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Role of preconception nutrition supplements in maternal anemia and intrauterine growth: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Impaired intrauterine growth, a significant global health problem, contributes to a higher burden of infant morbidity and mortality, mainly in resource-poor settings. Maternal anemia and undernutrition, two important causes of impaired intrauterine growth, are prioritized by global nutrition targets of 2030. We synthesized the evidence on the role of preconception nutrition supplements in reducing maternal anemia and improving intrauterine growth.

Methods We undertook a review of the randomized controlled trials (RCTs) assessing the effect of preconception nutrition supplements on maternal hemoglobin, an indicator to estimate maternal anemia, and markers of intrauterine growth including birth weight, length, head circumference, and small for gestational age. Additionally, we examined preterm birth as an important perinatal outcome. We searched PubMed, CINAHL, Web of Science, Cochrane Central, and Embase. We computed summary mean differences and risk ratios (RR) with 95% confidence intervals (CIs) using random-effect models. We employed I^2 and Cochran's Q test statistics to assess heterogeneity. We used a revised Cochrane risk-of-bias (RoB version 2.0) and GRADE (grading of recommendations, assessment, development, and evaluation) tools to assess the risk of bias and quality of evidence of eligible RCTs, respectively.

Results We identified 20 eligible RCTs ($n=27{,}659$ women). Preconception nutrition supplements (iron and folic acid, multiple micronutrients, and a lipid-based nutrient supplement) overall increased maternal hemoglobin by 0.30 g/dL ((0.03, 0.57); $I^2=79\%$; n=9). However, we did not find a significant effect of the supplements on birth weight (12.25 gm ((− 22.66, 47.16); $I^2=55\%$; n=10)), length (0.15 cm (− 0.26, 0.56); $I^2=68\%$; $n=5$), head circumference (− 0.23 cm (− 0.88, 0.43); $I^2=84\%$; n=4), small for gestational age (RR 0.91 (0.80, 1.04); $I^2=31\%$; n=8), or preterm birth (RR 0.93 (0.69,1.25); $I^2=57\%$; n=12). In general, the quality of evidence was assessed as very low to moderate.

Conclusion Preconception nutrition supplements studied to date appear to reduce maternal anemia. However, it is uncertain whether there are beneficial effects of the supplements on intrauterine growth. Low quality of evidence

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warrants future well-designed RCTs to produce solid scientific data, particularly of a more comprehensive package of preconception nutrition supplements that include both macro- and micronutrients.

Systematic review registration PROSPERO CRD42023464966.

Keywords Preconception nutrition supplements, Maternal anemia, Intrauterine growth, Systematic review, Meta-analysis

Background

The prevalence of impaired intrauterine growth is almost six times higher in low and middle-income countries (LMICs) than in high-income countries (HICs) [1]. Asia accounts for about 75% of the prevalence of impaired intrauterine growth, followed by Africa and Latin America [2]. Intrauterine growth is an inferred process with a small gestational age (SGA) considered a rough estimate of impaired fetal growth, which can only be calculated with reliable gestational age data [3]. Due to sparse data and measurement errors in gestational age, experts in the field of perinatal health typically rely on birth weight, length, and head circumference as markers to infer intrauterine growth [4]. Impaired intrauterine growth is associated with wasting and stunting, and about one-fifth of stunting in children in LMICs may have been directly impacted during the intrauterine period [5].

The adverse outcomes associated with impaired intrauterine growth such as stunting, wasting, cognitive decline, and neurological impairment are not only limited to infancy but span across life [5]. While the etiology of impaired intrauterine growth is multifactorial, maternal anemia and undernutrition are the main contributors to impaired intrauterine growth [6] and are prioritized in 2030 global nutrition targets by the World Health Assembly [7]. Addressing maternal undernutrition and nutritional anemia by appropriate intake of micro-and macronutrients is pivotal for optimal fetal growth [8]. Micro- and macronutrients are crucial for cell division, embryogenesis, enzymatic processes, and protein metabolism required for adequate fetal growth, development, and function [8]. Demand for micro-and macronutrients increases during pregnancy due to the formation of the placenta, maternal tissues, and fetal growth [9]. Failure to meet the demands may lead to maternal anemia, impaired intrauterine growth, preterm births, stillbirths, cognitive delays, and neonatal mortality [10].

Among socially disadvantaged women living in food-insecure areas, obtaining a nutritious diet to reduce the burden of maternal anemia and associated impaired fetal growth can be challenging without considering additional nutrition supplements [11, 12]. Such nutrition supplements include but are not limited to, iron and folic acid, multiple micronutrients, macronutrients, and nutrient-dense lipid-based supplements [12]. Nutrition supplements during pregnancy have been found to reduce maternal anemia as indicated by improved maternal hemoglobin levels [13, 14]. However, the effect of the nutrition supplements during pregnancy on intrauterine growth appears to be small to negligible, which has shifted the researchers' focus to the preconception period [15]. Providing nutrient supplements before conception may be crucial as the preconception window offers an opportunity to intervene for a relatively longer duration to rectify nutrient deficits before pregnancy [16]. Maximum gains can be achieved in terms of favorable birth outcomes by providing nutrient supplements to women during the preconception period, a crucial period for laying the foundation for a healthy pregnancy and favorable birth outcomes [17].

