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Preconception and periconception interventions to prevent low birth weight, small for gestational age and preterm birth: a systematic review and meta-analysis

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ABSTRACT

Background Low birth weight (LBW), including preterm birth (PTB) and small for gestational age (SGA), contributes a significant global health burden. We aimed to summarise current evidence on the effect of preconception and periconception interventions on LBW, SGA and PTB.

Methods In this systematic review and meta-analysis, we searched PubMed, Embase, Cochrane Library and WHO Global Index Medicus for randomised controlled trials and quasi-experimental studies published by 28 November 2020, which assessed interventions delivered in preconception and periconception or preconception and pregnancy. Primary outcomes were LBW, SGA and PTB. Studies were categorised by intervention type and delivery during preconception and periconception or during preconception and pregnancy. Estimates were pooled using fixed-effects or random-effects restricted maximum likelihood method meta-analyses. Quality of evidence for primary outcomes was assessed using the Grades of Recommendations, Assessment, Development and Evaluation approach.

Results We included 58 studies. Twenty-eight studies examined nutrition interventions (primarily micronutrient or food supplementation). Thirty studies (including one reporting a nutrition intervention) provided health interventions (general preconception health, early adverse pregnancy outcome prevention, non-communicable disease and infectious disease prevention and management). One study assessed a social intervention (reproductive planning). Studies varied in terms of specific interventions, including delivery across preconception or pregnancy, resulting in few studies for any single comparison. Overall, the evidence was generally very uncertain regarding the impact of any intervention on LBW, SGA and PTB. Additionally, preconception and periconception nutritional supplementation containing folic acid was associated with reduced risk of birth defects (10 studies, N=3 13 312, risk ratio: 0.37 (95% CI: 0.24 to 0.55), I^2: 74.33%).

Conclusion We found a paucity of evidence regarding the impact of preconception and periconception interventions on LBW, SGA and PTB. Further research on a wider range of interventions is required to clearly ascertain their potential effectiveness.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous reviews on the effect of maternal preconception status on low birth weight (LBW), small for gestational age (SGA) and preterm birth (PTB) and other adverse birth and pregnancy outcomes have identified potential preconception risk factors from observational evidence; assessed selected preconception interventions; and mainly studied outcomes such as micronutrient or disease status in the preconception period.

⇒ To our knowledge, no review has comprehensively and systematically examined the evidence directly linking interventions in the preconception period to the risk of adverse pregnancy outcomes such as LBW, SGA and PTB.

WHAT THIS STUDY ADDS

⇒ In this systematic review and meta-analysis, we identified 58 eligible studies on the impact of preconception and periconception interventions on LBW, PTB, SGA and other birth and maternal outcomes—however, there were few studies for any single comparison, for example, food supplementation in preconception and pregnancy versus pregnancy only to prevent PTB.

⇒ Studies reported mainly on health and nutrition interventions, with little research on other relevant areas such as environmental health, and the available evidence was generally very uncertain regarding the impact of these interventions on LBW, PTB and SGA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ This work highlights that there is currently not enough high-quality evidence to clearly understand the effect of a range of possible preconception and periconception interventions on LBW, PTB and SGA; further, well-designed research is required in this area.

Trial registration number This review was prospectively registered with PROSPERO (CRD42020220915).

INTRODUCTION

Low birth weight (LBW), including preterm and small for gestational age babies (preterm birth, PTB and SGA), presents a significant global health burden. Approximately 20.5 million (14.6%) live births globally were estimated to be LBW in 2015, with 91% of these occurring in low-income and middle-income countries (LMICs).[1] It is estimated that 14.84 million (10.6%) live births in 2014 were preterm, while approximately 23.3 million (19.3%) neonates were born SGA in LMICs in 2012.[2 3] LBW is associated with increased risk of mortality especially in the neonatal period and infancy,[4 5] and increased morbidity across the lifespan, including developmental and behavioural problems,[6 7] undernutrition in childhood[8] and cardiometabolic disease development in adulthood.[9] Much research and programmatic attention has focused on interventions during pregnancy to prevent LBW.[10] However, there is growing recognition of the need to identify additional windows for interventions prior to pregnancy for its prevention.[11 12]

Preconception is broadly understood as the period up to a few months before conception among women of reproductive age, although definitions encompassing a wider interval have also been proposed.[12 13] Recent research indicates that maternal morbidity and nutritional status in the preconception period have important influences on pregnancy outcomes and the health of offspring,[11 14 15] highlighting its value as a potentially critical window for preventative interventions. Although specific pathways have not been fully delineated, health and nutritional status up to conception are thought to inform physiological and epigenetic mechanisms during embryonic and fetal development, thereby influencing pregnancy and later life outcomes.[13 16]

While much research has been primarily from observational studies, evidence regarding potential preconception interventions to prevent adverse pregnancy outcomes has been growing.[11 17–19] This includes studies assessing interventions in the periconception period (until pregnancy is detected), and those examining interventions delivered from preconception throughout pregnancy. However, there is currently no comprehensive picture of the impact of such interventions. Previously published reviews on the preconception period have included observational studies of potential contributing risk factors,[11 14 15 17 20] examined endpoints other than pregnancy outcomes,[21] and restricted searches to specific interventions.[12 13 22] A better understanding of current data on the effect of interventions in the preconception period on pregnancy outcomes is key to identifying knowledge gaps and informing relevant and appropriate prevention strategies.

Objectives

We undertook a systematic review and meta-analysis aiming to summarise the current evidence regarding the impact of interventions delivered in the preconception and periconception period on the risks of LBW, SGA and PTB.

METHODS

Eligibility criteria

Eligibility criteria for this systematic review are outlined below:

- Population: Target participants were women in the preconception period, defined as any period in the life cycle prior to conception. This was guided by our conceptual framework (figure 1).
- Intervention: Interventions had to be delivered prior to conception, or prior to the detection of pregnancy (periconception).
- Comparator: Interventions were compared against no intervention, standard of care or routine care or placebo.
- Outcome: The primary outcomes were LBW, PTB and SGA. Where possible, we also aimed to examine these outcomes reported in combination, as outlined by Lee *et al*.[3] Secondary outcomes included other birth outcomes (birth weight, gestational age and birth weight for gestational age, stillbirth, birth defects, perinatal mortality, and large for gestational age) and maternal outcomes during pregnancy: (malnutrition (underweight, overweight and obesity), anaemia, haemoglobin concentrations, pre-eclampsia, gestational hypertension and gestational diabetes mellitus).
- Study design: We included randomised controlled trials (RCTs), cluster RCTs and quasi-experimental designs in this review. Quasi-experimental designs were included only if concurrent comparator groups were used.

Information sources and search strategy

We performed searches in PubMed, Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), the WHO Global Index Medicus and EMBASE. Searches were performed on 28 November 2020. A comprehensive search strategy was developed and agreed on by the authors, with key terms including variants of “preconception” and “periconception” and words related to outcomes of interest, but no terms relating to specific interventions to ensure the broadest search possible (see online supplemental appendix 1). This was informed by our conceptual framework (figure 1), which indicated a broad range of possible domains for interventions in the preconception and periconception period. Reference lists of records included in the full text assessment stage were examined for additional relevant studies. Searches were performed without restrictions on language or publication date.

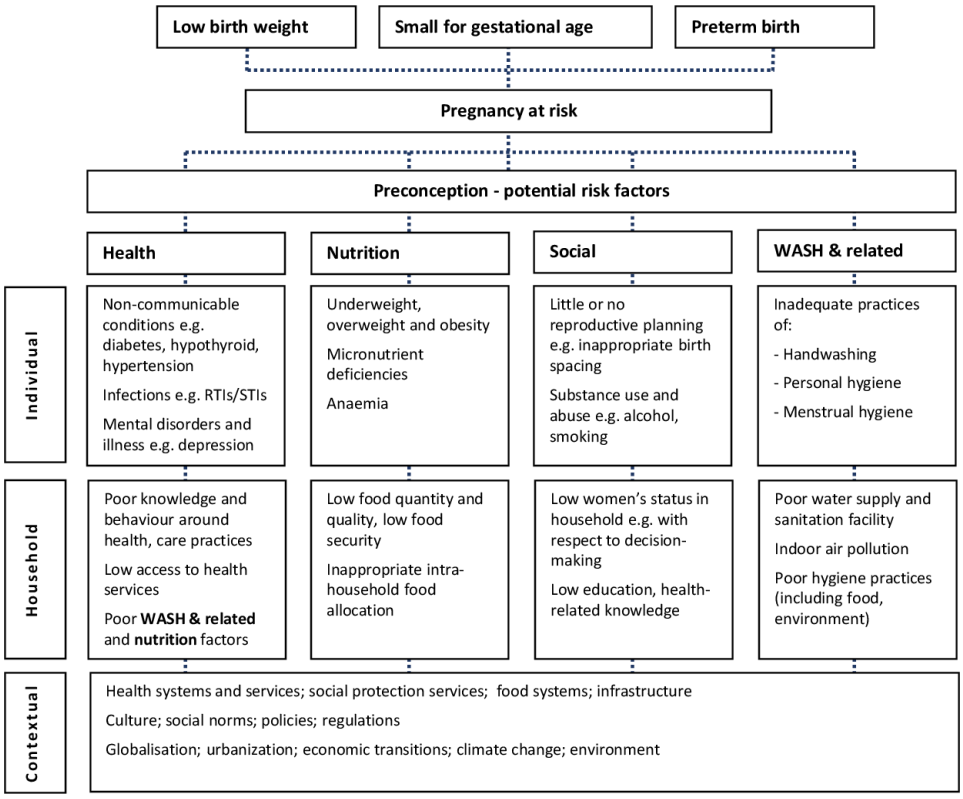

Figure 1 Conceptual framework outlining domains (morbidity, nutrition, social, WASH and related—at both individual and household level) for potential interventions to improve preconception health. While underlying, contextual risk factors are outlined in this framework, interventions are expected to have more direct effects on potential risk factors relevant to preconception health at the individual or household level. WASH: water, sanitation and hygiene; RTI: reproductive tract infection; STI: sexually transmitted infection.

Selection process, data collection process and data items

We used Covidence review management software (Veritas Innovation, Melbourne, Australia) to manage study selection. Two authors (RC and UP) independently assessed potential studies for inclusion through title and abstract screening, followed by full-text review. Studies with unclear eligibility during title and abstract screening were included for full-text review; where possible, further doubts regarding eligibility were clarified through corresponding with study authors during full-text review. Reports based on the same study were linked. Disagreements regarding eligibility of studies were resolved through discussion. Two authors (RC and UP) independently extracted data using a prespecified form. Broadly, data extracted included study population and setting, sample size (including initial number of participants recruited and analytical size), study design, participant characteristics, interventions and comparators and preconception phase in which these were delivered, outcomes and analytical strategy. We extracted both crude and adjusted effect estimates where possible. Relevant group level data were extracted for all reported study arms to facilitate comprehensive comparisons. For all outcomes, we noted and used definitions as described by the authors. Data were checked for accuracy, and we contacted study authors for further information if any relevant information was missing or unclear. Disagreements during data extraction were resolved by discussion or consultation with a third author.

Study risk of bias assessment

Risk of bias was assessed for studies examining primary outcomes of interest, and their corresponding continuous measures. Two authors (RC and UP) independently assessed risk of bias using the revised Cochrane Risk Of Bias tool (ROB 2 tool) for randomised trials,[23] the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool for non-randomised trials,[24] and the ROB 2 for Cluster Randomized Trials (ROB 2 CRT) tool for clustered studies.[25] Risk of bias was visualised using robvis.[26]

Effect measures

For binary outcomes, we used risk ratios (RR) or odds ratios (OR) where risk could not be calculated. For continuous outcomes, we used mean differences (see online supplemental appendix 1 for details on use of study estimates). Results adjusted for potential confounders were used in preference to unadjusted results; when these were not available, unadjusted results were used. For clustered studies, cluster-adjusted effect estimates as reported by the study or calculated independently (see online supplemental appendix 1) were used. Risk estimates were not included in meta-analyses if the outcome was a composite

measure, or if no outcome cases were observed in both intervention and comparator groups. We used estimates based on intention-to-treat analyses where possible.

Synthesis methods

For each outcome, included studies were categorised by intervention into three domains based on a predefined framework (see online supplemental appendix 1), and then into further subdomains. The domains were nutrition (subdomains: multiple micronutrient, iron and folic acid, folic acid or food supplementation and other); health (subdomains: general preconception health interventions, interventions to prevent early adverse pregnancy outcomes among women with a history of miscarriage, interventions to prevent or manage non-communicable diseases and interventions to prevent or manage infectious diseases); and social (subdomain: reproductive planning). Within subdomains, studies were additionally categorised by any other relevant study-specific characteristics (eg, high-dose vs low-dose supplementation, or potentially adverse effect hypothesised).

For our main analyses, we further divided studies according to two comparisons: (1) preconception and periconception intervention versus preconception and periconception no intervention, standard of care or routine care, or placebo, (2) or intervention in preconception and pregnancy versus same intervention in pregnancy only. Studies describing interventions delivered in preconception and pregnancy versus any other comparator in preconception and pregnancy were not included in main analyses, as these did not allow for examination of the effect of interventions in the preconception period alone. Where there were two or more studies for a specific comparison (eg, preconception and periconception folic acid supplementation to prevent LBW), data were pooled in a meta-analysis. Data were analysed using Stata V.16 (StataCorp). For health interventions, meta-analyses were only undertaken where study interventions were deemed to be sufficiently similar (eg, clinical interventions or lifestyle interventions); otherwise, studies were summarised individually.

Statistical heterogeneity among studies was examined through visual inspection of forest plots, assessment of the χ^2 test for homogeneity, and the I^2 value; notable heterogeneity was assessed as I^2 ≥50%.[27] Where no notable heterogeneity was observed, we pooled results using fixed-effects models using the inverse variance method. In situations of notable heterogeneity, we used random-effects restricted maximum likelihood models, and conducted subgroup analyses where meta-analyses included four or more studies.

Clinical heterogeneity was systematically explored in relation to three key variables, in prespecified subgroup analyses. In these analyses, we aimed to group and examine studies by (1) the number of months preconception in which interventions were delivered (<3 and 3+ months prior to conception), (2) the age of participants (<30 and 30+, or <24, 25–29 and 30+, years) and (3) study setting (LMIC vs high-income country as defined by the World Bank). Additionally, in sensitivity analyses, we restricted meta-analyses to only studies assessed as low risk of bias by the ROB-2,[23] ROBINS-I[24] or ROB 2 CRT tool.[25] These indicated the potential impact of risk of bias as a source of methodological heterogeneity on effect estimates. Although in the protocol we planned to undertake these assessments for all meta-analyses, as the number of studies for any single meta-analysis was generally low and studies assessing health and social interventions were highly variable with regards to setting and intervention type, we examined subgroup effects and conducted sensitivity analyses only for studies examining nutritional interventions and primary outcomes where four or more studies were included in meta-analyses.

Reporting bias assessment

Funnel plots and Egger's test were used to assess the presence of publication bias in cases where four or more studies were included in meta-analyses, or in cases where meta-analyses included less than four studies but interventions were being assessed for primary outcomes. This was different to our original aim of conducting such assessments for all analyses as noted in the protocol, and was done due to the small number of studies for any single meta-analysis. These methods of assessment are recognised to have low power when based on a small number (<10) of studies, as in our case[28]; and we took this into consideration when interpreting the results. Additionally, although in the protocol we planned to stratify analyses by study size to assess the impact of publication bias on the pooled estimate, we did not do this as in most cases there were too few studies to obtain meaningful conclusions.

Certainty of evidence

Quality assessment of the pooled estimates for the primary outcomes was conducted through the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach, consisting of a systematic assessment of risk of bias, consistency of effect, imprecision, indirectness and publication bias, as outlined in the Cochrane Handbook.[28] Quality assessments were undertaken using the GRADEPro GDT tool.[29]

Patient and public involvement

As this study was a systematic review with a broad remit, and given that no de novo data and sample and collection was involved, patients and the public were not involved in this research.

RESULTS

Study selection and characteristics

Summary of screened and included studies

We retrieved a total of 6268 records; following removal of duplicates, 5107 records were screened. Of these, full texts of 182 records were assessed, and 66 records based on 58 studies were included for this analysis (figure 2).

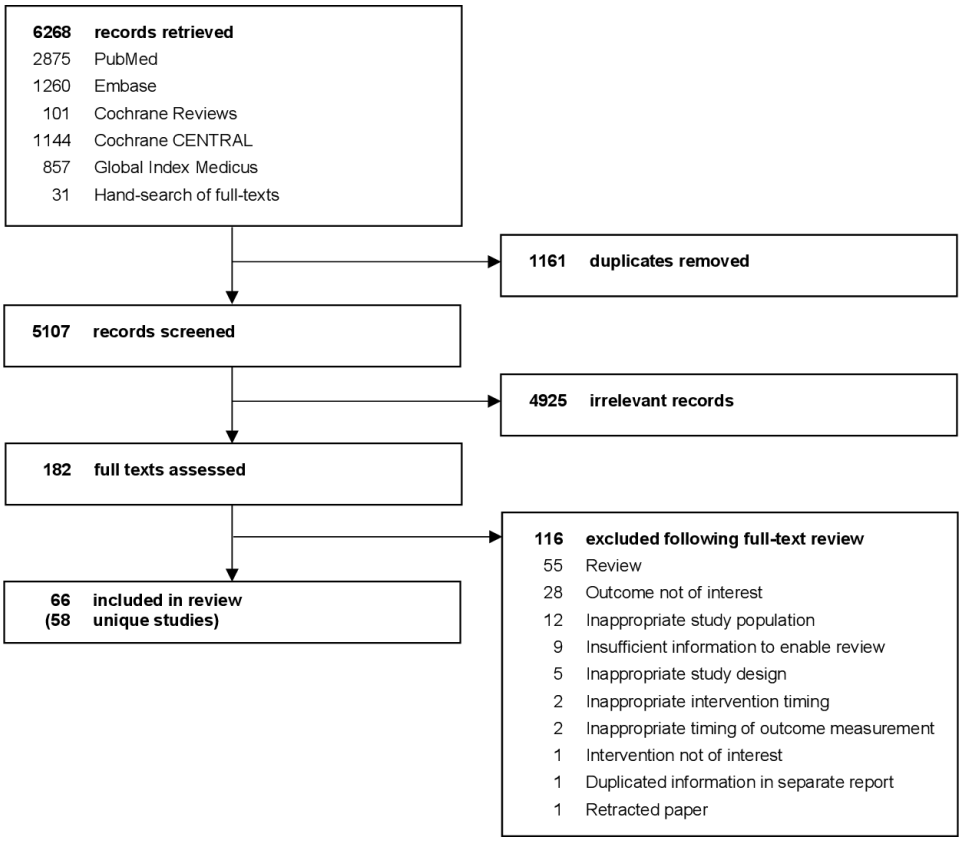

Figure 2 Study screening process.

Unique studies included 37 RCTs, 3 cluster RCTs and 18 quasi-experimental studies (table 1).[18 19 30–93]

Overall, studies varied widely in terms of interventions and comparators, and their delivery across the preconception and pregnancy phases. Generally, few and often diverse interventions were identified for any single comparison, especially for studies examining health interventions (table 1, online supplemental appendix 1).

Interventions

Twenty-eight studies examined nutritional interventions. Of these, 10 studies examined multiple micronutrient supplementation.[18 35 41 45 50 53 56 63 64 66 76 85 87 89] Five studies, including one study which also had a multiple micronutrient supplementation arm, examined iron and folic acid supplementation.[18 39 46 47 56 58 65] Six studies assessed folic acid supplementation,[32 42 48 52 83 84 86] and four studies assessed food supplementation.[19 30 38 43 57] Four studies reported on other nutrition interventions (calcium supplementation, iodine supplementation, vitamin A or beta carotene supplementation or inclusion of mushrooms in diet) (table 1).[31 61 80 82]

Thirty studies, including one also contributing information on a nutrition intervention,[70 76 89] assessed health interventions. Of these, five studies assessed general preconception health interventions.[34 37 44 51 55] Eight studies examined interventions to prevent early adverse pregnancy outcomes among women with a history of miscarriage.[36 49 60 67 69 73 75 88] Five studies assessed interventions to prevent or manage non-communicable diseases,[40 78 81 92 93] and 12 studies reported on interventions to prevent or manage infectious diseases (table 1).[33 59 62 68 70–72 74 77 79 90 91]

One study examined a social intervention (reproductive planning) (table 1).[54]

Outcomes

Forty studies reported on at least one primary outcome.[18 19 30 31 34 36–41 43 46 47 49 51 53–64 66–80 87–89 93] Eighteen studies assessed one or more secondary outcomes of interest.[32 33 35 42 44 45 48 50 52 65 81–86 90–92] We found no studies examining combinations of LBW, PTB and SGA (eg, SGA and preterm), and only one study that differentiated between spontaneous and iatrogenic PTB.[59] We found one or more studies on all secondary outcomes, except for maternal malnutrition measures (underweight, overweight, obesity) and perinatal mortality (no studies).

Results of syntheses

A summary of estimates is provided in table 2, and outlined in greater detail below.

Effect of interventions on LBW

Identified studies

We identified 18 studies reporting effects of 19 interventions on LBW where the preconception or periconception effect of interventions could be ascertained (table 2, figure 3, online supplemental appendix

Table 1 Summary of included studies

Study	Author and date	Study type	Country	Average age (years)	Specific subpopulation	Intervention	Comparator	Phase intervention delivered	Preconception time initiated (months)	Analytical sample size	Outcomes
Nutrition interventions											
1	Ramakrishnan 2016[18]	RCT	Vietnam (LMIC)	26.2	–	Intervention 1: Multiple micronutrient supplement Intervention 2: Iron and folic acid supplement	Folic acid supplement	Preconception and periconception	12	1599	Birth weight Low birth weight Gestational age at birth Preterm birth Small for gestational age Large for gestational age
	Nguyen 2016[56]	RCT	Vietnam (LMIC)	26.2	–	Intervention 1: Multiple micronutrient supplement Intervention 2: Iron and folic acid supplement	Folic acid supplement	Preconception and periconception	12	1581	Haemoglobin (<14 weeks gestation) Anaemia (<14 weeks gestation) Haemoglobin (14–27.9 weeks gestation) Anaemia (14–27.9 weeks gestation) Haemoglobin (≥28 weeks gestation) Anaemia (≥28 weeks gestation)
2	Owens 2015[66]	RCT	Gambia (LIC)	28.8	–	UNIMMAP multiple micronutrient supplement	Placebo	Preconception and periconception	6	376	Gestational age at birth Preterm birth Pre-eclampsia Gestational hypertension
	Cooper 2012[41]	RCT	Gambia (LIC)	28.8	–	UNIMMAP multiple micronutrient supplement	Placebo	Preconception- and periconception	6	58	Birth weight Gestational age at birth
3	Sumarmi 2015[63]	RCT	Indonesia (UMIC)	22.1	–	UNIMMAP multiple micronutrient supplement formulation	Placebo (preconception), iron and folic acid supplement (pregnancy)	Preconception+pregnancy	6	112	Preterm birth
	Sumarmi 2017[87]	RCT	Indonesia (UMIC)	22.1	–	UNIMMAP multiple micronutrient supplement formulation	Placebo (preconception), iron and folic acid supplement (pregnancy)	Preconception+pregnancy	6	112	Birth weight Low birth weight Gestational age at birth

Continued

Table 1 Continued

Study	Author and date	Study type	Country	Average age (years)	Specific subpopulation	Intervention	Comparator	Phase intervention delivered	Preconception time initiated (months)	Analytical sample size	Outcomes
4	Czeizel 1996[89]	RCT	Hungary (HIC)	26.9	–	Multivitamin supplement containing) folic acid	Capsule containing copper, manganese, zinc and vitamin C	Preconception and periconception	1	4375	Birth defects—major, including cardiovascular, urinary tract, pyloric stenosis, limb deficiencies, NTDs and orofacial clefts
	Czeizel 1994[76]	RCT	Hungary (HIC)	26.9	–	Multivitamin supplement containing) folic acid	Capsule containing copper, manganese, zinc and vitamin C	Preconception and periconception	1	5453	Stillbirth Birth weight Low birth weight Gestational age at birth Preterm birth
5	Czeizel 2004[53]	Quasi-experimental	Hungary (HIC)	27.4	–	Multivitamin supplement containing) folic acid	No supplementation	Preconception and periconception	1	6112	Birth defects - major, including cardiovascular, urinary tract, pyloric stenosis, limb deficiencies, NTDs, orofacial clefts Birth defects - other, non-major Birth weight Low birth weight Gestational age at birth Stillbirth
6	Smithells 1981[35]	Quasi-experimental	UK (HIC)	27.2	Women with previous NTD birth	Multivitamin supplement containing) folic acid	No supplementation	Preconception and periconception	1	561	Birth defects—NTDs
7	Smithells 1983[50]	Quasi-experimental	UK (HIC)	27	Women with previous NTD birth	Multivitamin supplement containing) folic acid	No supplementation	Preconception and periconception	1	544	Birth defects— NTDs
8	ICMR 2000[64]	RCT	India (LMIC)	25.9	Women with previous NTD birth	Multivitamin supplement containing) folic acid	Capsule containing iron and calcium	Preconception and periconception	1	279	Birth defects— NTDs Stillbirth Low birth weight
9	Chen 2008[85]	Quasi-experimental	China (UMIC)	25.9	–	Multivitamin supplement containing) folic acid	No supplementation	Preconception and periconception	3	52 043	Birth defects— NTDs
10	Widasari 2019[45]	RCT	Indonesia (UMIC)	NI	–	Multiple micronutrient supplement	Iron and folic acid supplement	Preconception+pregnancy	–	19	Birth weight

Continued

Table 1 Continued

Study	Author and date	Study type	Country	Average age (years)	Specific subpopulation	Intervention	Comparator	Phase intervention delivered	Preconception time initiated (months)	Analytical sample size	Outcomes
11	Brabin 2019[47]	RCT	Burkina Faso (LIC)	17.1	–	Iron and folic acid supplement	Folic acid supplement	Preconception and periconception	18	307	Birth weight Low birth weight Gestational age at birth Preterm birth Small for gestational age Haemoglobin (13–16 weeks gestation) Haemoglobin (33–36 weeks gestation) Gestational hypertension
	Gies 2018[46]	RCT	Burkina Faso (LIC)	17.1	–	Iron and folic acid supplement	Folic acid supplement	Preconception and periconception	18	437	Birth defects—congenital anomalies Stillbirth
12	Berger 2005[39]	Quasi-experimental	Vietnam (LMIC)	NI	–	Iron and folic acid supplement	Iron and folic acid supplement	Preconception+pregnancy	6	200	Haemoglobin (first trimester) Anaemia (first trimester) Haemoglobin (second trimester) Anaemia (second trimester) Haemoglobin (third trimester) Anaemia (third trimester) Birth weight Low birth weight
13	Passerini 2012[58]	Quasi-experimental	Vietnam (LMIC)	26.2	–	Iron and folic acid supplement and deworming	No supplementation or deworming	Preconception and periconception	16	463	Birth weight Low birth weight
14	Khambalia 2009[65]	RCT	Bangladesh (LMIC)	19	–	Iron and folic acid supplement	Folic acid supplement	Preconception and periconception	1	88	Haemoglobin (15 weeks gestation) Anaemia (15 weeks gestation)
15	Wehby 2013[52]	RCT	Brazil (UMIC)	26.7	Women with oral clefts or previous oral cleft birth	Folic acid supplement	Folic acid supplement	Preconception and periconception	48	234	Birth defects—oral clefts Birth weight Gestational age at birth Pre-eclampsia

Continued

Table 1 Continued

Study	Author and date	Study type	Country	Average age (years)	Specific subpopulation	Intervention	Comparator	Phase intervention delivered	Preconception time initiated (months)	Analytical sample size	Outcomes
16	MRC 1991[83]	RCT	UK, Hungary, Israel, Australia, Canada, Russia, France (HIC)	26.9	Women with previous NTD birth	Folic acid with/ without multivitamin supplement (groups combined for meta-analysis)	Capsule containing iron and calcium, or multivitamin supplement without folic acid (groups combined for meta-analysis)	Preconception and periconception	–	1195	Birth defects—NTDs
17	Vergel 1990[86]	Quasi-experimental	Cuba (UMIC)	NI	Women with previous NTD birth	Folic acid supplement	No folic acid supplementation in preconception (potentially some supplementation in early pregnancy)	Preconception and periconception	1	213	Birth defects—NTDs
18	Laurence 1981[42]	RCT	Wales (HIC)	NI	Women with previous NTD birth	Folic acid supplement	Placebo	Preconception and periconception	–	111	Birth defects—NTDs
19	Kirke 1992[32]	RCT	Ireland (HIC)	31.3	Women with previous NTD birth	Folic acid with/ without multivitamin supplement (groups combined for meta-analysis)	Multivitamin supplement without folic acid	Preconception and periconception	2	261	Birth defects—NTDs Stillbirth
20	Berry 1999[84]	Quasi-experimental	China (UMIC)	24.9	–	Folic acid	No supplementation	Preconception and periconception	35	247831	Birth defects—NTDs
	Myers 2001[48]	Quasi-experimental	China (UMIC)	24.9	–	Folic acid	No supplementation	Preconception and periconception	29	222314	Birth defects—imperforate anus
21	Potdar 2014[57]	RCT	India (LMIC)	25	–	Food supplement—snack containing dried fruit, green leafy vegetables, and milk	Snack made of low-micronutrient vegetables	Preconception+pregnancy	3	1360	Birth weight Low birth weight Gestational age at birth Preterm birth Small for gestational age Large for gestational age
	Sahariah 2016[30]	RCT	India (LMIC)	23.5	–	Food supplement—snack containing dried fruit, green leafy vegetables, and milk	Snack made of low-micronutrient vegetables	Preconception+pregnancy	3	1008	Gestational diabetes mellitus—WHO 1999 and 2013 criteria

Continued

Table 1 Continued

Study	Author and date	Study type	Country	Average age (years)	Specific subpopulation	Intervention	Comparator	Phase intervention delivered	Preconception time initiated (months)	Analytical sample size	Outcomes
22	Nga 2020[43]	RCT	Vietnam (LMIC)	21.4	–	Food supplement containing) local dark-green leafy vegetables and animal source foods, aiming to cover 50% of RDA of iron, zinc, folate, vitamin A, and Vitamin B_{12}	Comparator 1: Food supplementation in pregnancy only Comparator 2: Standard or routine care	Preconception+pregnancy	2	317	Birth weight Low birth weight Gestational age at birth Preterm birth Small for gestational age Haemoglobin (16 weeks gestation) Anaemia (16 weeks gestation) Haemoglobin (32 weeks gestation) Anaemia (32 weeks gestation)
23	Hambidge 2019[19]	RCT	Democratic Republic of the Congo, Guatemala, India, and Pakistan (LIC, LMIC)	24.2	–	Lipid-based micronutrient supplement (nutriset), providing micronutrients and polyunsaturated fats, and modest amount of protein (2.6 g) and energy (118 kcal). (Additionally, second daily lipid-based protein-energy supplement provided to women with BMI <20 kg/m^2 at any time while receiving Nutriset supplement or with weight gain less than IOM guidelines in second and third trimester).	Comparator 1: Food supplementation in pregnancy only Comparator 2: Standard or routine care	Preconception+pregnancy	3	2451	Birth weight Low birth weight Preterm birth Small for gestational age
24	Caan 1987[38]	Quasi-experimental	USA (HIC)	NI	–	Food supplement—coupons and cheques for specific food items provided through the Special Supplemental Nutrition Programme for Women, Infants, and Children (5–7 months)	Food supplement shorter duration - coupons and cheques for specific food items provided through the Special Supplemental Nutrition Programme for Women, Infants, and Children (0–2 months)	Preconception and periconception	36	642	Birth weight Low birth weight Gestational age at birth Haemoglobin (unspecified timepoint in pregnancy) Anaemia (unspecified time point in pregnancy)
25	Chaouki 1994[82]	Quasi-experimental	Algeria (LMIC)	29	–	Iodised oil (lipiodol), provided orally	Comparator 1: No supplementation Comparator 2: Iodised oil (lipiodol) provided in early pregnancy	Preconception and periconception	3	1536	Birth weight

Continued

Table 1 Continued

Study	Author and date	Study type	Country	Average age (years)	Specific subpopulation	Intervention	Comparator	Phase intervention delivered	Preconception time initiated (months)	Analytical sample size	Outcomes
26	Katz 2000[61]	cRCT	Nepal (LMIC)	24.5	–	Intervention 1: Vitamin A supplement Intervention 2: Beta carotene supplement	Placebo	Preconception+pregnancy	5	17 373	Preterm birth Stillbirth or miscarriage—composite
27	Hofmeyr 2019[80]	RCT	South Africa, Argentina, Zimbabwe (UMIC, LMIC)	29.3	Women with previous pre-eclampsia	Calcium supplement	Placebo	Preconception and periconception	3	579	Pre-eclampsia Gestational hypertension Low birth weight Preterm birth Stillbirth
28	Sun 2020[31]	RCT	China (UMIC)	31.3	–	100 g white mushrooms to be integrated into daily diet	Standard or routine care: no mushroom diet intervention - normal diet	Preconception and periconception	–	1162	Gestational hypertension Pre-eclampsia Gestational diabetes Preterm birth Birth weight Low birth weight
Health interventions											
29	de Jong-Potjer 2006[51]	cRCT	Netherlands (HIC)	28.7	–	Preconception counselling session with general practitioner	Standard or routine care—no preconception intervention and standard antenatal care	Preconception and periconception	12	1019	Adverse pregnancy outcomes—composite (miscarriage, stillbirth, preterm, disorder of the newborn)
30	Livingood 2010[55]	Quasi-experimental	USA (HIC)	NI	Low income women, high risk for poor pregnancy outcome	Preconception care including goal plan to build resilience to negative social determinants	Comparator 1: No intervention Comparator 2: No intervention	Preconception and periconception	–	2090	Low birth weight
31	Jourabchi 2018[37]	Quasi-experimental	Iran (UMIC)	25	–	Preconception care integrated with prenatal care	Standard or routine care—standard antenatal care	Preconception+pregnancy	4	365	Low birth weight Preterm birth
32	Lumley 2006[34]	RCT	Australia (HIC)	29	Low income women, high risk for poor pregnancy outcome	Home visit following first delivery, offering comprehensive preconception care	Standard or routine care—home visit from study midwife discussing first pregnancy and answering any questions	Preconception and periconception	36	786	Birth weight Low birth weight Gestational age at birth Preterm birth Small for gestational age Birth defects—congenital anomalies

Continued

Table 1 Continued

Study	Author and date	Study type	Country	Average age (years)	Specific subpopulation	Intervention	Comparator	Phase intervention delivered	Preconception time initiated (months)	Analytical sample size	Outcomes
33	Manandhar 2004[44]	cRCT	Nepal (LMIC)	26.7	–	Women's group meetings by local facilitator about perinatal health in each ward (one facilitator for each Village Development Committee, containing nine wards)	Standard or routine care—no women's group meetings in control Village Development Committees	Preconception+pregnancy	36	6275	Stillbirth
34	Ismail 2016[88]	RCT	Egypt (LMIC)	26.6	Women with ≥3 first or ≥2 second-trimester miscarriages and APS	Subcutaneous heparin and oral aspirin	Placebo	Preconception and periconception	12	126	Birth weight Gestational age at birth Preterm birth Small for gestational age Pre-eclampsia
35	Russu 2009[75]	Quasi-experimental	Romania (HIC)	28.7	Women with two previous miscarriages	Vaginal micronised progesterone	Placebo—muscle relaxant	Preconception+pregnancy	6	69	Birth weight Low birth weight Preterm birth Birth defects—congenital anomalies Stillbirth Gestational hypertension Gestational diabetes
36	Hooker 2020[73]	RCT	Netherlands (HIC)	34.5	Women with previous miscarriage	Hyaluronic acid gel applied after dilation and curettage	No intervention following dilation and curettage	Preconception and periconception	31	104	Gestational age Preterm birth Birth weight
37	Siklósi 2012[49]	RCT	Hungary (HIC)	31.2	Women with≥3 previous miscarriages	Clomiphene citrate	Placebo	Preconception and periconception	12	82	Low birth weight Small for gestational age Preterm birth Pre-eclampsia
38	Stephenson 2010[60]	RCT	USA, Canada (HIC)	35.5	Women with≥3 consecutive unexplained previous miscarriages	Intravenous immunoglobulin	Placebo–normal saline solution	Preconception and periconception	6	31	Preterm birth Pre-eclampsia
39	Schisterman 2014[69]	RCT	USA (HIC)	28.7	Women with one or two previous miscarriages	Low-dose aspirin	Placebo	Preconception+pregnancy	6	595	Gestational age at birth Preterm birth Birth weight Gestational hypertension Gestational diabetes mellitus Pre-eclampsia

Continued

Table 1 Continued

Study	Author and date	Study type	Country	Average age (years)	Specific subpopulation	Intervention	Comparator	Phase intervention delivered	Preconception time initiated (months)	Analytical sample size	Outcomes
40	Christiansen 1994[67]	RCT	Denmark (HIC)	29.5	Women with ≥3 consecutive previous miscarriages	Active immunisation with third party leukocytes	Placebo - participant's own blood, drawn immediately before transfusion	Preconception and periconception	3	39	Birth weight Preterm birth Birth defects—congenital anomalies
41	Kaandorp 2010[36]	RCT	Netherlands (HIC)	33.7	Women with≥2 previous miscarriages	Intervention 1: Aspirin in preconception and heparin in pregnancy Intervention 2: Aspirin in preconception and pregnancy	Placebo	Preconception+pregnancy	24	299	Gestational age at birth Preterm birth Small for gestational age Birth defects—congenital anomalies Pre-eclampsia
42	LeBlanc 2020[93]	RCT	USA (HIC)	31.3	Women with overweight or obesity	Individualised telephone counselling sessions with health coach, a trained behavioural interventionist, and access to a personalised intervention website	Usual care - information on having a healthy pregnancy was provided in the baseline visit	Preconception+pregnancy	24	169	Birth weight Preterm birth Birth weight for gestational age Small for gestational age Large for gestational age Gestational diabetes Gestational hypertension Birth defects—congenital anomalies
43	Rönö 2018[81]	RCT	Netherlands (HIC)	32	Women with with obesity or prior history of gestational diabetes	Lifestyle counselling with trained nurse	Standard antenatal care - same number of visits but only leaflets similar to antenatal care leaflets (healthy diet and exercise) provided	Preconception+pregnancy	4	128	Gestational diabetes Gestational hypertension Pre-eclampsia Birth weight Birth defects—congenital anomalies
44	Willhoite 1993[92]	Quasi-experimental	USA (HIC)	26.9	Women with pregestational diabetes (type one or 2)	Preconception counselling session with healthcare provider (following statewide campaign to educate healthcare providers and individuals)	No preconception counselling session recorded	Preconception and periconception	–	157	Gestational age at birth Birth weight Birth defects—congenital anomalies

