight to account for clustering effects of the cluster trials, as recommended by Uhlmann *et al.*[48], assuming a conservative intra-cluster correlation coefficient (ICC) value of 0.05. For each outcome, we performed sensitivity analyses by excluding cluster randomized clinical trials where the analyses were limited to individually randomized clinical trials only.

Risk of bias within and across studies

Each full text article was evaluated for reporting quality according to the Cochrane Risk of Bias Tool[49]. The risk of bias assessment within and across studies are provided in the *Extended data* (Supplementary Table 8)[19].

Results

We identified 5,297 abstracts from our database searches and hand searches of the bibliography of the published reviews (Figure 1). Of these, 377 studies underwent a full-text review, and 132 papers reporting on 101 trials met our inclusion criteria. In total, these trials included 206,531 pregnant women that were randomized to 245 unique interventions (Figure 2). The list of included and excluded studies (*Extended data*, Supplementary Tables 4 and 5)[19], as well as the trial and patient characteristics of the included studies (*Extended data*, Supplementary Tables 6 and 7)[19] are provided in the *Extended data*. Geographically, most trials were conducted in South Eastern Asian (n = 38 trials) and African (n = 26 trials) countries, with individual randomization (i.e. non-cluster trials, n = 85 trials) and double blinding (n = 52 trials) being the most common methodological features. Micronutrient supplements was the most common intervention domain that was investigated (n = 79 trials); only a few of these micronutrient trials compared interventions from other domains, such as balanced energy protein supplements (n = 15 trials) and deworming (n = 6 trials). There were no WASH trials reporting on the analyzed birth outcomes.

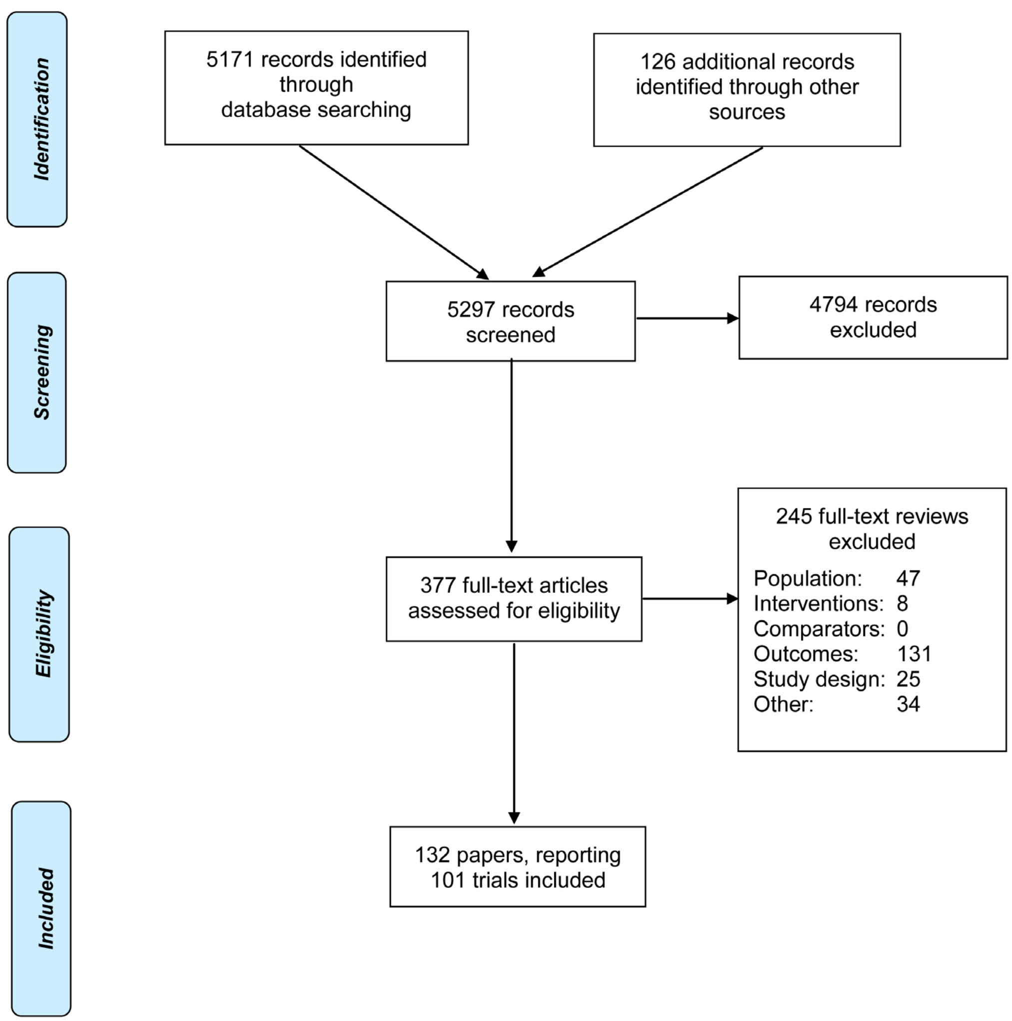

Figure 1. Study selection.

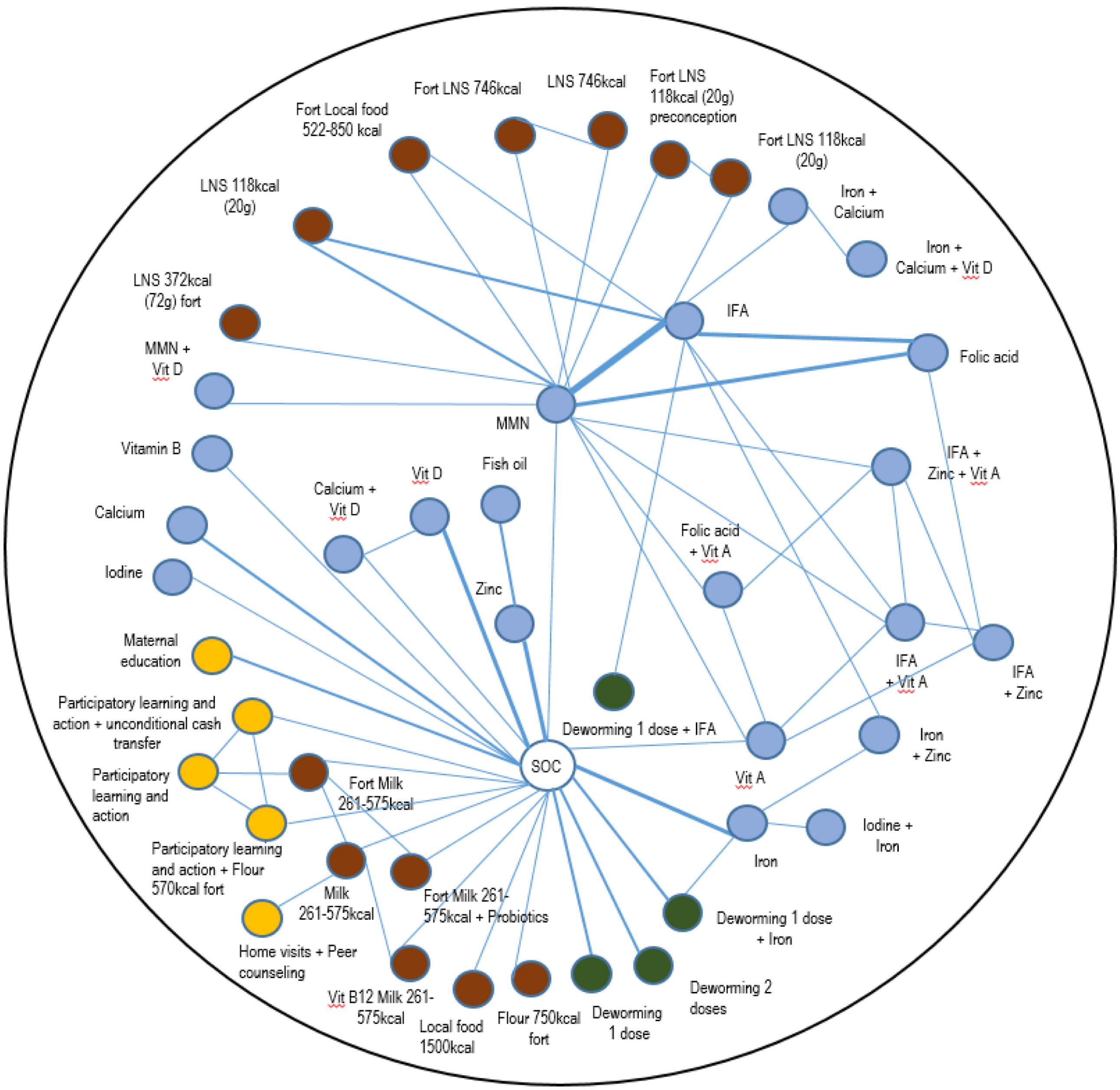

Figure 2. Overall network of the comparisons between interventions for pregnancy. Each node (circle) represents an intervention, each line represents a direct comparison between interventions, with the lines with width representing the number of trials with the direct comparisons in question (i.e. thicker width represents a direct comparison with larger numbers of trials). The different intervention domains are indicated with the following colors: blue for micronutrient supplements; brown for balanced energy protein supplements; yellow for education and counseling interventions; and green for deworming interventions. Vit, Vitamin; IFA, iron and folic Acid; LNS, lipid-based nutrient supplements; Fort, fortification; MMN, multiple micronutrients.