However, the epidemiological evidence for the significance of preconception nutrition is sparse and inconclusive, with a preponderance of animal and observational studies or natural experiments [18, 19]. Prior reviews on the preconception period have either synthesized the evidence from observational studies [20, 21], or have studied outcomes such as congenital anomalies or neural tube defects, neurodevelopment disorders, or only birth weight [22, 23]. Hence, the prior reviews have not comprehensively assessed the effect of preconception nutrition supplements on maternal anemia and all markers of intrauterine growth including birth weight, length, and head circumference. To address this knowledge gap, we undertook a systematic review and meta-analysis of the randomized controlled trials (RCTs) assessing the effect of preconception nutrition supplements on maternal anemia and the markers of intrauterine growth.

Material and methods

Sources of information and search strategy

We conducted this systematic review and meta-analysis in accordance with standard methodological practices, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3) [24]. The reporting of the review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines [25]. We searched electronic databases, including PubMed, CINAHL, Web of Science, Cochrane Central, and Embase from inception through June 30th,

2024. Additionally, we searched Google Scholar, clinical trials.gov, and reference lists of published primary and review articles to identify relevant publications not captured by electronic searches. Under the guidance of the research librarian, we carried out a search using combinations of search terms such as "preconception", "nutrient supplements" (iron and folic acid, multivitamins, multiple micronutrients, macronutrients, and lipid-based nutrient supplements), "maternal hemoglobin", "maternal anemia", and "intrauterine growth". Initially, we identified major concepts, including preconception, nutrient supplements, maternal hemoglobin, and intrauterine growth and their synonyms. Preconception-related synonyms included "before conception", "pre-pregnancy", "prior to pregnancy", "periconception", and "before pregnancy". For intrauterine growth, potentially related terms included 'birth weight,' 'birth length,' 'birth head circumference,' 'small for gestational age', 'newborn anthropometry,' and 'newborn size.' Next, we combined the major concepts using Boolean operators (AND, OR) (Supplemental Table S1).

Eligibility criteria

We used the PICO framework to group eligibility criteria into (1) population, (2) intervention, (3) comparison, and (4) outcome [26]. The population included non-pregnant women planning to conceive in the future. The intervention was a nutrition supplement including iron and folic acid, multivitamins, multiple micro or macronutrients, or lipid-based nutrient supplements. The comparison group was either a placebo, no intervention, routine antenatal care, or alternative supplement as standard of care. The outcomes included maternal hemoglobin (g/dL) and markers of intrauterine growth including birth weight (gm), length (cm), head circumference (cm), and small for gestational age (birth weight < 10th percentile for gestational age). While preterm birth (birth before 37 weeks of gestation) is not a marker of intrauterine growth and has distinct risk factors, it is a commonly reported perinatal outcome and has a strong effect on postnatal outcomes [27]. Hence, we studied preterm birth as an additional outcome in the current review. We included RCTs if they (1) investigated the effect of nutrient supplements, offered during the preconception period, on the above-mentioned outcomes; (2) reported effect sizes, i.e., mean differences or risk ratios for the continuous or binary outcomes, respectively or provided sufficient raw data to calculate the effect sizes; and (3) published in the English language. Additionally, we had access to unpublished hemoglobin data from a large multi-country Women First (WF) Preconception Nutrition trial. Hence, we included the data from the WF trial for the current review and meta-analysis. We excluded studies if they were observational studies, reviews, letters to the editors, commentaries, or animal studies. We did not apply restrictions on the publication year or study setting. We registered the study protocol to the PROSPERO database (registration number: CRD42023464966).

It is not uncommon to publish two to three separate papers on different outcomes using the data from the same RCT. For example, the researchers may design and conduct one RCT but two separate papers, one on maternal hemoglobin and the other on at least one marker of intrauterine growth, may be published from a single RCT. These multiple papers from one RCT were defined as records/citations in the current review and the number of records/citations included in the review may be greater than the number of unique RCTs.

Selection of studies

We uploaded all citations into Covidence review management software to read, screen, and filter abstracts and full-text manuscripts. After removing the duplicates, two independent reviewers (Sumera Aziz Ali (SAA) and Nayab Khowaja (NK)) screened titles and abstracts and removed irrelevant citations using the same protocol. Within Covidence, the reviewers marked "yes" if the title and/or abstract meets the inclusion criteria; otherwise, they marked "No." In case of doubt, the reviewers marked "maybe." If one reviewer considered "Yes" and the other marked "Maybe", the software moved the article to the second phase of "full-text screening." This approach was taken to avoid missing any relevant article because, very often, the abstract lacked the essential information that was obtained from reading the full text. Discrepancies between the two reviewers (e.g., one reviewer marked "Yes" and the other marked "No" or one marked "No" and the other marked "Maybe") were reflected under the domain of "resolve conflicts" within Covidence. Such discrepancies between the two reviewers were settled by discussion. Next, the two reviewers read, reviewed full texts, and scanned references for additional relevant citations.