Continued

Table 1 Continued

Study	Author and date	Study type	Country	Average age (years)	Specific subpopulation	Intervention	Comparator	Phase intervention delivered	Preconception time initiated (months)	Analytical sample size	Outcomes
45	DCCT Research Group 1996[78]	Quasi-experimental	USA (HIC)	23.9	Women with pregestational diabetes (type 1)	Intervention 1: Intensive therapy for diabetes - average of 40±25 months before conception Intervention 2: Intensive therapy for diabetes - average of 6.5±5.9 months before conception	Intensive therapy started after pregnancy detected	Preconception+pregnancy	Intervention 1: 40 Intervention 2: 6.5	191	Birth weight Low birth weight Gestational age at birth Birth defects—congenital anomalies Stillbirth
46	Feig 2017[40]	RCT	Canada, England, Scotland, Spain, Italy, Ireland, and the USA (HIC)	32.9	Women with pregestational diabetes (type 1)	Continuous glucose monitoring, in addition to capillary glucose monitoring	Usual care - capillary glucose monitoring	Preconception+pregnancy	6	25	Birth weight Gestational age at birth Preterm birth Birth weight for gestational age Large for gestational age Small for gestational age Stillbirth Birth defects—congenital anomalies Pre-eclampsia Gestational hypertension
47	Hoffman 2019[33]	RCT	Argentina, Botswana, Brazil, China, Haiti, Peru, Thailand, USA (LIC to HIC)	27.4	Women with HIV	Continue ART following delivery (within 42 days)	Discontinue ART after delivery (within 42 days); restart on detection of subsequent pregnancy in accordance with local guidelines (or for clinical indications)	Preconception+pregnancy	15	266	Stillbirth
48	Mugo 2014[74]	RCT	Kenya, Uganda (LMIC, LIC)	33	Women without HIV, who have partners with HIV	Intervention 1: HIV PreP: tenofovir disoproxil fumarate Intervention 2: HIV PreP: combination emtricitabine/tenofovir disoproxil fumarate	Placebo	Preconception and periconception	2	194	Preterm birth Birth defects—congenital anomalies
49	Taylor 2013[77]	RCTs	Botswana (UMIC)	28	Women with HIV	Long-term isoniazid prophylaxis	Placebo	Preconception+pregnancy	11	196	Preterm birth, stillbirth, low birth weight, birth defects— composite

Continued

Table 1 Continued

Study	Author and date	Study type	Country	Average age (years)	Specific subpopulation	Intervention	Comparator	Phase intervention delivered	Preconception time initiated (months)	Analytical sample size	Outcomes
50	Theron 2020[79]	RCT	India, Malawi, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe (LIC, LMIC)	27.3	Women with HIV	Continuation of ART following delivery or following breastfeeding cessation	Discontinue ART following delivery or breastfeeding cessation; restart on detection of next pregnancy	Preconception+pregnancy	52	186	Low birth weight
51	Makanani 2018[71]	RCT	Malawi, South Africa, Uganda, Zimbabwe (LIC, LMIC, UMIC)	23	Women without HIV	Dapivirine ring	Placebo	Preconception and periconception	24	181	Preterm birth Stillbirth Birth defects—congenital anomalies
52	Wacholder 2010[90]	RCT	Costa Rica, USA, Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Mexico, Philippines, Spain, Taiwan, Thailand, UK (LMIC, UMIC, HIC)	NI	–	HPV 16/18 vaccine (Cervarix) formulated with AS04 adjuvant system	Hepatitis A vaccine	Preconception and periconception	48	3506	Stillbirth
53	Garland 2009[72]	RCT	Multiple countries, not named (NI)	20.9	–	HPV type 6/11/16/18 (Gardasil/Silgard) vaccine	Placebo - not specified	Preconception and periconception	48	2871	Birth defects—congenital anomalies Preterm Small for gestational age Stillbirth
54	Chen 2019[91]	RCT	China (UMIC)	NI	–	HPV type 6/11/16/18 (Gardasil/Silgard) vaccine	Placebo - also containing 0.225 µg adjuvant	Preconception and periconception	77	932	Birth defects—congenital anomalies Stillbirth
55	Angelo 2014[68]	Quasi-experimental	40 countries, not named (NI)	NI	–	HPV 16/18 vaccine (Cervarix) formulated with AS04 adjuvant system – sometimes coadministered with another vaccine	Placebo, or other non-HPV vaccine (eg, Hepatitis A)	Preconception and periconception	2	571	Preterm birth

Continued

Table 1 Continued

Study	Author and date	Study type	Country	Average age (years)	Specific subpopulation	Intervention	Comparator	Phase intervention delivered	Preconception time initiated (months)	Analytical sample size	Outcomes
56	Cérbulo-Vázquez 2019[62]	RCT	Mexico (UMIC)	26.1	–	H1N1 Influenza vaccine	Placebo	Preconception and periconception	5	39	Pre-eclampsia Gestational hypertension Low birth weight
4*	Banhidy 2010[70]	Quasi-experimental	Hungary (HIC)	26.4	Women with sexually transmitted disease or vaginal candidiasis	Treatment of sexually transmitted disease or vaginal candidiasis	No intervention – no treatment for sexually transmitted disease or vaginal candidiasis	Preconception and periconception	–	2167	Preterm birth
57	Andrews 2006[59]	RCT	USA (HIC)	23.5	Women with previous spontaneous preterm birth	Azithromycin and metronidazole	Placebo	Preconception and periconception	15	124	Gestational age at birth Preterm birth Birth weight
Social interventions											
58	Baqui 2018[54]	Quasi-experimental	Bangladesh (LMIC)	26.6	–	Integrated postpartum family planning and maternal and newborn health interventions, delivered by trained community health workers	Standard maternal and newborn health services, delivered by community health workers	Preconception and periconception	28	1140	Preterm birth

*This study contributed data for both a nutrition intervention and a health intervention.
Average age is mean, median or a weighted average of age categories as provided by studies.
APS, antiphospholipid syndrome; ART, antiretroviral therapy; BMI, body mass index; cRCT, cluster-RCT; HIC, high-income country; IOM, Institute of Medicine; LIC, low-income country; LMIC, low-income and middle-income country; NI, no information; NTD, neural tube defect; PreP, pre-exposure prophylaxis; Quasi-experimental, quasi-experimental design; RCT, randomised controlled trial; RDA, recommended dietary allowance; UMIC, upper-middle income country; UNIMMAP, United Nations International Multiple Micronutrient Antenatal Preparation.

Table 2 Summary of evidence regarding the effect of preconception and periconception interventions to prevent LBW, SGA and PTB

	Intervention in preconception and periconception (vs no intervention, standard of care or routine care, or placebo)					Intervention in preconception and pregnancy (vs intervention in pregnancy only)				
	Studies	N	Risk Ratio (95% CI)	I^2 (%)	Certainty of evidence	Studies	N	Risk ratio (95% CI)	I^2 (%)	Certainty of evidence
LBW										
Nutrition interventions										
Multiple micronutrient supplementation[18 53 64 76]	4	12 054	1.06 (0.90 to 1.25)	0.00	Low	0	0	–	–	–
Iron and folic acid supplementation[18 39 47 58]	3	1831	0.74 (0.34 to 1.61)	83.10	Very low	1	200	0.28 (0.08 to 1.03)	–	Very low
Food supplementation*[19 38 43]	1	529	0.40 (0.14 to 1.12)	–	Very low	2	1134	1.00 (0.79 to 1.26)	0.00	Very low
Other: Calcium supplementation[80]	1	507	1.00 (0.76 to 1.30)	–	–	0	0	–	–	–
Other: Mushroom in diet[31]	1	1162	0.79 (0.46 to 1.35)	–	–	0	0	–	–	–
Health interventions										
General preconception health[34 55]	2	1188	1.27 (0.83 to 1.94)	39.11	Very low	0	0	–	–	–
Early adverse pregnancy outcome prevention[49]	1	82	0.23 (0.11 to 0.51)	–	Very low	0	0	–	–	–
NCD interventions (safety)†[78]	0	0	–		–	1	149	4.34 (0.55 to 34.34)	–	Very low
Infectious disease interventions (safety)†[62 79]	1	39	4.96 (0.27 to 89.87)	–	Very low	1	186	2.65 (1.20 to 5.81)	–	Very low
SGA										
Nutrition interventions										
Multiple micronutrient supplementation[20]	1	1084	1.02 (0.74 to 1.40)	–	Very low	0	0	–	–	–
Iron and folic acid supplementation[18 47]	2	1351	0.83 (0.66 to 1.05)	0.00	Low	0	0	–	–	–
Food supplementation[19 43]	0	0	–	–	–	2	1161	0.89 (0.78 to 1.02)	0.00	Low
Health interventions										
General preconception health[34]	1	760	1.13 (0.57 to 2.14)	–	Very low	0	0	–	–	–
Early adverse pregnancy outcome prevention[49 88]	2	208	0.35 (0.18 to 0.68)	0.00	Low	0	0	–	–	–

Continued

Table 2 Continued

	Intervention in preconception and periconception (vs no intervention, standard of care or routine care, or placebo)					Intervention in preconception and pregnancy (vs intervention in pregnancy only)				
	Studies	N	Risk Ratio (95% CI)	I^2 (%)	Certainty of evidence	Studies	N	Risk ratio (95% CI)	I^2 (%)	Certainty of evidence
Infectious disease interventions (safety)*[72]	1	2871	1.23 (0.33 to 4.57)	–	Very low	0	0	–	–	–
PTB										
Nutrition interventions										
Multiple micronutrient supplementation[18 53 66 76]	4	12235	1.03 (0.90 to 1.18)	39.04	Low	0	0	–	–	–
Iron and folic acid supplementation[18 47]	2	1360	1.42 (0.60 to 3.37)	87.79	Very low	0	0	–	–	–
Food supplementation[19 43]	0	0	–	–	–	2	1163	1.38 (1.06 to 1.79)	0.00	Very low
Other: Calcium supplementation[80]	1	579	0.90 (0.74 to 1.10)	–	–	0	0	–	–	–
Other: Mushroom in diet[31]	1	1162	0.93 (0.63 to 1.38)	–	–	0	0	–	–	–
Health interventions										
General preconception health[34]	1	786	1.41 (0.74 to 2.69)	–	Very low	0	0	–	–	–
Early adverse pregnancy outcome prevention[49 60 67 73 88]	5	382	0.32 (0.20 to 0.51)	5.13	Very low	0	0	–	–	–
Infectious disease interventions[59 70]	2	2275	0.62 (0.20 to 1.93)	95.34	Very low	0	0	–	–	–
Infectious disease interventions (safety†)[68 72 74]	3	3666	1.05 (0.71 to 1.57)	0.00	Very low	0	0	–	–	–
Infectious disease interventions (safety‡)[71]	1	181	0.06 (0.00 to 0.96)	–	Very low	0	0	–	–	–
Social interventions										
Reproductive planning[54]	1	1140	0.79 (0.63 to 0.99)	–	Very low	0	0	–	–	–

Certainty of evidence assessed using the GRADE tool.
Some studies included consisted of women with underlying conditions (eg, previous pre-eclampsia or HIV). These are identified in table 1 and figures 3–5.
*The identified study compared the effect of a longer duration of food supplementation with a shorter duration.; the OR is reported for this study as risk ratio could not be computed.
†The aim of interventions was not to prevent LBW, PTB or SGA, and the anticipated effect of interventions was not necessarily protective.
‡The aim of interventions was not to prevent PTB, and the anticipated effect of interventions was not necessarily protective; additionally, the effect estimate of this study could not be statistically combined with that of other studies due to its CI including the null.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; LBW, low birth weight; NCD, non-communicable disease; PTB, preterm birth; SGA, small for gestational age.

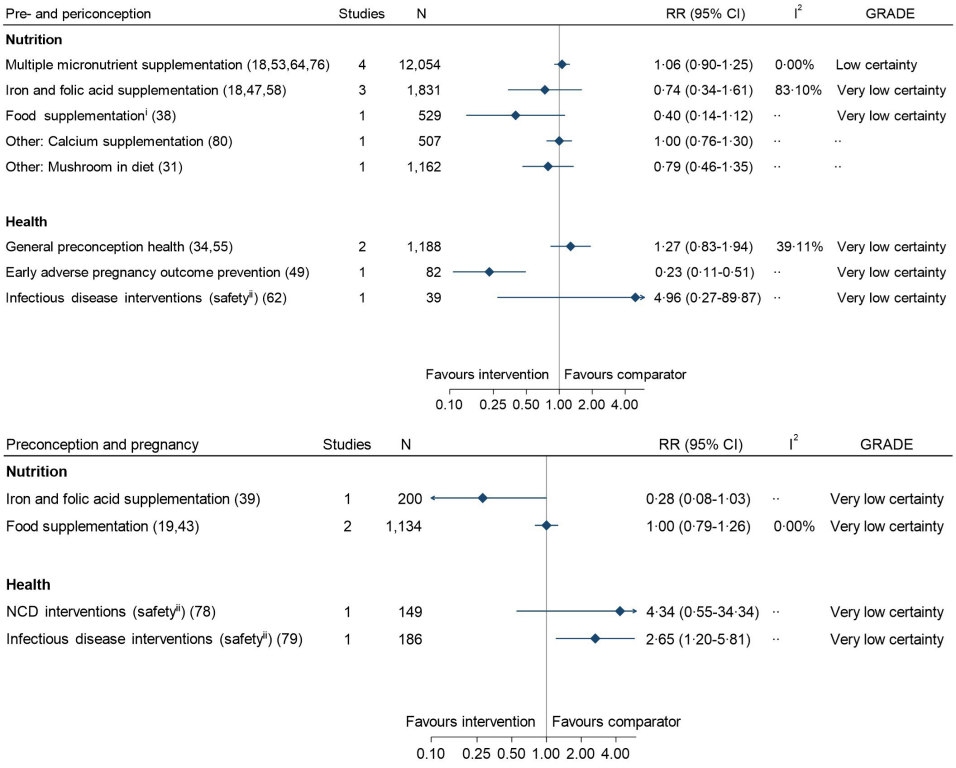

Figure 3 Summary of evidence regarding the effect of interventions delivered in the preconception and periconception period or preconception and pregnancy (vs pregnancy) period on low birth weight. The upper plot summarises the effect of interventions delivered in the preconception and periconception period compared with folic acid supplementation, other micronutrients (not folic acid), standard or routine care, placebo or no intervention (apart from food supplementation, see [i] below). The lower plot summarises the effect of interventions delivered in the preconception and pregnancy period compared with the same intervention delivered during pregnancy only. NCD interventions: NCD prevention and management. Infectious disease interventions: infectious disease prevention and management. Numbers in brackets denote the study reference. RR (95% CI): RR (95% CI). Grade: certainty of evidence assessment using the grading of recommendations assessment, development and evaluation tool. Preconception and periconception multiple micronutrient supplementation: one study was based among women with a previous birth with neural tube defect. Preconception and periconception calcium supplementation: the identified study was based among women with previous pre-eclampsia. Preconception and periconception early adverse pregnancy outcome prevention: the identified study was based among women with previous miscarriage. Preconception and pregnancy NCD interventions: the identified study was based among women with type one diabetes. Preconception and pregnancy infectious disease interventions: the identified study was based among women with HIV. [i]The identified study compared the effect of a longer duration of food supplementation with a shorter duration; the OR is reported for this study as risk ratio could not be computed. [ii]The aim of interventions was not to prevent low birth weight, and the anticipated effect of interventions was not necessarily protective. GRADE, Grades of Recommendations, Assessment, Development and Evaluation; NCD, non-communicable disease; RR, risk ratio.

1).[18 19 31 34 38 39 43 47 49 53 55 58 62 64 76 78–80] This included 14 interventions (10 nutrition[18 31 38 47 53 58 64 76 80] and 4 health[34 49 55 62]) delivered in preconception and periconception, and 5 (3 nutrition[19 39 43] and 2 health[78 79]) delivered in preconception and pregnancy (vs pregnancy-only intervention).

Interventions in preconception and periconception

We found two or more studies for two nutrition interventions delivered in preconception and periconception. These were preconception and periconception multiple micronutrient supplementation and preconception and periconception iron and folic acid supplementation. The evidence suggested that preconception and periconception multiple micronutrient supplementation results in little to no difference in LBW (four studies, N=12 054, RR: 1.06 (95% CI: 0.90 to 1.25), I^2: 0.00%, GRADE: low certainty).[18 53 64 76] Overall, the evidence was very uncertain about the effect of preconception and periconception iron and folic acid supplementation on LBW (three studies, N=1831, RR: 0.74 (95% CI: 0.34 to 1.61), I^2: 83.10%, GRADE: very low certainty).[18 47 58] Similarly, the evidence was very uncertain regarding the effect of preconception and periconception food supplementation on LBW (one study, N=529, OR: 0.40 (95% CI: 0.14 to 1.12), GRADE: very low certainty) (table 2, figure 3, online supplemental appendix 1).[38] We found only two single, non-comparable studies for other nutrition interventions, both of which reported no clear effect on LBW (table 2, figure 3, online supplemental appendix 1).[31 80]

Among health interventions, we found two studies for preconception and periconception general health interventions. The available evidence from these studies suggested that such interventions may increase LBW; however, the evidence was very uncertain (two studies, N=1188, RR: 1.27 (95% CI: 0.83 to 1.94), I^2: 39.11%, GRADE: very low certainty).[34 55] We found no studies examining effects on LBW of preconception and periconception interventions to prevent or manage non-communicable diseases, and only one small study (N<100 each) for each of the other health interventions (early adverse pregnancy outcome prevention among women with previous miscarriage: clomiphene citrate vs placebo,[49] and infectious disease interventions: H1N1 vaccine vs placebo[62]). The overall evidence was very uncertain regarding the effect of either of these interventions in the preconception and periconception period on LBW (early adverse pregnancy outcome prevention: one study, N=82, RR: 0.23 (95% CI: 0.11 to 0.51), GRADE: very low certainty; infectious disease interventions: one study: N=39, RR: 4.96 (95% CI: 0.27 to 89.87), GRADE: very low certainty) (table 2, figure 3, online supplemental appendix 1).

Interventions in preconception and pregnancy versus intervention in pregnancy only

We found two or more studies for only one nutrition intervention delivered in preconception and pregnancy vs pregnancy only: food supplementation.[19 43] Evidence from these studies suggested that preconception and pregnancy food supplementation may have little to no impact on LBW compared with pregnancy-only supplementation, but was very uncertain (two studies, N=1134, RR: 1.00 (95% CI: 0.79 to 1.26), I^2: 0.00%, GRADE: very low certainty).[19 43] We found one other small study (N=200) examining the effect of preconception and pregnancy iron supplementation (vs pregnancy-only supplementation) on LBW; overall, the evidence was very uncertain about its effect on LBW (one study, N=200, RR: 0.28 (95% CI: 0.08 to 1.03), GRADE: very low certainty).[39] We found no studies examining any other nutrition interventions (table 2, figure 3, online supplemental appendix 1).

For health interventions, we found only one small (N<200) study each reporting effects of a preconception and pregnancy versus pregnancy-only non-communicable disease intervention (intensive therapy for type 1 diabetes)[78] or infectious disease intervention (antiretroviral therapy)[79] (table 2, figure 3, online supplemental appendix 1).[79] Overall, the evidence was very uncertain about the effect of either of these interventions on LBW (non-communicable disease interventions: one study, N=149, RR: 4.34 (95% CI: 0.55 to 34.34), GRADE: very low certainty; infectious disease interventions: 1 study: N=186, RR: 2.65 (95% CI: 1.20 to 5.81), GRADE: very low certainty).

Effect of interventions on SGA

Identified studies

Eight studies reported the effect of nine interventions where the preconception or periconception impact of interventions on SGA could be examined.[18 19 34 43 47 49 72 88] Of these, seven interventions (three nutrition[18 47] and four health[34 49 72 88]) were delivered in preconception and periconception, while two (both nutrition[19 43]) were delivered in preconception and pregnancy versus pregnancy only (table 2, figure 4, online supplemental appendix 1).

Interventions in preconception and periconception

Among nutrition interventions, we found two studies assessing preconception and periconception iron and folic acid supplementation. The evidence suggested that preconception and periconception iron and folic acid supplementation reduces SGA (two studies, N=1351, RR: 0.83 (95% CI: 0.66 to 1.05), I^2: 0.00%, GRADE: low certainty).[18 47] Additionally, the evidence was very uncertain about the effect of preconception and periconception multiple micronutrient supplementation on SGA (one study, N=1084, RR: 1.02 (95% CI: 0.74 to 1.40), GRADE: very low certainty).[20] We found no studies for any other nutrition intervention (table 2, figure 4, online supplemental appendix 1).

Among health interventions, we found two studies examining heterogeneous preconception and periconception interventions to prevent early adverse pregnancy outcomes (clomiphene citrate[49] or aspirin and heparin vs placebo[88]) among women with previous miscarriage. The evidence suggested that such interventions result in a large reduction in SGA (two studies, N=208, RR: 0.35 (95% CI: 0.18 to 0.68), I^2: 0.00%, GRADE: low certainty).[49 88] No studies examined non-communicable disease interventions. One study each examined the impact on SGA of a general preconception health intervention (home visit following first delivery offering comprehensive preconception care vs standard or routine care)[34] or an infectious disease intervention (HPV vaccine vs placebo)[72] (table 2, figure 4, online supplemental appendix 1). The evidence was very uncertain regarding the effect of each of these interventions on SGA (general preconception health interventions: 1 study, N=760, RR: 1.13 (95% CI: 0.57 to 2.14) GRADE: very low certainty; infectious disease interventions: 1 study, N=2871, RR: 1.23 (95% CI: 0.33 to 4.57), GRADE: very low certainty).

Interventions in preconception and pregnancy versus intervention in pregnancy only

We found studies for only food supplementation interventions delivered in preconception and pregnancy versus pregnancy. The evidence from these studies suggested that preconception and pregnancy versus pregnancy-only food supplementation reduces SGA slightly (two studies, N=1161, RR: 0.89 (95% CI: 0.78 to 1.02), I^2: 0.00%, GRADE: low certainty).[19 43] No studies were found for any other nutrition or health intervention delivered

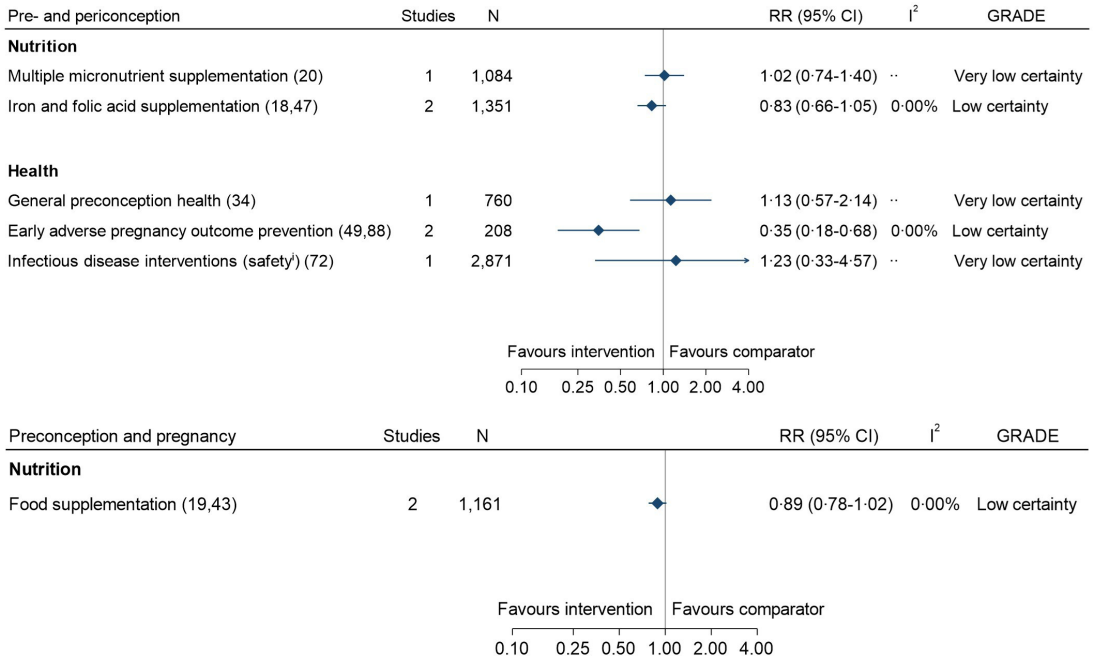

Figure 4 Summary of evidence regarding the effect of interventions delivered in the preconception and periconception period or preconception and pregnancy (vs pregnancy) period on small for gestational age. The upper plot summarises the effect of interventions delivered in the preconception and periconception period compared with folic acid supplementation, standard or routine care or placebo. The lower plot summarises the effect of interventions delivered in the preconception and pregnancy period compared with the same intervention delivered during pregnancy only. Infectious disease interventions: infectious disease prevention and management. Numbers in brackets denote the study reference. RR (95% CI): RR (95% CI). Grade: certainty of evidence assessment using the grading of recommendations assessment, development and evaluation tool. Preconception and periconception early adverse pregnancy outcome prevention: both studies were based among women with previous miscarriage; in one study, participants also had antiphospholipid syndrome. [i]The aim of interventions was not to prevent low birth weight, and the anticipated effect of interventions was not necessarily protective. GRADE, Grades of Recommendations, Assessment, Development and Evaluation; RR, risk ratio.

in preconception and pregnancy versus pregnancy only (table 2, figure 4, online supplemental appendix 1).

Effect of interventions on PTB

Identified studies

Twenty-three studies (24 interventions)[18 19 31 34 43 47 49 51 53 54 59 60 66–68 70–74 76 80 88] examining PTB were identified which estimated preconception or periconception effects of interventions. Most interventions were delivered during the preconception and periconception period (8 nutrition,[18 31 47 53 66 76 80] 13 health,[34 49 51 59 60 67 68 70–74 88] 1 social[54]). Only two interventions (both nutrition)[19 43] were delivered in preconception and pregnancy and compared with pregnancy-only intervention (table 2, figure 5, online supplemental appendix 1).

Interventions in preconception and periconception

We found two or more comparable studies for two nutrition interventions delivered in preconception and periconception that reported on PTB. These were preconception and periconception multiple micronutrient supplementation and preconception and periconception iron and folic acid supplementation. The evidence suggested that preconception and periconception micronutrient supplementation results in little to no difference in PTB (four studies, N=12 235, RR: 1.03 (95% CI: 0.90 to 1.18), I^2: 39.04%, GRADE: low certainty).[18 53 66 76] Furthermore, the evidence was very uncertain about the impact of preconception and periconception iron and folic acid supplementation on PTB (two studies, N=1360, RR: 1.42 (95% CI: 0.60 to 3.37), I^2: 87.79%, GRADE: very low certainty).[18 47] We found no studies examining preconception and periconception food supplementation, and two studies indicating no clear effect of other preconception and periconception nutrition interventions (calcium supplementation,[80] inclusion of mushrooms in diet[31]) on PTB (table 2, figure 5, online supplemental appendix 1).

We found two or more studies for two preconception and periconception health interventions. These were interventions to prevent early adverse pregnancy outcomes among women with previous miscarriage (five studies, N=382)[49 60 67 73 88] and infectious disease interventions. We subdivided infectious disease interventions into those that specifically aimed to reduce PTB risk (two studies, N=2275, GRADE: very low certainty),[59 70] and those with unclear or adverse hypothesised effect (three studies, N=3666, GRADE: very low certainty).[68 72 74] The available evidence suggested that preconception and periconception interventions to prevent early adverse pregnancy outcomes among women with previous miscarriage may

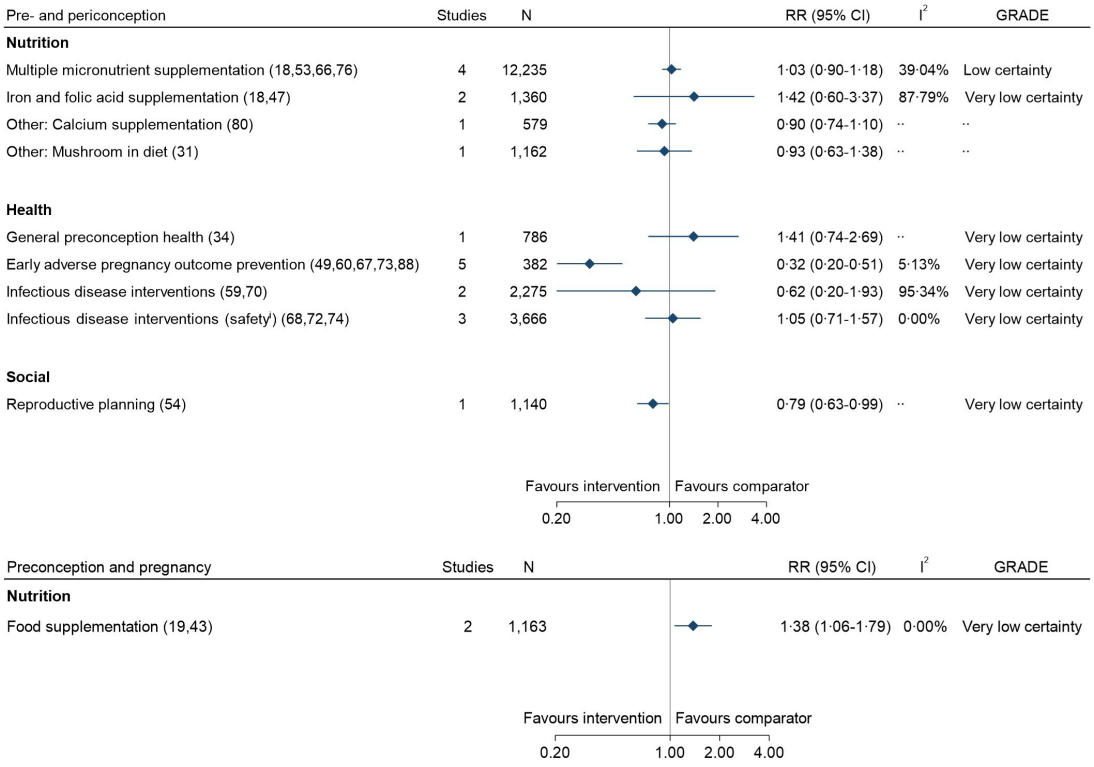

Figure 5 Summary of evidence regarding the effect of interventions delivered in the preconception and periconception period or preconception and pregnancy (vs pregnancy) period on preterm birth. The upper plot summarises the effect of interventions delivered in the preconception and periconception period compared with folic acid supplementation, other micronutrients (not folic acid), standard or routine care, placebo or no intervention. The lower plot summarises the effect of interventions delivered in the preconception and pregnancy period compared with the same intervention delivered during pregnancy only. Infectious disease interventions: infectious disease prevention and management. numbers in brackets denote the study reference. RR (95% CI). Grade: certainty of evidence assessment using the grading of recommendations assessment, development and evaluation tool. Preconception and periconception calcium supplementation: the identified study was based among women with previous pre-eclampsia. Preconception and periconception early adverse pregnancy outcome prevention: the identified study was based among women with previous miscarriage; in one study, participants also had antiphospholipid syndrome. [i]The aim of interventions was not to prevent low birth weight, and the anticipated effect of interventions was not necessarily protective. GRADE, Grades of Recommendations, Assessment, Development and Evaluation; RR, risk ratio.

reduce PTB; however, the evidence was very uncertain (five studies, N=382, RR: 0.32 (95% CI: 0.20 to 0.51), I^2: 5.13%, GRADE: very low certainty).[49 60 67 73 88] Importantly, these interventions were widely varying, and included clomiphene citrate,[49] aspirin and heparin,[88] intravenous immunoglobulin[60] or third party leucocyte transfusion vs placebo,[67] and intrauterine hyaluronic acid gel vs no intervention following dilation and curettage.[73] Furthermore, the evidence was very uncertain regarding the effect of preconception and periconception infectious disease interventions or general health interventions on PTB (general preconception health interventions: one study, N=786, RR: 1.41 (95% CI: 0.74 to 2.69), GRADE: very low certainty; infectious disease interventions to reduce PTB risk: two studies, N=2275, RR: 0.62 (95% CI: 0.20 to 1.93), I^2: 95.34%, GRADE: very low certainty; infectious disease interventions with potential unclear or adverse effects: three studies, N=3666, RR: 1.05 (95% CI: 0.71 to 1.57), I^2: 0.00%, GRADE: very low certainty).[34] We found no studies examining preconception and periconception non-communicable disease interventions (table 2, figure 5, online supplemental appendix 1).

Two studies examining health interventions were not presented in figure 5: one examined a preconception counselling intervention on a composite outcome including PTB (online supplemental appendix 1),[51] and one assessed effects of the dapivirine vaginal ring compared with a placebo ring, with no PTB cases in the intervention group and a resulting estimate that could not be pooled but which suggested no clear effect (one study, N=181, RR: 0.06 (95% CI: 0.00 to 0.96), GRADE: very low certainty) (table 2, online supplemental appendix 1).[71]

We found a single study on a preconception and periconception social intervention. This study examined the impact a reproductive planning intervention to increase interpregnancy interval on PTB risk. The available evidence suggested that such an intervention may reduce PTB, but the evidence was very uncertain (one study, N=1140, RR: 0.79 (95% CI: 0.63 to 0.99), GRADE: very low certainty) (table 2, figure 5, online supplemental appendix 1).[54]

Interventions in preconception and pregnancy versus intervention in pregnancy only

We identified studies for only food supplementation interventions delivered in preconception and pregnancy versus pregnancy. The evidence was very uncertain regarding the impact of preconception and pregnancy food supplementation compared with pregnancy-only supplementation on PTB (GRADE: very low certainty).[19 43] No other preconception and pregnancy versus pregnancy-only interventions were identified.

Subgroup and sensitivity analyses and reporting biases

Subgroup and sensitivity analyses indicated no clear trends or differences in findings, although these were limited by the small number of studies for any main meta-analysis (online supplemental appendix 1). We found no clear evidence of publication bias for studies assessing primary outcomes. In most cases, these analyses were based on ≤4 studies overall or within subgroups, insufficient to draw firm conclusions.

Risk of bias in studies and certainty of evidence

Only a small proportion of studies assessing the primary outcomes or their continuous measures were assessed as low risk of bias (LBW or birth weight: 6/35 studies, SGA or birth weight for gestational age: 4/12 studies, PTB or gestational age: 6/37 studies) (see online supplemental appendix 1). GRADE assessment suggested low or very low quality evidence overall (table 2, figures 3–5 and online supplemental appendix 1).

Effect of interventions on other birth and maternal outcomes

We observed some effect of interventions on some birth and maternal outcomes as well, although certainty of evidence was not examined for these secondary outcomes. Among other birth outcomes, preconception and periconception nutritional supplementation containing folic acid was associated with 63% reduced risk of birth defects, which were mainly neural tube defects (NTDs) (10 studies, N=313 312, RR: 0.37 (95% CI: 0.24 to 0.55), I^2: 74.33%) (online supplemental appendix 1).[32 35 42 48 50 53 64 83–85 89]

Limited evidence suggested 33%–39% reduced risk of maternal anaemia during pregnancy associated with preconception and pregnancy nutritional supplementation (iron and folic acid or food supplementation) compared with pregnancy-only supplementation (second trimester—two studies with N=307, RR: 0.61 (95% CI: 0.47 to 0.80), I^2: 0.00%, third trimester—two studies with N=289, RR: 0.67 (95% CI: 0.47 to 0.96), I^2: 0.00%).[39 43] A 61% reduced risk of maternal pre-eclampsia was associated with preconception and periconception early adverse pregnancy outcome prevention interventions (two studies, clomiphene citrate[49] or aspirin and heparin[88] vs placebo, N=208, RR: 0.39 (95% CI: 0.20 to 0.74), I^2: 0.00%) (online supplemental appendix 1).

DISCUSSION

This systematic review identified 58 studies examining the effect of interventions delivered during the preconception and periconception period or from preconception throughout pregnancy on LBW, SGA, PTB, and other birth and maternal outcomes. These studies mainly examined nutrition or health interventions, with only one study on a potential social intervention. Studies varied widely in terms of the nature of interventions and comparators and their delivery across preconception and pregnancy. This led to many comparisons, but few studies for any single comparison. Most studies examining LBW, SGA and PTB and their continuous measures were assessed as moderate or high risk of bias. In terms of effect sizes, our findings indicated no clear impact of preconception and periconception nutrition interventions on any primary outcome, although preconception and periconception interventions aiming to reduce early adverse pregnancy outcomes were associated with reduced risk of SGA and PTB among women with previous miscarriage. However, evidence regarding any specific intervention was sparse, limiting any conclusive interpretations. The overall quality of evidence regarding interventions in preconception and periconception or from preconception throughout pregnancy to prevent LBW, SGA and PTB was low or very low certainty. Thus, the evidence summarised here is very uncertain about the effect of most of the interventions examined on LBW, SGA and PTB, at best suggesting that some interventions may reduce these LBW, SGA and PTB. To our knowledge, this is the first comprehensive systematic review and meta-analysis examining the effect of preconception and periconception interventions on LBW, SGA, PTB and other birth and maternal outcomes.