In most trials, interventions were provided to pregnant women from enrollment until delivery (n = 87 trials). These trials generally involved women who were in the later part of their gestational age. For instance, only 5 trials enrolled women from or before conception (Owens[50], The women First Trial[51], CAP Trial[52], PRECONCEPT[53], and Brabin[54]), while the majority of trials recruited women who were in the later trimesters, such as the 2nd and 3rd trimesters (n = 69 trials).

Preterm birth (<37 weeks of gestational age)

The preterm birth network (*Extended data*, Supplementary Figure 1)[19] included 64 trials consisting of 85,546 pregnant women randomized to 152 intervention arms (ten cluster trials consisting of 1,998 clusters and 20,218 pregnant women). From the primary analysis, that included both cluster and non-cluster randomized clinical trials, only few interventions showed superiority over standard-of-care for preterm birth (Figure 3). For instance, compared to standard-of-care, intake of 1500 kcal of local food per day showed an RR of 0.36 (95% CrI: 0.16, 0.77) and calcium showed an RR of 0.76 (95% CrI: 0.56, 0.99). Other micronutrient supplements such as folic acid (RR: 0.71, 95% CrI: 0.43, 1.09), iron (RR: 0.70, 95% CrI: 0.47, 1.01), zinc (RR: 0.67, 95% CrI: 0.41, 1.04), and multiple micronutrients (MMN) (RR: 0.70, 95% CrI: 0.45, 1.02) showed a trend towards lower preterm birth risks compared to standard-of-care, but their Crls overlapped the null effect of 1.00. In comparison to standard-of-care, no balanced energy food supplements, other than 1500 kcal of local food showed reduction in preterm birth risks, and neither did maternal education interventions (e.g. participatory learning action[55]).

Mean birthweight (kg)

The mean birthweight network (*Extended data*, Supplementary Figure 3)[19] included of 81 trials that consisted of 130,315 pregnant women randomized to 196 intervention arms. Of these 81 trials, 14 were cluster trials that randomized 1,354 clusters (57,483 pregnant women) to 35 intervention arms. The results of the network meta-analysis on mean birthweight can be found in Figure 4. Among the micronutrient supplementation domain, compared to standard-of-care, MMN (mean difference: 0.27 kg; 95% CrI: 0.09, 0.45 kg), folic acid (mean difference: 0.21 kg; 95% CrI: 0.00, 0.42 kg), iron (mean difference: 0.18 kg; 95% CrI: 0.02, 0.34 kg), and iron + folic acid (IFA) (mean difference: 0.18 kg; 95% CrI: 0.00, 0.36 kg) showed improvements in birthweight. Among the balanced energy food supplements, unfortified lipid-based nutrient supplements of 20 grams (LNS20) showed improvements in birthweight compared to standard-of-care (mean difference: 0.27 kg; 95% CrI: 0.03, 0.51 kg). Deworming and maternal education interventions did not improve mean birth

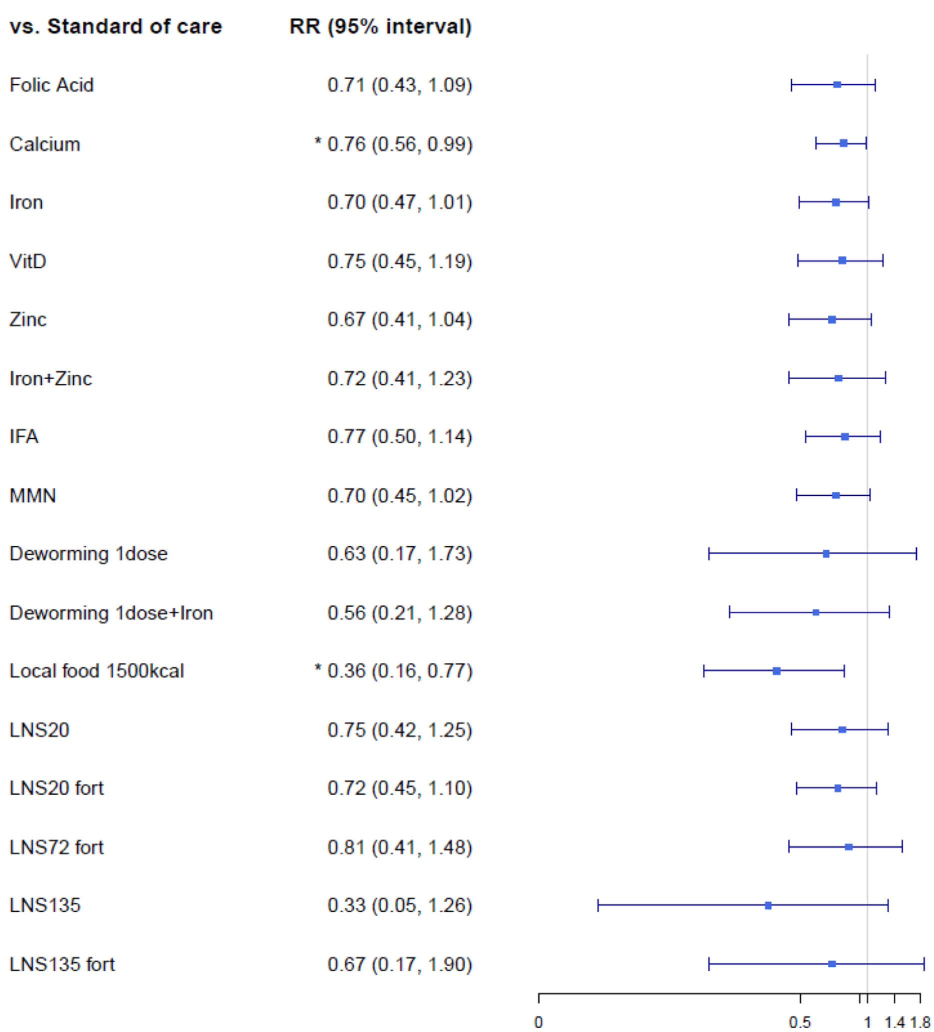

Figure 3. Forest plot for the effects of interventions on preterm birth, risk ratio. Vit, Vitamin; IFA, iron and folic Acid; LNS, lipid-based nutrient supplements; Fort, fortification; MMN, multiple micronutrients.

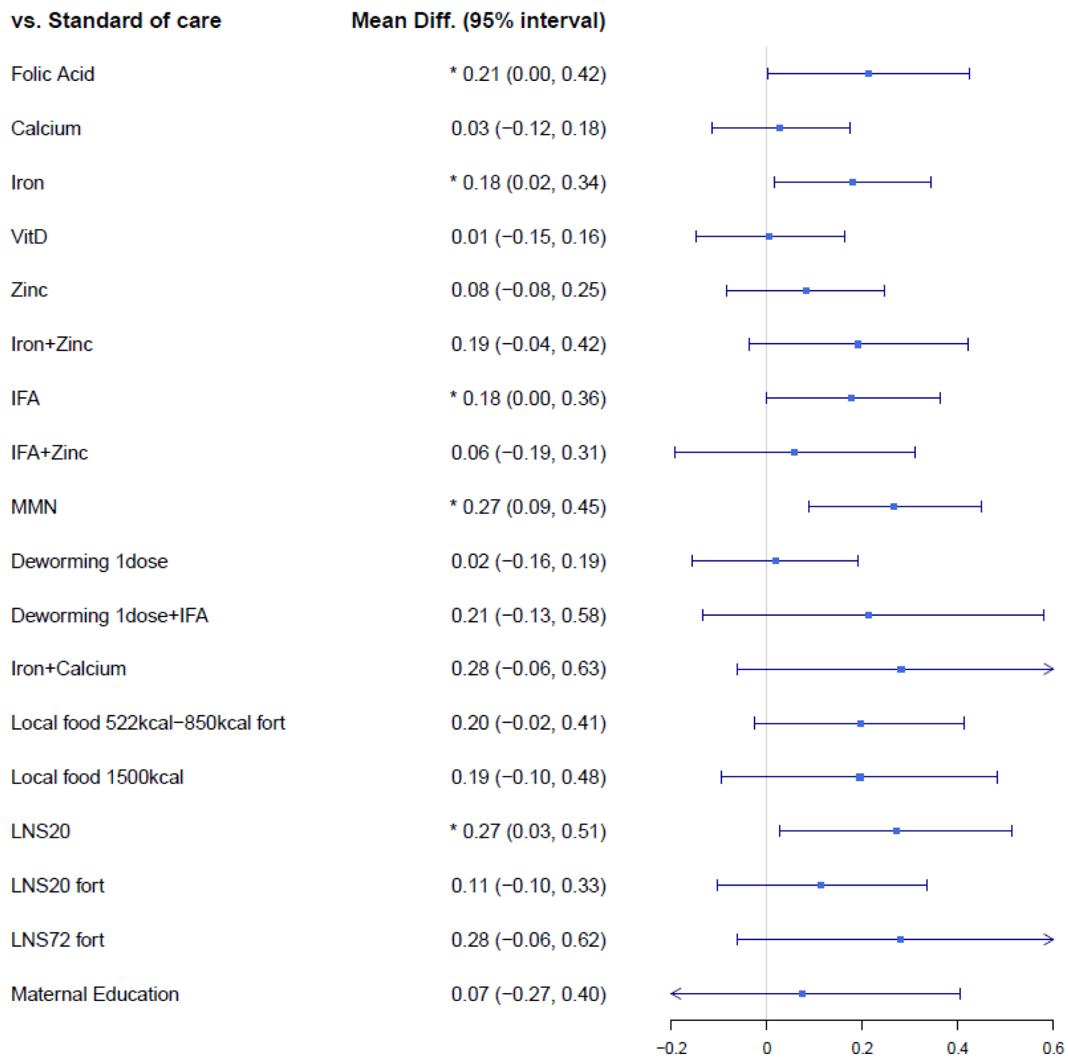

Figure 4. Forest plot for the effects of interventions on birthweight, mean difference in kg. Vit, Vitamin; IFA, iron and folic Acid; LNS, lipid-based nutrient supplements; Fort, fortification; MMN multiple micronutrients.