Data extraction

All identified studies proceeded to data extraction. Two independent reviewers used a pre-specified data extraction tool and extracted information on authors, title, publication year, study aims, study setting, sample size, intervention type, intervention groups, frequency and duration of intervention, compliance with the intervention, types of outcomes, methods to measure outcomes, follow-up time, age (in years) and body mass index (BMI in kg/m^2), effect modifiers tested if any, and key findings. For the continuous outcomes (hemoglobin (g/dL), birth weight (gm), birth length

(cm), and birth head circumference (cm)), we extracted data on sample size along with the mean and standard deviation of the outcomes in intervention and control groups. For binary outcomes (small for gestational age and preterm birth), we extracted data on sample size and number of events in intervention and control groups. We used the extracted raw data for intervention and control arms to compute mean differences and risk ratios for continuous and binary outcomes, respectively with their 95% confidence intervals (CIs). The terminology of "group/intervention/arm/control" follows the definitions used by the original study authors. To clarify this, we have added a column to Table 1 indicating which groups were analyzed for the forest plots. For studies with multiple intervention arms, similar arms were combined for comparison with the control arm. For example, in Ramakrishnan et al. [41], since there was no significant difference between Groups 2 and 3 (both intervention arms), we combined these groups into a single intervention arm and compared them with Group 1 (control). In Hambidge et al. [45], for outcomes other than hemoglobin, Arms 1 and 2 were combined due to no significant differences between them, and compared with Arm 3, the control arm. For Hambidge et al. (unpublished data), Arms 2 and 3 were both considered control arms; Arm 2 started the intervention only after the first trimester (12 weeks gestation) and was grouped with Arm 3 (control) for comparison with Arm 1 (intervention). Similarly, in Nga et al. [48], the preconception group was considered the primary intervention arm, and the pregnant and control groups (which showed no significant difference between them) were combined into a single control arm for comparison with the preconception group. This approach was applied consistently across studies with multiple arms, and the specific groupings and comparisons are detailed in Table 1.

Risk of bias assessment

Using a revised Cochrane risk-of-bias tool for RCTs (RoB version 2.0), we assessed the risk of bias in eligible RCTs [53]. The tool assessed the bias in five distinct domains including the randomization process, deviation from intended interventions, missing outcome data, outcome measurement, and selection of the reported results [53]. For each domain, we answered a series of signaling questions to make a decision for "low risk of bias", "some concerns", or "high risk of bias" [53]. The judgments about the risk of bias for each domain were derived by algorithms based on the answers to signaling questions, specific to each domain [53]. Next, the judgments for each domain lead to an "overall risk of bias" for the studied outcomes [53].

Quality of evidence using the GRADE tool

Two authors independently used the GRADE (grading of recommendations, assessment, development, and evaluation) tool [54] to assess the quality of evidence for outcomes including maternal hemoglobin, birth weight, birth length, birth head circumference, small for gestational age, and preterm birth. The GRADE assessment provides a degree of confidence in the pooled summary measure for a given outcome. The GRADE tool consists of five domains including risk of bias, inconsistency in the findings, indirectness of evidence, imprecision of the effect measures, and publication bias [54]. After assessing the certainty of evidence against the five domains, we summarized the quality of evidence as very low, low, moderate, or high quality [54]. Very low or low quality implies no confidence in the estimated pooled summary measure and further studies with robust methods will likely change the effect measures [54].

Statistical methods

Instead of reporting *Z*-scores for the continuous outcomes, almost all RCTs reported the data in absolute measurements (e.g., birth weight (gm), length (cm), and head circumference (cm)). Hence, for the primary analysis, we computed summary mean differences with 95% CIs for the continuous outcomes. However, to standardize for differences across studies, we also computed summary standardized mean differences for the continuous outcomes. For dichotomous outcomes (small for gestational age and preterm birth), we calculated summary risk ratios (RRs) and 95% CIs. We created forest plots to visualize point estimates for individual RCTs and a summary estimate for all RCTs with 95% CIs [55].