Recognition has grown in recent years of the preconception period as a window of opportunity to improve pregnancy outcomes.[13 16 94] Recent reports have noted the potential value of improving health, nutrition and psychosocial status during the preconception period, highlighting its importance given the global burden of malnutrition and morbidity among women of reproductive age and increasing observational evidence indicating associations between preconception health status and pregnancy outcomes.[13 16 95 96] Recent research has also assessed the impact of interventions delivered preconceptionally on preconception health outcomes, key to ensuring that women enter pregnancy in a healthy state.[11 17 21 97] However, previous evidence syntheses in this area have been limited, due to their assessment of specific interventions and non-pregnancy endpoints, or inclusion of observational studies.[11 12 14 15 17 21 22] Importantly, the available data directly linking preconception interventions to LBW, SGA, PTB and other outcomes have not yet been systematically examined and summarised. This systematic review bridges this gap, collating current evidence on preconception interventions across all possible domains and outlining their impact on these outcomes. Importantly, it highlights a dearth of relevant high-quality evidence in this area, and a need for much further research to accurately and reliably ascertain any impact.

Overall, the evidence is generally very uncertain about the effect of nutrition interventions delivered in the preconception and periconception period, including multiple micronutrient supplementation, iron and folic acid supplementation, folic acid supplementation and food supplementation, on LBW, SGA and PTB. Our observations may be explained by multiple reasons. First, evidence regarding any single comparison generally came from few studies, limiting the ability to examine the question and yield meaningful effects. Second, most studies provided nutritional supplementation for approximately 3–6 months before conception,[19 43 57 64 66 76] which may not be sufficient to achieve sustained improvement in preconception nutritional status to the extent that an effect could be observed on pregnancy outcomes. Third, while adherence was not systematically reported or assessed, certain studies noted poor adherence to interventions, which may have contributed to drawing true effects towards the null.[43 57] Finally, the specific interventions themselves may not be adequate.[43 57] Studies were conducted mainly in LMICs, where the burden of undernutrition remains high among women of reproductive age.[18 19 43 47 66] In this context, interventions such as single or multiple micronutrient supplementation or food supplementation alone may not be sufficient to improve pregnancy outcomes when delivered in the preconception period.

Notably, we found reduced risk of maternal anaemia during the second and third trimesters associated with preconception nutritional supplementation, supporting the notion that such interventions may confer some beneficial effects at least into pregnancy. These findings extend previous research establishing reduced risk of maternal anaemia with prenatal iron supplementation.[98 99] Given evidence that antenatal care is often started late in LMIC settings,[12 100] they suggest potential opportunities to further improve anaemia status by focusing on the periconception period. Additionally, we observed reduced risk of birth defects (primarily NTDs) associated with preconception and periconception nutritional supplementation containing folic acid, consistent with previous reviews in this area.[101] Multiple genetic and environmental factors are thought to contribute to the pathway between folate supplementation during preconception and periconception and reduced risk of NTDs.[101 102]

The totality of evidence identified regarding preconception and periconception health interventions was heterogeneous and inconsistent, preventing conclusive interpretations. Evidence from this review suggests that preconception and periconception interventions to prevent early adverse pregnancy outcomes on the may result in a large reduction in SGA. Although the evidence was very uncertain regarding the effect of such intervention on PTB and certainty of evidence was not ascertained for pre-eclampsia, effect estimates indicated that such interventions were associated with reduced risk of PTB and pre-eclampsia. However, these findings may have limited utility in terms of potential for wider application given the wide variability in the specific interventions, although the individual interventions may merit further investigation. Though the available studies contribute important data regarding preventative and adverse effects of specific strategies to address key diseases when delivered in preconception and periconception, there is scope for much future work addressing a wider range of conditions.

We found little to no literature regarding other important areas in which interventions delivered preconceptionally may have a positive impact on LBW, SGA and PTB. Although symptoms of most common mental disorders are noted to begin in adolescence and young adulthood,[103] and evidence has linked prepregnancy and pregnancy mental health to adverse pregnancy outcomes,[104 105] we found no studies assessing preconception mental health interventions. Additionally, no studies examined strategies to address environmental conditions contributing to poor preconception health, such as those improving water, sanitation and hygiene, which may increase the risk of chronic infectious conditions,[106–108] and those reducing indoor air pollution, which has been linked to LBW.[109] More research is also needed regarding interventions addressing sociocultural issues, including approaches to reduce smoking and substance abuse,[15] or to empower women of reproductive age in ways that may benefit maternal and child health, such as through preventing adolescent pregnancy or increasing interpregnancy interval.[110] We identified only a single study reporting reduced risk of PTB following integration of family planning services into late antenatal and postpartum care.[54] This community-based study from Bangladesh highlighted notable decreases in the proportion of women with a short (<24 month) interpregnancy interval in areas where the intervention was delivered, indicating the potential value of applying such approaches to similar settings and other aspects of reproductive planning.

It will be particularly important for future research to assess integrated, multicomponent interventions addressing different determinants of preconception health. This is essential given previous evidence that women of reproductive age may have a combination of risk factors or conditions which may interact, and that standalone interventions in pregnancy have not shown large effects on LBW and related outcomes.[13 94] More generally, evidence from countries such as Bangladesh, where rates of adverse maternal and neonatal outcomes have decreased in recent decades, suggests an important role of multisectoral advances, covering aspects from women's education, empowerment and equity to infrastructure, water supply and sanitation.[111 112] Additionally, further investigation is required of age and intervention timing and duration, or other underlying characteristics such as preconception nutritional status or geographic region, as factors affecting overall impact.[57] More broadly, research may need to consider how the preconception period is defined, with a view to informing appropriate

intervention and study design.[22] For example, lifestyle and nutrition interventions requiring sustained delivery may be more effective when starting in adolescence, rather than a prespecified number of months before women intend to become pregnant. In this regard, approaches that integrate preconception and adolescent health research may be an efficient way to maximise insight. This may be particularly valuable given increasing recognition of the need for further research into adolescent health.[113] Importantly, such approaches acknowledge the overlap in both periods, and recognise that potential benefits are twofold—to individuals regardless of whether they conceive, and to offspring once conception occurs.[22 103] However, such approaches must also take into account a potential need for continuity of interventions after adolescence to have some impact on birth outcomes, especially given global increases in age at first pregnancy to well beyond this period.[114]

There are limitations to this systematic review. Some of these relate to the evidence base. Our primary outcomes were often reported as secondary outcomes or as part of post hoc analyses in most studies examining health interventions and some studies examining nutrition interventions. Therefore, studies may not have been powered to identify clinically significant effects, and ascertainment and follow-up for outcomes may not have been rigorous. As may be expected, most studies had notable lost to follow-up (over 20%) due to participants not conceiving, or other reasons which were not always reported, suggesting potential for selection bias. Studies also had distinct inclusion and exclusion criteria, which may have had some impact on effect estimates and conclusions. We included quasi-experimental designs in our systematic review, which often did not adequately account for confounding, potentially affecting reported estimates. Such aspects were considered when assessing risk of bias and the certainty of evidence.

One limitation specific to the systematic review was that we examined a small set of sources of clinical and methodological heterogeneity. We did not assess other potentially relevant ones; for example, we did not differentiate studies that may have used varying definitions of SGA, PTB and other outcomes. We also did not examine potentially different effects by region, which may be relevant given the distinct geographical distribution of LBW, PTB, SGA.[1 2 115] As such, given the low number of studies for any single comparison, consideration of these would most likely not be particularly informative; due to the scarcity of studies for any single comparison, we were unable to parse potentially important effects of interventions by age, preconception period when interventions were conducted, and country income setting. Additionally, as we combined studies for distinct interventions within subgroups, particularly in the health domain, this review may offer only broad conclusions about their effect on the outcomes of interest. Finally, due to there being generally few studies per comparison, we did not conduct subgroup and sensitivity analyses or assess publication bias for all comparisons as we had originally planned in the protocol.

Importantly, many of these limitations may be viewed as important findings, justifying the call for further research in this area. Furthermore, this systematic review has several strengths. To our knowledge, this systematic review and meta-analysis is the first to comprehensively assess evidence on the effect of preconception interventions on the risk of LBW, SGA and PTB. We searched multiple databases for published evidence and did not place limits regarding specific intervention types or domains, language or publication date, allowing us to identify all possibly relevant interventions. We also considered evidence on other birth and maternal outcomes, and followed a systematic method to summarise, analyse and consider the quality of available evidence.

CONCLUSION

While interventions delivered during pregnancy have demonstrated the potential to reduce the risk of LBW and related outcomes, reported effects have generally been modest.[13 94] Consequently, the preconception period is increasingly considered as an additional window of opportunity where interventions may have larger impact on such outcomes. In this systematic review, we aimed to summarise current evidence on the effect of preconception and periconception interventions on LBW, SGA and PTB. We noted that the available evidence is generally very uncertain regarding any impact of such interventions. Importantly, our findings indicate that there is not yet sufficient high-quality evidence to understand their effect. Further, well-designed studies are required on the effectiveness of preconception nutrition, health, social and environmental interventions delivered either singly or in combination, in preventing LBW, SGA, PTB and other birth and maternal outcomes.

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REFERENCES

1 Blencowe H, Krasevec J, de Onis M, *et al*. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health* 2019;7:e849–60.
2 Chawanpaiboon S, Vogel JP, Moller A-B, *et al*. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019;7:e37–46.
3 Lee ACC, Kozuki N, Cousens S, *et al*. Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21 st standard: analysis of CHERG datasets. *BMJ* 2017;358:j3677.
4 O'Leary M, Edmond K, Floyd S, *et al*. A cohort study of low birth weight and health outcomes in the first year of life, Ghana. *Bull World Health Organ* 2017;95:574–83.
5 Watkins WJ, Kotecha SJ, Kotecha S. All-Cause mortality of low birthweight infants in infancy, childhood, and adolescence: population study of England and Wales. *PLoS Med* 2016;13:e1002018.
6 Zerbeto AB, Cortelo FM, C Filho Élio B. Association between gestational age and birth weight on the language development of Brazilian children: a systematic review. *J Pediatr* 2015;91:326–32.
7 Upadhyay RP, Naik G, Choudhary TS, *et al*. Cognitive and motor outcomes in children born low birth weight: a systematic review and meta-analysis of studies from South Asia. *BMC Pediatr* 2019;19:35.
8 Christian P, Lee SE, Donahue Angel M, *et al*. Risk of childhood undernutrition related to small-for-gestational age and preterm birth in low- and middle-income countries. *Int J Epidemiol* 2013;42:1340–55.
9 Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? *Physiol Rev* 2014;94:1027–76.
10 da Silva Lopes K, Ota E, Shakya P, *et al*. Effects of nutrition interventions during pregnancy on low birth weight: an overview of systematic reviews. *BMJ Glob Health* 2017;2:e000389.
11 Dean SV, Lassi ZS, Imam AM, *et al*. Preconception care: nutritional risks and interventions. *Reprod Health* 2014;11 Suppl 3:S3.
12 Dean SV, Lassi ZS, Imam AM, *et al*. Preconception care: closing the gap in the continuum of care to accelerate improvements in maternal, newborn and child health. *Reprod Health* 2014;11 Suppl 3:S1.
13 Stephenson J, Heslehurst N, Hall J, *et al*. Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. *Lancet* 2018;391:1830–41.
14 Lassi ZS, Imam AM, Dean SV, *et al*. Preconception care: screening and management of chronic disease and promoting psychological health. *Reprod Health* 2014;11 Suppl 3:S5.
15 Lassi ZS, Imam AM, Dean SV, *et al*. Preconception care: caffeine, smoking, alcohol, drugs and other environmental chemical/radiation exposure. *Reprod Health* 2014;11 Suppl 3:S6.
16 Fleming TP, Watkins AJ, Velazquez MA, *et al*. Origins of lifetime health around the time of conception: causes and consequences. *Lancet* 2018;391:1842–52.
17 Dean SV, Lassi ZS, Imam AM, *et al*. Preconception care: promoting reproductive planning. *Reprod Health* 2014;11 Suppl 3:S2.
18 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;146:1445S–52.
19 Hambidge KM, Westcott JE, Garcés 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;109:457–69.
20 Ramakrishnan U, Grant F, Goldenberg T, *et al*. Effect of women's nutrition before and during early pregnancy on maternal and infant outcomes: a systematic review. *Paediatr Perinat Epidemiol* 2012;26 Suppl 1:285–301.
21 Lassi ZS, Kedzior SG, Tariq W, *et al*. Effects of preconception care and Periconception interventions on maternal nutritional status and birth outcomes in low- and middle-income countries: a systematic review. *Nutrients* 2020;12:E606.
22 Barker M, Dombrowski SU, Colbourn T, *et al*. Intervention strategies to improve nutrition and health behaviours before conception. *Lancet* 2018;391:1853–64.
23 Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
24 Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
25 Eldridge S, Campbell M, Campbell M. Revised Cochrane risk of bias tool for randomized trials (rob 2); additional considerations for cluster-randomized trials (rob 2 crt), 2020. Available: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/rob-2-for-cluster-randomized-trials?authuser=0
26 McGuinness LA, Higgins JPT. Risk-of-bias visualization (robvis): an R package and shiny web APP for visualizing risk-of-bias assessments. *Res Synth Methods* 2021;12:55–61.
27 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
28 Higgins J, Thomas J, Chandler J. *Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated* September 2020). Cochrane, 2020. Available: www.training.cochrane.org/handbook
29 Evidence Prime. *GRADEpro GDT*. Hamilton, Ontario: : McMaster University (developed by Evidence Prime). Available: https://gradepro.org/ [Accessed 12 Oct 2020].
30 Sahariah SA, Potdar RD, Gandhi M, *et al*. A daily snack containing leafy green vegetables, fruit, and milk before and during pregnancy prevents gestational diabetes in a randomized, controlled trial in Mumbai, India. *J Nutr* 2016;146:1453S–60.
31 Sun L, Niu Z. A mushroom diet reduced the risk of pregnancy-induced hypertension and macrosomia: a randomized clinical trial. *Food Nutr Res* 2020;64. doi:10.29219/fnr.v64.4451. [Epub ahead of print: 08 06 2020].
32 Kirke PN, Daly LE, Elwood JH. A randomised trial of low dose folic acid to prevent neural tube defects. The Irish vitamin Study Group. *Arch Dis Child* 1992;67:1442–6.
33 Hoffman RM, Brummel SS, Britto P, *et al*. Adverse pregnancy outcomes among women who Conceive on antiretroviral therapy. *Clin Infect Dis* 2019;68:273–9.
34 Lumley J, Donohue L. Aiming to increase birth weight: a randomised trial of pre-pregnancy information, advice and counselling in inner-urban Melbourne. *BMC Public Health* 2006;6:299.
35 Smithells RW, Sheppard S, Schorah CJ, *et al*. Apparent prevention of neural tube defects by periconceptional vitamin supplementation. *Arch Dis Child* 1981;56:911–8.
36 Kaandorp SP, Goddijn M, van der Post JAM, *et al*. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *N Engl J Med* 2010;362:1586–96.
37 Jourabchi Z, Sharif S, Lye MS, *et al*. Association between preconception care and birth outcomes. *Am J Health Promot* 2019;33:363–71.
38 Caan B, Horgen DM, Margen S, *et al*. Benefits associated with WIC supplemental feeding during the interpregnancy interval. *Am J Clin Nutr* 1987;45:29–41.
39 Berger J, Thanh HTK, Cavalli-Sforza T, *et al*. Community mobilization and social marketing to promote Weekly iron-folic acid supplementation in women of reproductive age in Vietnam: impact on anemia and iron status. *Nutr Rev* 2005;63:95–108.

40 Feig DS, Donovan LE, Corcoy R, *et al*. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet* 2017;390:2347–59.
41 Cooper WN, Khulan B, Owens S, *et al*. DNA methylation profiling at imprinted loci after periconceptional micronutrient supplementation in humans: results of a pilot randomized controlled trial. *Faseb J* 2012;26:1782–90.
42 Laurence KM, James N, Miller MH, *et al*. Double-Blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural-tube defects. *Br Med J* 1981;282:1509–11.
43 Nga HT, Quyen PN, Chaffee BW, *et al*. Effect of a nutrient-rich, food-based supplement given to rural Vietnamese mothers prior to and/or during pregnancy on birth outcomes: a randomized controlled trial. *PLoS One* 2020;15:e0232197.
44 Manandhar DS, Osrin D, Shrestha BP, *et al*. Effect of a participatory intervention with women's groups on birth outcomes in Nepal: cluster-randomised controlled trial. *Lancet* 2004;364:970–9.
45 Widasari L, Chalid MT, Jafar N, *et al*. Effects of multimicronutrient and IFA supplementation in preconception period against birth length and birth weight: a randomized, double blind controlled trial in banggai regency, central Sulawesi. *Indian J Public Health Res Dev* 2019;10:338–43.
46 Gies S, Diallo S, Roberts SA, *et al*. Effects of Weekly iron and folic acid supplements on malaria risk in nulliparous women in Burkina Faso: a periconceptional, double-blind, randomized controlled Noninferiority trial. *J Infect Dis* 2018;218:1099–109.
47 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;18:161.
48 Myers MF, Li S, Correa-Villaseñor A, *et al*. Folic acid supplementation and risk for imperforate anus in China. *Am J Epidemiol* 2001;154:1051–6.
49 Siklósi GS, Bánhidy FG, Ács N. Fundamental role of folliculo-luteal function in recurrent miscarriage. *Arch Gynecol Obstet* 2012;286:1299–305.
50 Smithells RW, Nevin NC, Seller MJ, *et al*. Further experience of vitamin supplementation for prevention of neural tube defect recurrences. *Lancet* 1983;1:1027–31.
51 de Jong-Potjer LC, Elsinga J, le Cessie S, *et al*. GP-initiated preconception counselling in a randomised controlled trial does not induce anxiety. *BMC Fam Pract* 2006;7:66.
52 Wehby GL, Félix TM, Goco N, *et al*. High dosage folic acid supplementation, oral cleft recurrence and fetal growth. *Int J Environ Res Public Health* 2013;10:590–605.
53 Czeizel AE, Dobó M, Vargha P. Hungarian cohort-controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital abnormalities. *Birth Defects Res A Clin Mol Teratol* 2004;70:853–61.
54 Baqui AH, Ahmed S, Begum N, *et al*. Impact of integrating a postpartum family planning program into a community-based maternal and newborn health program on birth spacing and preterm birth in rural Bangladesh. *J Glob Health* 2018;8:020406.
55 Livingood WC, Brady C, Pierce K, *et al*. Impact of pre-conception health care: evaluation of a social determinants focused intervention. *Matern Child Health J* 2010;14:382–91.
56 Nguyen PH, Young M, Gonzalez-Casanova I, *et al*. Impact of preconception micronutrient supplementation on anemia and iron status during pregnancy and postpartum: a randomized controlled trial in rural Vietnam. *PLoS One* 2016;11:e0167416.
57 Potdar RD, Sahariah SA, Gandhi M, *et al*. Improving women's diet quality preconceptionally and during gestation: effects on birth weight and prevalence of low birth weight--a randomized controlled efficacy trial in India (Mumbai Maternal Nutrition Project). *Am J Clin Nutr* 2014;100:1257–68.
58 Passerini L, Casey GJ, Biggs BA, *et al*. Increased birth weight associated with regular pre-pregnancy deworming and Weekly iron-folic acid supplementation for Vietnamese women. *PLoS Negl Trop Dis* 2012;6:e1608.
59 Andrews WW, Goldenberg RL, Hauth JC, *et al*. Interconceptional antibiotics to prevent spontaneous preterm birth: a randomized clinical trial. *Am J Obstet Gynecol* 2006;194:617–23.
60 Stephenson MD, Kutteh WH, Purkiss S, *et al*. Intravenous immunoglobulin and idiopathic secondary recurrent miscarriage: a multicentered randomized placebo-controlled trial. *Hum Reprod* 2010;25:2203–9.
61 Katz J, West KP, Khatry SK, *et al*. Maternal low-dose vitamin A or beta-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal. *Am J Clin Nutr* 2000;71:1570–6.
62 Cérbulo-Vázquez A, Arriaga-Pizano L, Cruz-Cureño G, *et al*. Medical outcomes in women who became pregnant after vaccination with a virus-like particle experimental vaccine against influenza A (H1N1) 2009 virus tested during 2009 pandemic outbreak. *Viruses* 2019;11. doi:10.3390/v11090868. [Epub ahead of print: 17 09 2019].
63 Sumarmi S, Wirjatmadi B, *et al*. Micronutrients supplementation during preconception period improves fetal survival and cord blood insulin-like growth factor 1. *Asian Journal of Clinical Nutrition* 2015;7:33–44.
64 Central Technical Co-ordinating Unit, ICMRCentral Technical Co-ordinating Unit, ICMR.. Multicentric study of efficacy of periconceptional folic acid containing vitamin supplementation in prevention of open neural tube defects from India. *Indian J Med Res* 2000;112:206–11.
65 Khambalia AZ, O'Connor DL, Macarthur C, *et al*. Periconceptional iron supplementation does not reduce anemia or improve iron status among pregnant women in rural Bangladesh. *Am J Clin Nutr* 2009;90:1295–302.
66 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;102:1450–9.
67 Christiansen OB, Mathiesen O, Husth M, *et al*. Placebo-Controlled trial of active immunization with third Party leukocytes in recurrent miscarriage. *Acta Obstet Gynecol Scand* 1994;73:261–8.
68 Angelo M-G, David M-P, Zima J, *et al*. Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. *Pharmacoepidemiol Drug Saf* 2014;23:466–79.
69 Schisterman EF, Silver RM, Lesher LL, *et al*. Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. *Lancet* 2014;384:29–36.
70 Banhidy F, DudaS I, Czeizel AE. Preconceptional screening of sexually transmitted infections/diseases. *Central European Journal of Medicine* 2010;6:49–57.
71 Makanani B, Balkus JE, Jiao Y, *et al*. Pregnancy and infant outcomes among women using the Dapivirine vaginal ring in early pregnancy. *J Acquir Immune Defic Syndr* 2018;79:566–72.
72 Garland SM, Ault KA, Gall SA, *et al*. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. *Obstet Gynecol* 2009;114:1179–88.
73 Hooker AB, de Leeuw RA, Twisk JWR, *et al*. Pregnancy and neonatal outcomes 42 months after application of hyaluronic acid gel following dilation and curettage for miscarriage in women who have experienced at least one previous curettage: follow-up of a randomized controlled trial. *Fertil Steril* 2020;114:601–9.
74 Mugo NR, Hong T, Celum C, *et al*. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. *JAMA* 2014;312:362–71.
75 Russu M, Stanculescu R, Nastasia S. Pregnancy outcomes following preconception, early and late administration of vaginal micronized progesterone for recurrent pregnancy loss. *Gineco.ro* 2009;5:10–15.
76 Czeizel AE, Dudás I, Métneki J. Pregnancy outcomes in a randomised controlled trial of periconceptional multivitamin supplementation. final report. *Arch Gynecol Obstet* 1994;255:131–9.
77 Taylor AW, Mosimaneotsile B, Mathebula U, *et al*. Pregnancy outcomes in HIV-infected women receiving long-term isoniazid prophylaxis for tuberculosis and antiretroviral therapy. *Infect Dis Obstet Gynecol* 2013;2013:1–5.
78 The Diabetes Control Complications Trial Research Group. Pregnancy outcomes in the diabetes control and complications trial. *Am J Obstet Gynecol* 1996;174:1343–53.
79 Theron G, Brummel S, Fairlie L, *et al*. Pregnancy outcomes of women Conceiving on antiretroviral therapy (art) compared to those commenced on art during pregnancy. *Clin Infect Dis* 2021;73:e312–20.
80 Hofmeyr GJ, 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;393:330–9.
81 Rönö K, Stach-Lempinen B, Eriksson JG, *et al*. Prevention of gestational diabetes with a prepregnancy lifestyle intervention - findings from a randomized controlled trial. *Int J Womens Health* 2018;10:493–501.

82 Chaouki ML, Benmiloud M. Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy. *Eur J Endocrinol* 1994;130:547–51.
83 MRC. Prevention of neural tube defects: results of the medical Research Council vitamin study. MRC vitamin study Research Group. *Lancet* 1991;338:131–7.
84 Berry RJ, Li Z, Erickson JD, *et al*. Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative project for neural tube defect prevention. *N Engl J Med* 1999;341:1485–90.
85 Chen G, Song X, Ji Y, *et al*. Prevention of NTDs with periconceptional multivitamin supplementation containing folic acid in China. *Birth Defects Res A Clin Mol Teratol* 2008;82:592–6.
86 Vergel RG, Sanchez LR, Heredero BL, *et al*. Primary prevention of neural tube defects with folic acid supplementation: Cuban experience. *Prenat Diagn* 1990;10:149–52.
87 Sumarmi S, Melaniani S, Kuntoro K. Prolonging micronutrients supplementation 2-6 months prior to pregnancy significantly improves birth weight by increasing hPL production and controlling IL-12 concentration: a randomized double blind controlled study. *Ann Nutr Metab* 2017;71:554.
88 Ismail AM, Hamed AH, Saso S, *et al*. Randomized controlled study of pre-conception thromboprophylaxis among patients with recurrent spontaneous abortion related to antiphospholipid syndrome. *Int J Gynaecol Obstet* 2016;132:219–23.
89 Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. *Am J Med Genet* 1996;62:179–83.
90 Wacholder S, Chen BE, Wilcox A, *et al*. Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials. *BMJ* 2010;340:c712.
91 Chen W, Zhao Y, Xie X, *et al*. Safety of a quadrivalent human papillomavirus vaccine in a Phase 3, randomized, double-blind, placebo-controlled clinical trial among Chinese women during 90 months of follow-up. *Vaccine* 2019;37:889–97.
92 Willhoite MB, Bennert HW, Palomaki GE, *et al*. The impact of preconception counseling on pregnancy outcomes. The experience of the Maine diabetes in pregnancy program. *Diabetes Care* 1993;16:450–5.
93 LeBlanc ES, Smith NX, Vesco KK, *et al*. Weight loss prior to pregnancy and subsequent gestational weight gain: Prepare, a randomized clinical trial. *Am J Obstet Gynecol* 2021;224:99.e1–99.e14.
94 Taneja S, Chowdhury R, Dhabhai N, *et al*. Impact of an integrated nutrition, health, water sanitation and hygiene, psychosocial care and support intervention package delivered during the pre- and peri-conception period and/or during pregnancy and early childhood on linear growth of infants in the first two years of life, birth outcomes and nutritional status of mothers: study protocol of a factorial, individually randomized controlled trial in India. *Trials* 2020;21:127.
95 De-Regil LM, Harding KB, Roche ML. Preconceptional nutrition interventions for adolescent girls and adult women: global guidelines and gaps in evidence and policy with emphasis on micronutrients. *J Nutr* 2016;146:1461S–70.
96 Chowdhury R, Taneja S, Dhabhai N, *et al*. Burden of preconception morbidity in women of reproductive age from an urban setting in North India. *PLoS One* 2020;15:e0234768.
97 Gunaratna NS, Masanja H, Mrema S, *et al*. Multivitamin and iron supplementation to prevent periconceptional anemia in rural Tanzanian women: a randomized, controlled trial. *PLoS One* 2015;10:e0121552.
98 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.
99 Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, *et al*. Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev* 2015:CD004736.
100 Gross K, Alba S, Glass TR, *et al*. Timing of antenatal care for adolescent and adult pregnant women in south-eastern Tanzania. *BMC Pregnancy Childbirth* 2012;12:16.
101 De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, *et al*. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. *Cochrane Database Syst Rev* 2015:CD007950.
102 Bailey LB, Stover PJ, McNulty H, *et al*. Biomarkers of nutrition for Development-Folate review. *J Nutr* 2015;145:1636S–80.
103 Patton GC, Sawyer SM, Santelli JS, *et al*. Our future: a Lancet Commission on adolescent health and wellbeing. *Lancet* 2016;387:2423–78.
104 Witt WP, Wisk LE, Cheng ER, *et al*. Preconception mental health predicts pregnancy complications and adverse birth outcomes: a national population-based study. *Matern Child Health J* 2012;16:1525–41.
105 Spry EA, Wilson CA, Middleton M, *et al*. Parental mental health before and during pregnancy and offspring birth outcomes: a 20-year preconception cohort of maternal and paternal exposure. *EClinicalMedicine* 2020;27:100564.
106 Ademas A, Adane M, Sisay T, *et al*. Does menstrual hygiene management and water, sanitation, and hygiene predict reproductive tract infections among reproductive women in urban areas in Ethiopia? *PLoS One* 2020;15:e0237696.
107 Lauer JM, Duggan CP, Ausman LM, *et al*. Biomarkers of maternal environmental enteric dysfunction are associated with shorter gestation and reduced length in newborn infants in Uganda. *Am J Clin Nutr* 2018;108:889–96.
108 Padhi BK, Baker KK, Dutta A, *et al*. Risk of adverse pregnancy outcomes among women practicing poor sanitation in rural India: a population-based prospective cohort study. *PLoS Med* 2015;12:e1001851.
109 Pope DP, Mishra V, Thompson L, *et al*. Risk of low birth weight and stillbirth associated with indoor air pollution from solid fuel use in developing countries. *Epidemiol Rev* 2010;32:70–81.
110 Ganchimeg T, Ota E, Morisaki N, *et al*. Pregnancy and childbirth outcomes among adolescent mothers: a world Health organization multicountry study. *BJOG* 2014;121 Suppl 1:40–8.
111 Ministry of Health and Family Welfare Bangladesh, World Health Organization, World Bank. Success Factors for Women's and Children's Health: Bangladesh, 2015. Available: https://www.who.int/pmnch/knowledge/publications/bangladesh.pdf [Accessed 18 Dec 2021].
112 Rahman A, Rahman M, Pervin J, *et al*. Time trends and sociodemographic determinants of preterm births in pregnancy cohorts in Matlab, Bangladesh, 1990-2014. *BMJ Glob Health* 2019;4:e001462.
113 Lassi ZS, Moin A, Das JK, *et al*. Systematic review on evidence-based adolescent nutrition interventions. *Ann N Y Acad Sci* 2017;1393:34–50.
114 Bongaarts J, Mensch BS, Blanc AK. Trends in the age at reproductive transitions in the developing world: the role of education. *Popul Stud* 2017;71:139–54.
115 Lee ACC, Katz J, Blencowe H. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *Lancet Glob Health* 2013;1:e26–36.

Supplemental Appendix. Preconception interventions to prevent low birth weight, preterm birth and small for gestational age – a systematic review and meta-analysis

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1. Preconception interventions to prevent low birth weight, preterm birth and small for gestational age: Search strategy

(All searches run on 28 Nov 2020)

1.1. PubMed

1.1A. Combined search

Preconception + study type + LBW: ((1 AND 9) NOT 8) AND 2D = **2875 results**

1.1B. Search sub-blocks:

(1) **Preconception**

"preconception*"[tiab] OR "pre-conception*"[tiab] OR "periconception*"[tiab] OR "peri-conception*"[tiab] OR "conception*"[tiab] OR "pre-pregnancy"[tiab] OR "prepregnancy"[tiab] OR "pre pregnancy"[tiab] OR "before-pregnancy"[tiab] OR "before pregnancy"[tiab] OR "prior to pregnancy"[tiab] OR "pre-gestation"[tiab] OR "pre gestation"[tiab] OR "inter-pregnancy"[tiab] OR "inter pregnancy"[tiab] OR "inter-gestation"[tiab] OR "inter gestation"[tiab] OR "between pregnancy"[tiab] OR "between-pregnancy"[tiab] OR "interconception"[tiab] OR "inter-conception"[tiab] OR "inter conception"[tiab] OR "adolescen*"[tiab] OR "teenage*"[tiab]

Results: 375,166 on 28 Nov 2020

(2) Outcomes

"low birth weight"[tiab] OR "low birthweight"[tiab] OR "low-birthweight"[tiab] OR "LBW"[tiab] OR "birth weight"[tiab] OR "birthweight"[tiab] OR "weight at birth"[tiab] OR "preterm"[tiab] OR "pre-term"[tiab] OR "prematur*" OR "pre-matur*"[tiab] OR "PPROM"[tiab] OR "gestational age"[tiab] OR "gestational age at birth"[tiab] OR "fetal age"[tiab] OR "small for gestational age"[tiab] OR "small-for-gestational-age"[tiab] OR "small-for-gestational age"[tiab] OR "SGA"[tiab] OR "weight for gestational age"[tiab] OR "weight-for-gestational-age"[tiab] OR "weight-for-gestational age"[tiab] OR "birthweight for gestational age"[tiab] OR "birthweight-for-gestational-age"[tiab] OR "birthweight-for-gestational age"[tiab] OR ("weight"[tiab] AND "gestational age"[tiab]) OR ("birthweight"[tiab] AND "gestational age"[tiab]) OR ("birth-weight"[tiab] AND "gestational age"[tiab]) OR "intrauterine growth retardation"[tiab] OR "intra-uterine growth retardation"[tiab] OR "intrauterine growth restriction"[tiab] OR "intra-uterine growth restriction"[tiab] OR "IUGR"[tiab] OR "fetal growth retardation"[tiab] OR "fetal growth restriction"[tiab] OR "FGR"[tiab] OR "Infant, Low Birth Weight"[mh] OR "Birth Weight"[mh] OR "Premature Birth"[mh] OR "Fetal Membranes, Premature Rupture"[mh] OR "Gestational Age"[mh] OR "Infant, Small for Gestational Age"[mh] OR "Fetal Growth Retardation"[mh] OR (("maternal"[tiab] OR "mother*"[tiab] OR "pregnan*"[tiab]) AND ("underweight"[tiab] OR "under-weight"[tiab] OR "thin*"[tiab] OR "overweight"[tiab] OR "over-weight"[tiab] OR "obes*"[tiab] OR "undernourish*"[tiab] OR "under-nourish*"[tiab] OR "malnourish*"[tiab] OR "mal-nourish*"[tiab] OR "malnutrition"[tiab] OR "mal-nutrition"[tiab] OR "body mass index"[tiab] OR "body-mass index"[tiab] OR "BMI"[tiab] OR "body mass"[tiab] OR "anthropometr*"[tiab] OR "anaem*"[tiab] OR "anem*"[tiab] OR "haemoglobin"[tiab] OR "hemoglobin"[tiab] OR "Hb"[tiab] OR "deficien*"[tiab] OR "iron"[tiab] OR "hypertens*"[tiab] OR "blood pressure*"[tiab] OR "systolic"[tiab] OR "diastolic"[tiab] OR "SBP"[tiab] OR "DBP"[tiab] OR "proteinuria"[tiab] OR "diabet*"[tiab] OR "prediabet*"[tiab] OR "hyperglycemi*"[tiab] OR "dysglycemi*"[tiab] OR "blood glucose"[tiab] OR "fasting glucose"[tiab] OR "IGT"[tiab] OR "IFG"[tiab] OR "HbA1c"[tiab] OR "glycated hemoglobin"[tiab] OR "glycated haemoglobin"[tiab] OR "glucose tolerance"[tiab] OR "glucose intolerance"[tiab] OR "insulin"[tiab] OR "hyperinsulinaemia"[tiab] OR "hyperinsulinemia"[tiab])) OR "gestational hypertension"[tiab] OR "pre-eclampsia"[tiab] OR "preeclampsia"[tiab] OR "pre eclampsia"[tiab] OR "pregnancy-induced hypertension"[tiab] OR "pregnancy induced hypertension"[tiab] OR "gestational diabetes"[tiab] OR "stillbirth"[tiab] OR "still birth"[tiab] OR "still-birth"[tiab] OR "birth defect*"[tiab] OR "perinatal

mortality"[tiab] OR "peri natal mortality"[tiab] OR "peri-natal mortality"[tiab] OR "large for gestational age"[tiab] OR "large-for-gestational-age"[tiab] OR "large-for-gestational age"[tiab] OR "LGA"[tiab]

Results: 517,610 on 28 Nov 2020

Sub-blocks 8 and 9. Inclusions and exclusions based on study type, in order to focus the search.