weight; for instance, in comparison to standard-of-care, a single dose of deworming showed a mean difference of 0.02 kg (95% CrI: -0.16, 0.19 kg) and maternal education showed a mean difference of 0.07 kg (95% CrI: -0.27, 0.40 kg).

Low birthweight (<2.5 kg)

The low birthweight network (*Extended data*, Supplementary Figure 5)[19] consisted of 67 trials, with 84,675 patients randomized to 160 intervention arms (eleven cluster trials consisting of 792 clusters and 9,512 pregnant women). The results on low birthweight (kg) outcome can be found in Figure 5. High caloric local food intervention (1500 kcal per day) reduced the risk of low birthweight (RR: 0.17; 95% CrI: 0.09; 0.29). There was a trend towards reduced risks of low birthweight for other interventions such as calcium (RR: 0.87; 95% CrI: 0.69; 1.07), MMN (RR: 0.73; 95% CrI: 0.49, 1.07), and LNS20 (RR: 0.65; 95% CrI: 0.39, 1.07), fortified LNS20 (RR: 0.72, 95% CrI: 0.48, 1.03), but their 95% CrI contained the null effect of 1.00. A single dose of deworming during pregnancy did not show reduction in low birthweight when compared to standard-of-care (RR: 1.15, 95% CrI: 0.83, 1.58).

Sensitivity analysis

For all three outcomes, the results from the sensitivity analyses of studies limited to non-cluster randomized clinical trials can be found in the *Extended data* (Supplementary cross table excel file: Sensitivity Preterm, LBW, and Birthweight tabs)[19]. As fewer studies were available for the sensitivity analysis, the CrIs for many comparisons became wider, but the direction and the magnitude of comparative effects remained relatively stable. For instance, there were no individually randomized trials that evaluated the effectiveness of high

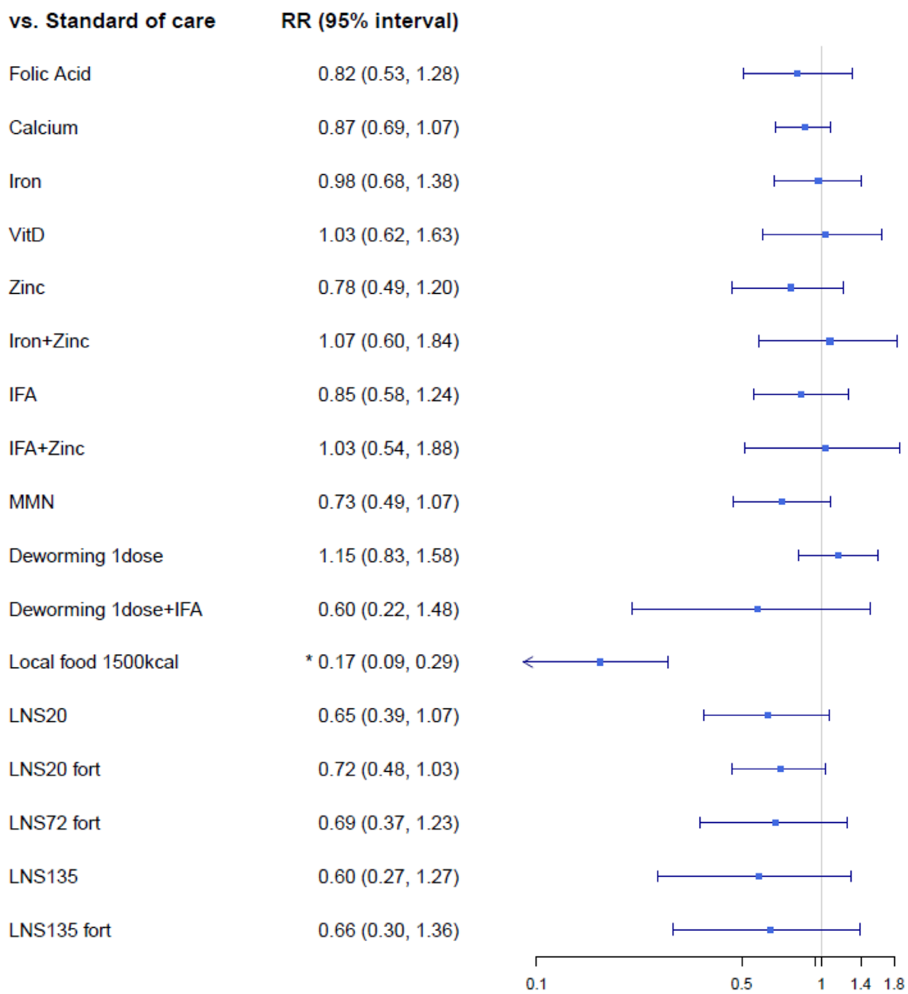

Figure 5. Forest plot for the effects of interventions on low birthweight, risk ratio. Vit, Vitamin; IFA, iron and folic Acid; LNS, lipid-based nutrient supplements; Fort, fortification; MMN multiple micronutrients.

caloric (1500 kcal per day) local food. In terms of micronutrient supplementation, MMN (mean difference: 0.10 kg; 95% CrI: 0.00, 0.20 kg) and iron (mean difference: 0.09 kg; 95% CrI: 0.02, 0.16 kg) improved mean birthweight by a small margin compared to standard-of-care. Similarly, unfortified lipid-based nutrient supplements (LNS20) did not improve mean birthweight to a great extent compared to standard-of-care (mean difference: 0.13 kg; 95% CrI: 0.01, 0.24 kg). Furthermore, in comparison to standard-of-care, maternal education (mean difference: 0.04 kg; 95% CrI: -0.13, 0.20 kg) and one dose of deworming (mean difference: 0.01 kg; 95% CrI: -0.04, 0.06 kg) did not have any effect on mean birthweight. As far as preterm birth is concerned, MMN (RR: 0.58; 95% CrI: 0.31, 1.00) showed a trend towards lower preterm birth risks compared to standard-of-care, but their Crls overlapped the null effect of 1.00.

Discussion

In this study, we used network meta-analysis to compare the effectiveness of interventions across several domains ranging from nutrition, infection control, and education that can be provided to pregnant women living in LMICs. Several micronutrient supplements demonstrated decreased risks for preterm birth and/or improve mean birthweight, compared with standard-of-care for pregnant women. For example, MMN interventions showed reduction in preterm birth risks and improved mean birthweight. In comparison to standard-of-care, IFA, calcium, iron, and zinc also demonstrated a trend towards decreasing preterm birth risks. However, the evidence for other intervention domains were limited. For instance, among balanced energy protein supplements, only consumption of 1500 kcal of local food supplement lowered the risks of preterm birth and low birthweight; and only unfortified LNS 20 demonstrated improvement in mean birthweight. Nevertheless, these findings pertaining to balanced energy protein supplements corresponded to only three trials in the study[56–58]. There was a limited number of trials available for maternal education and deworming intervention; no WASH trials reporting on preterm birth and birthweight outcomes were available.

The main strength of this study was the use of network meta-analysis to assess the effectiveness of different interventions from a large network of evidence compared to standard-of-care. Unlike previous reviews that have focused on one intervention within a single domain, we used a broad evidence base that included multiple interventions from different domains. As well, appropriate statistical adjustments were made for clustering effects of cluster randomized clinical trials to enable the convergence of cluster and non-cluster trials for our network meta-analysis. Nevertheless, the existing evidence base limited our analyses. Few trials reported low birthweight, and the majority of randomized clinical trial evidence base was confined to a single domain of micronutrient supplementation. Another possible limitation was that there was notable variation in the enrollment of pregnant women in terms of trimesters and gestational age. While we did not find that time of enrollment relative to gestational age was a treatment effect modifier in our analyses, we acknowledge that this variation may have introduced heterogeneity in our meta-analyses. Prior evidence has also demonstrated mixed evidence as to whether the time at which treatment is initiated influences overall treatment efficacy, and this varies by treatment type[25,35,41]. Lastly, our assumption of a conservative ICC (0.05) may also have affected the results. However, this was necessary in order to assess for the entire evidence base of interventions for pregnancy, as most cluster randomized trials did not report ICC for each outcome.