Anticipating heterogeneity across the RCTs, we pooled results using random-effects models. This approach accounts for variability both within and between studies, which may arise due to differences in study populations, interventions, and other factors. We applied weights to each study using the inverse variance method, giving more weight to studies with larger sample sizes or more precise estimates [56]. To assess heterogeneity across the RCTs, we calculated the I^2 statistic and conducted Cochran's Q test [56]. The I^2 statistic quantifies the proportion of total variability in effect estimates that is due to heterogeneity rather than chance, with values of $< 50\%$, 50–75%, and $> 75\%$ indicating low, moderate, and high heterogeneity, respectively. Cochran's Q test provides a statistical test for heterogeneity, with a significant result indicating that the observed variation is unlikely to be

Table 1 Characteristics of the RCTs included in the systematic review and meta-analysis ($n = 25$ records and 20 unique RCTs) [28–52]

Author, Year	Setting	n	Intervention (Frequency)	Age (years)	BMI (Kg/m^2)	Intervention groups	Outcomes	Intervention and control Arms for meta-analysis
MRC Vitamin Study Research group., 1991[28]	UK, Australia, Hungary, Canada, Russia, France, and Israel	1145	Multivitamin supplement (daily capsule)	26.8±NR	NR	**Group 1:** Multivitamins and folic acid **Group 2:** Multivitamins **Group 3:** Folic acid	Birth weight and birth head circumference	**Group 1 and 2:** Intervention **Group 3:** Control We did not include in the meta-analysis due to insufficient data on outcome
Czeizel, 1994[29]	Hungary	5453	Multivitamin supplement (daily tablet)	26±3.0	weight (kg) 57.3±7.3	**Intervention:** A multivitamin supplement including 0.8 mg folic acid, vitamins A, B1, B2, B6, nicotinamide, calcium, phosphorus, zinc, and manganese, biotin, B12, E, C, **Control:** Trace element only containing copper, manganese, zinc, and vitamin C	Birth weight and preterm birth	We used intervention and control arms from the article as defined by author
Rolschau et al., 1999[30]	Denmark	7824	Folic acid supplement (Daily)	NR	NR	**Group 1:** Folic acid supplement preconceptionally **Group 2:** Folic acid supplement during the first half of pregnancy (first 19 weeks)	**Birth weight, small for gestational age, and preterm birth**	**Group 1:** Intervention **Group 2:** Control
ICMR, 2000[31]	India	279	Multivitamin supplement (Daily capsule)	26.1±4.0	NR	**Intervention:** Multivitamin preparation containing folic acid, calcium, iron, zinc, and vitamins A, B1, B2, B6, C, D, and nicotinamide **Control:** Calcium and iron only	Low birth weight	Not included in the meta-analysis because of insufficient data on outcome
Katz et al., 2000[32]	Nepal	3000	Vitamin A or beta carotene supplement (weekly capsule)	<20 years: 22%	NR	**Group 1:** Vitamin A supplement **Group 2:** Beta carotene supplement	Preterm birth	**Group 1:** Intervention **Group 2:** Control
Gilgen et al., 2001[33]	Bangladesh	280	Iron and folic acid supplement (weekly capsule)	39.6 (14-66)	17.1 (11-24)	**Group 1**: Iron and Folic acid **Group 2:** Placebo	**Hemoglobin and maternal anemia**	**Group 1:** Intervention **Group 2:** Control
Moriarty_Craig et al. 2004[34]	Mexico	152	Multiple micronutrients (6 days/week)	28.6±7.8	NR	**Group 1:** MM supplement (Vitamins A, B complex, C, D, E, and K, iron, zinc, and mg) **Group 2:** Iron alone	**Hemoglobin and maternal anemia**	**Group 1:** Intervention **Group 2:** Control
Khambalia et al., 2009[35]	Rural Bangladesh	234	Iron and folic acid supplement (daily powder sachets)	20.6±4.4	21.4±3.3	**Group 1:** Iron and folic acid containing 60mg iron and 400ug folic acid **Group 2:** 400ug folic acid	**Hemoglobin and maternal anemia during pregnancy**	**Group 1:** Intervention **Group 2:** Control
Potdar et al., 2014[36]	India (poor and low-resource areas of Mumbai)	1360	Snack prepared from vegetables, fruits, and milk (Daily)	25 (22, 28)	20.1 (17.9, 22.9)	**Intervention**: A daily energy snack (prepared from vegetables, fruits, and milk: consumed daily before conception until delivery: 0.69 megajoules of energy **Control**: low-micronutrient snack:0.37 megajoules of energy	**Birth weight**, birth length and small for gestational age	We used intervention and control arms from the article as defined by author
Gunaratna et al, 2015[37]	Rural Tanzania	561	Multiple micronutrients or Iron and Folic acid supplement (Daily Pill)	21.2±4.5	21.6±4.1	**Group 1**: folic acid alone **Group 2**: Iron and Folic acid **Group 3**: iron, folic acid, and vitamins A, B-complex, C, E	**Periconceptional anemia and hemoglobin**	**Group 1 and 2:** Combined to represent control arm **Group 3:** Intervention
Owens et al., 2015[38]	Gambia	376	Multiple micronutrient supplement (Daily Tablet)	28.9 (23.7-34.8)	20.9 (19.4-23.3)	**Intervention**: UNICEF/WHO/United Nations University multiple micronutrient preparation (UNIMMAP) **Control:** Placebo	Preterm birth	We used intervention and control arms from the article as defined by author
Cooper et al., 2012[39]		58					Birth weight, length, head circumference	
Gulati et al., 2009[40]		293		25.2±7.9	21.1±3.2		Maternal anemia and hemoglobin levels	
Ramakrishnan et al., 2016[41]	Rural Vietnam	1599	Multiple nutrient supplements (Weekly Capsules)	26±4.5	19.6±2.1	**Group 1**: 2800 ug folic acid only **Group 2**: 60 mg iron and 2800 ug folic acid **-Group 3**: 60 mg iron and 2800 ug folic acid plus multiple micronutrients **-**Preconception weekly supplements until pregnancy **-**All pregnant women took iron and folic acid	**Birth weight, preterm birth,** and small for gestational age	**Group 1:** Control **Group 2 and 3:** Intervention. Since there was no difference between group 2 and 3 (two intervention arms), we combined these together.
Nguyen et al., 2016 [42]		1581					Anemia during pregnancy	