(8) **Exclusions**
(Address[ptyp] OR Autobiography[ptyp] OR Bibliography[ptyp] OR Biography[ptyp] OR pubmed books[filter] OR Case Reports[ptyp] OR Congress[ptyp] OR Consensus Development Conference[ptyp] OR Directory[ptyp] OR Duplicate Publication[ptyp] OR Editorial[ptyp] OR Festschrift[ptyp] OR Guideline[ptyp] OR Interview[ptyp] OR Lecture[ptyp] OR Legal Case[ptyp] OR News[ptyp] OR Newspaper Article[ptyp] OR Personal Narrative[ptyp] OR Portrait[ptyp] OR Retracted Publication[ptyp] OR Twin Study[ptyp] OR Video-Audio Media[ptyp])

Results: 3,323,471 on 28 Nov 2020

(9) **Inclusions for study type**. Based on the Cochrane sensitivity- and precision-maximising search for RCTs, and adding in the following possible study types: Clinical Study, Clinical Trial, Evaluation Study, Meta-Analysis, Pragmatic Clinical Trial, Preprint, Randomized Controlled Trial, Review, Systematic Review)
(randomized controlled trial[pt] OR controlled clinical trial[pt] OR Clinical Study[pt] OR Clinical Trial[pt] OR Meta-Analysis[pt] OR Pragmatic Clinical Trial[pt] OR Preprint[pt] OR Evaluation Study[pt] OR Systematic Review[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))

Results: 1,879,320 on 28 Nov 2020

1.2. Embase

1.2A. Combined search

Search A: 1 and 2: **42 396 results**

Search B: limit A to (human and embase and (meta analysis or "systematic review" or clinical trial or randomized controlled trial or controlled clinical trial or multicenter study) and (article or article in press) and journal): **1260 results**

1.2B. Search sub-blocks

(1) **Preconception**

preconception*.ab,ti OR pre-conception*.ab,ti OR periconception*.ab,ti OR peri-conception*.ab,ti OR conception*.ab,ti OR pre-pregnancy.ab,ti OR prepregnancy.ab,ti OR pre pregnancy.ab,ti OR before-pregnancy.ab,ti OR before pregnancy.ab,ti OR prior to pregnancy.ab,ti OR pre-gestation.ab,ti OR pre gestation.ab,ti OR inter-pregnancy.ab,ti OR inter pregnancy.ab,ti OR inter-gestation.ab,ti OR inter gestation.ab,ti OR between pregnancy.ab,ti OR between-pregnancy.ab,ti OR interconception.ab,ti OR inter-conception.ab,ti OR inter conception.ab,ti OR adolescen*.ab,ti OR teenage*.ab,ti

Results: 456,304 (map term to subject heading on) on 28 Nov 2020

(2) **Low birth weight, small for gestational age, preterm birth**

low birth weight.ab,ti OR low birthweight.ab,ti OR low-birthweight.ab,ti OR LBW.ab,ti OR birth weight.ab,ti OR birthweight.ab,ti OR weight at birth.ab,ti OR preterm.ab,ti OR pre-term.ab,ti OR prematur*.ab,ti OR pre-matur*.ab,ti OR PPROM.ab,ti OR gestational age.ab,ti OR gestational age at birth.ab,ti OR fetal age.ab,ti OR small for gestational age.ab,ti OR small-for-gestational-age.ab,ti OR small-for-gestational age.ab,ti OR SGA.ab,ti OR weight for gestational age.ab,ti OR weight-for-gestational-age.ab,ti OR weight-for-gestational age.ab,ti OR birthweight for gestational age.ab,ti OR birthweight-for-gestational-age.ab,ti OR birthweight-for-gestational age.ab,ti OR (weight adj25 gestational age).ab,ti OR (birthweight adj25 gestational age).ab,ti OR (birth-weight adj25 gestational age).ab,ti OR intrauterine growth retardation.ab,ti OR intra-uterine growth retardation.ab,ti OR intrauterine growth restriction.ab,ti OR intra-uterine growth restriction.ab,ti OR IUGR.ab,ti OR fetal growth retardation.ab,ti OR fetal growth restriction.ab,ti OR FGR.ab,ti OR ((maternal OR mother* OR pregnan*).ab,ti AND (underweight OR under-weight OR thin* OR overweight OR over-weight OR obes* OR undernourish* OR under-nourish* OR malnourish* OR mal-nourish* OR malnutrition OR mal-nutrition OR body mass index OR body-mass index OR BMI OR body mass OR anthropometr* OR anaem* OR anem* OR haemoglobin OR hemoglobin OR Hb OR deficien* OR iron OR hypertens* OR blood pressure* OR systolic OR diastolic OR SBP OR DBP OR proteinuria OR diabet* OR prediabet* OR hyperglycemi* OR dysglycemi* OR blood glucose OR fasting glucose OR IGT OR IFG OR HbA1c OR glycated hemoglobin OR glycated haemoglobin OR glucose tolerance OR glucose intolerance OR insulin OR hyperinsulinaemia OR hyperinsulinemia).ab,ti) OR gestational hypertension.ab,ti OR pre-eclampsia.ab,ti OR preeclampsia.ab,ti OR pre eclampsia.ab,ti OR pregnancy-induced hypertension.ab,ti OR pregnancy induced hypertension.ab,ti OR gestational diabetes.ab,ti OR stillbirth.ab,ti OR still birth.ab,ti OR still-birth.ab,ti OR birth defect*.ab,ti OR perinatal mortality.ab,ti OR peri natal mortality.ab,ti OR peri-natal mortality.ab,ti OR large for gestational age.ab,ti OR large-for-gestational-age.ab,ti OR large-for-gestational age.ab,ti OR LGA.ab,ti OR exp low birth weight/ OR exp birth weight/ OR exp premature fetus membrane rupture/ OR exp premature labor/ OR exp "immature and premature labor"/ OR exp small for date infant/ OR exp intrauterine growth retardation/ OR exp gestational age/

Results: 661,217 (map term to subject heading on) on 28 Nov 2020

1.3. Cochrane Library
(Also includes records from WHO ICTRP and ClinicalTrials.gov)

1.3A. Combined search

Overall search: 1 AND (2 OR 3), limits: Cochrane reviews or trials = 1245 results (101 reviews, 1144 trials)

1.3B. Search sub-blocks:

1 Preconception

Search in title, abstract, keyword: "preconception*" OR "pre-conception*" OR "periconception*" OR "peri-conception*" OR "conception*" OR "pre-pregnancy" OR "prepregnancy" OR "pre pregnancy" OR "before-pregnancy" OR "before pregnancy" OR "prior to pregnancy" OR "pre-gestation" OR "pre gestation" OR "inter-pregnancy" OR "inter pregnancy" OR "inter-gestation" OR "inter gestation" OR "between pregnancy" OR "between-pregnancy" OR "interconception" OR "inter-conception" OR "inter conception" OR "adolescen*" OR "teenage*"

Results: 3907 on 28 Nov 2020

2 Outcomes – non-MeSH terms

Search in title, abstract, keyword: "low birth weight" OR "low birthweight" OR "low-birthweight" OR "LBW" OR "birth weight" OR "birthweight" OR "weight at birth" OR "preterm" OR "pre-term" OR "prematur*" OR "pre-matur*" OR "PPROM" OR "gestational age" OR "gestational age at birth" OR "fetal age" OR "small for gestational age" OR "small-for-gestational-age" OR "small-for-gestational age" OR "SGA" OR "weight for gestational age" OR "weight-for-gestational-age" OR "weight-for-gestational age" OR "birthweight for gestational age" OR "birthweight-for-gestational-age" OR "birthweight-for-gestational age" OR ("weight" AND "gestational age") OR ("birthweight" AND "gestational age") OR ("birth-weight" AND "gestational age") OR "intrauterine growth retardation" OR "intra-uterine growth retardation" OR "intrauterine growth restriction" OR "intra-uterine growth restriction" OR "IUGR" OR "fetal growth retardation" OR "fetal growth restriction" OR "FGR" OR (("maternal" OR "mother*" OR "pregnan*") AND ("underweight" OR "under-weight" OR "thin*" OR "overweight" OR "over-weight" OR "obes*" OR "undernourish*" OR "under-nourish*" OR "malnourish*" OR "mal-nourish*" OR "malnutrition" OR "mal-nutrition" OR "body mass index" OR "body-mass index" OR "BMI" OR "body mass" OR "anthropometr*" OR "anaem*" OR "anem*" OR "haemoglobin" OR "hemoglobin" OR "Hb" OR "deficien*" OR "iron" OR "hypertens*" OR "blood pressure*" OR "systolic" OR "diastolic" OR "SBP" OR "DBP" OR "proteinuria" OR "diabet*" OR "prediabet*" OR "hyperglycemi*" OR "dysglycemi*" OR "blood glucose" OR "fasting glucose" OR "IGT" OR "IFG" OR "HbA1c" OR "glycated hemoglobin" OR "glycated haemoglobin" OR "glucose tolerance" OR "glucose intolerance" OR "insulin" OR "hyperinsulinaemia" OR "hyperinsulinemia")) OR "gestational hypertension" OR "pre-eclampsia" OR "preeclampsia" OR "pre eclampsia" OR "pregnancy-induced hypertension" OR "pregnancy induced hypertension" OR "gestational diabetes" OR "stillbirth" OR "still birth" OR "still-birth" OR "birth defect*" OR "perinatal mortality" OR "peri natal mortality" OR "peri-natal mortality" OR "large for gestational age" OR "large-for-gestational-age" OR "large-for-gestational age" OR "LGA" (title, abstract, keyword)

Results: 34,798 on 28 Nov 2020

3 Outcomes – MeSH terms

Entered directly in search box: mh "Infant, Low Birth Weight" OR mh "Birth Weight" OR mh "Premature Birth" OR mh "Fetal Membranes, Premature Rupture" OR mh "Gestational Age" OR mh "Infant, Small for Gestational Age" OR mh "Fetal Growth Retardation"

Results: 470 on 28 Nov 2020

1.4. WHO Global Index Medicus

1.4A. Combined search

(1 AND (2 OR 3 OR 4))) AND 5 = 857 results

1.4B. Search sub-blocks

(1) Preconception

preconception* OR pre-conception* OR periconception* OR peri-conception* OR conception* OR pre-pregnancy OR prepregnancy OR pre pregnancy OR before-pregnancy OR before pregnancy OR prior to pregnancy OR pre-gestation OR pre gestation OR inter-pregnancy OR inter pregnancy OR inter-gestation OR inter gestation OR between pregnancy OR between-pregnancy OR interconception OR inter-conception OR inter conception OR adolescen* OR teenage* **(title, abstract, subject)**

Results: 1,404,188 28 Nov 2020

(2) Outcomes – LBW

low birth weight OR low birthweight OR low-birthweight OR LBW OR birth weight OR birthweight OR weight at birth OR preterm OR pre-term OR prematur* OR pre-matur* OR PPROM OR gestational age OR gestational age at birth OR fetal age OR small for gestational age OR small-for-gestational-age OR small-for-gestational age OR SGA OR weight for gestational age OR weight-for-gestational-age OR weight-for-gestational age OR birthweight for gestational age OR birthweight-for-gestational-age OR birthweight-for-gestational age OR (weight AND gestational age) OR (birthweight AND gestational age) OR (birth-weight AND gestational age) OR intrauterine growth retardation OR intra-uterine growth retardation OR intrauterine growth restriction OR intra-uterine growth restriction OR IUGR OR fetal growth retardation OR fetal growth restriction OR FGR **(title, abstract, subject)**

Results: 259 on 28 Nov 2020

(3) Outcomes – maternal 1

(maternal OR mother* OR pregnan*) AND (underweight OR under-weight OR thin* OR overweight OR over-weight OR obes* OR undernourish* OR under-nourish* OR malnourish* OR mal-nourish* OR malnutrition OR mal-nutrition OR body mass index OR body-mass index OR BMI OR body mass OR anthropometr* OR anaem* OR anem* OR haemoglobin OR hemoglobin OR Hb OR deficien* OR iron OR hypertens* OR blood pressure* OR systolic OR diastolic OR SBP OR DBP OR proteinuria OR diabet* OR prediabet* OR hyperglycemi* OR dysglycemi* OR blood glucose OR fasting glucose OR IGT OR IFG OR HbA1c OR glycated hemoglobin OR glycated haemoglobin OR glucose tolerance OR glucose intolerance OR insulin OR hyperinsulinaemia OR hyperinsulinemia) **(title, abstract, subject)**

Results: 4252 on 28 Nov 2020

(4) Outcomes – maternal 2 and other adverse outcomes

gestational hypertension OR pre-eclampsia OR preeclampsia OR pre eclampsia OR pregnancy-induced hypertension OR pregnancy induced hypertension OR gestational diabetes OR stillbirth OR still birth OR still-birth OR birth defect* OR perinatal mortality OR peri natal mortality OR peri-natal mortality OR large for gestational age OR large-for-gestational-age OR large-for-gestational age OR LGA **(title, abstract, subject)**

Results: 127 on 28 Nov 2020

(5) Key words for study type

"trial" OR "randomized" OR "randomised" OR "intervention" OR "review" OR "meta-analysis"

2. Preconception interventions to prevent low birth weight, preterm birth and small for gestational age: Additional details regarding data analysis

Use of estimates from studies

- Where studies reported median and interquartile range, estimates were approximated to mean and standard error in accordance with the Cochrane Handbook (Chapter 6.5.2.5).[1]
- Where two intervention or comparator groups were combined for the purposes of consistent comparisons, these were done in accordance with the Cochrane Handbook (Chapter 6.5.2.10).[1]
- For studies where the standard deviation or standard error for a continuous measure was reported to be 0 for any intervention or comparator group, the corresponding statistic for another group was used.
- Where studies reported risk ratios, the adjusted estimate was included in analyses. Where only categorical cell counts were reported, crude risk ratios were calculated. If odds ratios were reported, these were converted to risk ratios in accordance with the Cochrane Handbook (Chapter 15.4.4.4),[1] using the proportion of outcomes in the comparator group as the assumed comparator risk. If information on the proportion of outcomes in the comparator group was missing and could not be retrieved, the odds ratio was not included in meta-analysis and was reported separately.
- If studies did not report risk ratios and reported no outcomes in one or more groups, an approximate estimate for the risk ratio was calculated by adding 0.5 to each empty cell (Cochrane Handbook Chapter 10.4.4.1).[1] If studies reported no outcomes in both groups, the estimate was noted, but not included as part of meta-analyses (Cochrane Handbook Chapter 10.4.4.2).[1]
- For cluster-randomized trials or clustered studies, cluster-adjusted effect estimates as reported by the study or calculated independently were combined with other outcome data. If these were not available, to account for clustering, we contacted study authors for relevant data (e.g. number of clusters and ICC) to estimate the effective sample size or adjust estimates' standard errors (Cochrane Handbook Chapter 23.1.5).[1] If no information was forthcoming, we adjusted estimates assuming a design effect of 2, in line with previous reports on child health indicators.[2]

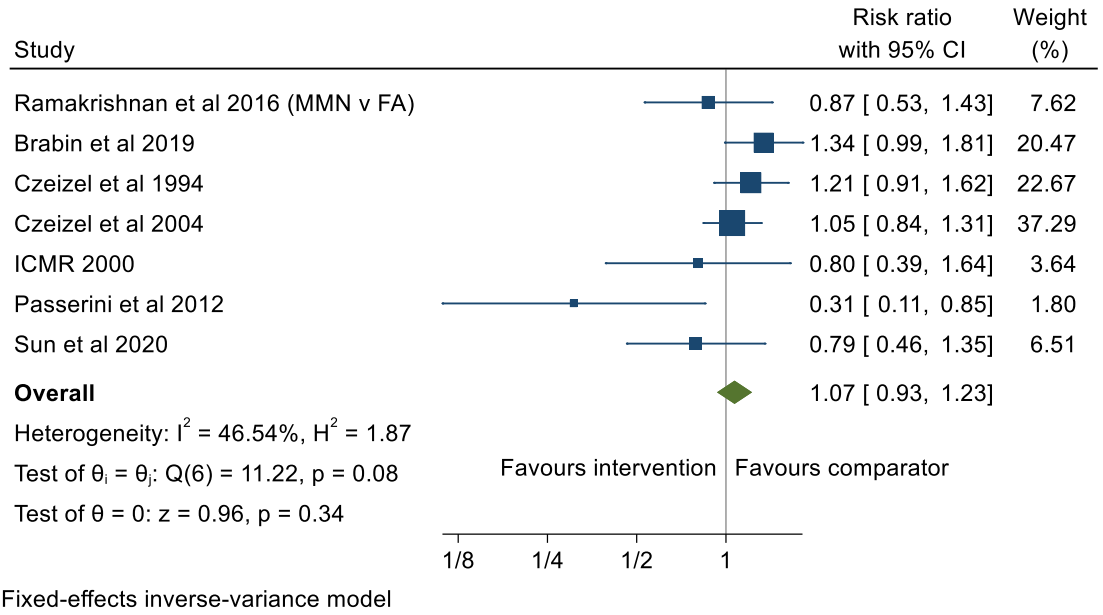
Synthesis of effect estimates

Where appropriate, similar intervention and comparator groups were combined for the purposes of meta-analysis, following procedures outlined in the Cochrane Handbook (Chapter 6.5.2.10);[1] disaggregated estimates were also noted and summarized. Where multiple similar outcomes from the same studies were reported (for example, distinct birth defects), we used the measure most consistent with other studies included in meta-analysis, and described any other measures.

3. Preconception interventions to prevent low birth weight, preterm birth and small for gestational age: Meta-analyses for primary outcomes

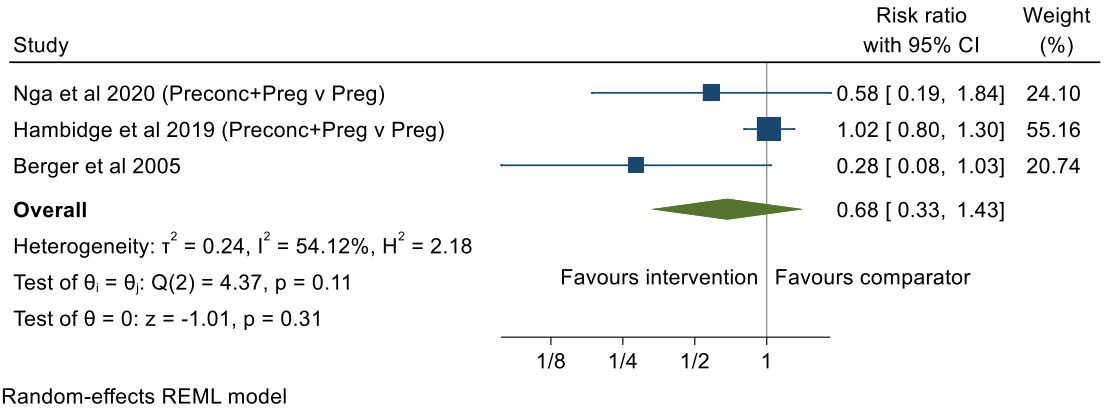
3.1. Low birth weight

3.1A. Interventions in nutrition - overall



Supplementary Figure 1. Meta-analysis of reported estimates: any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), standard or routine care, or no intervention to prevent low birth weight.

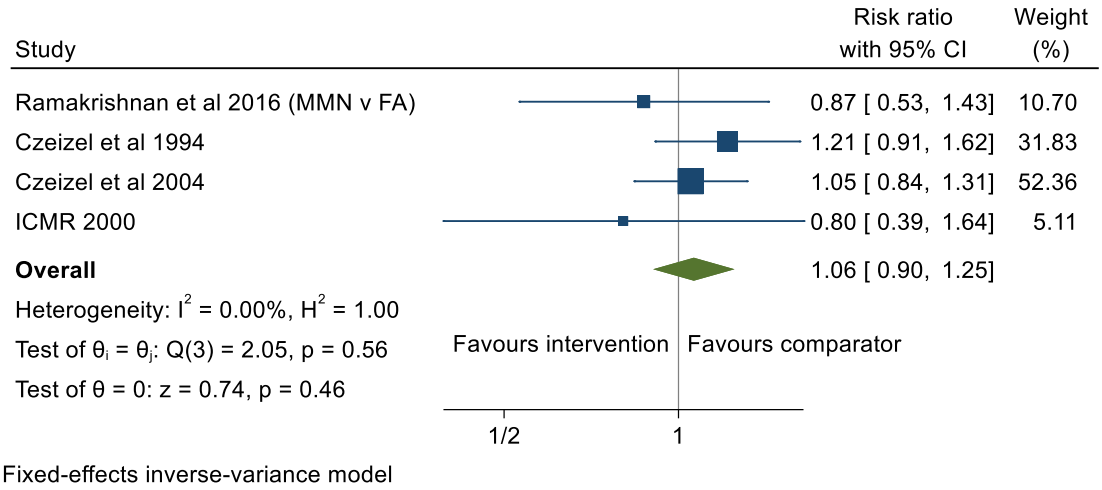
7 studies, N=13,973: Ramakrishnan et al 2016 (MMN supplementation v FA supplementation) [3], Czeizel et al 1994 (MMN supplementation v supplement containing only copper, manganese, zinc and Vitamin C) [4], Czeizel et al 2004 (MMN supplementation v no supplementation) [5], ICMR 2000 (MMN supplementation v supplement containing only iron and calcium; population: women with previous birth with neural tube defect) [6], Brabin et al 2019 (IFA supplementation v FA supplementation) [7], Passerini et al 2012 (IFA supplementation with deworming v no supplementation or deworming) [8], and Sun et al 2020 (100g mushroom daily v standard or routine care [normal diet]) [9].



Supplementary Figure 2. Meta-analysis of reported estimates: any general population-based nutritional intervention from preconception throughout pregnancy compared with pregnancy-only intervention to prevent low birth weight.

3 studies, N=1334: Berger et al 2005 (preconception throughout pregnancy IFA supplementation v pregnancy-only supplementation) [10], Nga et al 2020 (preconception throughout pregnancy food supplement containing dark-green leafy vegetables and animal source foods v pregnancy-only supplementation) [11], Hambidge et al 2019 (preconception throughout pregnancy Nutriset [and additional lipid-based protein energy supplement for women with BMI <20 kg/m^2 or gestational weight gain <Institute of Medicine recommendations] v pregnancy-only supplementation) [12].

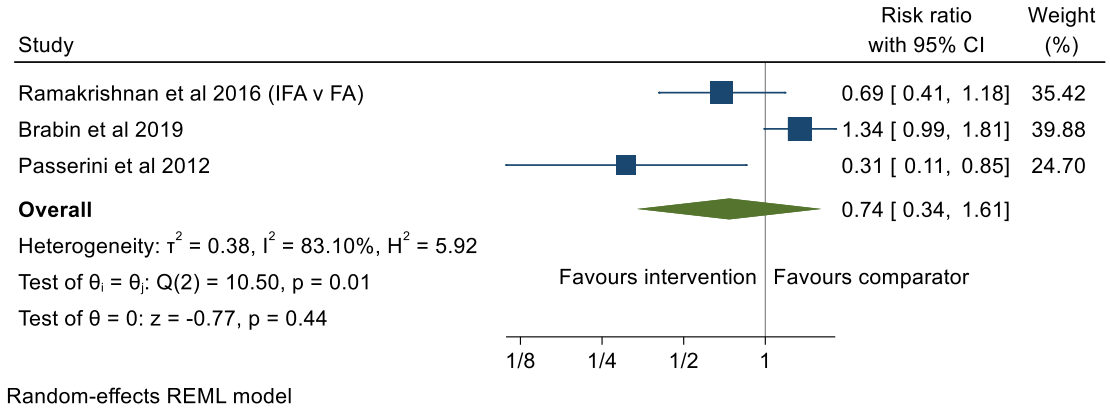
3.1B. Multiple micronutrient supplementation including IFA



Supplementary Figure 3. Meta-analysis of reported estimates: pre- and periconception MMN including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), or no intervention to prevent low birth weight.

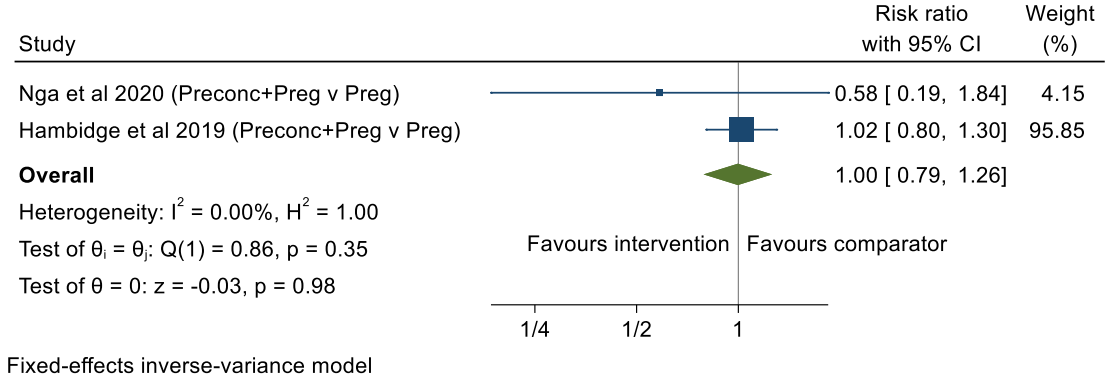
4 studies, N=12,054: Ramakrishnan et al 2016 (MMN supplementation v FA supplementation) [3], Czeizel et al 1994 (MMN supplementation v supplement containing only copper, manganese, zinc and Vitamin C) [4], Czeizel et al 2004 (MMN supplementation v no supplementation) [5], ICMR 2000 (MMN supplementation v supplement containing only iron and calcium; population: women with previous birth with neural tube defect) [6].

3.1C. Iron and folic acid supplementation

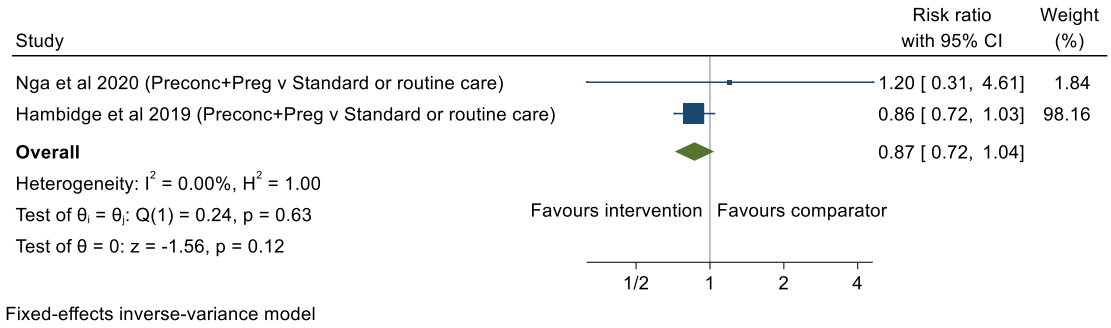


Supplementary Figure 4. Meta-analysis of reported estimates: pre- and periconception IFA supplementation versus pre- and periconception FA supplementation or no intervention to prevent low birth weight.
3 studies, N=1831: Brabin et al 2019 (IFA supplementation v FA supplementation) [7], Ramakrishnan et al 2016 (IFA supplementation v FA supplementation) [3], Passerini et al 2012 (IFA supplementation with deworming v no supplementation or deworming) [8].

3.1D. Food supplementation



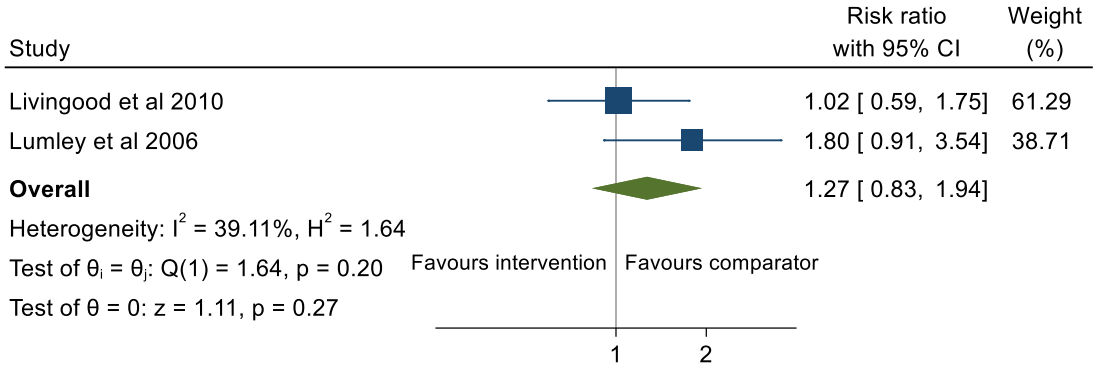
Supplementary Figure 5. Meta-analysis of reported estimates: preconception and pregnancy food supplementation versus pregnancy-only food supplementation to prevent low birth weight.
2 studies, N=1134: Nga et al 2020 (preconception throughout pregnancy food supplement containing dark-green leafy vegetables and animal source foods v pregnancy-only supplementation) [11], Hambidge et al 2019 (preconception throughout pregnancy Nutriset [and additional lipid-based protein energy supplement for women with BMI <20 kg/m^2 or gestational weight gain <Institute of Medicine recommendations] v pregnancy-only supplementation) [12].



Supplementary Figure 6. Meta-analysis of reported estimates: preconception and pregnancy food supplementation versus standard or routine care to prevent low birth weight.
2 studies, N=1078: Nga et al 2020 (preconception throughout pregnancy food supplement containing dark-green leafy vegetables and animal source foods v standard or routine care) [11], Hambidge et al 2019 (preconception throughout pregnancy Nutriset [and additional lipid-based protein energy supplement for women with BMI <20 kg/m^2 or gestational weight gain <Institute of Medicine recommendations] v standard or routine care) [12].

3.1E. General health interventions

General health interventions are those that provide care aiming to directly address aspects of preconception health. As examples, such interventions include preconception counseling, or a package of care comprising of services such as counseling, screening, vaccination, and linkage with appropriate clinical or community resources.

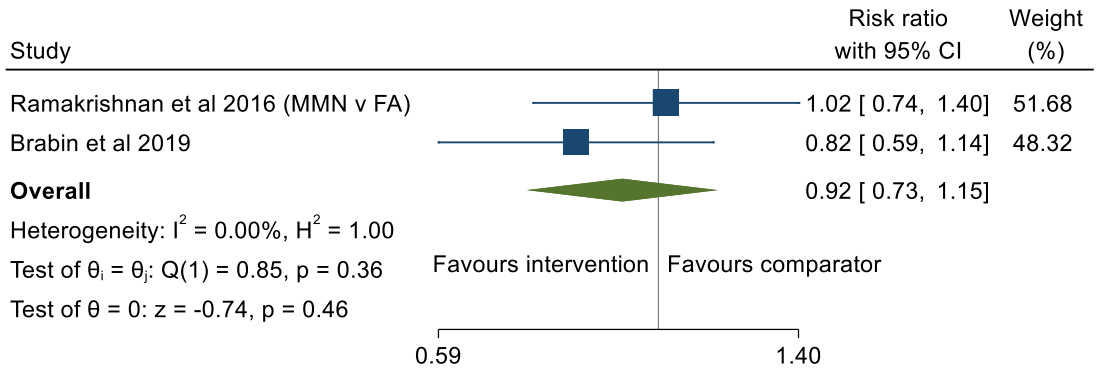


Supplementary Figure 7. Meta-analysis of reported estimates: pre- and periconception general health interventions versus pre- and periconception standard or routine care to prevent low birth weight.

2 studies, N=1188: Lumley et al 2006 (postpartum home visit offering comprehensive preconception care v standard or routine care; population: low income women) [13], Livingood et al 2010 (preconception care including goal plan to build resilience to negative social determinants v standard or routine care; population: low income women) [14].

3.2. Small for gestational age

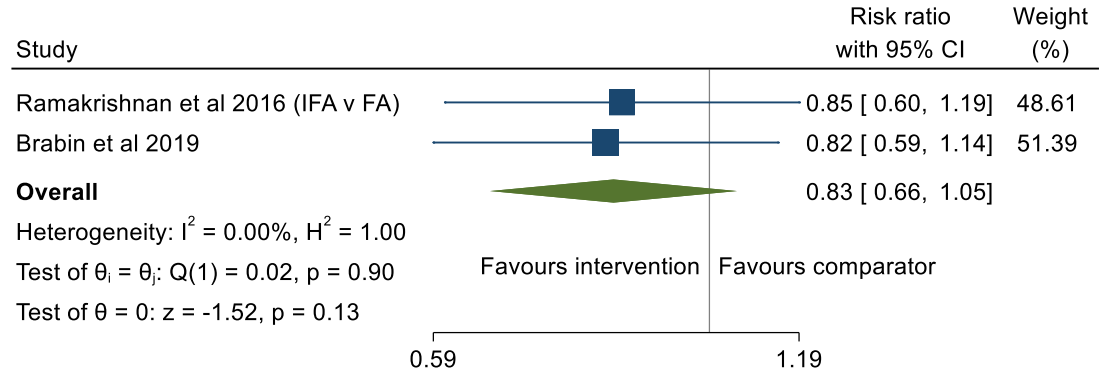
3.2A. Interventions in nutrition - overall



Supplementary Figure 8. Meta-analysis of reported estimates: any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation to prevent small for gestational age.

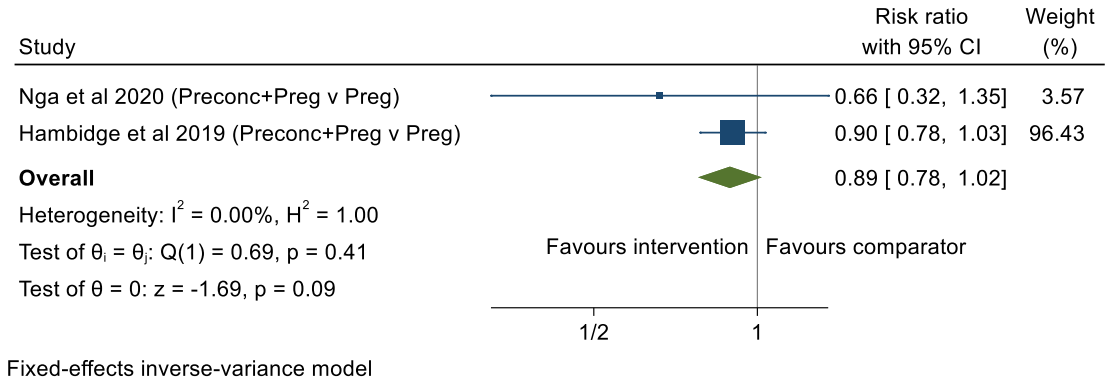
2 studies, N=1361: Ramakrishnan et al 2016 (MMN supplementation v FA supplementation) [3], Brabin et al 2019 (IFA supplementation v FA supplementation) [7].

3.2B Iron and folic acid supplementation

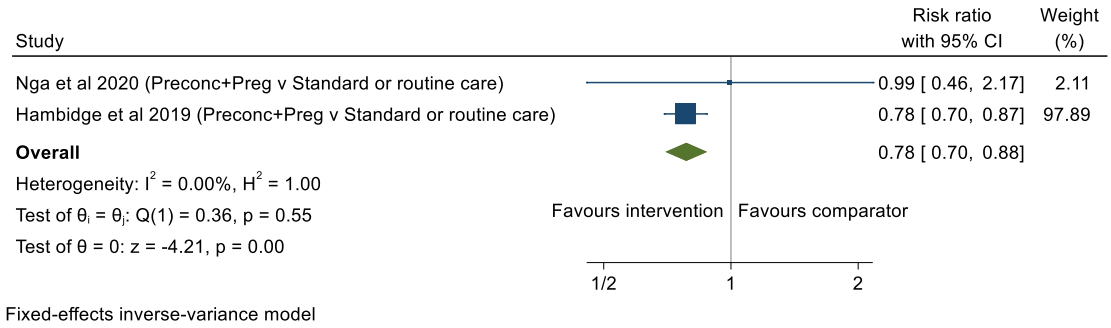


Supplementary Figure 9. Meta-analysis of reported estimates: pre- and periconception IFA supplementation versus pre- and periconception FA supplementation to prevent small for gestational age.
2 studies, N=1351: Brabin et al 2019 (IFA supplementation v FA supplementation) [7] and Ramakrishnan et al 2016 (IFA supplementation v FA supplementation) [3].

3.2C. Food supplementation



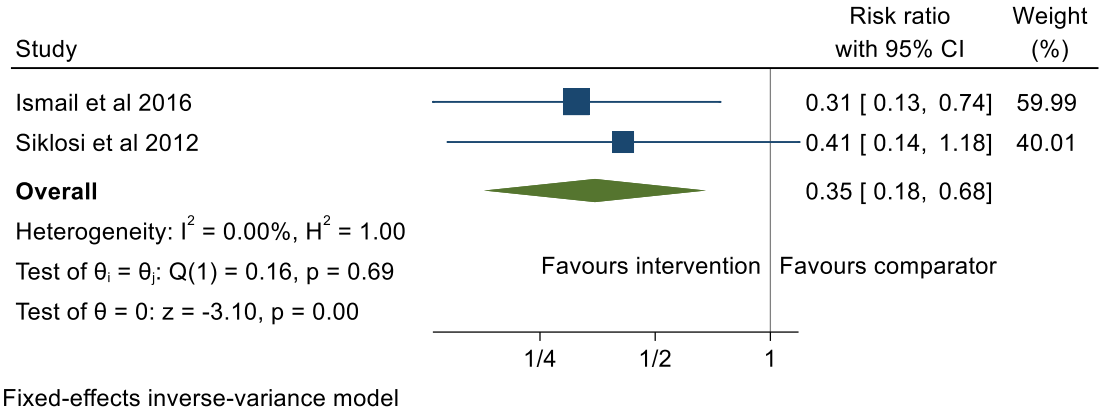
Supplementary Figure 10. Meta-analysis of reported estimates: preconception and pregnancy food supplementation versus pregnancy-only food supplementation to prevent small for gestational age.
2 studies, N=1161: Hambidge et al 2019 (preconception throughout pregnancy Nutriset [and additional lipid-based protein energy supplement for women with BMI <20 kg/m^2 or gestational weight gain <Institute of Medicine recommendations] v pregnancy-only supplementation) [12] and Nga et al 2020 (preconception throughout pregnancy food supplement containing dark-green leafy vegetables and animal source foods v pregnancy-only supplementation) [11].



Supplementary Figure 11. Meta-analysis of reported estimates: preconception and pregnancy food supplementation versus preconception and pregnancy standard or routine care to prevent small for gestational age.
2 studies, N=1108: Hambidge et al 2019 (preconception throughout pregnancy Nutriset [and additional lipid-based protein energy supplement for women with BMI <20 kg/m^2 or gestational weight gain <Institute of Medicine recommendations] v standard or routine care) and Nga et al 2020 (preconception throughout pregnancy food supplement containing dark-green leafy vegetables and animal source foods v standard or routine care).

3.2D. Interventions to prevent adverse outcomes in early pregnancy

Early adverse pregnancy outcome interventions include studies aiming primarily to prevent miscarriage or other early adverse outcomes in subsequent pregnancies in populations of women with at least one previous miscarriage.