Despite these limitations, the findings of this study were generally similar to that of other existing reviews. For instance, among the micronutrient supplements, other reviews have shown that iron (RR=0.82, 95%Crl 0.72, 0.94)[59] and MMN (RR=0.88, 95%Crl 0.85, 0.90)[35] reduced the risks of low birthweight versus standard-of-care. Moreover, calcium (RR=0.76, 95%Crl 0.60, 0.97)[25] and zinc (RR=0.86, 95%Crl 0.76, 0.97)[41] supplements reduced the risks of preterm birth, and we have found that intake of combined MMN reduced the risks of preterm birth and improved mean birthweight. Similar to this study, Salam[28] found no improvements in low birthweight and preterm birth for deworming versus standard-of-care. There were no reviews on WASH available that looked at the role of WASH interventions on birthweight and preterm birth.

Our findings identified several directions for future research. First, there is a need to combine interventions that consist of compelling and evidence-based interventions of different domains as a package, moving away from a reductionist approach that is reflected in the majority of clinical trials conducted so far. Instead of a singling out interventions from one domain, there is a need for more evidence of packaged interventions because a combined set of interventions will likely result in the greatest improvement for adverse birth outcomes. Second, more research is needed to assess the longevity of interventions and its effectiveness across multiple life stages. For instance, only 17 out of 101 trials conducted follow-ups of women after birth delivery into the postpartum period. It is also important to note that the median follow-up of pregnant women beyond delivery was 8 weeks and only three trials[23,60,61] conducted follow-ups with women and their newborns up to 6 months of age.

Overall, we identified a number of interventions for pregnancy with clear and compelling supportive evidence for effectiveness for preventing adverse birth outcomes. In midst of the World Health Organization's Global Nutrition Targets 2025[62], which focuses on improving maternal, infant, and young children nutrition, national and local MNCH programs should consider adopting and adapting effective interventions identified in this review based on their local resource availability and program priorities. This may provide an opportunity to evaluate the benefits of these interventions in routine practice for pregnancy, and a step towards reaching the 2025 Global Nutrition Target of reducing the global prevalence of low birthweight by 30%[63].

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Extended data

Open Science Framework: Interventions to improve birth outcomes of pregnant women living in low- and middle-income countries: a systematic review and network meta-analysis.

https://doi.org/10.17605/OSF.IO/JK3AQ[19].

This project contains the following extended data:

- Pregnancy NMA - Supplementary tables and figures - v2.0:
    - Appendix 1. Literature search strategy. (Contains Supplementary Tables 1–3.)
    - Appendix 2. Details of statistical analyses.
    - Appendix 3. List of included and excluded studies are full-text review. (Contains Supplementary Tables 4 and 5.)
    - Appendix 4. Details of the evidence base. (Contains Supplementary Tables 6 and 7.)
    - Appendix 5. Bias Assessment. (Contains Supplementary Table 8.)
    - Appendix 6. Intervention networks for birth outcomes (Supplementary Figures 1–6.)

- ○ Appendix 7. Primary analysis leverage and consistency plots. (Supplementary Figures 7–12.)
- ○ Appendix 8. Sensitivity analysis forest plots, non-cluster trials. (Supplementary Figures 13–15.)
- ○ Appendix 9. Sensitivity analysis leverage plots, non-cluster trials. (Supplementary Figures 16–18.)

- Pregnancy NMA - Supplementary crosstables - v1.0

Reporting guidelines

Open Science Framework: PRISMA checklist for "Interventions to improve birth outcomes of pregnant women living in low- and middle-income countries: a systematic review and network meta-analysis." https://doi.org/10.17605/OSF.IO/JK3AQ[19].

Author contributions

JJHP, KT, and EJM conceptualized and designed the study. JJHP, OH, ES, MZ, LD, NEZ, RTL, KT, and EJM acquired, analyzed, and interpreted data. JJHP drafted the manuscript. All authors critically revised the manuscript for important intellectual content. JJHP, OH, KT, and EJM did the statistical analysis. EJM obtained funding. KT and EJM provided administrative, technical, or material support. KT and EJM supervised the study.

KT and EJM had full access to all of the data in the study. EJM was responsible for the integrity of the data, accuracy of the data analysis, and the final decision to submit for publication.

References

1. Black RE, Victora CG, Walker SP, *et al.*: **Maternal and child undernutrition and overweight in low-income and middle-income countries.** *Lancet.* 2013; **382**(9890): 427–51.
PubMed Abstract | Publisher Full Text

2. Bhutta ZA, Das JK, Rizvi A, *et al.*: **Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost?** *Lancet.* 2013; **382**(9890): 452–77.
PubMed Abstract | Publisher Full Text

3. Vaivada T, Gaffey MF, Das JK, *et al.*: **Evidence-based interventions for improvement of maternal and child nutrition in low-income settings: what's new?** *Curr Opin Clin Nutr Metab Care.* 2017; **20**(3): 204–10.
PubMed Abstract | Publisher Full Text

4. Gernand AD, Schulze KJ, Stewart CP, *et al.*: **Micronutrient deficiencies in pregnancy worldwide: health effects and prevention.** *Nat Rev Endocrinol.* 2016; **12**(5): 274–89.
PubMed Abstract | Publisher Full Text | Free Full Text

5. Darnton-Hill I, Mkparu UC: **Micronutrients in pregnancy in low- and middle-income countries.** *Nutrients.* 2015; **7**(3): 1744–68.
PubMed Abstract | Publisher Full Text | Free Full Text

6. Campbell OM, Benova L, Gon G, *et al.*: **Getting the basic rights - the role of water, sanitation and hygiene in maternal and reproductive health: a conceptual framework.** *Trop Med Int Health.* 2015; **20**(3): 252–67.
PubMed Abstract | Publisher Full Text | Free Full Text

7. Sappenfield E, Jamieson DJ, Kourtis AP: **Pregnancy and susceptibility to infectious diseases.** *Infect Dis Obstet Gynecol.* 2013; **2013**: 752852.
PubMed Abstract | Publisher Full Text | Free Full Text

8. Campbell SJ, Nery SV, Wardell R, *et al.*: **Water, Sanitation and Hygiene (WASH) and environmental risk factors for soil-transmitted helminth intensity of infection in Timor-Leste, using real time PCR.** *PLoS Negl Trop Dis.* 2017; **11**(3): e0005393.
PubMed Abstract | Publisher Full Text | Free Full Text

9. Benova L, Cumming O, Campbell OM: **Systematic review and meta-analysis: association between water and sanitation environment and maternal mortality.** *Trop Med Int Health.* 2014; **19**(4): 368–87.
PubMed Abstract | Publisher Full Text

10. Christian P: **Fetal growth restriction and preterm as determinants of child growth in the first two years and potential interventions.** *Nestle Nutr Inst Workshop Ser.* Karger Publishers. 2014: **78**: 81–91.
PubMed Abstract | Publisher Full Text

11. Sinha B, Taneja S, Chowdhury R, *et al.*: **Low-birthweight infants born to short-stature mothers are at additional risk of stunting and poor growth velocity: Evidence from secondary data analyses.** *Matern Child Nutr.* 2018; **14**(1): e12504.
PubMed Abstract | Publisher Full Text | Free Full Text

12. Kanters S, Ford N, Druyts E, *et al.*: **Use of network meta-analysis in clinical guidelines.** *Bull World Health Organ.* 2016; **94**(10): 782–4.
PubMed Abstract | Publisher Full Text | Free Full Text

13. Thorlund K, Druyts E, Toor K, *et al.*: **Comparative efficacy of golimumab, infliximab, and adalimumab for moderately to severely active ulcerative colitis: a network meta-analysis accounting for differences in trial designs.** *Expert Rev Gastroenterol Hepatol.* 2015; **9**(5): 693–700.
PubMed Abstract | Publisher Full Text

14. Hutton B, Salanti G, Chaimani A, *et al.*: **The quality of reporting methods and results in network meta-analyses: an overview of reviews and suggestions for improvement.** *PLoS One.* 2014; **9**(3): e92508.
PubMed Abstract | Publisher Full Text | Free Full Text

15. Mills EJ, Thorlund K, Ioannidis JP: **Demystifying trial networks and network meta-analysis.** *BMJ.* 2013; **346**: f2914.
PubMed Abstract | Publisher Full Text

16. Zafari Z, Thorlund K, FitzGerald JM, *et al.*: **Network vs. pairwise meta-analyses: a case study of the impact of an evidence-synthesis paradigm on value of information outcomes.** *Pharmacoeconomics.* 2014; **32**(10): 995–1004.
PubMed Abstract | Publisher Full Text

17. Hutton B, Salanti G, Caldwell DM, *et al.*: **The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations.** *Ann Intern Med.* 2015; **162**(11): 777–84.
PubMed Abstract | Publisher Full Text