Table 1 (continued)

Sumarmi et al.,2015 [43] Sumarmi et al., 2017[44]	**Indonesia**	112 115	Multiple micronutrient supplement (Capsule every other day)	22.4±3.9	21.0±3.8	**Group 1:** Multiple micronutrient supplement containing 15 micronutrients **Group 2:** iron and folic acid	**Preterm birth** Birth weight	**Group 1:** Intervention **Group 2:** Control
Hambidge et al., 2019[45]	**India, Pakistan, Guatemala, and DRC**	2451	Lipid-based nutrient supplement: Micronutrients, polyunsaturated fats, and modest quantities of protein and energy (Daily Sachet).			**-Arm 1**: Daily Lipid-based nutrient supplement: Micronutrients, polyunsaturated fats, and modest quantities of protein and energy ≥3 months before pregnancy until delivery **-Arm 2**: The same supplement from the second trimester until delivery	**Birth length,** birth weight, birth head circumference, small for gestational age, and preterm birth, and	**Arm 1 and 2:** Intervention **Arm 3:** Control Since there was no difference between Arms 2 and 3 (two intervention arms), we combined these together.
Women First Study (Unpublished)		2320		23.2±4.2	20.6±2.6	**-Arm 3**: No supplement (routine antenatal care)	Anemia during pregnancy	**Arm 1:** Intervention **Arm 2 and 3:** Control Since Arm 2 had not started the intervention until first trimester (12 weeks gestation), it was considered control arm like Arm 3.
Brabin et al., 2019[46] Giest et al., 2018[47]	**Burkina Faso**	307 315	Iron folic acid supplement (Weekly Capsule)	16.8 ± 1.8	19.7 ±2.2	**Intervention:** Weekly iron folic acid supplement 60 mg elemental iron and 2.8 mg folic acid, **Control**: 2.8 mg folic acid alone	Birth weight and preterm birth Maternal anemia	We used intervention and control arms from the article as defined by author
Nga et al., 2020[48]	**Rural Vietnam**	317	A food-based nutritious supplement prepared from animal-source foods and vegetables (protein, energy, vitamin A, B12, iron and folic acid, and zinc) (5 days/week)	21.1±2.6	19.8±1.9	**Preconception**: A food-based nutritious supplement from preconception until birth **Pregnant women**: Supplement from mid-gestation to birth. **Control arm**: No supplement	**Birth weight, birth length, preterm birth,** and head circumference	**Preconception:** Intervention **Pregnant women and control arm:** Control Since preconception arm was considered a primary intervention arm and author compared preconception to pregnant and control groups (no significant difference between the two), we combined pregnant and control groups into control arm and compared to preconception (intervention) group.
Sun et al., 2020[49]	**China**	1162	100gms of white button Mushrooms (low in calories and rich in fiber) contain various nutrients such as niacin, riboflavin, phosphorus, Pantothenic acid, copper, selenium, vit-B12, ergosterol, and ergothioneine (daily)	31.4±4.3	22.6±4.0	**Group 1:** 100 gm mushroom integrated into daily diet daily **Group 2:** Placebo	Birth weight, Preterm birth, and Low birth weight	**Group 1:** Intervention **Group 2:** Control
Widasari et al., 2020 [50]	**Indonesia**	19	Multiple micronutrients (Daily)	NR	NR	**Group 1:** UNICEF/WHO/United Nations University multiple micronutrient preparation (UNIMMAP: 15 micronutrients) **Group 2:** Iron and Folic acid	**Birth weight and birth length**	**Group 1:** Intervention **Group 2:** Control
Bortolus et al., 2021[51]	**Italy**	431	High dose folic acid (Daily)	32.3±4.0	21.9±2.8	**Group 1:** 4.0mg folic acid **Group 2:** 0.4mg folic acid	Preterm birth, small for gestational age, and birth weight	**Group 1:** Intervention **Group 2:** Control
Godfrey et al., 2021[52]	**Singapore, UK, and New Zealand**	586	Myoinositol, probiotics, and multiple micronutrients (powdered sachets: twice Daily)	30.14±3.3	23.7 (21.3-27.5)	**Group 1:** Myoinositol, probiotics, and multiple micronutrients **Group 2:** Multiple Micronutrients	Birth weight, preterm birth, and small for gestational age	**Group 1:** Intervention **Group 2:** Control