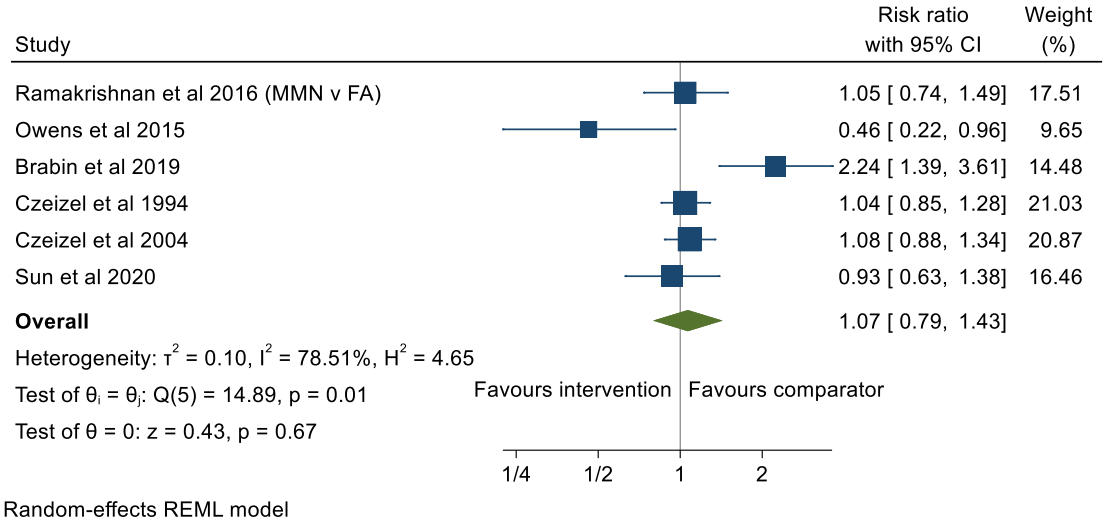


Supplementary Figure 12. Meta-analysis of reported estimates: pre- and periconception early adverse pregnancy outcome prevention interventions versus placebo to prevent small for gestational age.

2 studies, N=208: Ismail et al 2016 (oral aspirin + subcutaneous heparin v placebo; population: women with ≥2 previous miscarriages and antiphospholipid syndrome) [15] and Siklosi et al 2012 (clomiphene citrate v placebo; population: women with ≥3 previous miscarriages) [16].

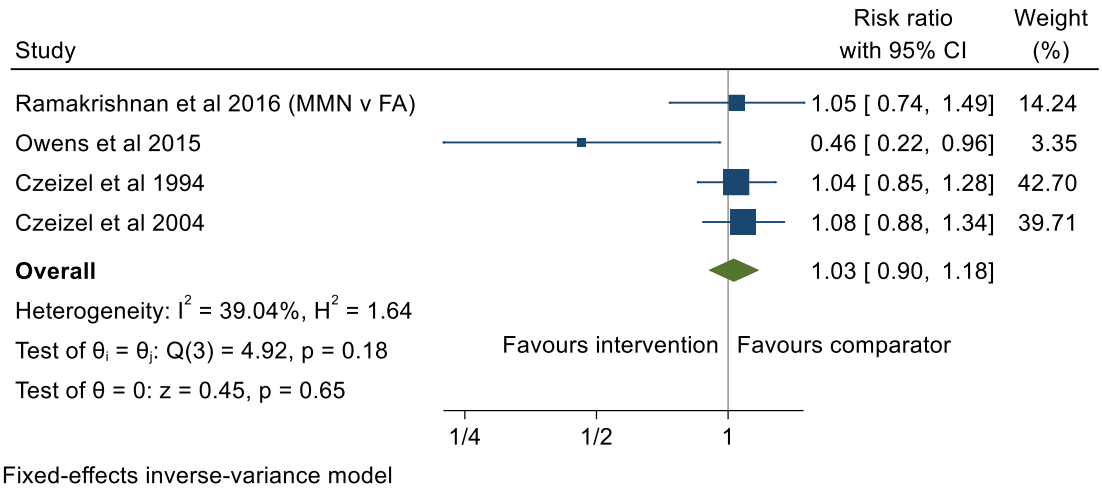
3.3. Preterm birth

3.3A. Interventions in nutrition – overall



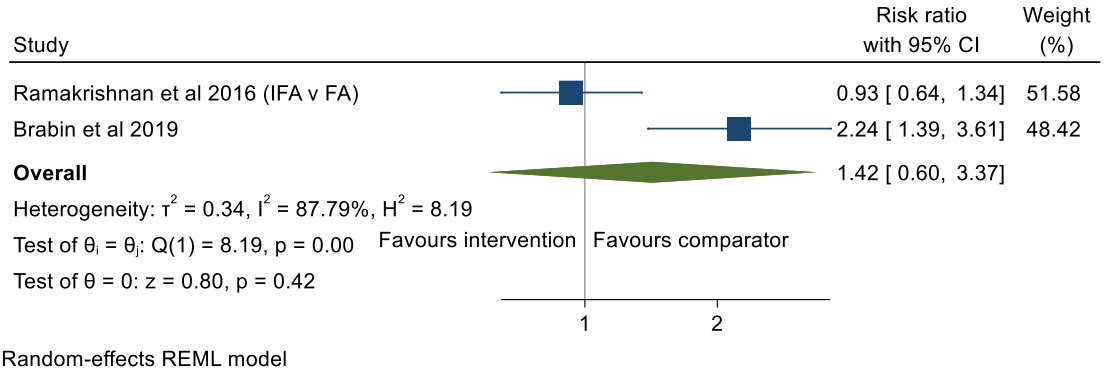
Supplementary Figure 13. Meta-analysis of reported estimates: any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), placebo, standard or routine care, or no intervention to prevent preterm birth.
6 studies, N=13,683: Ramakrishnan et al 2016 (MMN supplementation v FA supplementation) [3], Czeizel et al 1994 (MMN supplementation v supplement containing only copper, manganese, zinc and Vitamin C) [4], Czeizel et al 2004 (MMN supplementation v no supplementation) [5], Owens et al 2015 (MMN supplementation v placebo) [17], Brabin et al 2019 (IFA supplementation v FA supplementation) [7], Sun et al 2020 (100g mushroom daily v standard or routine care [normal diet]) [9].

3.3B. Multiple micronutrient supplementation including IFA



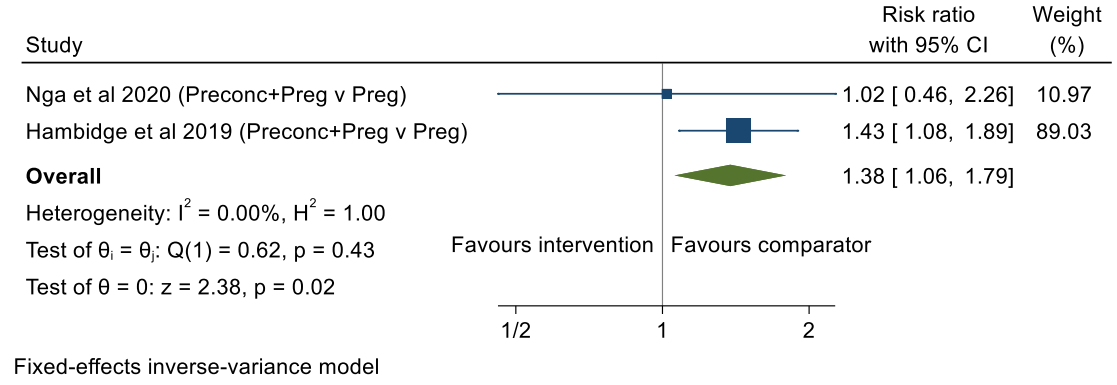
Supplementary Figure 14. Meta-analysis of reported estimates: pre- and periconception MMN supplementation including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), placebo or no intervention to prevent preterm birth.
4 studies, N=12,235: Ramakrishnan et al 2016 (MMN supplementation v FA supplementation) [3], Czeizel et al 1994 (MMN supplementation v supplement containing only copper, manganese, zinc and Vitamin C) [4], Czeizel et al 2004 (MMN supplementation v no supplementation) [5], Owens et al 2015 (MMN supplementation v placebo) [17].

3.3C. Iron and folic acid supplementation

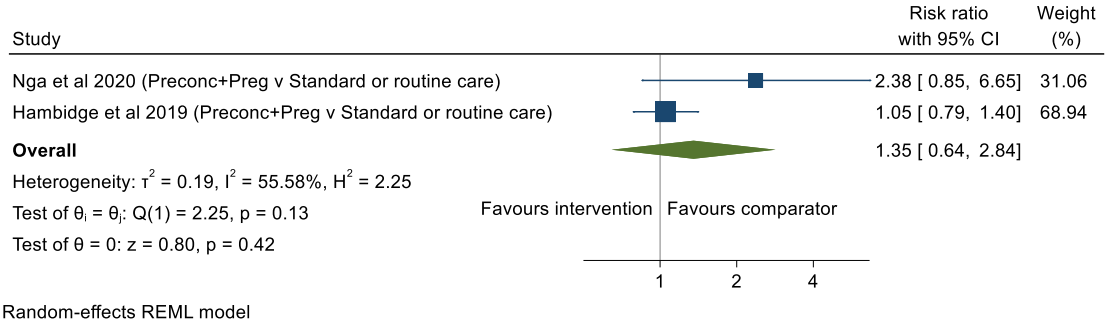


Supplementary Figure 15. Meta-analysis of reported estimates: pre- and periconception IFA supplementation versus pre- and periconception FA supplementation to prevent preterm birth.
2 studies, N=1360: Brabin et al 2019 (IFA supplementation v FA supplementation) [7], Ramakrishnan et al 2016 (IFA supplementation v FA supplementation) [3].

3.3D. Food supplementation



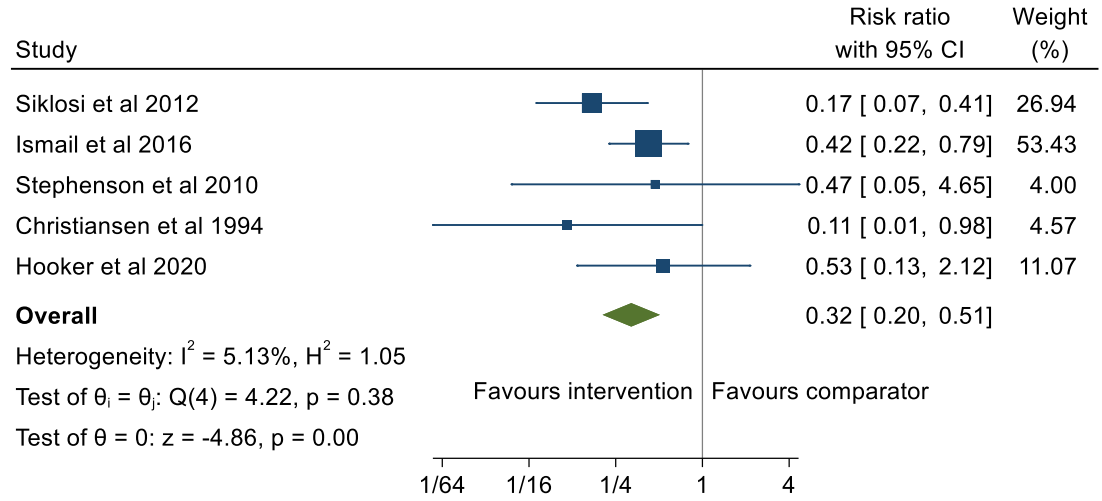
Supplementary Figure 16. Meta-analysis of reported estimates: preconception and pregnancy food supplementation versus pregnancy-only food supplementation to prevent preterm birth.
2 studies, N=1163: Nga et al 2020 (preconception throughout pregnancy food supplement containing dark-green leafy vegetables and animal source foods v pregnancy-only supplementation) [11], Hambidge et al 2019 (preconception throughout pregnancy Nutriset [and additional lipid-based protein energy supplement for women with BMI <20 kg/m^2 or gestational weight gain <Institute of Medicine recommendations] v pregnancy-only supplementation) [12].



Supplementary Figure 17. Meta-analysis of reported estimates: preconception and pregnancy food supplementation versus preconception and pregnancy standard or routine care to prevent preterm birth.
2 studies, N=1110: Nga et al 2020 (preconception throughout pregnancy food supplement containing dark-green leafy vegetables and animal source foods v standard or routine care) [11], Hambidge et al 2019 (preconception throughout pregnancy Nutriset [and additional lipid-based protein energy supplement for women with BMI <20 kg/m^2 or gestational weight gain <Institute of Medicine recommendations] v standard or routine care) [12].

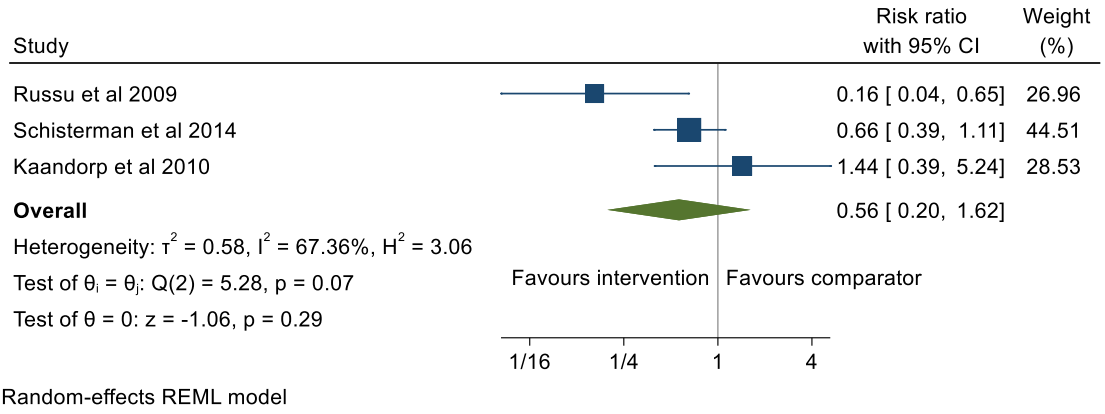
3.3E. Interventions to prevent adverse outcomes in early pregnancy

Early adverse pregnancy outcome interventions include studies aiming primarily to prevent miscarriage or other early adverse outcomes in subsequent pregnancies in populations of women with at least one previous miscarriage.



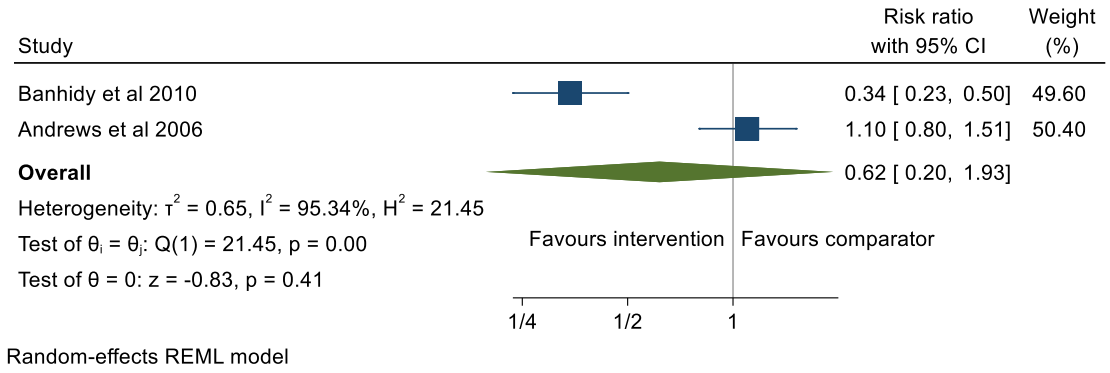
Supplementary Figure 18. Meta-analysis of reported estimates: pre- and periconception early adverse pregnancy outcome prevention interventions versus pre- and periconception placebo or no intervention to prevent preterm birth.

5 studies, N=382: Siklosi et al 2012 (clomiphene citrate v placebo; population: women with ≥3 previous miscarriages) [16], Ismail et al 2016 (oral aspirin + subcutaneous heparin v placebo; population: women with ≥2 previous miscarriages and antiphospholipid syndrome) [15], Hooker et al 2020 (intrauterine hyaluronic acid gel v no intervention following dilation and curettage; population: women with miscarriage undergoing dilation and curettage) [18], Stephenson et al 2010 (intravenous immunoglobulin v placebo [normal saline solution]; population: women with ≥3 consecutive previous miscarriages) [19], Christiansen et al 1994 (active immunization with third party leukocytes v placebo [participant's own blood, drawn immediately before transfusion]; population: women with ≥3 consecutive previous miscarriages) [20].



Supplementary Figure 19. Meta-analysis of reported estimates: preconception and pregnancy early adverse pregnancy outcome prevention interventions versus placebo and/or no intervention to prevent preterm birth.
3 studies, N=864: Russu et al 2009 (vaginal micronized progesterone v placebo [muscle relaxant]; population: women with 2 previous miscarriages) [21], Schisterman et al 2014 (oral aspirin v placebo; population: women with 1-2 previous miscarriages) [22], Kaandorp et al 2010 (oral aspirin or oral aspirin + subcutaneous heparin v placebo [for aspirin only]; population: women with ≥2 previous miscarriages) [23].

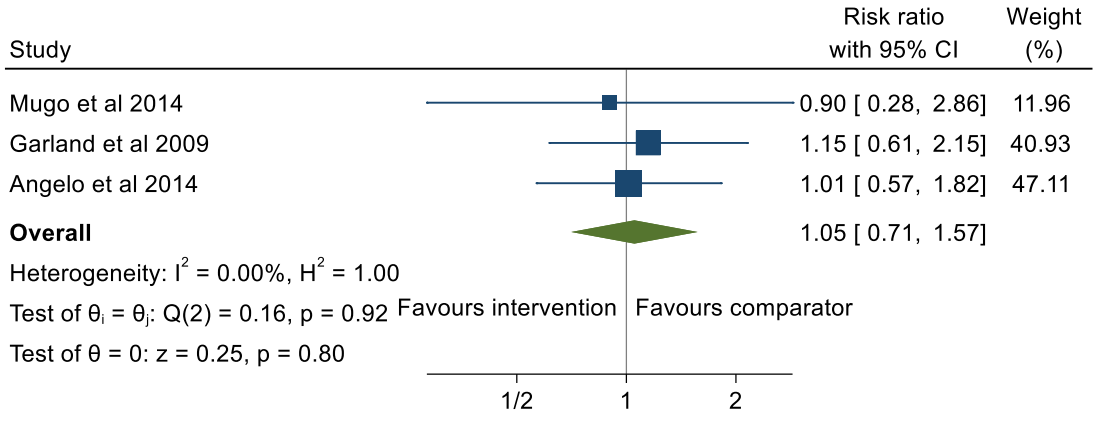
3.3F. Interventions to prevent or manage infectious diseases



Random-effects REML model

Infectious disease interventions include studies examining interventions to prevent infectious diseases in the preconception period (e.g. HIV prevention or HPV vaccination), and studies examining interventions to manage infectious diseases in preconception (e.g. HIV management with ART).

Supplementary Figure 20. Meta-analysis of reported estimates: pre- and periconception infectious disease interventions versus placebo or no intervention to prevent preterm birth.
2 studies, N=2275: Andrews et al 2006 (azithromycin + metronidazole v placebo; population: women with a previous spontaneous preterm birth) [24], Banhidy et al 2010 (treatment of sexually transmitted diseases and/or vaginal candidiasis v no treatment; population: women with sexually transmitted diseases or vaginal candidiasis) [25].
Risk ratio for Andrews et al if restricted to spontaneous preterm births only: 1.12 (95% CI: 0.76, 0.64) (27/52 babies in intervention group and 26/56 in comparator group born spontaneously preterm).



Fixed-effects inverse-variance model

Supplementary Figure 21. Meta-analysis of reported estimates: pre- and periconception infectious disease interventions versus pre- and periconception placebo or alternative intervention that may affect preterm birth.
4 studies, 3 included in meta-analyses (N=3666): Mugo et al 2014 (TDF+FTC or TDF v placebo; population: women with partners with HIV) [26], Garland et al 2009 (HPV vaccine [Gardasil] v placebo) [27], Angelo et al 2014 (HPV vaccine [Cervarix] v placebo or other vaccine) [28].

Makanani et al 2018 (dapivirine vaginal ring v placebo vaginal ring), N=181: reported separately as no preterm birth cases [29]: 0/87 preterm births among women assigned to use a dapivirine vaginal ring (HIV PreP) pre- and periconceptionally compared with 9/94 preterm births among women assigned to a placebo ring (calculated RR: 0.06 [95% CI: 0.00, 0.96]) (Makanani et al 2018) [29].

4. Preconception interventions to prevent low birth weight, preterm birth and small for gestational age: summary of estimates for all outcomes

	Supplementary Table 1. Summary of evidence from included studies – nutrition interventions for low birth weight.					
Period	**Any nutrition**	**MMN supplementation including IFA**	**IFA supplementation**	**FA supplementation**	**Food supplementation**	**Other nutritional**
Pre- + Periconc	7 studies, N=13,973[3–9] Comp: FA, other micronutrients (not FA), standard care, no int Popn: 1 study: previous NTD birth RR: 1.07 (95% CI: 0.93, 1.23), I^2: 46.54% **GRADE: Very low certainty**	4 studies, N=12,054[3–6] Comp: FA, other micronutrients (not FA), no int Popn: 1 study: previous NTD birth RR: 1.06 (95% CI: 0.90, 1.25), I^2: 0.00% **GRADE: Low certainty**	3 studies, N=1831[3,7,8] RR: 0.74 (95% CI: 0.34, 1.61), I^2: 83.10% Int: 1 study: IFA+deworming Comp: FA, no int **GRADE: Very low certainty**	No studies	1 study, N=529[30] 5-7 months v 0-2 months Popn: Low-income OR: 0.40 (95% CI: 0.14, 1.12) *(No case ns to calculate assumed comparator risk & RR)* **GRADE: Very low certainty**	(1) 1 study, N=507[31] Popn: previous pre-eclampsia Calcium supp v placebo RR: 1.00 (95% CI: 0.76, 1.30) (2) 1 study, N=1162[9] Mushroom in diet v standard care RR: 0.79 (95% CI: 0.46, 1.35)
Preconc + Preg v Preg only int	3 studies, N=1334[10–12] RR: 0.68 (95% CI: 0.33, 1.43), I^2: 54.12% **GRADE: Very low certainty**	No studies	1 study, N=200[10] RR: 0.28 (95% CI: 0.08, 1.03) **GRADE: Very low certainty**	No studies	2 studies, N=1134[11,12] RR: 1.00 (95% CI: 0.79, 1.26), I^2: 0.00% **GRADE: Very low certainty**	No studies
Preconc + Preg v Other (specified)	NA	1 study, N=108[32] Comp: Placebo (Preconc) and IFA (Preg) RR: 0.05 (95% CI: 0.00, 0.82)	No studies	No studies	(1) 1 study, N=1360[33] High v Low nutrition value snack (Preconc+Preg) RR: 0.89 (95% CI: 0.76, 1.03) (2) 2 studies, N=1078[11,12] Comp: Standard care (Preconc+Preg) RR: 0.87 (95% CI: 0.72, 1.04), I^2: 0.00	No studies

NTD: Neural tube defect, MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.
Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

Supplementary Table 2. Summary of evidence from included studies – health and social interventions for low birth weight.

	Health interventions				Social interventions
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**	**Reproductive planning**
Pre- + Periconc	2 studies, N=1188[13,14] Popn: Low income Int: Preconc health care Comp: Standard care RR: 1.27 (95% CI: 0.83, 1.94), I^2: 39.11% **GRADE: Very low certainty**	1 study, N=82[16] Popn: Previous miscarriage Clomiphene citrate v placebo RR: 0.23 (95% CI: 0.11, 0.51) **GRADE: Very low certainty**	No studies	1 study, N=39[34] H1N1 vaccine v placebo RR: 4.96 (95% CI: 0.27, 89.87) **GRADE: Very low certainty**	No studies
Preconc + Preg v Preg only int	No studies	No studies	1 study, N=149[35] Popn: T1DM Int: Intensive DM management RR: 4.34 (95% CI: 0.55, 34.34) **GRADE: Very low certainty**	1 study, N=186[36] Popn: HIV Int: Antiretroviral therapy RR: 2.65 (95% CI: 1.20, 5.81) **GRADE: Very low certainty**	No studies
Preconc + Preg v Other (specified)	1 study, N=349[37] Int: Integrated preconc and antenatal care Comp: Standard care (Preconc+Preg) RR: 0.44 (95% CI: 0.19, 0.97)	1 study, N=69[21] Popn: Previous miscarriage Int: Vaginal micronized progesterone Comp: Placebo (Preconc+Preg) RR: 0.09 (95% CI: 0.01, 0.65)	1 study, N=134[35] Popn: T1DM Int: Intensive DM management Preconc+Preg; 40 v 7 months Preconc RR: 1.60 (95% CI: 0.35, 7.37)	1 study, N=196[38] Popn: HIV Int: Isoniazid Comp: Placebo (Preconc+Preg), Outcome: Composite including LBW RR: 0.72 (95% CI: 0.43, 1.05)	No studies

DM: Diabetes mellitus, T1DM: Type 1 diabetes mellitus, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.
Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

	Supplementary Table 3. Summary of evidence from included studies – nutrition interventions for birth weight.					
Period	**Any nutrition**	**MMN supplementation including IFA**	**IFA supplementation**	**FA supplementation**	**Food supplementation**	**Other nutritional**
Pre- + Periconc	8 studies, N=15,040[3–5,7–9,39,40] Comp: FA, other micronutrients (not FA), standard care, placebo, no int MD: -13.98g (95% CI: -51.69, 23.74), I^2: 67.42%	4 studies, N=11,926[3–5,39] Comp: FA, other micronutrients (not FA), placebo, no int MD: -18.26g (95% CI: -62.15, 25.62), I^2: 74.28%	3 studies, N=1831[3,7,8] Int: 1 study: IFA+deworming Comp: FA, no int MD: 6.59g (95% CI: -116.54, 129.72), I^2: 81.09%	1 study, N=234[41] Popn: Oral cleft, previous oral cleft birth 4mg FA v 0.4 mg FA MD: -69g (SE: 62)	1 study, N=529[30] Popn: low-income 5-7 months v 0-2 months MD: 131g (SE: 43)	(1) 1 study, N=1195[40] Iodine supp v no supp MD: 200g (SE: 283) (2) 1 study, N=1162[9] Mushroom in diet v standard care MD: -4g (SE: 23) (3) 1 study, N=551[40] Iodine supp Preconc v Preg MD: 0g (SE: 283)
Preconc + Preg v Preg only int	3 studies, N=1971[10–12] MD: 7.03g (95% CI: -30.19, 44.25), I^2: 10.66%	No studies	1 study, N=200[10] MD: 81g (SE: 53)	No studies	2 studies, N=1771[11,12] MD: -3.76g (95% CI: -43.60, 36.08), I^2: 0.00%	No studies
Preconc + Preg v Other (specified)	NA	2 studies, N=127[32,42] Comp: Placebo (Preconc+Preg), Placebo (Preconc) and IFA (Preg) MD: 295.96g (95% CI: 158.55, 433.37), I^2: 0.00%	No studies	No studies	(1) 1 study, N=1360[33] High v Low nutrition value snack (Preconc+Preg) MD: 26g (SE: 21) (2) 2 studies, N=1745[11,12] Comp: Standard care (Preconc+Preg) MD: 41.86g (95% CI: 1.36, 82.37), I^2: 0.00	No studies

MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, MD: mean difference, 95% CI: 95% confidence interval, SE: standard error.
Yellow shaded cells indicate statistically notable results (95% CIs not overlapping 0) from meta-analyses.

Supplementary Table 4. Summary of evidence from included studies – health and social interventions for birth weight.

	Health interventions				Social interventions
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**	**Reproductive planning**
Pre- + Periconc	1 study, N=781[13] Popn: Low income Int: Preconc health care Comp: Standard care MD: -97g (SE: 36)	3 studies, N=269[15,18,20] Popn: Previous miscarriage, 1 study: APS Aspirin + heparin v placebo, Intrauterine hyaluronic acid gel v no int post D&C, Third party leukocytes transfusion v placebo MD: 279.46g (95% CI: -292.95, 851.87), I^2: 91.80%	1 study, N=157[43] Popn: T1DM or T2DM Counseling session for DM v standard care MD: 99g (SE: 139)	1 study, N=108[44] Popn: Previous PTB Azithromycin+Metronidazole v placebo MD: -418g (SE: 220)	No studies
Preconc + Preg v Preg only int	No studies	No studies	1 study, N=149[35] Popn: T1DM Int: Intensive DM management MD: 45g (SE: 112)	No studies	No studies
Preconc + Preg v Other (specified)	No studies	2 studies, N=664[21,22] Popn: Previous miscarriage Int: Aspirin, Vaginal micronized progesterone Comp: Placebo (Preconc+Preg) MD: 299.67g (95% CI: -294.28, 893.61), I^2: 93.75%	(1) 1 study, N=134[35] Popn: T1DM Int: Intensive DM management Preconc+Preg; 40 v 7 months Preconc MD: -21g (SE:126) (2) 1 study, N=25[45] Popn: T1DM Int: Continuous glucose monit Comp: Standard care (Preconc+Preg) MD: -327g (SE: 244) (3) 2 studies, N=289[46,47] Popn: Overweight/obese and/or previous GDM Int: Lifestyle change counseling Comp: Standard care (Preconc+Preg) MD: -81.15g (95% CI: -205.97, 43.67), I^2: 0.00%	No studies	No studies

DM: Diabetes mellitus, T1DM: Type 1 diabetes mellitus, T2DM: Type 2 diabetes mellitus, GDM: Gestational diabetes mellitus, APS: Antiphospholipid syndrome, D&C: Dilation and curettage, Continuous glucose monit: Continuous glucose monitoring, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care. MD: mean difference, 95% CI: 95% confidence interval, SE: standard error.

Yellow shaded cells indicate statistically notable results (95% CIs not overlapping 0) from meta-analyses.

	Supplementary Table 5. Summary of evidence from included studies – nutrition interventions for small for gestational age.					
Period	**Any nutrition**	**MMN supplementation including IFA**	**IFA supplementation**	**FA supplementation**	**Food supplementation**	**Other nutritional**
Pre- + Periconc	2 studies, N=1361[3,7] Comp: FA RR: 0.92 (95% CI: 0.73, 1.15), I^2: 0.00% **GRADE: Low certainty**	1 study, N=1084[3] Comp: FA RR: 1.02 (95% CI: 0.74, 1.40) **GRADE: Very low certainty**	2 studies, N=1351[3,7] Comp: FA RR: 0.83 (95% CI: 0.66, 1.05), I^2: 0.00% **GRADE: Low certainty**	No studies	No studies	No studies
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	2 studies, N=1161[11,12] RR: 0.89 (95% CI: 0.78, 1.02), I^2: 0.00% **GRADE: Low certainty**	No studies
Preconc + Preg v Other (specified)	NA	No studies	No studies	No studies	(1) 1 study, N=1360[33] High v Low nutrition value snack (Preconc+Preg) RR: 0.96 (95% CI: 0.88, 1.04) (2) 2 studies, N=1108[11,12] Comp: Standard care (Preconc+Preg) RR: 0.78 (95% CI: 0.70, 0.88), I^2: 0.00%	No studies

MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.

Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

Supplementary Table 6. Summary of evidence from included studies – health and social interventions for small for gestational age.

	Health interventions				Social interventions
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**	**Reproductive planning**
Pre- + Periconc	1 study, N=760[13] Popn: Low income Int: Preconc health care Comp: Standard care RR: 1.13 (95% CI: 0.57, 2.14) **GRADE: Very low certainty**	2 studies, N=208[15,16] Popn: Previous miscarriage, 1 study: APS Clomiphene citrate v placebo, Aspirin + heparin v placebo RR: 0.35 (95% CI: 0.18, 0.68), I^2: 0.00% **GRADE: Low certainty**	No studies	1 study, N=2871[27] HPV vaccine v placebo RR: 1.23 (95% CI: 0.33, 4.57) **GRADE: Very low certainty**	No studies
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	No studies	1 study, N=200[23] Popn: Previous miscarriage Int: Aspirin or Aspirin + heparin Comp: Placebo + standard care (Preconc+Preg) RR: 1.40 (95% CI: 0.52, 3.77)	(1) 1 study, N=25 (no SGA cases)[45] Popn: T1DM Int: Continuous glucose monit Comp: Standard care (Preconc+Preg) RR: 1.45 (95% CI: 0.03, 67.95) (2) 1 study, N=161[46] Popn: Overweight/obese Int: Lifestyle change counseling Comp: Standard care (Preconc+Preg) RR: 5.37 (95% CI: 0.67, 29.82)	No studies	No studies

T1DM: Type 1 diabetes mellitus, APS: Antiphospholipid syndrome, Continuous glucose monit: Continuous glucose monitoring, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.

Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

Supplementary Table 7. Summary of evidence from included studies – nutrition interventions for birth weight for gestational age.

Period	Any nutrition	MMN supplementation including IFA	IFA supplementation	FA supplementation	Food supplementation	Other nutritional
Pre- + Periconc	No studies	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	NA	No studies	No studies	No studies	No studies	No studies

Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy.

Supplementary Table 8. Summary of evidence from included studies – health and social interventions for birth weight for gestational age.

	Health interventions				Social interventions
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**	**Reproductive planning**
Pre- + Periconc	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	No studies	No studies	(1) 1 study, N=25[45] Popn: T1DM Int: Continuous glucose monit Comp: Standard care (Preconc+Preg) MD: -3.90 centiles (SE: 4.48) (2) 1 study, N=161[46] Popn: Overweight/obese Int: Lifestyle change counseling Comp: Standard care MD: -0.10 centiles (SE: 0.15)	No studies	No studies

T1DM: Type 1 diabetes mellitus, Continuous glucose monit: Continuous glucose monitoring, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care, MD: mean difference, 95% CI: 95% confidence interval, SE: standard error.
Yellow shaded cells indicate statistically notable results (95% CIs not overlapping 0) from meta-analyses.

Supplementary Table 9. Summary of evidence from included studies – nutrition interventions for preterm birth.

Period	Any nutrition	MMN supplementation including IFA	IFA supplementation	FA supplementation	Food supplementation	Other nutritional
Pre- + Periconc	6 studies, N=13,683[3–5,7,9,17] Comp: FA, other micronutrients (not FA), standard care, placebo, no int RR: 1.07 (95% CI: 0.79, 1.43), I^2: 78.51%) **GRADE: Very low certainty**	4 studies, N=12,235[3–5,17] Comp: FA, other micronutrients (not FA), placebo, no int RR: 1.03 (95% CI: 0.90, 1.18), I^2: 39.04% **GRADE: Low certainty**	2 studies, N=1360[3,7] Comp: FA RR: 1.42 (95% CI: 0.60, 3.37), I^2: 87.79% **GRADE: Very low certainty**	No studies	No studies	(1) 1 study, N=579[31] Popn: Previous pre-eclampsia Calcium supp v placebo RR: 0.90 (95% CI: 0.74, 1.10) (2) 1 study, N=1162[9] Mushroom in diet v standard care RR: 0.93 (95% CI: 0.63, 1.38)
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	2 studies, N=1163[11,12] RR: 1.38 (95% CI: 1.06, 1.79), I^2: 0.00% **GRADE: Very low certainty**	No studies
Preconc + Preg v Other (specified)	NA	1 study, N=112[48] Comp: Placebo (Preconc) and IFA (Preg) RR: 0.32 (95% CI: 0.07, 1.53)	No studies	No studies	(1) 1 study, N=1360[33] High v Low nutrition value snack (Preconc+Preg) RR: 1.08 (95% CI: 0.81, 1.43) (2) 2 studies, N=1110[11,12] Comp: Standard care (Preconc+Preg) RR: 1.35 (95% CI: 0.64, 2.84), I^2: 55.58%	1 study, N=17,373[49] Vit A supp or B carotene v Placebo (Preconc+Preg) Vit A prevalence: 314/1000 pregnancies B carotene prevalence: 284/1000 pregnancies Placebo prevalence: 282/1000 pregnancies

MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.

Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

Supplementary Table 10. Summary of evidence from included studies – health and social interventions for preterm birth.