18. Ruel MT, Alderman H, Maternal and Child Nutrition Study Group: **Nutrition-sensitive interventions and programmes: how can they help to accelerate progress in improving maternal and child nutrition?** *Lancet.* 2013; **382**(9891): 536–51.
PubMed Abstract | Publisher Full Text

19. Park JJ, Harari O, Siden E, *et al.*: **Interventions to improve birth outcomes of pregnant women living in low- and middle-income countries: a systematic review and network meta-analysis**. 2019.
http://www.doi.org/10.17605/OSF.IO/JK3AQ

20. Imdad A, Bhutta ZA: **Effect of balanced protein energy supplementation during pregnancy on birth outcomes.** *BMC Public Health.* 2011; **11 Suppl 3**: S17.
PubMed Abstract | Publisher Full Text | Free Full Text

21. Imdad A, Bhutta ZA: **Maternal nutrition and birth outcomes: effect of balanced protein-energy supplementation.** *Paediatr Perinat Epidemiol.* 2012; **26 Suppl 1**: 178–90.
PubMed Abstract | Publisher Full Text

22. Liberato SC, Singh G, Mulholland K: **Effects of protein energy supplementation during pregnancy on fetal growth: a review of the literature focusing on contextual factors.** *Food Nutr Res.* 2013; **57**.
PubMed Abstract | Publisher Full Text | Free Full Text

23. Stevens B, Buettner P, Watt K, *et al.*: **The effect of balanced protein energy supplementation in undernourished pregnant women and child physical growth in low- and middle-income countries: a systematic review and meta-analysis.** *Matern Child Nutr.* 2015; **11**(4): 415–32.
PubMed Abstract | Publisher Full Text

24. Buppasiri P, Lumbiganon P, Thinkhamrop J, *et al.*: **Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes.** *Cochrane Database Syst Rev.* 2015; (2): CD007079.
PubMed Abstract | Publisher Full Text

25. Hofmeyr GJ, Lawrie TA, Atallah AN, *et al.*: **Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems.** *Cochrane Database Syst Rev.* 2014; (6): CD001059.
PubMed Abstract | Publisher Full Text

26. Bassani DG, Arora P, Wazny K, *et al.*: **Financial incentives and coverage of**

child health interventions: a systematic review and meta-analysis. *BMC Public Health.* 2013; **13 Suppl 3**: S30.
PubMed Abstract | Publisher Full Text | Free Full Text

27. Glassman A, Duran D, Fleisher L, *et al.*: **Impact of conditional cash transfers on maternal and newborn health.** *J Health Popul Nutr.* 2013; **31**(4 Suppl 2): 48–66.
PubMed Abstract | Free Full Text

28. Salam RA, Haider BA, Humayun Q, *et al.*: **Effect of administration of antihelminthics for soil-transmitted helminths during pregnancy.** *Cochrane Database Syst Rev.* 2015; (6): CD005547.
PubMed Abstract | Publisher Full Text

29. Lassi ZS, Salam RA, Haider BA, *et al.*: **Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes.** *Cochrane Database Syst Rev.* 2013; (3): CD006896.
PubMed Abstract | Publisher Full Text

30. Yang Z, Huffman SL: **Review of fortified food and beverage products for pregnant and lactating women and their impact on nutritional status.** *Matern Child Nutr.* 2011; **7 Suppl 3**: 19–43.
PubMed Abstract | Publisher Full Text

31. Bratton KN, Wardle MT, Orenstein WA, *et al.*: **Maternal influenza immunization and birth outcomes of stillbirth and spontaneous abortion: a systematic review and meta-analysis.** *Clin Infect Dis.* 2015; **60**(5): e11–9.
PubMed Abstract | Publisher Full Text

32. Nunes MC, Aqil AR, Omer SB, *et al.*: **The Effects of Influenza Vaccination during Pregnancy on Birth Outcomes: A Systematic Review and Meta-Analysis.** *Am J Perinatol.* 2016; **33**(11): 1104–14.
PubMed Abstract | Publisher Full Text

33. Peña-Rosas JP, Viteri FE: **Effects and safety of preventive oral iron or iron+folic acid supplementation for women during pregnancy.** *Cochrane Database Syst Rev.* 2009; (4): CD004736.
PubMed Abstract | Publisher Full Text

34. Suchdev PS, Peña-Rosas JP, De-Regil LM: **Multiple micronutrient powders for home (point-of-use) fortification of foods in pregnant women.** *Cochrane Database Syst Rev.* 2015; (6): CD011158.
PubMed Abstract | Publisher Full Text

35. Haider BA, Bhutta ZA: **Multiple-micronutrient supplementation for women during pregnancy.** *Cochrane Database Syst Rev.* 2017; **4**: CD004905.
PubMed Abstract | Publisher Full Text | Free Full Text

36. Imhoff-Kunsch B, Briggs V, Goldenberg T, *et al.*: **Effect of n-3 long-chain polyunsaturated fatty acid intake during pregnancy on maternal, infant, and child health outcomes: a systematic review.** *Paediatr Perinat Epidemiol.* 2012; **26 Suppl 1**: 91–107.
PubMed Abstract | Publisher Full Text

37. Thorne-Lyman AL, Fawzi WW: **Vitamin A and carotenoids during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis.** *Paediatr Perinat Epidemiol.* 2012; **26 Suppl 1**: 36–54.
PubMed Abstract | Publisher Full Text | Free Full Text

38. De-Regil LM, Palacios C, Lombardo LK, *et al.*: **Vitamin D supplementation for women during pregnancy.** *Cochrane Database Syst Rev.* 2016; (1): CD008873.
PubMed Abstract | Publisher Full Text

39. Pérez-López FR, Pasupuleti V, Mezones-Holguin E, *et al.*: **Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials.** *Fertil Steril.* 2015; **103**(5): 1278–88 e4.
PubMed Abstract | Publisher Full Text

40. Thorne-Lyman A, Fawzi WW: **Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis.** *Paediatr Perinat Epidemiol.* 2012; **26 Suppl 1**: 75–90.
PubMed Abstract | Publisher Full Text | Free Full Text

41. Ota E, Mori R, Middleton P, *et al.*: **Zinc supplementation for improving pregnancy and infant outcome.** *Cochrane Database Syst Rev.* 2015; (2): CD000230.
PubMed Abstract | Publisher Full Text

42. Goudet SM, Bogin BA, Madise NJ, *et al.*: **Nutritional interventions for preventing stunting in children (birth to 59 months) living in urban slums in low- and middle-income countries (LMIC).** *Cochrane Database Syst Rev.* 2019; **6**: CD011695.
PubMed Abstract | Publisher Full Text | Free Full Text

43. R Development Core Team: **R: A Language Environment for Statistical Computing**. In: Team RC, editor. Vienna, Austria: *R Foundation for Statistical Computing*. 2017.
Reference Source

44. Sturtz S, Ligges U, Gelman A: **R2OpenBUGS: a package for running OpenBUGS from R.** *J Stat Softw.* 2005; **12**(3): 1–16.
Reference Source

45. Dias S, Sutton AJ, Ades AE, *et al.*: **Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials.** *Med Decis Making.* 2013; **33**(5): 607–17.
PubMed Abstract | Publisher Full Text | Free Full Text

46. Rhodes KM, Turner RM, Higgins JP: **Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data.** *J Clin Epidemiol.* 2015; **68**(1): 52–60.
PubMed Abstract | Publisher Full Text | Free Full Text

47. Turner RM, Jackson D, Wei Y, *et al.*: **Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis.** *Stat Med.* 2015; **34**(6): 984–98.
PubMed Abstract | Publisher Full Text | Free Full Text

48. Uhlmann L, Jensen K, Kieser M: **Bayesian network meta-analysis for cluster randomized trials with binary outcomes.** *Res Synth Methods.* 2017; **8**(2): 236–50.
PubMed Abstract | Publisher Full Text

49. Higgins JPT, Chandler J, Cumpston M, *et al.*: **Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019).** *Cochrane Reviews.* 2019.
Reference Source

50. Owens S, Gulati R, Fulford AJ, *et al.*: **Periconceptional multiple-micronutrient supplementation and placental function in rural Gambian women: a double-blind, randomized, placebo-controlled trial.** *Am J Clin Nutr.* 2015; **102**(6): 1450–9.
PubMed Abstract | Publisher Full Text | Free Full Text

51. Hambidge KM, Westcott JE, Garces A, *et al.*: **A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the Women First trial.** *Am J Clin Nutr.* 2019; **109**(2): 457–69.
PubMed Abstract | Publisher Full Text | Free Full Text

52. Hofmeyr G, Betrán AP, Singata-Madliki M, *et al.*: **Prepregnancy and early pregnancy calcium supplementation among women at high risk of pre-eclampsia: a multicentre, double-blind, randomised, placebo-controlled trial.** *Lancet.* 2019; **393**(10169): 330–339.
PubMed Abstract | Publisher Full Text | Free Full Text

53. Ramakrishnan U, Nguyen PH, Gonzalez-Casanova I, *et al.*: **Neither Preconceptional Weekly Multiple Micronutrient nor Iron-Folic Acid Supplements Affect Birth Size and Gestational Age Compared with a Folic Acid Supplement Alone in Rural Vietnamese Women: A Randomized Controlled Trial.** *J Nutr.* 2016; **146**(7): 1445S–52S.
PubMed Abstract | Publisher Full Text