UK United Kingdom, *DRC* Democratic Republic of Congo, *NR* not reported. Study participants in all RCTs were non-pregnant women of reproductive age planning to become pregnant. Countries in blue are high-income countries and countries bolded in black are low-middle income countries. Nutrient supplements written in red are iron and folic acid or folic acid, supplements written in black are multiple micronutrients, interventions in purple are multivitamins, and nutrient supplements in pink is a lipid-based nutrient supplement (both micro and macronutrients). Outcomes written in green were measured as primary outcomes in the individual RCTs

due to random sampling error alone [56]. Meta-regression was performed to explore potential sources of heterogeneity across the included studies. We analyzed a range of study-level factors, including study setting (LMICs vs. HICs), publication year (1991–2021), type of nutrient supplement (e.g., multiple micronutrients vs. iron and folic acid), frequency of supplement consumption (weekly vs. daily), type of control (alternative vs. placebo or standard of care), risk of bias (low or high vs. some concerns), mean age (years), and mean body mass index (BMI) of study participants (kg/m^2). The contribution of each study-level factor to the overall heterogeneity was quantified using meta-regression R^2, which represents the proportion of variance in the effect estimates explained by these variables. We interpreted the meta-regression results by reporting beta-coefficients for all study-level factors along with their respective 95% CIs.

To assess publication bias, we visually inspected funnel plots for asymmetry. Asymmetry in the funnel plot may indicate potential publication bias, where smaller studies with non-significant results are less likely to be published [56]. Additionally, we performed Egger's regression test, which provides a formal statistical test for funnel plot asymmetry, helping to identify the presence of publication bias. We performed the analysis using the meta package in R [57].

Results

We identified 3,078 citations from the databases. After removing 554 duplicates, we screened 2524 studies for their titles and abstracts. We excluded 2432 irrelevant citations by reviewing their titles and abstracts. Of the remaining 92 citations, we excluded 67 citations after reviewing their full texts because (1) they were reviews/commentaries/ letters to the editor/protocols ($n=15$); (2) the intervention was other than a nutrient supplement in 27 records (we excluded 27 additional records because the intervention in the 27 records comprised of resilience to negative social determinants during preconception, preconception counseling sessions with health care providers, women's group meetings in villages, heparin and oral aspirin, vaginal micronized progesterone, hyaluronic acid gel, clomiphene citrate, immunoglobulin, and active immunization with leukocytes); (3) outcome was other than maternal hemoglobin and markers of intrauterine growth for 12 citations (we excluded 12 more citations because they examined outcomes such as neural tube defects, oral defects, neurodevelopment disorders, stillbirth, preeclampsia, and gestational diabetes mellitus); and (4) design was not RCT ($n=13$). Hence, we included 25 records in the current review and meta-analysis as shown in Fig. 1.

Number of RCTs and study settings

Overall, 25 records, identified from 20 unique RCTs ($n=27,659$ women), were published between 1991 and 2021 (Table 1). Of the 25 records, 16 examined at least one marker of intrauterine growth and 9 investigated maternal hemoglobin. All studies on maternal hemoglobin were from LMICs including Bangladesh ($n=2$) [33, 35], Vietnam ($n=2$) [42, 48], Mexico ($n=1$) [34], Gambia ($n=1$) [40], Tanzania ($n=1$) [37], Burkina Faso ($n=1$) [47], and one multi-country RCT conducted in Pakistan, India, the Democratic Republic of Congo (DRC), and Guatemala [58]. Of the 16 RCTs examining markers of intrauterine growth, 11 RCTs were from LMICs [31, 32, 36, 38, 41, 44–46, 48–50], and 5 RCTs were from HICs [28–30, 51, 52]. RCTs from LMICs were conducted in India ($n=2$) [31, 36], Vietnam ($n=2$) [41, 48], Nepal ($n=1$) [32], Gambia ($n=1$) [38], Burkina Faso ($n=1$) [46], China ($n=1$) [49], Indonesia ($n=2$) [44, 50], and one multi-country RCT conducted in Pakistan, India, DRC, and Guatemala [45]. RCTs conducted in HICs were from Hungary ($n=1$) [29], Italy ($n=1$) [51], Denmark ($n=1$) [30], and 2 multi-country RCTs, one was conducted in the United Kingdom (UK), Australia, Hungary, Canada, Russia, France, and Israel [28] and another was conducted in Singapore, UK, and New Zealand [52]. Details of the 20 unique RCTs and 25 records are given in Table 1.