	Health interventions				Social interventions
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**	**Reproductive planning**
Pre- + Periconc	(1) 1 study, N=786[13] Popn: Low income Int: Preconc health care Comp: Standard care RR: 1.41 (95% CI: 0.74, 2.69) **GRADE: Very low certainty** (2) 1 study, N=1816[50] Int: Preconc counselling Comp: Standard care Outcome: Composite including PTB RR: 0.96 (95% CI: 0.81, 1.14)	5 studies, N=382[15,16,18–20] Popn: Previous miscarriage, 1 study: APS Clomiphene citrate v placebo, Aspirin + heparin v placebo, Intrauterine hyaluronic acid gel v no int post D&C, Intravenous immunoglobulin v placebo, Third party leukocytes transfusion v placebo RR: 0.32 (95% CI: 0.20, 0.51), I^2: 5.13% **GRADE: Very low certainty**	No studies	(1) 2 studies, N=2275[25,44] Specific aim: reduce PTB Popn: 1 study: previous PTB Azithromycin+Metronidazole v placebo, Treatment of STD/VC v no int RR: 0.62 (95% CI: 0.20, 1.93), I^2: 95.34% **GRADE: Very low certainty** (2) 3 studies, N=3666[26–28] Popn: 1 study: partner with HIV HIV PreP (TDF or TDF+FTC) v placebo, HPV vaccine v placebo, HPV vaccine v placebo or alternative int RR: 1.05 (95% CI: 0.71, 1.57), I^2: 0.00% **GRADE: Very low certainty** (3) 1 study, N=181 (no PTB cases)[29] Dapivirine vaginal ring HIV PreP v placebo RR: 0.06 (95% CI: 0.00, 0.96) **GRADE: Very low certainty**	1 study, N=1140[51] Comp: Standard care RR: 0.79 (95% CI: 0.63, 0.99) **GRADE: Very low certainty**
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	1 study, N=364[37] Int: Integrated preconc and antenatal care Comp: Standard care RR: 0.33 (95% CI: 0.13, 0.77)	3 studies, N=864[21–23] Popn: Previous miscarriage Int: Aspirin or Aspirin + heparin, Aspirin, Vaginal micronized progesterone Comp: Placebo and/or standard care (Preconc+Preg) RR: 0.56 (95% CI: 0.20, 1.62), I^2: 67.36%	(1) 1 study, N=25[45] Popn: T1DM Int: Continuous glucose monit Comp: Standard care (Preconc+Preg) RR: 1.88 (95% CI: 0.66, 5.32) (2) 1 study, N=161[46] Popn: Overweight/obese Int: Lifestyle change counseling Comp: Standard care (Preconc+Preg) RR: 1.37 (95% CI: 0.44, 3.85)	1 study, N=196[38] Popn: HIV Int: Isoniazid Comp: Placebo (Preconc+Preg), Outcome: Composite including PTB RR: 0.72 (95% CI: 0.43, 1.05)	No studies

PTB: Preterm birth, T1DM: Type 1 diabetes mellitus, APS: Antiphospholipid syndrome, D&C: Dilation and curettage, TDF: Tenofovir disoproxil fumarate, FTC: Emtricitabine, STD: Sexually transmitted disease, VC: Vaginal Candidiasis, Continuous glucose monit: Continuous glucose monitoring, Preconc:

Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.
Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

	Supplementary Table 11. Summary of evidence from included studies – nutrition interventions for gestational age.					
Period	**Any nutrition**	**MMN supplementation including IFA**	**IFA supplementation**	**FA supplementation**	**Food supplementation**	**Other nutritional**
Pre- + Periconc	5 studies, N=12,212[3–5,7,39] Comp: FA, other micronutrients (not FA), placebo, no int MD: -0.01wk (95% CI: -0.07, 0.05), I^2: 36.82%	4 studies, N=11,926[3–5,39] Comp: FA, other micronutrients (not FA), placebo, no int MD: 0.00wk (95% CI: -0.06, 0.06), I^2: 0.00%	2 studies, N=1360[3,7] Comp: FA MD: -0.32wk (95% CI: -1.05, 0.40), I^2: 81.58%	1 study, N=231[41] Popn: Oral cleft, previous oral cleft birth 4mg FA v 0.4 mg FA MD: 0.1wk (SE: 0.2)	1 study, N=533[30] Popn: Low income 5-7 months v 0-2 months MD: 0.1wk (SE: 0.2)	No studies
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	1 study, N=157[11] MD: 0.1wk (SE: 0.3)	No studies
Preconc + Preg v Other (specified)	NA	1 study, N=112[32] Comp: Placebo (Preconc) and IFA (Preg) MD: 1.7wk (SE: 1.2)	No studies	No studies	(1) 1 study, N=1360[33] High v Low nutrition value snack (Preconc+Preg) MD: -0.10wk (SE: 0.08) (2) 1 study, N=162[11] Comp: Standard care (Preconc+Preg) MD: -0.5wk (SE: 0.3)	No studies

MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, MD: mean difference, 95% CI: 95% confidence interval, SE: standard error.
Yellow shaded cells indicate statistically notable results (95% CIs not overlapping 0) from meta-analyses.

Supplementary Table 12. Summary of evidence from included studies – health and social interventions for gestational age.

	Health interventions				Social interventions
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**	**Reproductive planning**
Pre- + Periconc	1 study, N=786[13] Popn: Low income Int: Preconc health care Comp: Standard care MD: -0.2wk (SE: 0.1)	2 studies, N=230[15,18] Popn: Previous miscarriage, 1 study: APS Aspirin + heparin v placebo, Intrauterine hyaluronic acid gel v no int post D&C MD: 1.56wk (95% CI: -3.44, 6.55), I^2: 99.21%	1 study, N=157[43] Popn: T1DM or T2DM Counseling session for DM v standard care MD: -0.4wk (SE: 0.4)	1 study, N=124[44] Popn: Previous PTB Azithromycin+Metronidazole v placebo MD: -2.4wk (SE: 1.3)	No studies
Preconc + Preg v Preg only int	No studies	No studies	1 study, N=149[35] Popn: T1DM Int: Intensive DM management MD: -0.9wk (SE: 0.3)	No studies	No studies
Preconc + Preg v Other (specified)	No studies	2 studies, N=795[22,23] Popn: Previous miscarriage Int: Aspirin or Aspirin + heparin v placebo, Aspirin v placebo Comp: Placebo and/or standard care (Preconc+Preg) MD: -0.30wk (95% CI: -0.98, 0.38), I^2: 75.27%	(1) 1 study, N=134[35] Popn: T1DM Int: Intensive DM management Preconc+Preg; 40 v 7 months Preconc MD: -1.1wk (SE: 0.3) (2) 1 study, N=25[45] Popn: T1DM Int: Continuous glucose monit Comp: Standard care (Preconc+Preg) MD: -0.6wk (SE: 0.4)	No studies	No studies

DM: Diabetes mellitus, T1DM: Type 1 diabetes mellitus, T2DM: Type 2 diabetes mellitus, GDM: Gestational diabetes mellitus, APS: Antiphospholipid syndrome, D&C: Dilation and curettage, TDF: Tenofovir disoproxil fumarate, FTC: Emtricitabine, Continuous glucose monit: Continuous glucose monitoring, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care, MD: mean difference, 95% CI: 95% confidence interval, SE: standard error.
Yellow shaded cells indicate statistically notable results (95% CIs not overlapping 0) from meta-analyses.

	Supplementary Table 13. Summary of evidence from included studies – nutrition interventions for birth defects.					
Period	**Any nutrition**	**MMN supplementation including IFA**	**IFA supplementation**	**FA supplementation**	**Food supplementation**	**Other nutritional**
Pre- + Periconc	(1) 10 studies, N=313,312[5,6,52–59] Popn: 6 studies: previous NTD birth Int: MMN including IFA, or FA Comp: MMN no FA, other micronutrients (not FA), placebo, no int RR: 0.37 (95% CI: 0.24, 0.55), I^2: 74.33% (2) 1 study, N=222,314[60] Dataset already included in (1) for different birth defect Comp: No int RR: 0.59 (95% CI: 0.33, 1.07)	6 studies, N=63,914[5,6,52–55] Popn: 3 studies: previous NTD birth Comp: MMN no FA, no int RR: 0.37 (95% CI: 0.22, 0.61), I^2: 63.89%	1 study, N=437[61] Comp: FA RR: 0.07 (95% CI: 0.00, 1.21)	(1) 4 studies, N=249,398[56–59] Popn: 3 studies: previous NTD birth Int: FA or MMN containing FA Comp: MMN no FA, other micronutrients (not FA), placebo, no int RR: 0.38 (95% CI: 0.18, 0.77), I^2: 77.58% (2) 1 study, N=222,314[60] Dataset already included in (1) for different birth defect Comp: No int RR: 0.59 (95% CI: 0.33, 1.07) (3) 1 study, N=213[62] Popn: Previous NTD birth Pre + periconc only v Early preg only FA RR: 0.13 (95% CI: 0.01, 2.34) (4) 1 study, N=224[41] Popn: Oral cleft or previous oral cleft birth 4mg FA v 0.4mg FA RR: 0.59 (95% CI: 0.10, 3.45)	No studies	No studies
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	NA	No studies	No studies	No studies	No studies	No studies

NTD: Neural tube defect, MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.
Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

Supplementary Table 14. Summary of evidence from included studies – health and social interventions for birth defects.

	Health interventions				Social interventions
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**	**Reproductive planning**
Pre- + Periconc	1 study, N=786[13] Popn: Low income Int: Preconc health care Comp: Standard care RR: 2.51 (95% CI: 0.49, 12.87)	1 study, N=39[20] Popn: Previous miscarriage Third party leukocytes transfusion v placebo RR: 0.34 (95% CI: 0.02, 5.01)	1 study, N=187[43] Popn: T1DM or T2DM Counseling session for DM v standard care RR: 0.25 (95% CI: 0.04, 1.88)	4 studies, N=5300[26,27,29,63] Popn: 1 study: partner with HIV Dapivirine vaginal ring HIV PreP v placebo, HPV vaccine v placebo (2 studies), HIV PreP (TDF or TDF+FTC) v placebo, RR: 1.36 (95% CI: 0.93, 1.99), I^2: 0.00%	No studies
Preconc + Preg v Preg only int	No studies	No studies	1 study, N=149[35] Popn: T1DM Int: Intensive DM management RR: 0.15 (95% CI: 0.02, 1.35)	No studies	No studies
Preconc + Preg v Other (specified)	No studies	2 studies, N=269[21,23] Popn: Previous miscarriage Int: Aspirin or Aspirin + heparin, Vaginal micronized progesterone Comp: Placebo and/or standard care (Preconc+Preg) RR: 1.19 (95% CI: 0.34, 4.10), I^2: 42.91%	(1) 1 study, N=134[35] Popn: T1DM Int: Intensive DM management Preconc+Preg; 40 v 7 months Preconc RR: 0.11 (95% CI: 0.01, 0.99) (2) 1 study, N=25 (no BD cases)[45] Popn: T1DM Int: Continuous glucose monit Comp: Standard care (Preconc+Preg) RR: 1.45 (95% CI: 0.03, 67.95) (3) 2 studies, N=297[46,47] Popn: Overweight/obese and/or previous GDM Int: Lifestyle change counseling Comp: Standard care (Preconc+Preg) RR: 1.04 (95% CI: 0.37, 2.96), I^2: 0.00%	1 study, N=196[38] Popn: HIV Int: Isoniazid Comp: Placebo (Preconc+Preg), Outcome: Composite including BD RR: 0.72 (95% CI: 0.43, 1.05)	No studies

BD: Birth defects, DM: Diabetes mellitus, T1DM: Type 1 diabetes mellitus, T2DM: Type 2 diabetes mellitus, GDM: Gestational diabetes mellitus, TDF: Tenofovir disoproxil fumarate, FTC: Emtricitabine, Continuous glucose monit: Continuous glucose monitoring, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.

Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

	Supplementary Table 15. Summary of evidence from included studies – nutrition interventions for stillbirth.					
Period	**Any nutrition**	**MMN supplementation including IFA**	**IFA supplementation**	**FA supplementation**	**Food supplementation**	**Other nutritional**
Pre- + Periconc	5 studies, N=12,684[4–6,31,57] Popn: 2 studies: previous NTD birth, 1 study: previous pre-eclampsia Comp: MMN no FA, other micronutrients (not FA), placebo, no int RR: 0.83 (95% CI: 0.57, 1.21), I^2: 0.00%	3 studies, N=11,844[4–6] Popn: 1 study: previous NTD birth Comp: Other micronutrients (not FA), no int RR: 1.03 (95% CI: 0.56, 1.90), I^2: 0.00%	1 study, N=437[61] Comp: FA RR: 0.68 (95% CI: 0.34, 1.37)	1 study, N=261[57] Popn: Previous NTD birth Int: FA or MMN containing FA Comp: MMN no FA RR: 0.10 (95% CI: 0.01, 2.14)	No studies	1 study, N=579[31] Popn: Previous pre-eclampsia Calcium supp v placebo RR: 0.78 (95% CI: 0.48, 1.27)
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	NA	No studies	No studies	No studies	No studies	1 study, N=17,373[49] Vit A supp or B carotene v Placebo (Preconc+Preg) Outcome: Miscarriage + SB Vit A (N=11,723) RR: 1.06 (95% CI: 0.91, 1.25) B carotene (N=11,303) RR: 1.03 (95% CI: 0.87, 1.19)

NTD: Neural tube defect, MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.
Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

Supplementary Table 16. Summary of evidence from included studies – health and social interventions for stillbirth.

	Health interventions				Social interventions
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**	**Reproductive planning**
Pre- + Periconc	1 study, N=1816[50] Int: Preconc counselling Comp: Standard care Outcome: Composite including SB RR: 0.96 (95% CI: 0.81, 1.14)	No studies	No studies	4 studies, N=8656[27,29,63,64] Dapivirine vaginal ring HIV PreP v placebo, HPV vaccine v placebo (3 studies) RR: 1.20 (95% CI: 0.74, 1.93), I^2: 0.00%	No studies
Preconc + Preg v Preg only int	No studies	No studies	1 study, N=218[35] Popn: T1DM Int: Intensive DM management RR: 0.31 (95% CI: 0.03, 3.34)	1 study, N=266[65] Popn: HIV Int: Antiretroviral therapy RR: 2.70 (95% CI: 0.55, 13.14)	No studies
Preconc + Preg v Other (specified)	1 study, N=6275[66] Int: Women's groups on perinatal care Comp: Standard care (Preconc+Preg) RR: 1.06 (95% CI: 0.76, 1.45)	1 study, N=69[21] Popn: Previous miscarriage Int: Vaginal micronized progesterone Comp: Placebo (Preconc+Preg) RR: 0.73 (95% CI: 0.07, 7.69)	(1) 1 study, N=187[35] Popn: T1DM Int: Intensive DM management Preconc+Preg; 40 v 7 months Preconc RR: 0.39 (95% CI: 0.02, 6.05) (2) 1 study, N=25 (no SB cases)[45] Popn: T1DM Int: Continuous glucose monit Comp: Standard care (Preconc+Preg) RR: 1.45 (95% CI: 0.03, 67.95)	1 study, N=196[38] Popn: HIV Int: Isoniazid Comp: Placebo (Preconc+Preg), Outcome: Composite including SB RR: 0.72 (95% CI: 0.43, 1.05)	No studies

DM: Diabetes mellitus, T1DM: Type 1 diabetes mellitus, Continuous glucose monit: Continuous glucose monitoring, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.

Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

	Supplementary Table 17. Summary of evidence from included studies – nutrition interventions for large for gestational age.					
Period	**Any nutrition**	**MMN supplementation including IFA**	**IFA supplementation**	**FA supplementation**	**Food supplementation**	**Other nutritional**
Pre- + Periconc	No studies	1 study, N=1084[3] Comp: FA RR: 1.06 (95% CI: 0.75, 1.51)	1 study, N=1074[3] Comp: FA RR: 1.05 (95% CI: 0.73, 1.49)	No studies	No studies	No studies
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	NA	No studies	No studies	No studies	1 study, N=1360[33] High v Low nutrition value snack (Preconc+Preg) RR: 1.05 (95% CI: 0.21, 5.21)	No studies

MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.

Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

Supplementary Table 18. Summary of evidence from included studies – health and social interventions for large for gestational age.

	Health interventions				Social interventions
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**	**Reproductive planning**
Pre- + Periconc	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	No studies	No studies	(1) 1 study, N=25[45] Popn: T1DM Int: Continuous glucose monit Comp: Standard care (Preconc+Preg) RR: 0.82 (95% CI: 0.45, 1.48) (2) 1 study, N=161[46] Popn: Overweight/obese Int: Lifestyle change counseling Comp: Standard care (Preconc+Preg) RR: 0.97 (95% CI: 0.47, 1.82)	No studies	No studies

T1DM: Type 1 diabetes mellitus, Continuous glucose monit: Continuous glucose monitoring, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.

Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

Supplementary Table 19. Summary of evidence from included studies – nutrition interventions for maternal anaemia.

Period	Any nutrition	MMN supplementation including IFA	IFA supplementation	FA supplementation	Food supplementation	Other nutritional
Pre- + Periconc	2 studies, N=1060[67,68] Int: MMN including IFA or FA Comp: FA Trimester: 1 RR: 1.01 (95% CI: 0.83, 1.24), I^2: 0.00%	(1) 1 study, N=972[67] Comp: FA Trimester: 1 RR: 1.01 (95% CI, 0.77, 1.32) (2) 1 study, N=973[67] Comp: FA Trimester: 2 RR: 0.95 (95% CI: 0.81, 1.11) (3) 1 study, N=974[67] Trimester: 3 Comp: FA RR: 1.07 (95% CI: 0.89, 1.28)	(1) 2 studies, N=1060[67,68] Comp: FA Trimester: 1 RR: 1.13 (95% CI: 0.93, 1.37), I^2: 0.00% (2) 1 study, N=971[67] Comp: FA Trimester: 2 RR: 1.02 (95% CI: 0.88, 1.19) (3) 1 study, N=986[67] Comp: FA Trimester: 3 RR: 1.05 (95% CI: 0.87, 1.25)	No studies	1 study, N=368[30] Popn: Low income 5-7 months v 0-2 months OR: 0.65 (95% CI: 0.45, 1.07) *(No case ns to calculate assumed comparator risk & RR)*	No studies
Preconc + Preg v Preg only int	(1) 2 studies, N=307[10,11] Int: Food supp or IFA Trimester: 2 RR: 0.61 (95% CI: 0.47, 0.80), I^2: 0.00% (2) 2 studies, N=289[10,11] Int: Food supp or IFA Trimester: 3 RR: 0.67 (95% CI: 0.47, 0.96), I^2: 0.00%	No studies	(1) 1 study, N=191[10] Trimester: 1 RR: 0.50 (95% CI: 0.31, 0.78) (2) 1 study, N=201[10] Trimester: 2 RR: 0.60 (95% CI: 0.45, 0.79) (3) 1 study, N=175[10] Trimester: 3 RR: 0.64 (95% CI: 0.43, 0.94)	No studies	(1) 1 study, N=106[11] Trimester: 2 RR: 0.78 (95% CI: 0.30, 2.03) (2) 1 study, N=114[11] Trimester: 3 RR: 0.89 (95% CI: 0.37, 2.14)	No studies
Preconc + Preg v Other (specified)	NA	No studies	No studies	No studies	(1) 1 study, N=112[11] Trimester: 2 Comp: Standard care (Preconc+Preg) RR: 0.77 (95% CI: 0.30, 1.98) (2) 1 study, N=123[11] Trimester: 3 Comp: Standard care (Preconc+Preg) RR: 1.03 (95% CI: 0.43, 2.49)	No studies

MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.
Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

	Supplementary Table 20. Summary of evidence from included studies – health interventions for maternal anaemia.			
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**
Pre- + Periconc	No studies	No studies	No studies	No studies
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	No studies	No studies	No studies	No studies
Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy.				

	Supplementary Table 21. Summary of evidence from included studies – nutrition interventions for maternal haemoglobin.					
Period	**Any nutrition**	**MMN supplementation including IFA**	**IFA supplementation**	**FA supplementation**	**Food supplementation**	**Other nutritional**
Pre- + Periconc	(1) 2 studies, N=1060[67,68] Int: MMN including IFA or FA Comp: FA Trimester: 1 MD: 0.14g/dL (95% CI: -0.02, 0.31), I^2: 43.61% (2) 2 studies, N=1259[7,67] Int: MMN including IFA or FA Comp: FA Trimester: 2 MD: -0.06g/dL (95% CI: -0.20, 0.09), I^2: 0.00% (3) 2 studies, N=1217[7,67] Int: MMN including IFA or FA Comp: FA Trimester: 3 MD: -0.08g/dL (95% CI: -0.22, 0.07), I^2: 0.00%	(1) 1 study, N=972[67] Comp: FA Trimester: 1 MD: 0.18g/dL (SE: 0.09) (2) 1 study, N=973[67] Comp: FA Trimester: 2 MD: -0.07g/dL (SE: 0.08) (3) 1 study, N=974[67] Comp: FA Trimester: 3 MD: -0.07g/dL (SE:0.08)	(1) 2 studies, N=1060[67,68] Comp: FA Trimester: 1 MD: -0.04g/dL (95% CI: -0.20, 0.11), I^2: 0.00% (2) 2 studies, N=1257[7,67] Comp: FA Trimester: 2 MD: -0.07g/dL (95% CI: -0.21, 0.07), I^2: 0.00% (3)2 studies, N=1229[7,67] Comp: FA Trimester: 3 MD: -0.06g/dL (95% CI: -0.21, 0.09), I^2: 0.00%	No studies	1 study, N=368[30] Popn: Low income 5-7 months v 0-2 months MD: 0.29g/dL (SE: 0.11)	No studies
Preconc + Preg v Preg only int	(1) 2 studies, N=307[10,11] Int: Food supp or IFA Trimester: 2 MD: 0.29g/dL (95% CI: -0.48, 1.05), I^2: 85.97% (2) 2 studies, N=289[10,11] Int: Food supp or IFA Trimester: 3 MD: 0.06g/dL (95% CI: -0.64, 0.77), I^2: 85.44%	No studies	(1) 1 study, N=191[10] Trimester: 1 MD: 0.83g/dL (SE: 0.21) (2) 1 study, N=201[10] Trimester: 2 MD: 0.68g/dL (SE: 0.21) (3) 1 study, N=175[10] Trimester: 3 MD: 0.42g/dL (SE: 0.19)	No studies	(1) 1 study, N=106[11] Trimester: 2 MD: -0.10g/dL (SE: 0.20) (2) 1 study, N=114[11] Trimester: 3 MD: -0.30g/dL (SE: 0.20)	No studies
Preconc + Preg v Other (specified)	NA	No studies	No studies	No studies	(1) 1 study, N=112[11] Trimester: 2 Comp: Standard care (Preconc+Preg) MD: 0.00g/dL (SE: 0.21) (2) 1 study, N=123[11] Trimester: 3 Comp: Standard care (Preconc+Preg) MD: -0.10g/dL (SE: 0.19)	No studies

MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, MD: mean difference, 95% CI: 95% confidence interval, SE: standard error.
Yellow shaded cells indicate statistically notable results (95% CIs not overlapping 0) from meta-analyses.

	Supplementary Table 22. Summary of evidence from included studies – health interventions for maternal anaemia.			
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**
Pre- + Periconc	No studies	No studies	No studies	No studies
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	No studies	No studies	No studies	No studies
Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy.				

	Supplementary Table 23. Summary of evidence from included studies – nutrition interventions for maternal gestational diabetes mellitus.					
Period	**Any nutrition**	**MMN supplementation including IFA**	**IFA supplementation**	**FA supplementation**	**Food supplementation**	**Other nutritional**
Pre- + Periconc	No studies	No studies	No studies	No studies	No studies	1 study, N=1162[9] Mushroom in diet v standard care RR: 0.72 (95% CI: 0.42, 1.21)
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	NA	No studies	No studies	No studies	1 study, N=1008[69] High v Low nutrition value snack (Preconc+Preg) RR: 0.81 (95% CI: 0.55, 1.17)	No studies
MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval. Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.						

	Supplementary Table 24. Summary of evidence from included studies – health interventions for maternal gestational diabetes mellitus.			
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**
Pre- + Periconc	No studies	No studies	No studies	No studies
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	No studies	(1) 1 study, N=69 (No GDM cases)[21] Popn: Previous miscarriage Int: Vaginal micronized progesterone Comp: Placebo (Preconc+Preg) RR: 1.45 (95% CI: 0.03, 70.93) (2) 1 study, N=728[22] Popn: Previous miscarriage Int: Aspirin Comp: Placebo (Preconc+Preg) RR: 0.93 (95% CI: 0.41, 2.11)	2 studies, N=297[46,47] Popn: Overweight/obese and/or previous GDM Int: Lifestyle change counseling Comp: Standard care (Preconc+Preg) RR: 1.01 (95%CI: 0.78, 1.31), I^2: 36.92%	No studies
GDM: Gestational diabetes mellitus, APS: Antiphospholipid syndrome, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval. Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.				

Supplementary Table 25. Summary of evidence from included studies – nutrition interventions for maternal gestational hypertension.

Period	Any nutrition	MMN supplementation including IFA	IFA supplementation	FA supplementation	Food supplementation	Other nutritional
Pre- + Periconc	(1) 2 studies, N=1741[9,31] Popn: 1 study: previous pre-eclampsia Comp: Placebo, standard care RR: 0.72 (95% CI: 0.39, 1.32), I^2: 84.54% (2) 1 study, N=243 (no GHT cases)[7] Comp: FA RR: 0.98 (95% CI: 0.02, 48.79) (3) 1 study, N=363 (Pregnancy HT; unclear if GHT specifically)[17] Comp: Placebo RR: 1.15 (95% CI: 0.49, 2.57)	1 study, N=363 (Pregnancy HT; unclear if GHT specifically)[17] Comp: Placebo RR: 1.15 (95% CI: 0.49, 2.57)	1 study, N=243 (no GHT cases)[7] Comp: FA RR: 0.98 (95% CI: 0.02, 48.79)	No studies	No studies	(1) 1 study, N=579[31] Popn: Previous pre-eclampsia Calcium supp v placebo RR: 0.94 (95% CI: 0.84, 1.05) (2) 1 study, N=1162[9] Mushroom in diet v standard care RR: 0.50 (95% CI: 0.31, 0.80)
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	NA	No studies	No studies	No studies	No studies	No studies

MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.

Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

Supplementary Table 26. Summary of evidence from included studies – health interventions for maternal gestational hypertension.

Period	General health	Prevention of early adverse pregnancy outcomes	Prevention or management of non-communicable disease	Prevention or management of infectious disease
Pre- + Periconc	No studies	No studies	No studies	1 study, N=39[34] Int: H1N1 vaccine RR: 2.13 (95% CI: 0.09, 49.08)
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	No studies	2 studies, N=797[21,22] Popn: Previous miscarriage Int: Vaginal micronized progesterone, Aspirin Comp: Placebo (Preconc+Preg) RR: 0.76 (95% CI: 0.17, 3.53)	(1) 1 study, N=25[45] Popn: T1DM Int: Continuous glucose monit Comp: Standard care (Preconc+Preg) RR: 0.30 (95% CI: 0.04, 2.20) (2) 2 studies, N=297[46,47] Popn: Overweight/obese and/or previous GDM Int: Lifestyle change counseling Comp: Standard care (Preconc+Preg RR: 1.05 (95% CI: 0.55, 2.03), I^2: 0.00%	No studies

T1DM: Type 1 diabetes mellitus, GDM: Gestational diabetes mellitus, Continuous glucose monit: Continuous glucose monitoring, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.

Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

	Supplementary Table 27. Summary of evidence from included studies – nutrition interventions for maternal pre-eclampsia.					
Period	**Any nutrition**	**MMN supplementation including IFA**	**IFA supplementation**	**FA supplementation**	**Food supplementation**	**Other nutritional**
Pre- + Periconc	3 studies, N=2156[9,17,31] Popn: 1 study: previous pre-eclampsia Comp: Placebo, standard care RR: 0.78 (95% CI: 0.60, 1.01), I^2: 29.53%	1 study, N=415[17] Comp: Placebo RR: 1.39 (95% CI: 0.31. 5.89)	No studies	1 study, N=233[41] Popn: Oral cleft or previous oral cleft birth 4mg FA v 0.4 mg FA RR: 1.30 (95% CI: 0.38, 4.47)	No studies	(1) 1 study, N=579[31] Popn: Previous pre-eclampsia Calcium supp v placebo RR: 0.80 (95% CI: 0.61, 1.06) (2) 1 study, N=1162[9] Mushroom in diet v standard care RR: 0.33 (95% CI: 0.11, 1.02)
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	NA	No studies	No studies	No studies	No studies	No studies

MMN: Multiple micronutrient, IFA: Iron and folic acid, FA: Folic acid, Supp: Supplementation, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, No int: No intervention, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.

Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

	Supplementary Table 28. Summary of evidence from included studies – health interventions for maternal pre-eclampsia.			
Period	**General health**	**Prevention of early adverse pregnancy outcomes**	**Prevention or management of non-communicable disease**	**Prevention or management of infectious disease**
Pre- + Periconc	No studies	2 studies, N=208[15,16] Popn: Previous miscarriage, 1 study: APS Clomiphene citrate v placebo, Aspirin + heparin v placebo RR: 0.39 (95% CI: 0.20, 0.74), I^2: 0.00%	No studies	1 study, N=39[34] Int: H1N1 vaccine RR: 3.54 (95% CI: 0.18, 69.18)
Preconc + Preg v Preg only int	No studies	No studies	No studies	No studies
Preconc + Preg v Other (specified)	No studies	2 studies, N=928[22,23] Popn: Previous miscarriage Int: Aspirin or Aspirin + heparin, Aspirin Comp: Placebo and/or standard care (Preconc+Preg) RR: 1.01 (95% CI: 0.63, 1.61), I^2: 0.00%	(1) 1 study, N=25[45] Popn: T1DM Comp: Standard care (Preconc+Preg) RR: 0.48 (95% CI: 0.02, 10.84) (2) 1 study, N=128[47] Popn: Obese and/or previous GDM Comp: Standard care RR: 0.48 (95% CI: 0.05, 5.21)	No studies

T1DM: Type 1 diabetes mellitus, GDM: Gestational diabetes mellitus, APS: Antiphospholipid syndrome, Preconc: Preconception, Periconc: Periconception, Preg: Pregnancy, Int: Intervention, Comp: Comparator, Popn: Population, Standard care: Standard or routine care, RR: relative risk, 95% CI: 95% confidence interval.

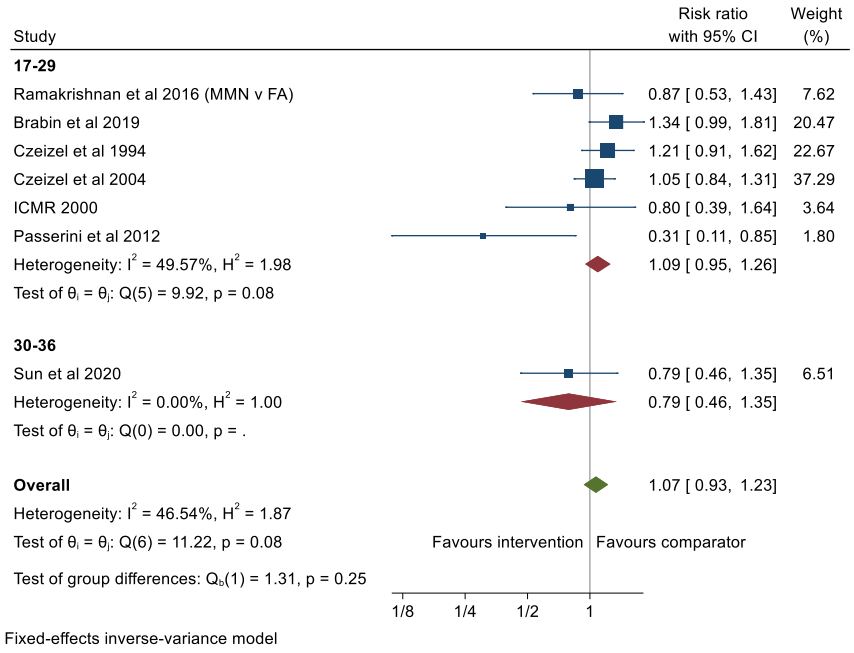
Grey shaded and yellow shaded cells indicate statistically notable results (95% CIs not overlapping 1) from single studies and meta-analyses respectively.

5. Preconception interventions to prevent low birth weight, preterm birth and small for gestational age: Subgroup and sensitivity analyses for primary outcomes and nutrition interventions

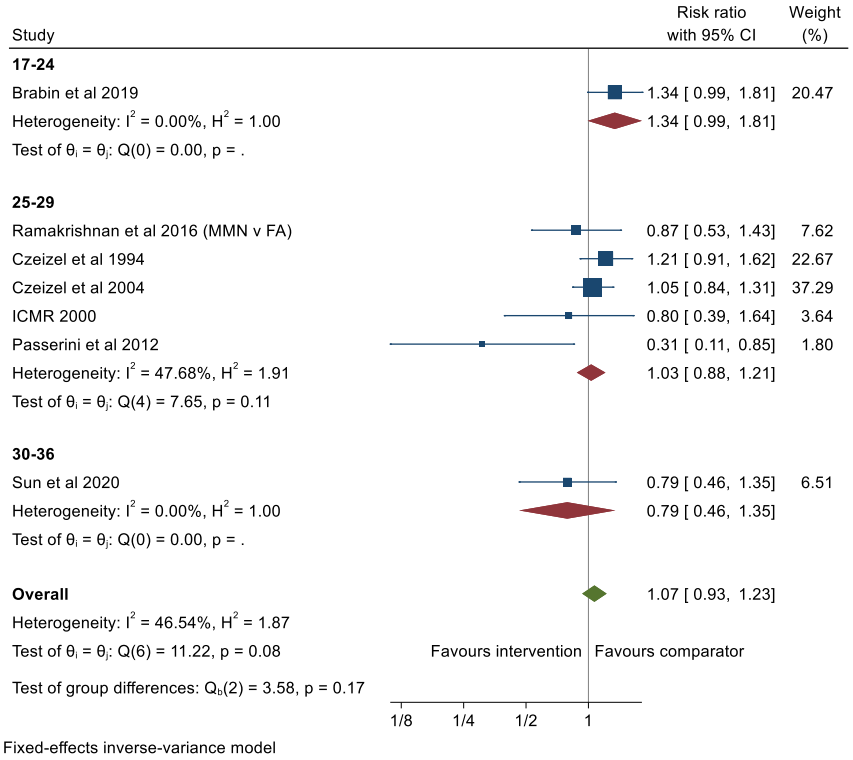
Note: subgroup and sensitivity analyses were only conducted for meta-analyses including ≥4 studies.

5.1. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), standard or routine care, or no intervention to prevent low birth weight

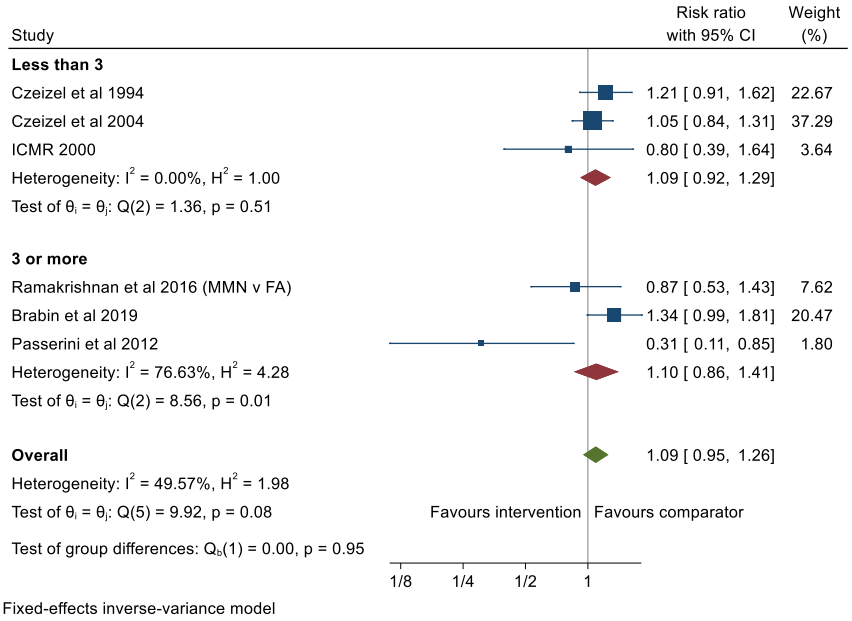
7 studies, N=13,973: Ramakrishnan et al 2016 (MMN supplementation v FA supplementation) [3], Czeizel et al 1994 (MMN supplementation v supplement containing only copper, manganese, zinc and Vitamin C) [4], Czeizel et al 2004 (MMN supplementation v no supplementation) [5], ICMR 2000 (MMN supplementation v supplement containing only iron and calcium; population: women with previous birth with neural tube defect) [6], Brabin et al 2019 (IFA supplementation v FA supplementation) [7], Passerini et al 2012 (IFA supplementation with deworming v no supplementation or deworming) [8], and Sun et al 2020 (100g mushroom daily v standard or routine care [normal diet]) [9].



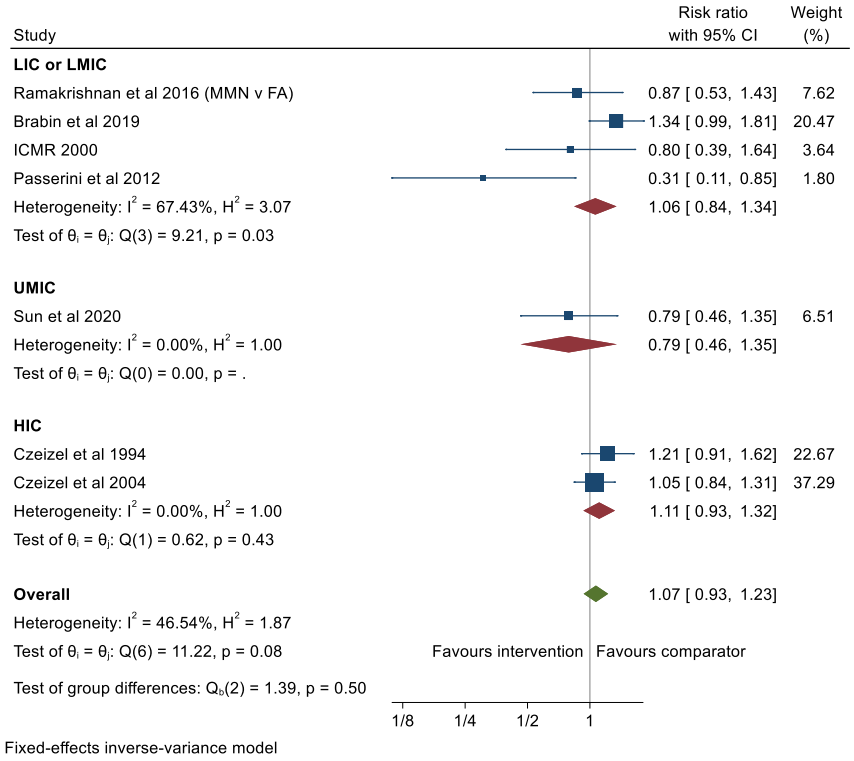
Supplementary Figure 22. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), standard or routine care, or no intervention to prevent low birth weight: subgroup effects by age (as two categories: 17-29 and 30-36 years).



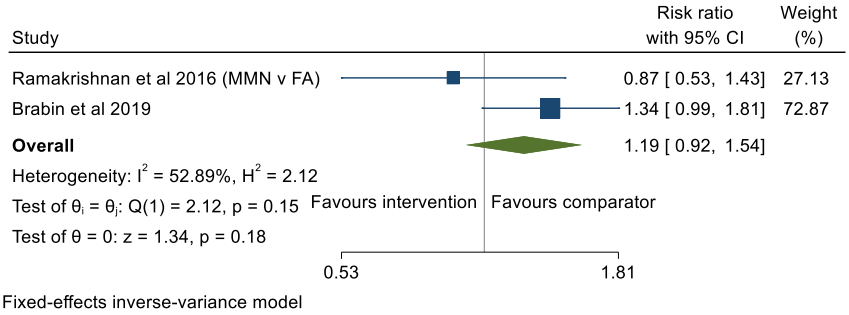
Supplementary Figure 23. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), standard or routine care, or no intervention to prevent low birth weight: subgroup effects by age (as three categories: 17-24, 25-29 and 30-36 years).