54. Brabin B, Gies S, Roberts SA, *et al.*: **Excess risk of preterm birth with periconceptional iron supplementation in a malaria endemic area: analysis of secondary data on birth outcomes in a double blind randomized controlled safety trial in Burkina Faso.** *Malar J.* 2019; **18**(1): 161.
PubMed Abstract | Publisher Full Text | Free Full Text

55. Saville NM, Shrestha BP, Style S, *et al.*: **Impact on birth weight and child growth of Participatory Learning and Action women's groups with and without transfers of food or cash during pregnancy: Findings of the low birth weight South Asia cluster-randomised controlled trial (LBWSAT) in Nepal.** *PLoS One.* 2018; **13**(5): e0194064.
PubMed Abstract | Publisher Full Text | Free Full Text

56. Tabrizi JS, Asghari A, Pourali F, *et al.*: **Effects of Food Supplementation During Pregnancy on Maternal Weight Gain, Hemoglobin Levels and Pregnancy Outcomes in Iran.** *Matern Child Health J.* 2019; **23**(2): 258–64.
PubMed Abstract | Publisher Full Text

57. Adu-Afarwuah S, Lartey A, Okronipa H, *et al.*: **Lipid-based nutrient supplement increases the birth size of infants of primiparous women in Ghana.** *Am J Clin Nutr.* 2015; **101**(4): 835–46.
PubMed Abstract | Publisher Full Text

58. Ashorn P, Alho L, Ashorn U, *et al.*: **Supplementation of Maternal Diets during Pregnancy and for 6 Months Postpartum and Infant Diets Thereafter with Small-Quantity Lipid-Based Nutrient Supplements Does Not Promote Child Growth by 18 Months of Age in Rural Malawi: A Randomized Controlled Trial.** *J Nutr.* 2015; **145**(6): 1345–53.
PubMed Abstract | Publisher Full Text

59. Haider BA, Olofin I, Wang M, *et al.*: **Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis.** *BMJ.* 2013; **346**: f3443.
PubMed Abstract | Publisher Full Text | Free Full Text

60. Ahmad SM, Hossain MB, Monirujjaman M, *et al.*: **Maternal zinc supplementation improves hepatitis B antibody responses in infants but decreases plasma zinc level.** *Eur J Nutr.* 2016; **55**(5): 1823–9.
PubMed Abstract | Publisher Full Text

61. Nair N, Tripathy P, Sachdev HS, *et al.*: **Effect of participatory women's groups and counselling through home visits on children's linear growth in rural eastern India (CARING trial): a cluster-randomised controlled trial.** *Lancet Glob Health.* 2017; **5**(10): e1004–e16.
Publisher Full Text

62. **WHO Global Targets 2025**. 2019.
Reference Source

63. Dhillon S: **Roxadustat: First Global Approval.** *Drugs.* 2019; **79**(5): 563–72.
PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ? ? ?

Version 1

Reviewer Report 16 July 2020

https://doi.org/10.21956/gatesopenres.14223.r29004

?

Sonali Kochhar

[1] Department of Global Health, University of Washington, Seattle, WA, USA

[2] Global Healthcare Consulting, New Delhi, Delhi, India

- The comparative effectiveness of interventions across different domains to address adverse birth outcomes such as preterm birth, low birth weight, and birth weight for LMIC-based pregnant women is not known. This network meta-analysis study aims to compare interventions across domains like micronutrients, balanced energy protein supplements, maternal education, deworming, and WASH. Most clinical trials have compared within a domain, and summaries of the evidence for pregnancy interventions have used a pairwise meta-analysis to compare a single intervention with a comparator. Utilizing network meta-analysis, the study has prepared a network of interventions connected via the comparisons that have been made in head-to-head trials, with the interventions being compared indirectly via the common comparators.

- The study has been carefully designed and conducted and well reported. The results are not as significant as would have been expected. The author's conclusions of the reasons for this are valid and include the limited existing evidence and low number of trials per comparison in the network.

- There are significant theoretical advantages of the network meta-analysis mentioned, but these are not clearly demonstrated in the study. The authors conclude that the findings of the study are generally similar to that of other existing reviews. The practical advantages of utilizing network meta-analysis in the study could be highlighted.

- It is not clear why some of the interventions were chosen as the common criteria are not immediately obvious. What was the maternal education about - nutrition or birth weight or?

- There was considerable variation in the enrollment of pregnant women in terms of the trimesters and gestational age. A number of studies involved women who were in their 2nd and 3rd trimesters. It is not expected that nutritional interventions in the later trimesters would have a significant impact on low birth weight or preterm birth. The authors acknowledge this. The authors could perhaps consider if there are there any other criteria that would be more beneficial to analyze.

- The authors mention that more research is needed to follow up women into the post-partum period. It would be useful if they substantiated this statement.

- This is a well-designed and conducted study. It would be useful if there was some thought was paid to the points mentioned above to increase the value of the study

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Maternal Immunization, Maternal and Child Research, Adverse Maternal and neonatal outcomes

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Aug 2020
Edward Mills, MTEK Sciences, Vancouver, Canada

Dear Dr. Kochhar:

Thank you for your thorough review of our manuscript. Our responses to your recommendations and comments are marked with bullets below.

Sincerely,
Edward J. Mills

The study has been carefully designed and conducted and well reported. The results are not as significant as would have been expected. The author’s conclusions of the reasons for this are valid and include the limited existing evidence and low number of trials per comparison in the network.

- *Thank you for the comment. We appreciate the time you took to review this article.*

There are significant theoretical advantages of the network meta-analysis mentioned, but these are not clearly demonstrated in the study. The authors conclude that the findings of the study are generally similar to that of other existing reviews. The practical advantages of utilizing network meta-analysis in the study could be highlighted.

- *Thank you for this comment. We have highlighted in the introduction and discussion sections that network meta-analysis allows the indirect comparison of multiple interventions connected via a common comparator when direct head-to-head evidence between interventions is not available. Since this direct evidence between interventions across multiple domains is very limited for pregnancy studies, we used network meta-analysis to compare the effectiveness of interventions across several domains. Figure 2 in the article demonstrates how the interventions are connected to each other via standard of care. Each line between the nodes represents a direct comparison between the interventions. Supplementary figures 1-6 demonstrate intervention networks for each outcome. Supplementary cross tables file provides effectiveness of different interventions domains relative to standard of care. Supplementary files can be found here (https://doi.org/10.17605/OSF.IO/JK3AQ). The forest plots provided in figures 3, 4, and 5 also demonstrate the comparative effectiveness of interventions relative to standard of care.*

It is not clear why some of the interventions were chosen as the common criteria are not immediately obvious. What was the maternal education about - nutrition or birth weight or?

- *The interventions were selected based on our PICOS criteria provided in Table 2 in page 5. The PICOS criteria was formulated based on existing reviews that have analyzed interventions for pregnant women. The list of existing reviews is provided in Table 1 in page 4.*
- *We have amended the results section to include the following:*

“Maternal education was captured in only one trial where the education component was in the form of participatory learning action (PLA) with government-mandated women’s groups. PLA involved awareness of the problem of LBW and malnutrition, and strategies to overcome barriers to improved health and nutrition.” [Page 6, second column]

There was considerable variation in the enrollment of pregnant women in terms of the trimesters and gestational age. A number of studies involved women who were in their 2nd and 3rd trimesters. It is not expected that nutritional interventions in the later trimesters would have a significant impact on low birth weight or preterm birth. The authors acknowledge this. The authors could perhaps consider if there are there any other criteria that would be more beneficial to analyze.

- *We have highlighted several areas of future research, such as looking at how combined set of interventions can impact adverse birth outcomes and assessing the longevity of*

- *interventions and its effectiveness across multiple life stages.*

The authors mention that more research is needed to follow up women into the post-partum period. It would be useful if they substantiated this statement.

- *We have indicated in the discussion section that only 17 out of 101 (16%) trials conducted follow-ups of women after delivery into the post-partum period. This is particularly important to assess the duration of effectiveness of interventions. This demonstrates the need to conduct more research in this area.*

This is a well-designed and conducted study. It would be useful if there was some thought was paid to the points mentioned above to increase the value of the study.

- *We are very thankful for your thorough review of our article and feedback. We hope that our responses sufficiently address the issues you have pointed out.*

Competing Interests: No competing interests were disclosed.

Reviewer Report 14 July 2020

https://doi.org/10.21956/gatesopenres.14223.r29007

?

Elizabeth M. McClure
Social, Statistical and Environmental Health Sciences, RTI International, Durham, NC, USA

This is a novel approach to compare disparate interventions' impact on common adverse pregnancy outcomes. Most RCTs compare interventions within a domain in a common environment and most meta-analyses follow this approach. Attempting to compare the impact of interventions within different domains present methodologic challenges. The authors note an important limitation of the gestational age at which women were enrolled may have varied across these trials. Another potential factor that should be addressed is the potential for disparities in the populations as well as the environments. In particular, when comparing maternal nutritional interventions, understanding the effect of low BMI, maternal anemia and other relevant factors is important. Similarly, the environments, including access to high quality EMONC and other care can impact outcomes. It would be helpful if the authors could comment on these potential influences on their findings.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, maternal and newborn health in LMICs

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Aug 2020
Edward Mills, MTEK Sciences, Vancouver, Canada

Dear Dr. McClure:

Thank you for your thorough review of our manuscript. Our responses to your recommendations and comments are marked with bullets below.