Type of interventions and outcomes studied

Out of 20 unique RCTs, 10 RCTs tested multiple micronutrient supplementation [34, 36–38, 41, 43, 48–50, 52] (7 in the form of tablet/capsule/powder sachets [34, 37, 38, 41, 43, 50, 52] and 3 were food-based nutritious supplements [36, 48, 49], 4 RCTs assessed multivitamins [28, 29, 31, 32], 5 RCTs investigated either iron and folic acid or folic acid alone [30, 33, 35, 46, 51], and one multi-country RCT [45] tested a comprehensive lipid-based nutrient supplement, comprised of multiple micronutrients, vitamins, minerals, iron and folic acid, proteins, energy, and fatty acids (Table 1). Regarding outcomes, 9 RCTs studied maternal hemoglobin [33–35, 37, 40, 42, 47, 48, 58], 15 RCTs examined birth weight (14 RCTs reported birth weight as a continuous outcome in gms and one RCT reported binary outcome of low birth weight) [28–31, 36, 38, 41, 43, 45, 46, 48–52], 5 RCTs studied birth length [36, 39, 45, 48, 50], 4 RCTs assessed head circumference at birth [36, 39, 45, 48], 8 RCTs

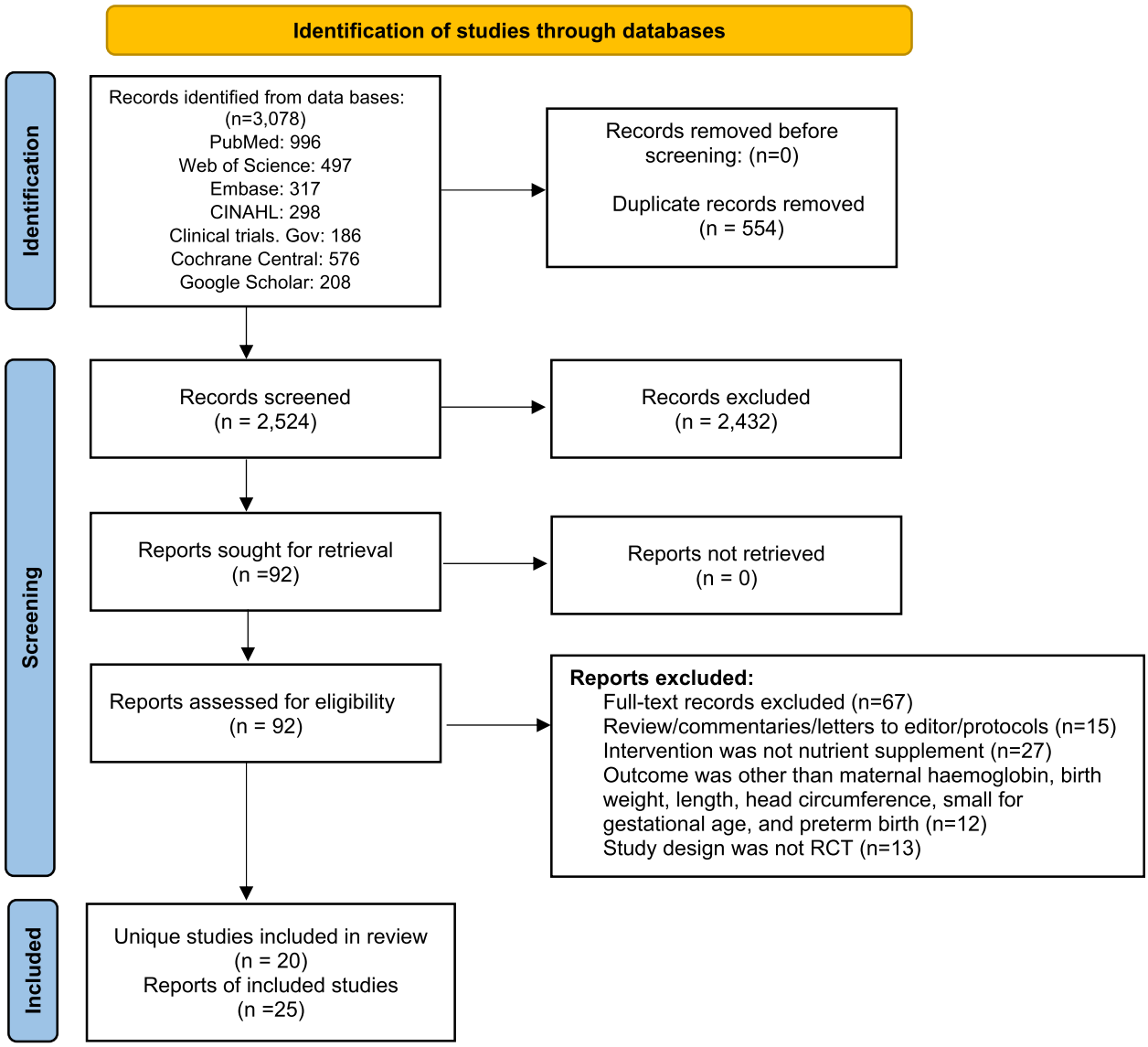


Fig. 1 PRISMA Flow chart summarizing the identification, inclusion, and exclusion of research papers

investigated small for gestational age [30, 36, 41, 45, 46, 48, 51, 52], and 12 RCTs studied preterm birth [30, 32, 36, 38, 41, 43, 45, 46, 48, 49, 51, 52] as shown in Tables 1 and 2.