Supplementary Figure 24. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), standard or routine care, or no intervention to prevent low birth weight: subgroup effects by months prior to conception intervention started (no information for Sun et al 2020).

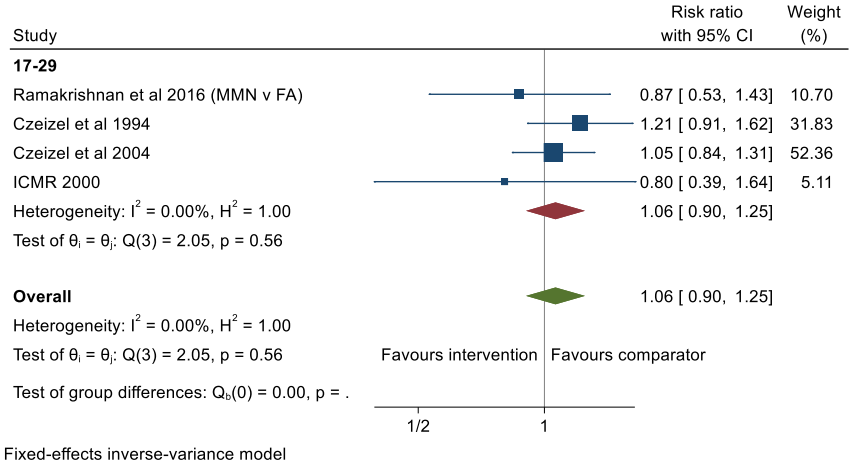


Supplementary Figure 25. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), standard or routine care, or no intervention to prevent low birth weight: subgroup effects by country income status.

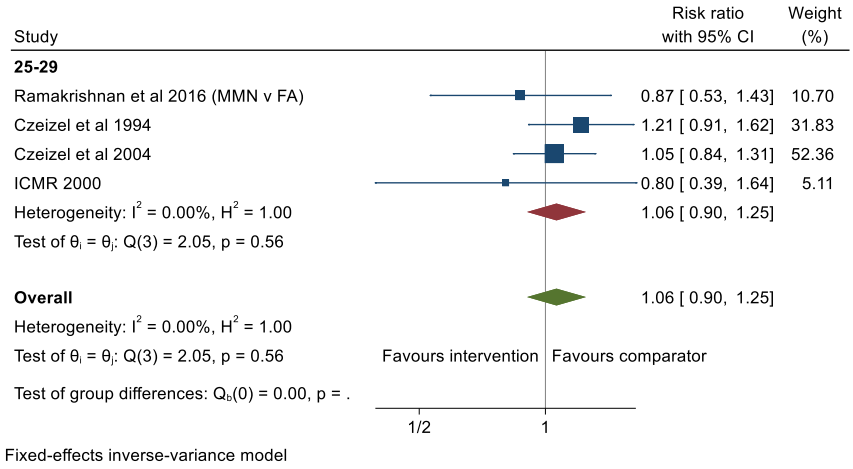


Supplementary Figure 26. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), standard or routine care, or no intervention to prevent low birth weight: sensitivity analysis – including only studies at low risk of bias.

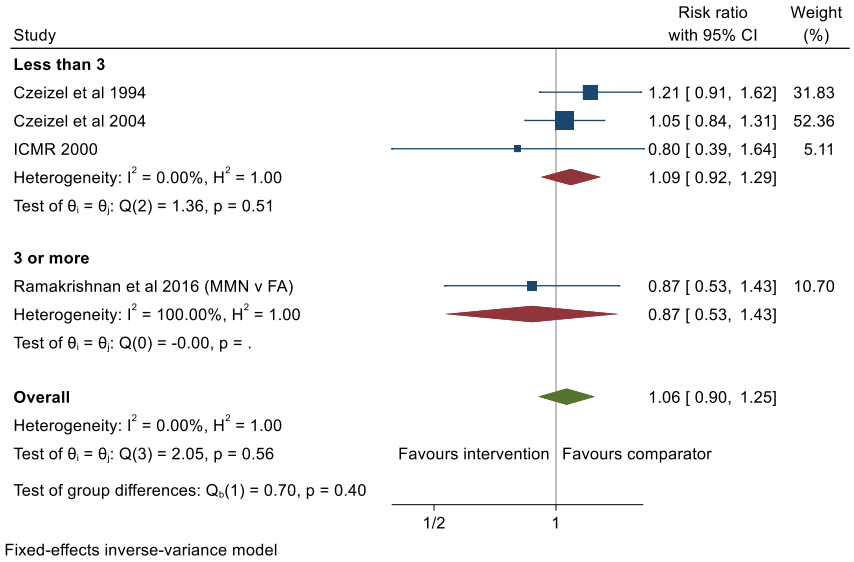
5.2. Pre- and periconception MMN including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), or no intervention to prevent low birth weight.
4 studies, N=12,054: Ramakrishnan et al 2016 (MMN supplementation v FA supplementation) [3], Czeizel et al 1994 (MMN supplementation v supplement containing only copper, manganese, zinc and Vitamin C) [4], Czeizel et al 2004 (MMN supplementation v no supplementation) [5], ICMR 2000 (MMN supplementation v supplement containing only iron and calcium; population: women with previous birth with neural tube defect) [6].



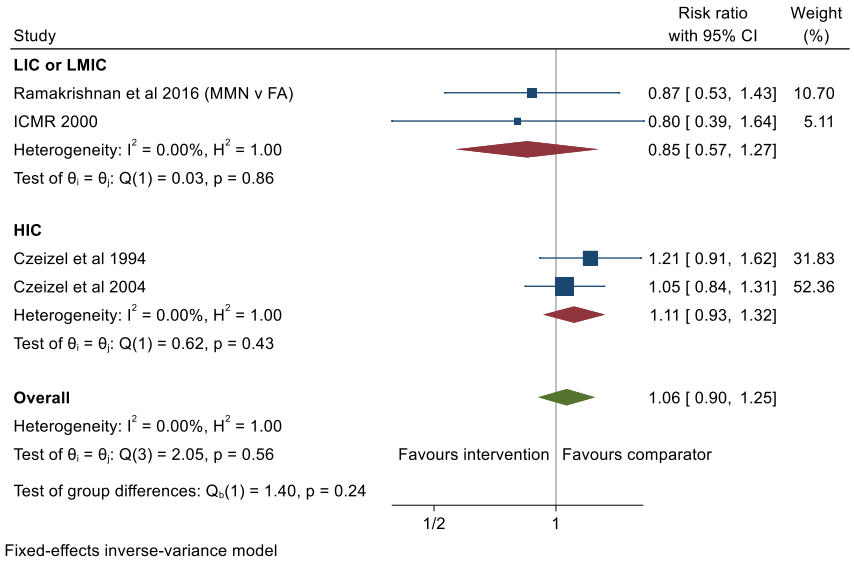
Supplementary Figure 27. Pre- and periconception MMN including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), or no intervention to prevent low birth weight: subgroup effects by age (as two categories: 17-29 and 30-36 years).



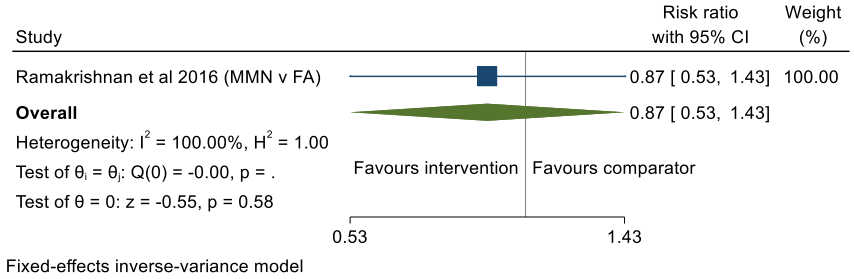
Supplementary Figure 28. Pre- and periconception MMN including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), or no intervention to prevent low birth weight: subgroup effects by age (as three categories: 17-24, 25-29 and 30-36 years).



Supplementary Figure 29. Pre- and periconception MMN including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), or no intervention to prevent low birth weight: subgroup effects by months prior to conception intervention started.



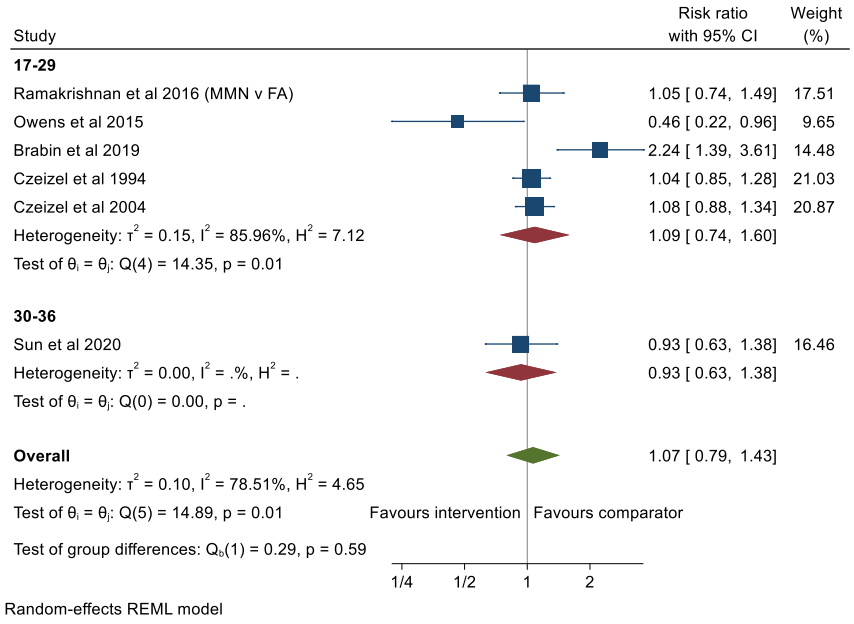
Supplementary Figure 30. Pre- and periconception MMN including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), or no intervention to prevent low birth weight: subgroup effects by country income status.



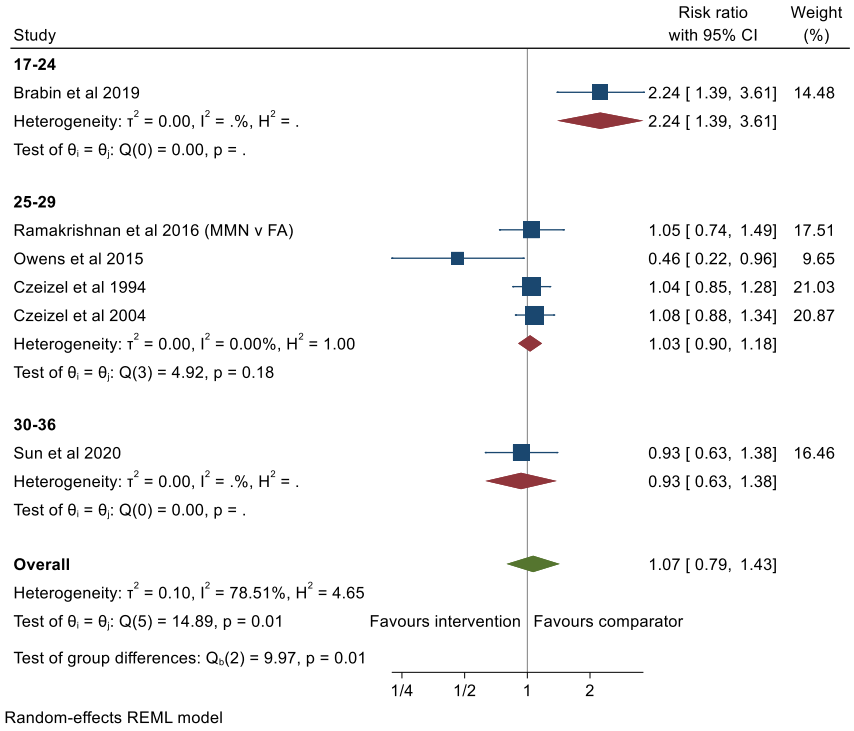
Supplementary Figure 31. Pre- and periconception MMN including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), or no intervention to prevent low birth weight: sensitivity analysis – including only studies at low risk of bias.

5.3. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), placebo, standard or routine care, or no intervention to prevent preterm birth

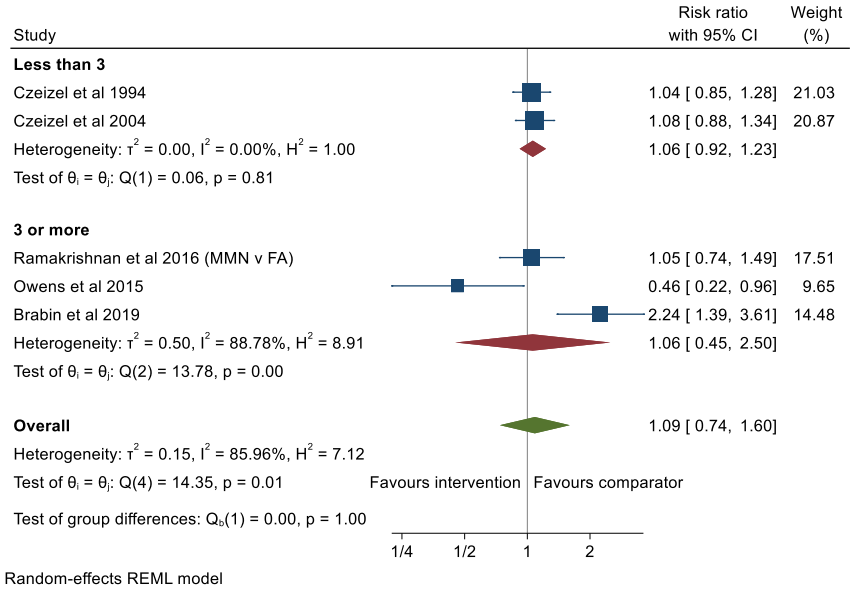
6 studies, N=13,683: Ramakrishnan et al 2016 (MMN supplementation v FA supplementation) [3], Czeizel et al 1994 (MMN supplementation v supplement containing only copper, manganese, zinc and Vitamin C) [4], Czeizel et al 2004 (MMN supplementation v no supplementation) [5], Owens et al 2015 (MMN supplementation v placebo) [17], Brabin et al 2019 (IFA supplementation v FA supplementation) [7], Sun et al 2020 (100g mushroom daily v standard or routine care [normal diet]) [9].



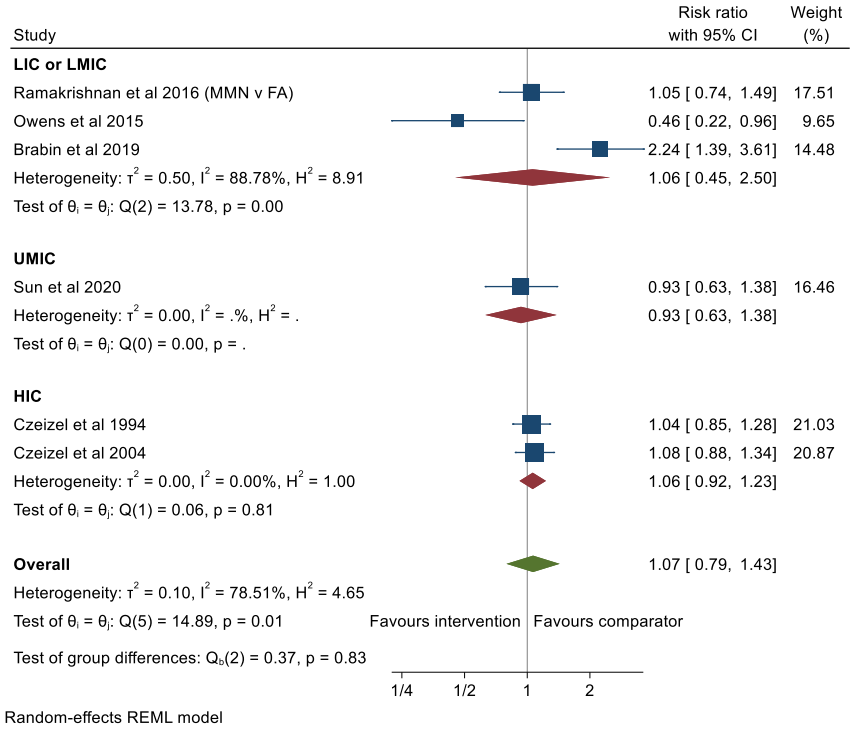
Supplementary Figure 32. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), placebo, standard or routine care, or no intervention to prevent preterm birth: subgroup effects by age (as two categories: 17-29 and 30-36 years).



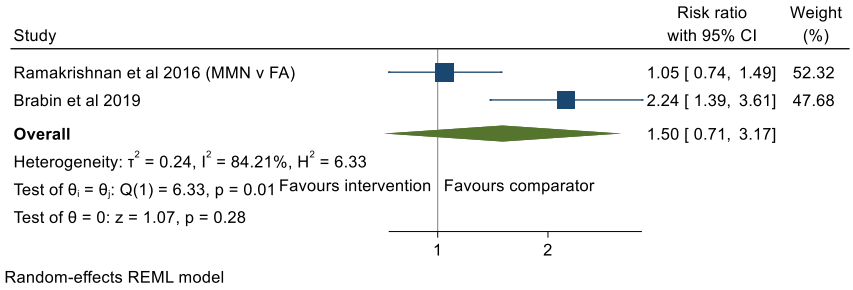
Supplementary Figure 33. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), placebo, standard or routine care, or no intervention to prevent preterm birth: subgroup effects by age (as three categories: 17-24, 25-29 and 30-36 years).



Supplementary Figure 34. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), placebo, standard or routine care, or no intervention to prevent preterm birth: subgroup effects by months prior to conception intervention started (no information for Sun et al 2020).



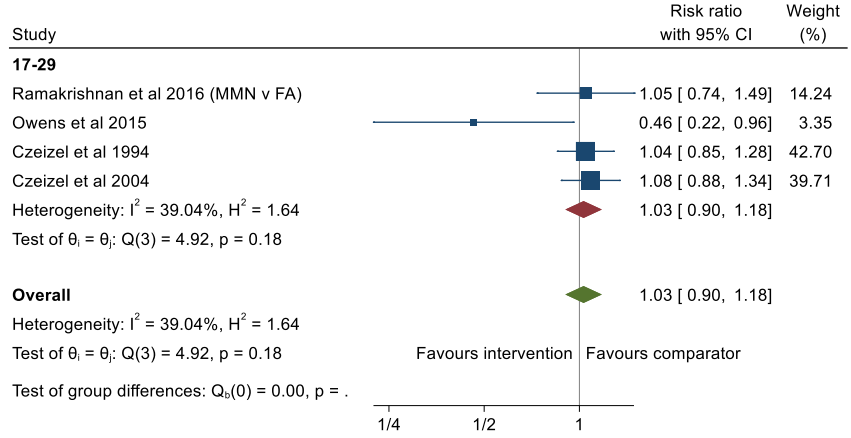
Supplementary Figure 35. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), placebo, standard or routine care, or no intervention to prevent preterm birth: subgroup effects by country income status.



Supplementary Figure 36. Any general population-based nutritional intervention in the pre- and periconception period compared with FA supplementation, supplementation with other micronutrients (not FA), placebo, standard or routine care, or no intervention to prevent preterm birth: sensitivity analysis – including only studies at low risk of bias.

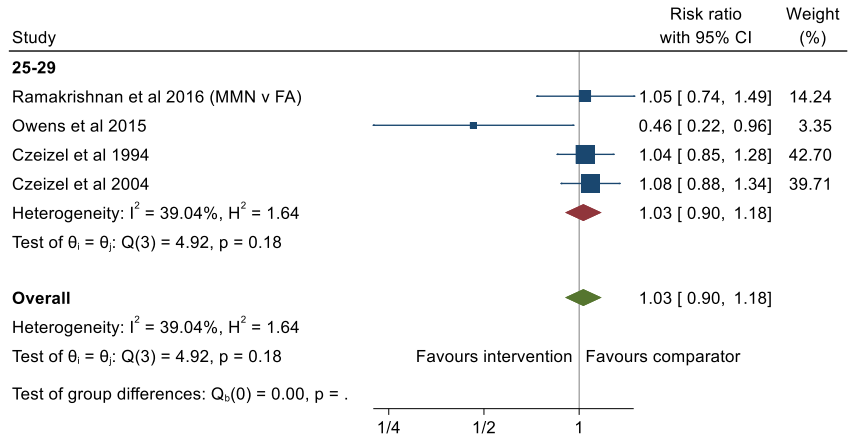
5.4. Pre- and periconception MMN supplementation including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), placebo or no intervention to prevent preterm birth.

4 studies, N=12,235: Ramakrishnan et al 2016 (MMN supplementation v FA supplementation) [3], Czeizel et al 1994 (MMN supplementation v supplement containing only copper, manganese, zinc and Vitamin C) [4], Czeizel et al 2004 (MMN supplementation v no supplementation) [5], Owens et al 2015 (MMN supplementation v placebo) [17].



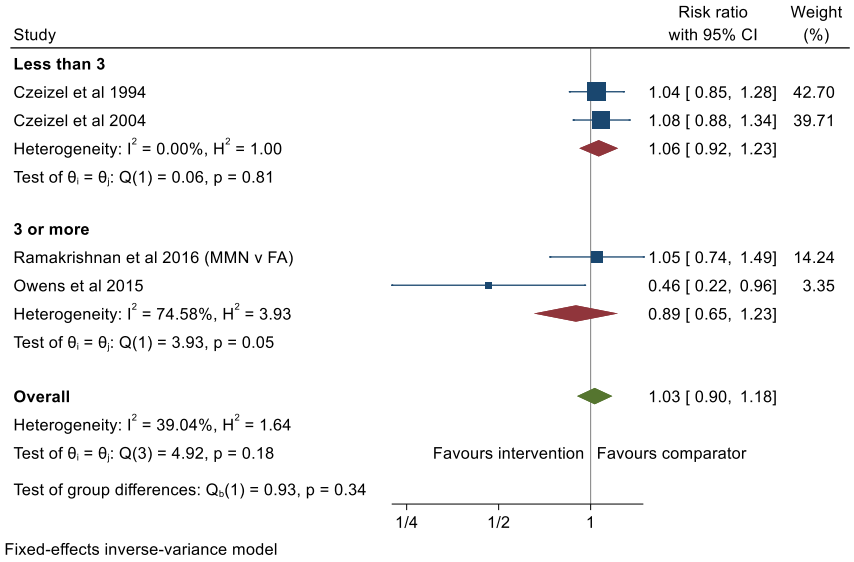
Fixed-effects inverse-variance model

Supplementary Figure 37. Pre- and periconception MMN supplementation including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), placebo or no intervention to prevent preterm birth: subgroup effects by age (as two categories: 17-29 and 30-36 years).

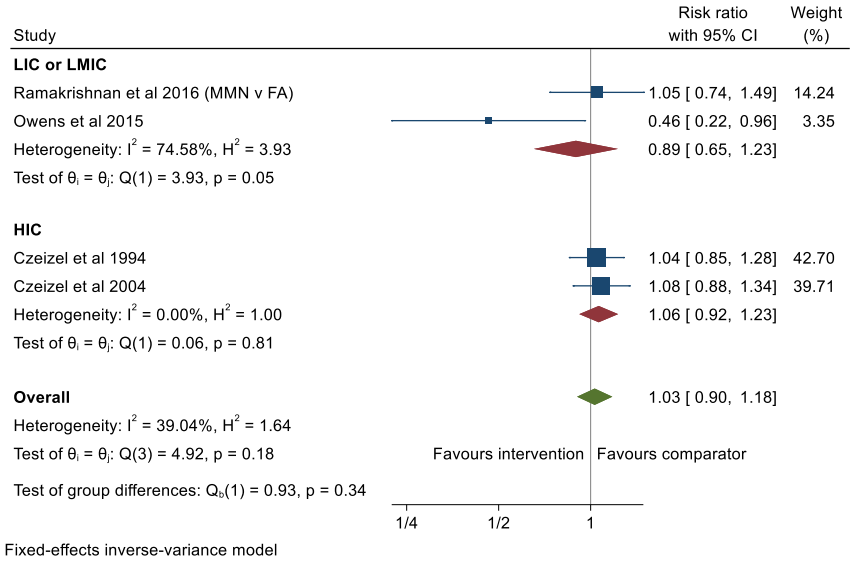


Fixed-effects inverse-variance model

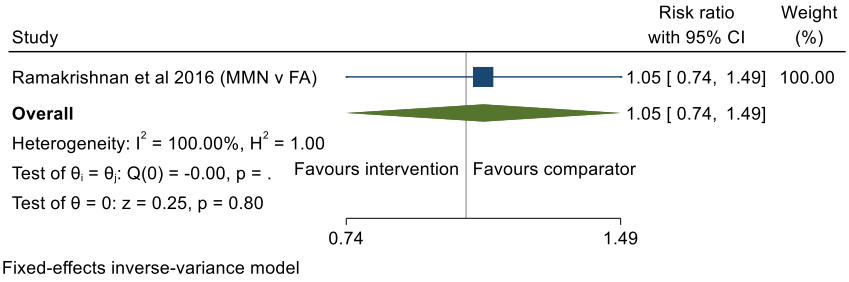
Supplementary Figure 38. Pre- and periconception MMN supplementation including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), placebo or no intervention to prevent preterm birth: subgroup effects by age (as three categories: 17-24, 25-29 and 30-36 years).



Supplementary Figure 39. Pre- and periconception MMN supplementation including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), placebo or no intervention to prevent preterm birth: subgroup effects by months prior to conception intervention started.



Supplementary Figure 40. Pre- and periconception MMN supplementation including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), placebo or no intervention to prevent preterm birth: subgroup effects by country income status.



Supplementary Figure 41. Pre- and periconception MMN supplementation including IFA versus pre- and periconception FA supplementation, supplementation with other micronutrients (not FA), placebo or no intervention to prevent preterm birth: sensitivity analysis – including only studies at low risk of bias.

6. Preconception interventions to prevent low birth weight, preterm birth and small for gestational age: Risk of bias assessments

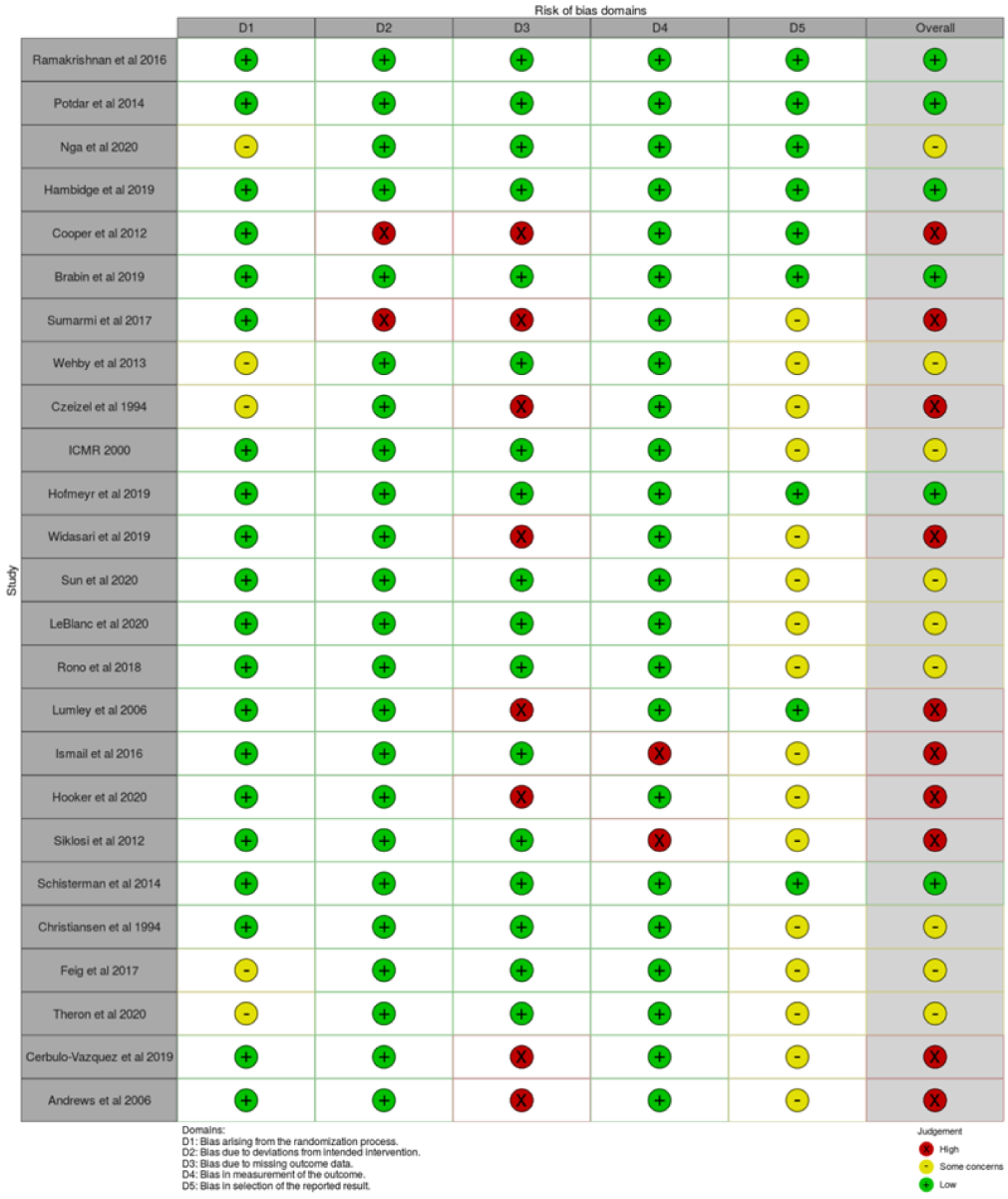
Notes

1. Risk of bias assessments for RCTs were undertaken using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (v 22Aug2019) tool[70], assessments for cluster RCTs were done using the Revised Cochrane risk-of-bias tool for cluster-randomized trials (RoB 2 CRT) (v 10Nov2020) tool[71], and assessments for qRCTs were done using Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) (v 01Aug2016) tool[72].

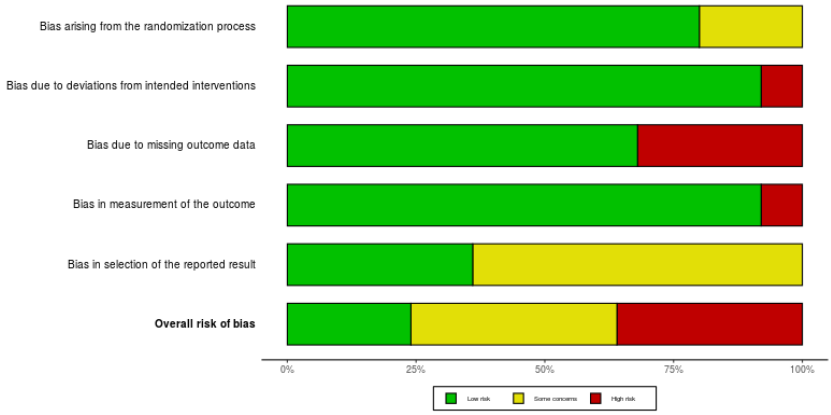
2. Traffic light plots and summary plots were generated using the robvis tool (https://mcguinlu.shinyapps.io/robvis/) [73].

6.1. Low birth weight and birth weight

6.1A. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (v 22Aug2019)



Supplementary Figure 42. RoB2 assessment for studies assessing low birth weight and birth weight: traffic light plot.



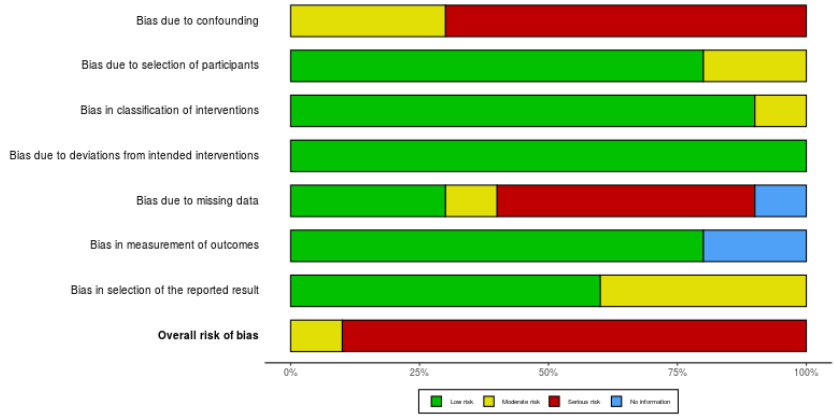
Supplementary Figure 43. RoB2 assessment for studies assessing low birth weight and birth weight: summary plot.

6.1B. Revised Cochrane risk-of-bias tool for cluster-randomized trials (RoB 2 CRT) (v 10Nov2020)

No studies

6.1C. Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) (v 01Aug2016)

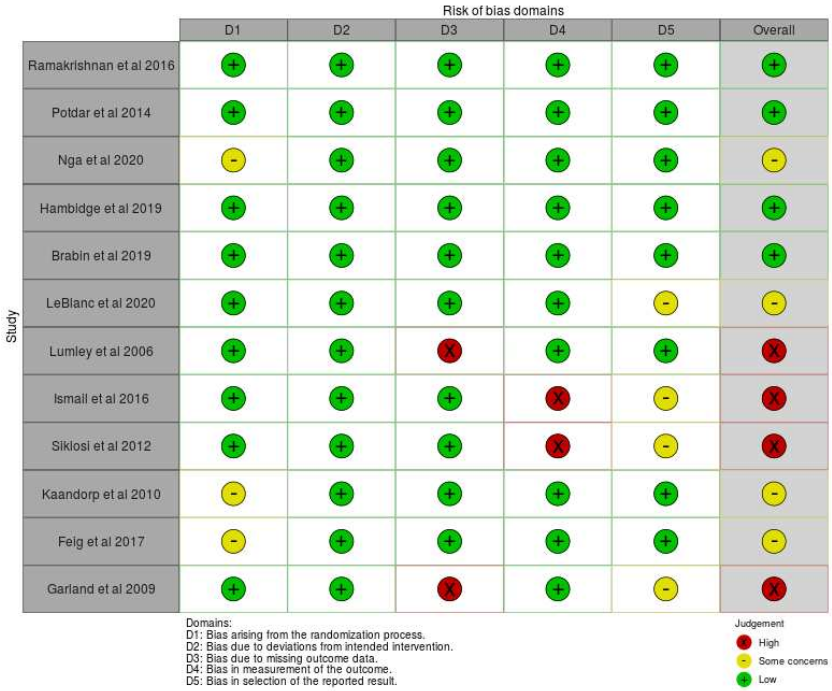
Supplementary Figure 44. ROBINS assessment for studies assessing low birth weight and birth weight: traffic light plot.



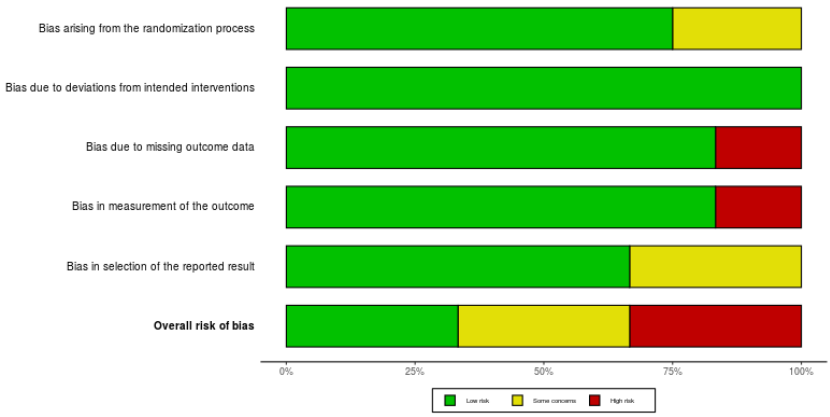
Supplementary Figure 45. ROBINS assessment for studies assessing low birth weight and birth weight: summary plot.

6.2. Small for gestational age and birth weight for gestational age

6.2A. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (v 22Aug2019)



Supplementary Figure 46. RoB2 assessment for studies assessing small for gestational age and birth weight for gestational age: traffic light plot.



Supplementary Figure 47. RoB2 assessment for studies assessing small for gestational age and birth weight for gestational age: summary plot.