Sincerely,
Edward J. Mills

This is a novel approach to compare disparate interventions' impact on common adverse pregnancy outcomes. Most RCTs compare interventions within a domain in a common environment and most meta-analyses follow this approach. Attempting to compare the impact of interventions within different domains present methodologic challenges. The authors note an important limitation of the gestational age at which women were enrolled may have varied across these trials. Another potential factor that should be addressed is the potential for disparities in the populations as well as the environments. In particular, when comparing maternal nutritional interventions, understanding the effect of low BMI, maternal anemia and other relevant factors is important. Similarly, the environments, including access to high quality EMONC and other care can impact outcomes. It would be helpful if the authors could comment on these potential influences on their findings.

- *Thank you for your comment. Network meta-analysis offers the advantage of making indirect comparison of multiple interventions connected via a common comparator. By employing network meta-analysis techniques, we were able to compare effectiveness of interventions across multiple domains.*
- *We acknowledge that there is substantial heterogeneity observed in the data. To address*

the heterogeneity in trials, we employed random-effects model for our network meta-analysis. It is also expected that nutritional interventions will positively impact maternal health parameters, such as BMI and anemia which in turn will reduce the incidence of adverse birth outcomes. External factors, such as access to quality EMONC and other care settings are outside the scope of our research article.

Competing Interests: No competing interests were disclosed.

Reviewer Report 10 July 2020

https://doi.org/10.21956/gatesopenres.14223.r28944

?

R Rima Jolivet
Women & Health Initiative, Harvard T.H. Chan School, Boston, MA, USA

- This is a carefully conducted study with great attention to study quality, using and diligently reporting best available criteria for quality in meta analytic studies. The results are somewhat less significant than could have been hoped for given the breadth of the search and network analytic design. I agree largely with the authors' assessment of the study limitations, which mostly have to do with limitations in the existing evidence base.

- While I have not had enough volume or very recent experience conducting meta analyses to feel overly confident critiquing the statistical or interpretational decisions made, I do have some relatively minor questions about the design and the conclusions.

- I am not familiar with the network meta analytic methodology; however, it is hard to see the added value afforded by the network approach, since there is no discussion of intersectionality, synergies, or correlations between domains of intervention. Thus, the additional value afforded by the network meta analysis is never clearly described. This may be because the underlying studies did not allow for such comparison, but the description of the methodology suggests that it would allow the researchers to take single intervention RCTs and combine their results to evaluate a web of effects. That does not come through in the paper. Despite this, the authors list the methodology as the paper's greatest strength.

- The authors state, "The purpose of this study was to assess the comparative effectiveness across intervention domains in micronutrient supplements, balanced energy protein supplements, deworming, maternal education, and WASH interventions…" In addition to the previous comment, I wondered on what basis the interventions were selected, as a unifying hypothesis was not given. The studies listed include several whose interventions have nothing to do with nutrition (financial incentives; flu immunization), and it was not clear why they were included. In addition, the authors do not specify whether maternal education, one of the intervention domains, was education specific to nutrition, or to preterm birth and birthweight? If not, it is unclear how the educational intervention serves as a comparator or how it relates to the nutritional interventions listed in the study aims.

- The authors state that the majority of trials recruited women who were in the later trimesters (n=69). This is potentially significant, given that nutritional determinants of preterm birth and low birth weight are likely to have their origin well before the time of study enrollment, and it is not surprising that the effects of nutritional interventions may not be observed in such a short period of time. This limitation is acknowledged by the authors. However, it raises the question of whether additional outcomes more likely to show a difference, such as mean difference in Hgb and Hct, might have been good to explore.

- While I agree largely with the authors' assessment of the study limitations and commend them for their attention to quality, and for adjusting for the clustering effects and choosing a conservative ICC, I differ with some points made in the Discussion section. The authors state that, "The main strength of this study was the use of network meta analysis to assess the effectiveness of different interventions from a large network of evidence compared to standard-of-care." However, the value of this approach and what it showed compared to a simple meta analysis was not adequately demonstrated and could perhaps be further emphasized.

- The authors state that "there is a need for more evidence of packaged interventions because a combined set of interventions will likely result in the greatest improvement for adverse birth outcomes" but they do not present any evidence for this hypothesis in the current study, as would be expected based on their assertions about network meta analysis. There does not appear to be any statistical analysis that shows that combined interventions resulted in a greater effect size or better outcomes.

- Finally, the discussion of the lack of postpartum follow-up with women (while valuable in its own right) is also hard to understand in the context of this study whose outcomes focused on the effects of maternal nutrition in pregnancy on gestational age and birthweight, since there were no outcomes related to the postnatal period for mothers or newborns.

- Overall, this is a well conducted study, that reflects possibly some areas for improvement in the description of the study aims, justification of the choice of methodology, and interpretation of the results (factors within the author's control), and well as limitations in the underlying evidence base (factors outside the authors' control).

Other minor comments:

- Exclusion of non-English pubs could be significant given the target of LMIC populations.

- The authors state, "All reviews were systematic literature reviews with pairwise meta-analysis, except for Glassman 2013 and Yang 2011", but do not clarify what kind of studies these two were.

- I was unable to find the network diagrams and thus could not evaluate this aspect of the study. The narrative in the paper does not seem to adequately address the elements of synergy/relationship between the intervention domains, or the lack thereof found through the analysis.

- The reported relative risk for preterm birth for iron supplementation contains 1: (iron: RR=0.70, 95% credible interval [CrI] 0.47, 1.01).

- I appreciate that the authors performed adjustments for the clustering effect of cluster randomization as well as sensitivity analyses to remove those trials, since other independent variables come into play in results observed with cluster randomization vs individual allocation. This study demonstrates the reason why individual allocation is valuable for exploring effectiveness of interventions whose mechanism of action is at the person level.

- The fact that the authors' search uncovered no individually randomized trials that evaluated the effectiveness of high caloric (1500 kcal per day) local food for pregnant women on birth outcomes demonstrates the problem that funder-driven trends in research design pose. The lack of nuance in the preference for implementation research aimed at scaling up interventions contributes to an inability to evaluate the effectiveness of potentially impactful interventions on one hand, and to the spread of interventions unproven at scale. This is not the within the authors' scope of responsibility but it is an important finding.

- The interventions described in the opening to the Discussion should match those described in the research question, but do not (the Discussion describes "several domains ranging from nutrition, infection control, and education"). This raises the question again of the underlying framework or hypothesis guiding the selection of intervention domains (is it nutrition or broader?), and if broader what kinds of correlation or interaction a network analysis was expected to show.

- I wonder why the effect of the 1500 kcal local food supplement is de-emphasized, since a statistically significant RR of 0.17 for preterm birth seems like it would be worth highlighting more than the RR = 0.70 for iron that contains 1.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Partly

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public health, maternal health, measurement, qualitative and quantitative research.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Aug 2020

Edward Mills, MTEK Sciences, Vancouver, Canada

Dear Dr. Jolivet:

Thank you for these thorough reviews of our manuscript. Our responses to your recommendations and comments are marked with bullets below.

Sincerely,
Edward J. Mills

This is a carefully conducted study with great attention to study quality, using and diligently reporting best available criteria for quality in meta analytic studies. The results are somewhat less significant than could have been hoped for given the breadth of the search and network analytic design. I agree largely with the authors' assessment of the study limitations, which mostly have to do with limitations in the existing evidence base. While I have not had enough volume or very recent experience conducting meta analyses to feel overly confident critiquing the statistical or interpretational decisions made, I do have some relatively minor questions about the design and the conclusions.

I am not familiar with the network meta analytic methodology; however, it is hard to see the added value afforded by the network approach, since there is no discussion of intersectionality, synergies, or correlations between domains of intervention. Thus, the additional value afforded by the network meta analysis is never clearly described. This may be because the underlying studies did not allow for such comparison, but the description of the methodology suggests that it would allow the researchers to take single intervention RCTs and combine their results to evaluate a web of effects. That does not come through in the paper. Despite this, the authors list the methodology as the paper's greatest strength.

- *Thank you for this comment. Network meta-analysis allows the indirect comparison of multiple interventions connected via a common comparator. Given that there is a scarcity of direct head-to-head randomized clinical trials (RCTs) between existing interventions in pregnancy, we felt this analytical approach was the most optimal way to summarize the current evidence base for this important life-stage. Figure 2 in the article demonstrates how the interventions are connected to each other via standard of care. Each line between the nodes represents a direct comparison between the interventions. Supplementary figures 1-6 demonstrate intervention networks for each outcome. Moreover, under the results section from pages 7-9, we discussed how some of the interventions impact the* *outcomes of interest. Forrest plots have also been provided to show the effects of interventions on our outcomes of interest.*

The authors state, “The purpose of this study was to assess the comparative effectiveness across intervention domains in micronutrient supplements, balanced energy protein supplements, deworming, maternal education, and WASH interventions…” In addition to the previous comment, I wondered on what basis the interventions were selected, as a unifying hypothesis was not given. The studies listed include several whose interventions have nothing to do with nutrition (financial incentives; flu immunization), and it was not clear why they were included.

- *We apologize for the confusion. We have removed mention of the studies related to financial incentives and flu immunization in Table 1. [New version of the manuscript has been submitted to Gates Open Research]*
- *We selected the scope of the interventions based on existing reviews that have analyzed interventions for pregnant women based on the hallmark paper by Bhutta 2013 (Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, Webb P, Lartey A, Black RE, Group TL, Maternal and Child Nutrition Study Group. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? The Lancet. 2013 Aug 3;382(9890):452-77.). We have updated the manuscript to provide justifications of our study scope.*

"***The scope of our research study and the corresponding search strategy** was developed after first reviewing the papers published in the Lancet’s 2013 Maternal and Child Nutrition series, including the umbrella review on evidence- based interventions by Bhutta and colleagues, for an overview of the literature*."

In addition, the authors do not specify whether maternal education, one of the intervention domains, was education specific to nutrition, or to preterm birth and birthweight? If not, it is unclear how the educational intervention serves as a comparator or how it relates to the nutritional interventions listed in the study aims.

- *There was only one study pertaining to maternal education (https://pubmed.ncbi.nlm.nih.gov/29742136/) which also included a combination of financial incentive program to encourage pregnant mothers to buy food. Description of intervention domains for each included study has been provided in Supplementary table 7. We have not included any study that involves flu immunization.*
- *We have amended the results section to include the following: “Maternal education was captured in only one trial where the education component was in the form of participatory learning action (PLA) with government-mandated women’s groups. PLA involved awareness of the problem of LBW and malnutrition, and strategies to overcome barriers to improved health and nutrition.” [Page 6, second column]*

The authors state that the majority of trials recruited women who were in the later trimesters (n=69). This is potentially significant, given that nutritional determinants of preterm birth and low birth weight are likely to have their origin well before the time of study enrollment, and it is not surprising that the effects of nutritional interventions may not be observed in such a short period of time. This limitation is acknowledged by the authors. However, it raises the question of whether additional outcomes more likely to show a difference, such as mean difference in Hgb and Hct, might have been good to explore.

- *Thank you for this comment. The decision to limit the scope of our study to preterm birth, low birthweight and mean birthweight outcomes was done based on our initial review of Bhutta et al 2013 and other important reviews during the project planning stage. While other outcomes such as Hgb and Hct are undoubtedly important, this is beyond the scope of our study.*

While I agree largely with the authors' assessment of the study limitations and commend them for their attention to quality, and for adjusting for the clustering effects and choosing a conservative ICC, I differ with some points made in the Discussion section. The authors state that, "The main strength of this study was the use of network meta analysis to assess the effectiveness of different interventions from a large network of evidence compared to standard-of-care." However, the value of this approach and what it showed compared to a simple meta analysis was not adequately demonstrated and could perhaps be further emphasized.

- *We have pointed out in the methods section that traditional pairwise meta-analysis only offers quantitative assessment of a single intervention versus a comparator. In network meta-analysis, we were able to strengthen the evidence base by analyzing both direct and indirect evidence collectively. Other existing reviews that have conducted a pairwise meta-analysis have pooled cluster and individually randomized clinical trials without adjusting for the intracluster correlation, so their effect estimates were heavily influenced by the cluster randomized clinical trials that were generally larger in sample size. While the most of cluster randomized clinical trials did not report their ICC value, this approach of pooling these two types of clinical trials is clearly inappropriate. We were forced to make an assumption of 0.05 ICC. We have acknowledged that this is a limitation while being more appropriate than previous analytical approaches that have been used for existing reviews.*

The authors state that "there is a need for more evidence of packaged interventions because a combined set of interventions will likely result in the greatest improvement for adverse birth outcomes" but they do not present any evidence for this hypothesis in the current study, as would be expected based on their assertions about network meta analysis. There does not appear to be any statistical analysis that shows that combined interventions resulted in a greater effect size or better outcomes.

- *Thank you for your comment. We have demonstrated through random effects network meta-analysis models that several micronutrient supplements decreased risks of pre-term birth and improved mean birthweight, compared to standard of care. Estimates from these analyses are provided in the forest plots as well as the cross-tables in the supplementary file. We have also pointed out in the discussion section that while network meta-analysis allows us to compare interventions indirectly across multiple domains, due to limited evidence base, our analyses was limited as well. The evidence base consisting of trials that report only on a single domain of intervention is a big limiting factor.*

Finally, the discussion of the lack of postpartum follow-up with women (while valuable in its own right) is also hard to understand in the context of this study whose outcomes focused on the effects of maternal nutrition in pregnancy on gestational age and birthweight, since there were no outcomes related to the postnatal period for mothers or newborns.

- *Thank you for this comment. We highlighted the need for follow-ups of women after birth delivery into the post-partum period in order to provide future direction of research to assess the longevity of interventions and its effectiveness across multiple life stages.*

Overall, this is a well conducted study, that reflects possibly some areas for improvement in the description of the study aims, justification of the choice of methodology, and interpretation of the results (factors within the author's control), and well as limitations in the underlying evidence base (factors outside the authors' control).

- *Thank you for this compliment.*

Exclusion of non-English pubs could be significant given the target of LMIC populations.

- *While we acknowledge that inclusion of non-English studies will reduce bias in reviews, including non-English studies will require services of professional translators, and the research process will become costly and time-consuming as a result.*

The authors state, "All reviews were systematic literature reviews with pairwise meta-analysis, except for Glassman 2013 and Yang 2011", but do not clarify what kind of studies these two were.

- *Table 1 provides details, such as title, interventions used, types of studies included, of existing reviews on pregnancy interventions. We have removed Glassman 2013 from the table. Description of Yang 2011 is provided in Table 1.*

I was unable to find the network diagrams and thus could not evaluate this aspect of the study. The narrative in the paper does not seem to adequately address the elements of synergy/relationship between the intervention domains, or the lack thereof found through the analysis.

- *The Supplementary tables and figures file can be found here: https://doi.org/10.17605/OSF.IO/JK3AQ (Click on Files section). Networks diagrams for birth outcomes are provided in supplementary figures 1-6. Supplementary cross tables file provides effectiveness of different interventions domains relative to standard of care. Figure 2 in the article demonstrates how the interventions are related to one another through standard of care.*

The reported relative risk for preterm birth for iron supplementation contains 1: (iron: RR=0.70, 95% credible interval [CrI] 0.47, 1.01).

- *This is correct which is why we interpreted this as a trend towards lower preterm birth risks compared to standard of care but the CrI overlapped the null effect of 1.*

I appreciate that the authors performed adjustments for the clustering effect of cluster randomization as well as sensitivity analyses to remove those trials, since other independent variables come into play in results observed with cluster randomization vs individual allocation. This study demonstrates the reason why individual allocation is valuable for exploring effectiveness of interventions whose mechanism of action is at the person level.

- *We thank you for this feedback.*

The fact that the authors' search uncovered no individually randomized trials that evaluated the effectiveness of high caloric (1500 kcal per day) local food for pregnant women on birth outcomes demonstrates the problem that funder-driven trends in research design pose. The lack of nuance in the preference for implementation research aimed at scaling up interventions contributes to an inability to evaluate the effectiveness of potentially impactful interventions on one hand, and to the spread of interventions unproven at scale. This is not the within the authors' scope of responsibility but it is an important finding.

- *We agree with you. While beyond the scope of this study, you are absolutely correct in your assertion here.*

The interventions described in the opening to the Discussion should match those described in the research question, but do not (the Discussion describes "several domains ranging from nutrition, infection control, and education"). This raises the question again of the underlying framework or hypothesis guiding the selection of intervention domains (is it nutrition or broader?), and if broader what kinds of correlation or interaction a network analysis was expected to show.

- *Thank you for this comment. We have amended the discussion section to include the following:*

"*We used network meta-analysis to compare the effectiveness of interventions across several domains* ***consisting of micronutrient supplements, balanced energy protein supplements, deworming, maternal education, and WASH interventions*** *that can be provided to pregnant women living in LMICs". [Page 10, 2nd column]*

- *Our objective was to compare the effectiveness of interventions not only involving nutrition but also deworming and WASH in impacting birth outcomes in LMICs. Due to limited evidence base, we didn't find any concrete findings in regards to how maternal education and deworming affected birth outcomes. And there were no WASH trials that reported on our outcomes of interest.*

I wonder why the effect of the 1500 kcal local food supplement is de-emphasized, since a statistically significant RR of 0.17 for preterm birth seems like it would be worth highlighting more than the RR = 0.70 for iron that contains 1.

- *We have mentioned both under results and discussion sections that consumption of 1500 kcal of local food supplement lowered the risks of preterm birth and low birthweight. For iron (RR: 0.70, 95% CrI: 0.47, 1.01), we have indicated that it showed a trend towards lower preterm birth risks compared to standard-of-care, but the Crl overlapped the null effect of 1.00.*

Competing Interests: No competing interests were disclosed.