6.2B. Revised Cochrane risk-of-bias tool for cluster-randomized trials (RoB 2 CRT) (v 10Nov2020)

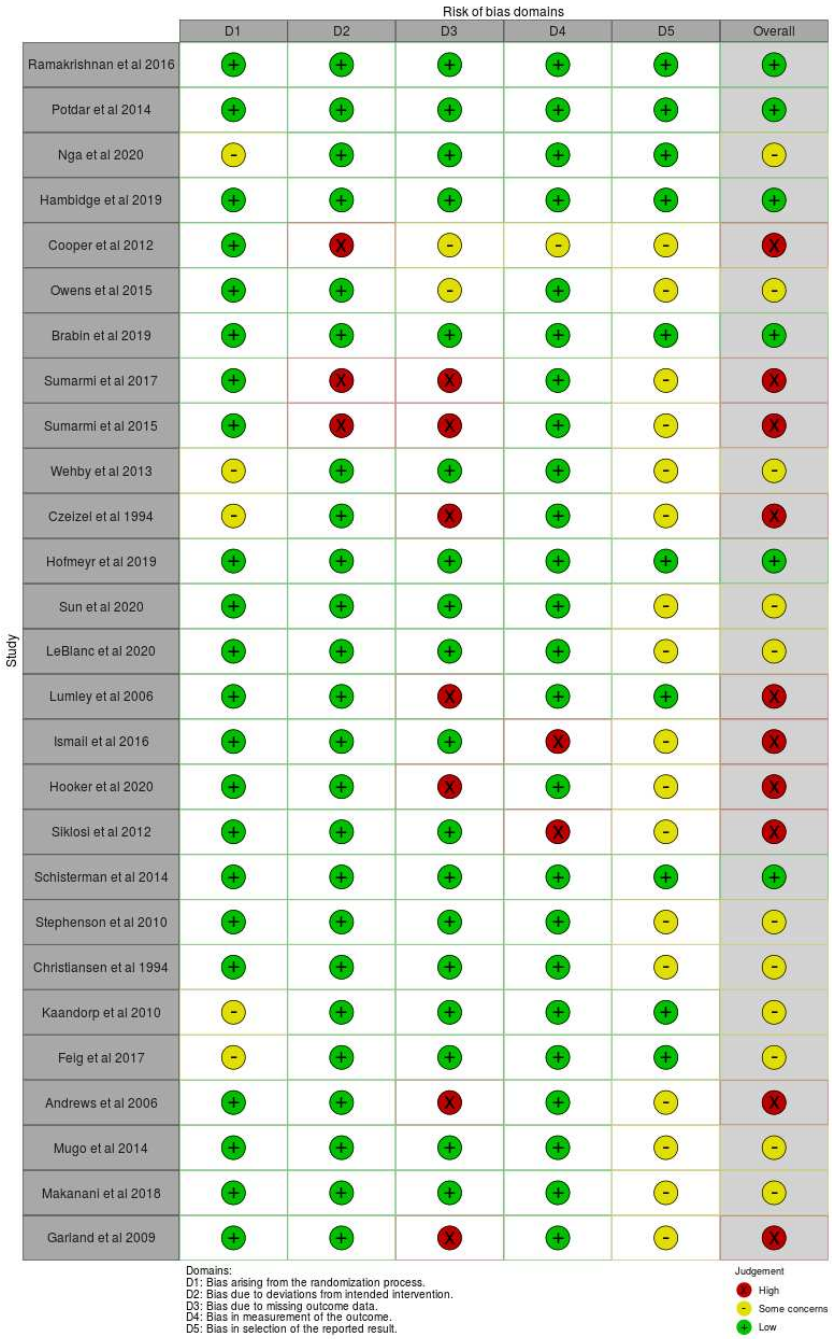
No studies

6.2C. Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) (v 01Aug2016)

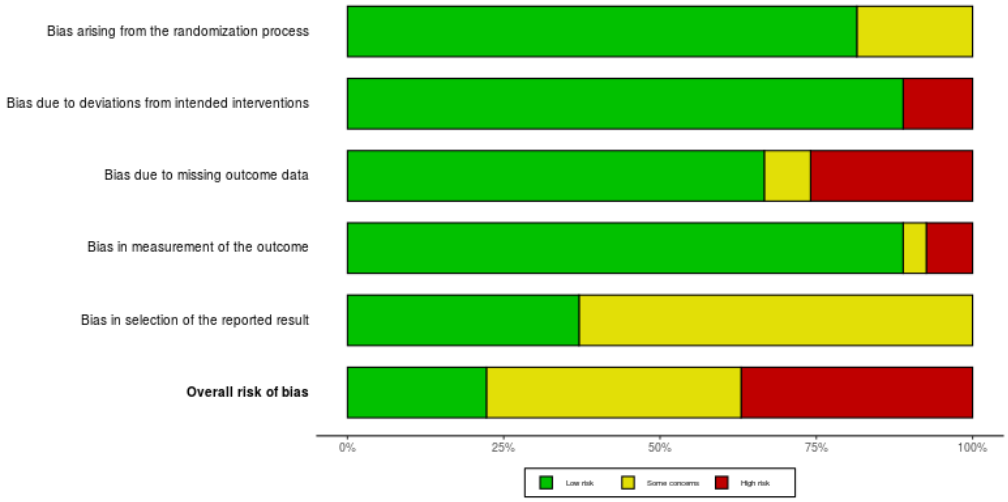
No studies

6.3. Preterm birth and gestational age

6.3A. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (v 22Aug2019)

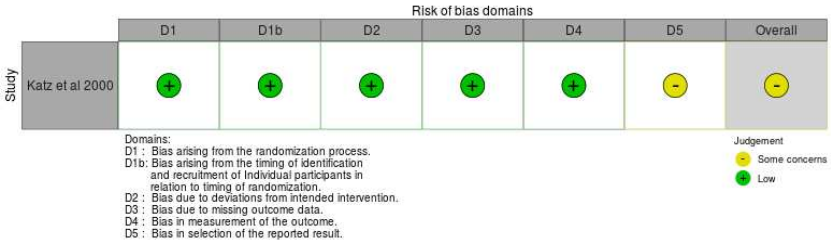


Supplementary Figure 48. RoB2 assessment for studies assessing preterm birth and gestational age: traffic light plot.



Supplementary Figure 49. RoB2 assessment for studies assessing preterm birth and gestational age: summary plot.

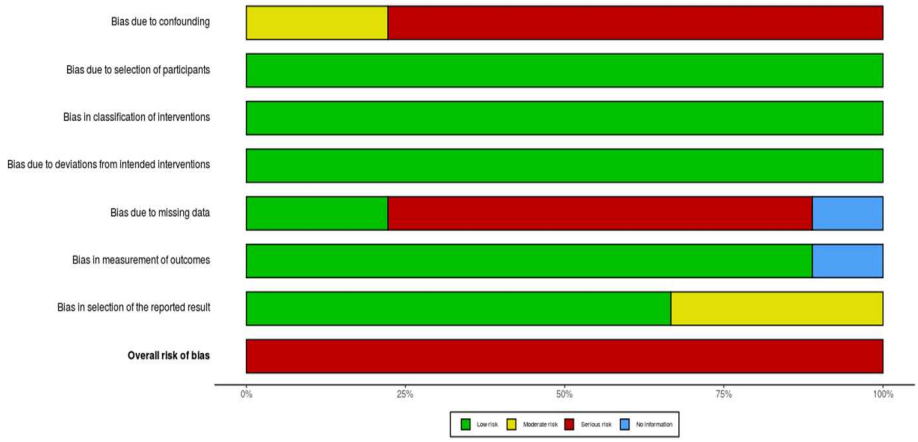
6.3B. Revised Cochrane risk-of-bias tool for cluster-randomized trials (RoB 2 CRT) (v 10Nov2020)



Supplementary Figure 50. RoB2 CRT assessment for studies assessing preterm birth and gestational age: traffic light plot.

6.3C. Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) (v 01Aug2016)

Supplementary Figure 51. ROBINS assessment for studies assessing preterm birth and gestational age: traffic light plot.



Supplementary Figure 52. ROBINS assessment for studies assessing preterm birth and gestational age: summary plot.

7. Preconception interventions to prevent low birth weight, preterm birth and small for gestational age: GRADE assessments

Notes

1. For all assessments, both available RCTs and qRCTS were assessed. Since only one option could be selected for study design, "randomised trials" was selected.

2. Studies in which the outcome of interest was part of a composite were not included. Based on this, one study was not included in analyses – de Jong-Potjer et al 2006 (comparison: pre- and periconception health interventions, outcome: composite including preterm birth).

3. Comparisons for which studies examining interventions that may affect low birth weight, small for gestational age and preterm birth were assessed separately to those examining interventions that may prevent these outcomes (signalled in the title).

4. Studies with no events of the outcome of interest were assessed separately, similarly to their treatment in meta-analyses (not included but reported separately).

5. GRADE assessments were performed and tables were generated using GRADEPro GDT (https://gradepro.org/)[74] .

Supplementary Table 29. GRADE assessment: Any general population-based nutritional intervention in the pre- and periconception period compared to folic acid supplementation, supplementation with other micronutrients (not folic acid), placebo, standard or routine care or no intervention for preventing low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**any general population-based nutritional intervention in the pre- and periconception period**	**folic acid supplementation, placebo or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Low birth weight												
7	randomised trials	serious [a]	serious [b]	not serious	not serious	publication bias strongly suspected [c]	372/6949 (5.4%)	362/7024 (5.2%)	**RR 1.07** (0.93 to 1.23)	**4 more per 1,000** (from 4 fewer to 12 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Small for gestational age												
2	randomised trials	not serious	not serious	serious	serious [d]	none	106/668 (15.9%)	116/693 (16.7%)	**RR 0.92** (0.73 to 1.15)	**13 fewer per 1,000** (from 45 fewer to 25 more)	⨁⨁◯◯ LOW	IMPORTANT
Preterm birth												
6	randomised trials	serious [e]	serious [f]	not serious	serious [g]	none	498/6856 (7.3%)	468/6827 (6.9%)	**RR 1.07** (0.79 to 1.43)	**5 more per 1,000** (from 14 fewer to 29 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. Out of 7 studies, 2 studies were high risk of bias, 3 were moderate/some concerns, and 2 were low risk.

b. There was wide variation in effects between studies, and evidence of moderate heterogeneity (I^2 46.54%).
c. Egger's test P value <0.05.
d. Optimal information size criterion not met.
e. Out of 6 studies, 2 studies were high risk of bias, 2 had some concerns, and 2 were low risk.
f. There was wide variation in effects between studies, and evidence of substantial heterogeneity (I^2 78.51%).
g. Optimal information size criterion met but 95% CIs fail to exclude important harm.

Supplementary Table 30. GRADE assessment: Any general population-based nutritional intervention from preconception throughout pregnancy compared to pregnancy-only intervention for preventing low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**any nutritional intervention from preconception throughout pregnancy**	**pregnancy-only intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Low birth weight												
3	randomised trials	serious [a]	serious [b]	serious	serious [c]	publication bias strongly suspected [d]	125/662 (18.9%)	135/672 (20.1%)	**RR 0.68** (0.33 to 1.43)	**64 fewer per 1,000** (from 135 fewer to 86 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Small for gestational age												
0									not estimable		-	
Preterm birth												
0									not estimable		-	

CI: Confidence interval; **RR:** Risk ratio

a. Out of 3 studies, 1 study was low risk of bias, 1 had some concerns and one was high risk.

b. There was variation in effect estimates, and evidence of moderate heterogeneity (I^2 54.12%).

c. Optimal information size criterion not met.

d. Egger's test P value <0.05.

Supplementary Table 31. GRADE assessment: Pre- and periconception multiple micronutrient supplementation containing iron and folic acid compared to pre- and periconception folic acid supplementation, supplementation with other micronutrients (not folic acid), placebo or no intervention for preventing low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pre- and periconception multiple micronutrient supplementation containing iron and folic acid**	**pre- and periconception folic acid supplementation, placebo or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Low birth weight												
4	randomised trials	serious [a]	serious [b]	not serious	not serious	none	290/6044 (4.8%)	271/6010 (4.5%)	**RR 1.06** (0.90 to 1.25)	**3 more per 1,000** (from 5 fewer to 11 more)	⨁⨁◯◯ LOW	IMPORTANT
Small for gestational age												
1	randomised trials	not serious	serious [c]	serious	serious [d]	none	65/525 (12.4%)	68/559 (12.2%)	**RR 1.02** (0.74 to 1.40)	**2 more per 1,000** (from 32 fewer to 49 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Preterm birth												
4	randomised trials	serious [a]	serious [b]	not serious	not serious	none	413/6125 (6.7%)	402/6110 (6.6%)	**RR 1.03** (0.90 to 1.18)	**2 more per 1,000** (from 7 fewer to 12 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. Out of 4 studies, 1 study was low risk of bias, 1 had some concerns, and 2 were high risk of bias.

b. There was notable variation in effect size point estimates, though heterogeneity was low.

c. Single study.

d. Optimal information size criterion not met.

Supplementary Table 32. GRADE assessment: Pre- and periconception iron and folic acid supplementation compared to pre- and periconception folic acid supplementation or no intervention for preventing low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pre- and periconception iron and folic acid supplementation**	**pre- and periconception folic acid supplementation or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Low birth weight												
3	randomised trials	serious [a]	serious [b]	serious	serious [c]	publication bias strongly suspected [d]	80/838 (9.5%)	95/993 (9.6%)	**RR 0.74** (0.34 to 1.61)	**25 fewer per 1,000** (from 63 fewer to 58 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Small for gestational age												
2	randomised trials	not serious	not serious	serious	serious [c]	none	94/658 (14.3%)	116/693 (16.7%)	**RR 0.83** (0.66 to 1.05)	**28 fewer per 1,000** (from 57 fewer to 8 more)	⨁⨁◯◯ LOW	IMPORTANT
Preterm birth												
2	randomised trials	not serious	serious [e]	serious	serious [c]	none	89/664 (13.4%)	75/696 (10.8%)	**RR 1.42** (0.60 to 3.37)	**45 more per 1,000** (from 43 fewer to 255 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. Out of 3 studies, 1 was moderate risk of bias, while 2 were low risk.

b. There was wide variation in effect estimates, with high heterogeneity (I^2 83.10%).

c. Optimal information size criterion not met.

d. Egger's test P value <0.05.

e. There was wide variation in effect estimates, with high heterogeneity (I^2 87.79%).

Supplementary Table 33. GRADE assessment: Preconception and pregnancy iron and folic acid supplementation compared to pregnancy-only iron and folic acid supplementation for preventing low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**preconception and pregnancy iron and folic acid supplementation**	**Pregnancy-only iron and folic acid supplementation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Low birth weight												
1	randomised trials	serious [a]	serious [b]	serious	serious [c]	all plausible residual confounding would reduce the demonstrated effect	3/144 (2.1%)	8/86 (9.3%)	**RR 0.28** (0.08 to 1.03)	**67 fewer per 1,000** (from 86 fewer to 3 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Small for gestational age												
0									not estimable		-	
Preterm birth												
0									not estimable		-	

CI: Confidence interval; **RR:** Risk ratio

a. The single identified study was rated as high risk of bias.

b. Single study.

c. Optimal information size criterion not met.

Supplementary Table 34. GRADE assessment: Pre- and periconception food supplementation longer duration compared to shorter duration of food supplementation for preventing low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pre- and periconception food supplementation longer duration**	**shorter duration of food supplementation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Low birth weight												
1	randomised trials	serious [a]	serious [b]	serious	serious [c]	none	-/273	-/256	**OR 0.40** (0.14 to 1.12)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Small for gestational age												
0									not estimable		-	
Preterm birth												
0									not estimable		-	

CI: Confidence interval; **OR:** Odds ratio

a. The single identified study was rated as high risk of bias.

b. Single study.

c. Optimal information size criterion not met.

Supplementary Table 35. GRADE assessment: Preconception and pregnancy food supplementation compared to pregnancy-only food supplementation for preventing low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**preconception and pregnancy food supplementation**	**pregnancy-only food supplementation**	**Relative (95% CI)**	**Absolute (95% CI)**		
Low birth weight												
2	randomised trials	not serious	serious [a]	serious	serious [b]	none	122/548 (22.3%)	127/586 (21.7%)	**RR 1.00** (0.79 to 1.26)	**0 fewer per 1,000** (from 46 fewer to 56 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Small for gestational age												
2	randomised trials	not serious	not serious	serious	serious [b]	none	171/562 (30.4%)	202/599 (33.7%)	**RR 0.89** (0.78 to 1.02)	**37 fewer per 1,000** (from 74 fewer to 7 more)	⨁⨁◯◯ LOW	IMPORTANT
Preterm birth												
2	randomised trials	not serious	serious [a]	serious	serious [b]	none	73/563 (13.0%)	57/600 (9.5%)	**RR 1.38** (1.06 to 1.79)	**36 more per 1,000** (from 6 more to 75 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. There was notable variation in effect size estimates, although there was no evidence of heterogeneity.

b. Optimal information size criterion not met.

Supplementary Table 36. GRADE assessment: Pre- and periconception general health interventions compared to standard or routine care for preventing low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pre- and periconception general health interventions**	**standard or routine care or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Low birth weight												
2	randomised trials	very serious [a]	not serious	serious	serious [b]	none	39/476 (8.2%)	66/712 (9.3%)	**RR 1.27** (0.83 to 1.94)	**25 more per 1,000** (from 16 fewer to 87 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Small for gestational age												
1	randomised trials	very serious [c]	serious [d]	serious	serious [b]	none	40/378 (10.6%)	31/382 (8.1%)	**RR 1.13** (0.57 to 2.14)	**11 more per 1,000** (from 35 fewer to 93 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Preterm birth												
1	randomised trials	very serious [c]	serious [d]	serious	serious [b]	none	24/392 (6.1%)	17/394 (4.3%)	**RR 1.41** (0.74 to 2.69)	**18 more per 1,000** (from 11 fewer to 73 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. Both studies identified were high risk of bias.

b. Optimal information size criterion not met.

c. The single study identified was assessed as high risk of bias.

d. Single study.

Supplementary Table 37. GRADE assessment: Pre- and periconception interventions to prevent early adverse pregnancy outcomes compared to placebo or no intervention for preventing low birth weight, small for gestational age, or preterm birth, among women with one or more previous miscarriages.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pre- and periconception interventions to prevent early adverse pregnancy outcomes**	**placebo or no intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Low birth weight												
1	randomised trials	very serious [a]	serious [b]	serious	serious [c]	strong association	7/52 (13.5%)	17/30 (56.7%)	**RR 0.23** (0.11 to 0.51)	**436 fewer per 1,000** (from 504 fewer to 278 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Small for gestational age												
2	randomised trials	very serious [d]	not serious	not serious	serious [c]	strong association	11/119 (9.2%)	24/89 (27.0%)	**RR 0.35** (0.18 to 0.68)	**175 fewer per 1,000** (from 221 fewer to 86 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Preterm birth												
5	randomised trials	very serious [e]	serious [f]	not serious	serious [c]	strong association	21/219 (9.6%)	50/163 (30.7%)	**RR 0.32** (0.20 to 0.51)	**209 fewer per 1,000** (from 245 fewer to 150 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. The single identified study was assessed as high risk of bias.

b. Single study.

c. Optimal information size criterion not met.

d. Both identified studies were assessed as high risk of bias.

e. Out of 5 studies, 3 studies were high risk of bias and 2 had some concerns.

f. There was notable variation in effect size point estimates, though heterogeneity was low.

Supplementary GRADE assessment: Preconception and pregnancy interventions to prevent or manage non-communicable diseases compared to pregnancy-only intervention that may affect low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**preconception and pregnancy interventions to prevent or manage non-communicable diseases**	**pregnancy-only intervention**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Low birth weight												
1	randomised trials	very serious [a]	serious [b]	serious	serious [c]	all plausible residual confounding would suggest spurious effect, while no effect was observed	7/92 (7.6%)	1/57 (1.8%)	**RR 4.34** (0.55 to 34.34)	**59 more per 1,000** (from 8 fewer to 585 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Small for gestational age												
0									not estimable		-	
Preterm birth												
0									not estimable		-	

CI: Confidence interval; **RR:** Risk ratio

a. The single study identified was assessed as high risk of bias.

b. Single study.

c. Optimal information size criterion not met.

Supplementary Table 39. GRADE assessment: Pre- and periconception interventions to prevent or manage infectious diseases compared to placebo or no intervention for preventing low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pre- and periconception interventions to prevent or manage infectious diseases	placebo or no intervention	Relative (95% CI)	Absolute (95% CI)		
Low birth weight												
0									not estimable		-	
Small for gestational age												
0									not estimable		-	
Preterm birth												
2	randomised trials	very serious [a]	serious [b]	serious	serious [c]	none	131/2009 (6.5%)	62/266 (23.3%)	**RR 0.62** (0.20 to 1.93)	**89 fewer per 1,000** (from 186 fewer to 217 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. Both identified studies were high risk of bias.

b. There was wide variation in effects between studies, and evidence of substantial heterogeneity (I^2 95.34%).

c. Optimal information size criterion not met.

Supplementary Table 40. GRADE assessment: Pre- and periconception interventions to prevent or manage infectious diseases compared to placebo or alternative intervention, or no intervention that may affect low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pre- and periconception interventions to prevent or manage infectious diseases	placebo or no intervention	Relative (95% CI)	Absolute (95% CI)		
Low birth weight												
1	randomised trials	very serious [a]	serious [b]	serious	serious [c]	none	3/23 (13.0%)	0/16 (0.0%)	**RR 4.96** (0.27 to 89.87)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Small for gestational age												
1	randomised trials	very serious [a]	serious [b]	serious	serious [d]	none	5/1447 (0.3%)	4/1424 (0.3%)	**RR 1.23** (0.33 to 4.57)	**1 more per 1,000** (from 2 fewer to 13 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Preterm birth												
3	randomised trials	very serious [e]	not serious	not serious	serious [c]	none	49/1872 (2.6%)	43/1794 (2.4%)	**RR 1.05** (0.71 to 1.57)	**1 more per 1,000** (from 7 fewer to 14 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Preterm birth (single study no events intervention group)												
1	randomised trials	serious [f]	serious [b]	serious	serious [c]	strong association	0/87 (0.0%)	9/94 (9.6%)	**RR 0.06** (0.00 to 0.96)	**90 fewer per 1,000** (from 4 fewer to --)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. The single study identified was assessed as high risk of bias.

b. Single study.

c. Optimal information size criterion not met.

d. Optimal information size criterion met but 95% CIs fail to exclude important benefit or harm.
e. Out of 3 studies, 2 were high risk of bias and one had some concerns.
f. The identified study had some concerns for risk of bias.

Supplementary Table 41. GRADE assessment: Preconception and pregnancy interventions to prevent or manage infectious diseases compared to pregnancy-only intervention that may affect low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**preconception and pregnancy interventions to prevent or manage infectious diseases**	**pregnancy-only intervention**	**Relative (95% CI)**	**Absolute (95% CI)**		
Low birth weight												
1	randomised trials	serious [a]	serious [b]	serious	serious [c]	strong association	19/90 (21.1%)	9/96 (9.4%)	**RR 2.65** (1.20 to 5.81)	**155 more per 1,000** (from 19 more to 451 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Small for gestational age												
0									not estimable		-	
Preterm birth												
0									not estimable		-	

CI: Confidence interval; **RR:** Risk ratio

a. The single study identified was assessed to have some concerns for risk of bias.

b. Single study.

c. Optimal information size criterion not met.

Supplementary Table 42. GRADE assessment: Pre- and periconception interventions to promote reproductive planning compared to standard or routine care for preventing low birth weight, small for gestational age, or preterm birth.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pre- and periconception interventions to promote reproductive planning	standard or routine care	Relative (95% CI)	Absolute (95% CI)		
Low birth weight												
0									not estimable		-	
Small for gestational age												
0									not estimable		-	
Preterm birth												
1	randomised trials	very serious [a]	serious [b]	serious	serious [c]	none	122/603 (20.2%)	140/537 (26.1%)	**RR 0.79** (0.63 to 0.99)	**55 fewer per 1,000** (from 96 fewer to 3 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

a. The single identified study was high risk of bias.

b. Single study.

c. Optimal information size criterion not met.

References

1 Higgins J, Thomas J, Chandler J, *et al.*, editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020 www.training.cochrane.org/handbook.

2 Hulland EN, Blanton CJ, Leidman EZ, Bilukha OO. Parameters associated with design effect of child anthropometry indicators in small-scale field surveys. *Emerging Themes in Epidemiology* 2016; **13**: 13.

3 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**: 1445S-52S.

4 Czeizel AE, Dudás I, Métneki J. Pregnancy outcomes in a randomised controlled trial of periconceptional multivitamin supplementation. Final report. *Arch Gynecol Obstet* 1994; **255**: 131–9.

5 Czeizel AE, Dobó M, Vargha P. Hungarian cohort-controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital abnormalities. *Birth Defects Res A Clin Mol Teratol* 2004; **70**: 853–61.

6 ICMR. Multicentric study of efficacy of periconceptional folic acid containing vitamin supplementation in prevention of open neural tube defects from India. *Indian J Med Res* 2000; **112**: 206–11.

7 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**: 161.

8 Passerini L, Casey GJ, Biggs BA, *et al.* Increased birth weight associated with regular pre-pregnancy deworming and weekly iron-folic acid supplementation for Vietnamese women. *PLoS Negl Trop Dis* 2012; **6**: e1608.

9 Sun L, Niu Z. A mushroom diet reduced the risk of pregnancy-induced hypertension and macrosomia: a randomized clinical trial. *Food Nutr Res* 2020; **64**. DOI:10.29219/fnr.v64.4451.

10 Berger J, Thanh HTK, Cavalli-Sforza T, *et al.* Community mobilization and social marketing to promote weekly iron-folic acid supplementation in women of reproductive age in Vietnam: impact on anemia and iron status. *Nutr Rev* 2005; **63**: S95-108.

11 Nga HT, Quyen PN, Chaffee BW, Diep Anh NT, Ngu T, King JC. Effect of a nutrient-rich, food-based supplement given to rural Vietnamese mothers prior to and/or during pregnancy on birth outcomes: A randomized controlled trial. *PLoS One* 2020; **15**: e0232197.

12 Hambidge KM, Westcott JE, Garcés 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**: 457–69.

13 Lumley J, Donohue L. Aiming to increase birth weight: a randomised trial of pre-pregnancy information, advice and counselling in inner-urban Melbourne. *BMC Public Health* 2006; **6**: 299.

14 Livingood WC, Brady C, Pierce K, Atrash H, Hou T, Bryant T 3rd. Impact of pre-conception health care: evaluation of a social determinants focused intervention. *Matern Child Health J* 2010; **14**: 382–91.

15 Ismail A.M., Hamed A.H., Saso S., Abu-Elhasan A.M., Abu-Elghar M.M., Abdelmeged A.N. Randomized controlled study of pre-conception thromboprophylaxis among patients with recurrent spontaneous abortion related to antiphospholipid syndrome. *International Journal of Gynecology and Obstetrics* 2016; **132**: 219–23.

16 Siklósi GS, Bánhidy FG, Ács N. Fundamental role of folliculo-luteal function in recurrent miscarriage. *Arch Gynecol Obstet* 2012; **286**: 1299–305.

17 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**: 1450–9.

18 Hooker A.B., de Leeuw R.A., Twisk J.W.R., Brolmann H.A.M., Huirne J.A.F. Pregnancy and neonatal outcomes 42 months after application of hyaluronic acid gel following dilation and curettage for miscarriage in women who have experienced at least one previous curettage: follow-up of a randomized controlled trial. *Fertility and Sterility* 2020; **114**: 601–9.

19 Stephenson M.D., Kutteh W.H., Purkiss S., *et al.* Intravenous immunoglobulin and idiopathic secondary recurrent miscarriage: A multicentered randomized placebo-controlled trial. *Human Reproduction* 2010; **25**: 2203–9.

20 Christiansen OB, Mathiesen O, Husth M, Lauritsen JG, Grunnet N. Placebo-controlled trial of active immunization with third party leukocytes in recurrent miscarriage. *Acta Obstetricia et Gynecologica Scandinavica* 1994; **73**: 261–8.

21 Russu M., Stanculescu R., Nastasia S., *et al.* Pregnancy outcomes following preconception, early and late administration of vaginal micronized progesterone for recurrent pregnancy loss. *Gineco.ro* 2009; **5**: 10–5.

22 Schisterman EF, Silver RM, Lesher LL, *et al.* Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. *Lancet* 2014; **384**: 29–36.

23 Kaandorp SP, Goddijn M, van der Post JAM, *et al.* Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *N Engl J Med* 2010; **362**: 1586–96.

24 Andrews WW, Goldenberg RL, Hauth JC, Cliver SP, Copper R, Conner M. Interconceptional antibiotics to prevent spontaneous preterm birth: a randomized clinical trial. *Am J Obstet Gynecol* 2006; **194**: 617–23.

25 Banhidy F., DudaS I., Czeizel A.E. Preconceptional screening of sexually transmitted infections/diseases. *Central European Journal of Medicine* 2010; **6**: 49–57.

26 Mugo NR, Hong T, Celum C, *et al.* Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. *JAMA* 2014; **312**: 362–71.

27 Garland SM, Ault KA, Gall SA, *et al.* Pregnancy and Infant Outcomes in the Clinical Trials of a Human Papillomavirus Type 6/11/16/18 Vaccine: A Combined Analysis of Five Randomized Controlled Trials. *Obstetrics & Gynecology* 2009; **114**: 1179–88.

28 Angelo M-G, David M-P, Zima J, *et al.* Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. *Pharmacoepidemiol Drug Saf* 2014; **23**: 466–79.

29 Makanani B, Balkus JE, Jiao Y, *et al.* Pregnancy and Infant Outcomes Among Women Using the Dapivirine Vaginal Ring in Early Pregnancy. *J Acquir Immune Defic Syndr* 2018; **79**: 566–72.

30 Caan B, Horgen DM, Margen S, King JC, Jewell NP. Benefits associated with WIC supplemental feeding during the interpregnancy interval. *Am J Clin Nutr* 1987; **45**: 29–41.

31 Hofmeyr GJ, 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**: 330–9.

32 Sumarmi S, Melaniani S, Kuntoro K, *et al.* Prolonging micronutrients supplementation 2-6 months prior to pregnancy significantly improves birth weight by increasing HPL production and controlling IL-12 concentration: a randomized double blind controlled study. *Ann Nutr Metab* 2017; **71**: 554-.

33 Potdar RD, Sahariah SA, Gandhi M, *et al.* Improving women's diet quality preconceptionally and during gestation: effects on birth weight and prevalence of low birth weight-a randomized controlled efficacy trial in India (Mumbai Maternal Nutrition Project). *Am J Clin Nutr* 2014; **100**: 1257–68.

34 Cérbulo-Vázquez A, Arriaga-Pizano L, Cruz-Cureño G, *et al.* Medical Outcomes in Women Who Became Pregnant after Vaccination with a Virus-Like Particle Experimental Vaccine against Influenza A (H1N1) 2009 Virus Tested during 2009 Pandemic Outbreak. *Viruses* 2019; **11**. DOI:10.3390/v11090868.

35 The Diabetes Control Complications Trial Research Group. Pregnancy outcomes in the Diabetes Control and Complications Trial. *Am J Obstet Gynecol* 1996; **174**: 1343–53.

36 Theron G, Brummel S, Fairlie L, *et al.* Pregnancy outcomes of women conceiving on antiretroviral therapy (ART) compared to those commenced on ART during pregnancy. *Clin Infect Dis* 2020. DOI:10.1093/cid/ciaa805.

37 Jourabchi Z, Sharif S, Lye MS, Saeed A, Khor GL, Tajuddin SHS. Association Between Preconception Care and Birth Outcomes. *Am J Health Promot* 2018; **33**: 363–71.

38 Taylor AW, Mosimaneotsile B, Mathebula U, *et al.* Pregnancy outcomes in HIV-infected women receiving long-term isoniazid prophylaxis for tuberculosis and antiretroviral therapy. *Infect Dis Obstet Gynecol* 2013; **2013**: 195637.

39 Cooper WN, Khulan B, Owens S, *et al.* DNA methylation profiling at imprinted loci after periconceptional micronutrient supplementation in humans: results of a pilot randomized controlled trial. *FASEB J* 2012; **26**: 1782–90.

40 Chaouki ML, Benmiloud M. Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy. *Eur J Endocrinol* 1994; **130**: 547–51.

41 Wehby GL, Félix TM, Goco N, *et al.* High Dosage Folic Acid Supplementation, Oral Cleft Recurrence and Fetal Growth. *Int J Environ Res Public Health* 2013; **10**: 590–605.

42 Widasari L. Effects of multimicronutrient supplementation in preconception period against VEGF/SFLT-1 ratio and birth weight: a randomized, double blind controlled trial in Banggai regency, Central Sulawesi. 2019; **75**: 99-.

43 Willhoite MB, Bennert HWJ, Palomaki GE, *et al.* The impact of preconception counseling on pregnancy outcomes. The experience of the Maine Diabetes in Pregnancy Program. *Diabetes Care* 1993; **16**: 450–5.

44 Andrews WW, Goldenberg RL, Hauth JC, Cliver SP, Copper R, Conner M. Interconceptional antibiotics to prevent spontaneous preterm birth: a randomized clinical trial. *Am J Obstet Gynecol* 2006; **194**: 617–23.

45 Feig D, Donovan L, Corcoy R, *et al.* Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet* 2017; **(no pagination)**. DOI:10.1016/S0140-6736%2817%2932400-5.

46 LeBlanc ES, Smith NX, Vesco KK, Paul IM, Stevens VJ. Weight loss prior to pregnancy and subsequent gestational weight gain: Prepare, a randomized clinical trial. *Am J Obstet Gynecol* 2020. DOI:10.1016/j.ajog.2020.07.027.

47 Rönö K, Stach-Lempinen B, Eriksson JG, *et al.* Prevention of gestational diabetes with a prepregnancy lifestyle intervention – findings from a randomized controlled trial. International Journal of Women's Health. 2018; **10**: 493–501.

48 Sumarmi S, Wirjatmadi B, Kuntoro, Gumilar E, Adriani M, Retnowati E. Micronutrients Supplementation during Preconception Period Improves Fetal Survival and Cord Blood Insulin-Like Growth Factor 1. *Asian Journal of Clinical Nutrition* 2015; **7**: 33–44.

49 Katz J, West KPJ, Khatry SK, *et al.* Maternal low-dose vitamin A or beta-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal. *Am J Clin Nutr* 2000; **71**: 1570–6.

50 de Jong-Potjer L, Elsinga J, le Cessie S, *et al.* GP-initiated preconception counselling in a randomised controlled trial does not induce anxiety. *BMC Family Practice* 2006; **7**: 66.

51 Baqui AH, Ahmed S, Begum N, *et al.* Impact of integrating a postpartum family planning program into a community-based maternal and newborn health program on birth spacing and preterm birth in rural Bangladesh. *J Glob Health* 2018; **8**: 020406.

52 Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. *Am J Med Genet* 1996; **62**: 179–83.

53 Smithells RW, Sheppard S, Schorah CJ, *et al.* Apparent prevention of neural tube defects by periconceptional vitamin supplementation. *Arch Dis Child* 1981; **56**: 911–8.

54 Smithells RW, Seller MJ, Harris R, *et al.* FURTHER EXPERIENCE OF VITAMIN SUPPLEMENTATION FOR PREVENTION OF NEURAL TUBE DEFECT RECURRENCES. *The Lancet* 1983; **321**: 1027–31.

55 Chen G, Song X, Ji Y, *et al.* Prevention of NTDs with periconceptional multivitamin supplementation containing folic acid in China. *Birth Defects Res A Clin Mol Teratol* 2008; **82**: 592–6.

56 MRC. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. *Lancet* 1991; **338**: 131–7.

57 Kirke PN, Daly LE, Elwood JH. A randomised trial of low dose folic acid to prevent neural tube defects. The Irish Vitamin Study Group. *Arch Dis Child* 1992; **67**: 1442–6.

58 Laurence KM, James N, Miller MH, Tennant GB, Campbell H. Double-blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural-tube defects. *Br Med J (Clin Res Ed)* 1981; **282**: 1509–11.

59 Berry RJ, Li Z, Erickson JD, *et al.* Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. *N Engl J Med* 1999; **341**: 1485–90.

60 Myers MF, Li S, Correa-Villaseñor A, *et al.* Folic Acid Supplementation and Risk for Imperforate Anus in China. *American Journal of Epidemiology* 2001; **154**: 1051–6.

61 Gies S, Diallo S, Roberts SA, *et al.* Effects of Weekly Iron and Folic Acid Supplements on Malaria Risk in Nulliparous Women in Burkina Faso: A Periconceptional, Double-Blind, Randomized Controlled Noninferiority Trial. *J Infect Dis* 2018; **218**: 1099–109.

62 Vergel RG, Sanchez LR, Heredero BL, Rodriguez PL, Martinez AJ. Primary prevention of neural tube defects with folic acid supplementation: Cuban experience. *Prenat Diagn* 1990; **10**: 149–52.

63 Chen W, Zhao Y, Xie X, *et al.* Safety of a quadrivalent human papillomavirus vaccine in a Phase 3, randomized, double-blind, placebo-controlled clinical trial among Chinese women during 90 months of follow-up. *Vaccine* 2019; **37**: 889–97.

64 Wacholder S, Chen BE, Wilcox A, *et al.* Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials. *BMJ* 2010; **340**: c712.

65 Hoffman RM, Brummel SS, Britto P, *et al.* Adverse Pregnancy Outcomes Among Women Who Conceive on Antiretroviral Therapy. *Clin Infect Dis* 2019; **68**: 273–9.

66 Manandhar DS, Osrin D, Shrestha BP, *et al.* Effect of a participatory intervention with women's groups on birth outcomes in Nepal: cluster-randomised controlled trial. *The Lancet* 2004; **364**: 970–9.

67 Nguyen PH, Young M, Gonzalez-Casanova I, *et al.* Impact of Preconception Micronutrient Supplementation on Anemia and Iron Status during Pregnancy and Postpartum: A Randomized Controlled Trial in Rural Vietnam. *PLoS One* 2016; **11**: e0167416.

68 Khambalia AZ, O'Connor DL, Macarthur C, Dupuis A, Zlotkin SH. Periconceptional iron supplementation does not reduce anemia or improve iron status among pregnant women in rural Bangladesh. *Am J Clin Nutr* 2009; **90**: 1295–302.

69 Sahariah SA, Potdar RD, Gandhi M, *et al.* A Daily Snack Containing Leafy Green Vegetables, Fruit, and Milk before and during Pregnancy Prevents Gestational Diabetes in a Randomized, Controlled Trial in Mumbai, India. *J Nutr* 2016; **146**: 1453S-60S.

70 Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**. DOI:10.1136/bmj.l4898.

71 Eldridge S, Campbell M, Campbell M, *et al.* Revised Cochrane risk of bias tool for randomized trials (RoB 2); Additional considerations for cluster-randomized trials (RoB 2 CRT). .

72 Sterne JA, Hernán MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**. DOI:10.1136/bmj.i4919.

73 McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods* 2020; **n/a**. DOI:10.1002/jrsm.1411.

74 Evidence Prime. GRADEpro GDT. Hamilton, Ontario: McMaster University (developed by Evidence Prime) https://gradepro.org/ (accessed Oct 12, 2020).