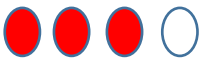
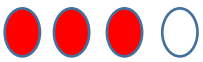
Effect of preconception nutrition supplements on maternal hemoglobin (g/dL)

Figure 2 shows the overall pooled effect of preconception nutrition supplements (iron and folic acid, multiple micronutrients, and a lipid-based nutrient supplement) on maternal hemoglobin (g/dL). Preconception nutrient supplements including iron and folic acid, multiple micronutrients, and a lipid-based nutrient supplement improved maternal hemoglobin by 0.30 g/dL (95% CIs 0.03, 0.57; $n=9$). We observed substantial heterogeneity for maternal hemoglobin ($I^2=79\%$, $Q=37.62$; p-value <0.01) as shown in Fig. 2.

Effect of preconception nutrition supplements on markers of intrauterine growth

Looking at the overall pooled effect of preconception nutrition supplements on markers of intrauterine growth (Fig. 3), we found that the supplements (iron and folic did or folic acid alone, multiple micronutrients, and

Table 2 Summary of findings for the quality of evidence for maternal hemoglobin, birth weight, birth length, birth head circumference, small for gestational age, and preterm birth using a GRADE assessment tool

Outcomes	Number of RCTs (study participants)	Pooled summary measure[a] and 95% CIs	I^2 (%)	Quality of evidence (GRADE)[b]	Final rating for quality
Maternal hemoglobin (g/dL)	9 (5,630)	0.30 g/dL (0.03, 0.57)	79		Moderate
Birth weight (gm)	10 (12,929)[c]	12.25 gm (−22.66, 47.16)	55		Very low
Birth length (cm)	5 (4,212)	0.15 cm (−0.26, 0.56)	68		Very low
Birth head circumference (cm)	4 (4,178)	−0.23 cm (−0.88, 0.43)	84		Very low
Small for gestational age	8 (13,856)	RR 0.91 (0.80, 1.04)	31		Moderate
Preterm birth	12 (18,413)	RR 0.93 (0.69 1.25)	57		Very low

RR risk ratios, *95% CIs* 95% Confidence intervals

[a] Pooled summary measures are mean differences for outcomes on a continuous scale including maternal hemoglobin (g/dL), birth weight (gm), birth length (cm), and head circumference (cm) and risk ratios (RR) for dichotomized outcomes (small for gestational age and preterm birth)

[b] Five GRADE criteria (Risk of bias, inconsistency, imprecision, indirectness, and publication bias) were used to assess the quality of evidence (see Supplementary Table S4 for details)

[c] Overall, 15 RCTs measured birth weight; however, only 10 RCTs provided sufficient raw data to compute the pooled mean difference in birth weight (gm) between intervention and control Arms

The four circles with the red color represent the rating for the quality of evidence. High quality of evidence: all four circles were made red; Moderate quality: three circles were colored red; Low quality of evidence: two circles were made red; Very low quality of evidence: only one circle was made red

Very low: the calculated effect size is very different from the truth

Low: the measured effect size may be substantially different from the truth

Moderate: The calculated effect measure may be close to the truth, but one may find a substantial difference between the estimated mean difference and the truth

High: there is a high confidence that calculated estimate is very close to the truth, and further studies may not find a substantial difference

a lipid-based nutrient supplement) had no significant effect on birth weight (12.25 gm (95% CIs − 22.66, 47.16); $n=10$), birth length (0.15 cm (95% CIs: −0.26, 0.56); $n=5$), and birth head circumference (−0.23 cm (95% CIs − 0.88, 0.43); $n=4$). We observed moderate heterogeneity for the analysis of birth weight ($I^2=55\%$; $Q=20.08$; $p=0.02$)) and birth length ($I^2=68\%$, $Q=12.44$; $p=0.01$). However, we observed substantial heterogeneity in the analysis of birth head circumference ($I^2=84\%$, $Q=19.04$; p-value <0.01).

Additionally, we found that preconception nutrition supplements (iron, and folic did or folic acid alone, multiple micronutrients, and a lipid-based nutrient supplement) did not appear to reduce the risk of small for gestational age (RR: 0.91 (95% CIs 0.80,1.04); $n=8$) as illustrated in Supplemental Figure S1. We observed low and non-significant heterogeneity ($I^2=31\%$, $Q=10.10$; $p=0.18$) while analyzing the data for small for gestational age (Supplemental Figure S1).

Effect of preconception nutrition supplements on preterm birth

Overall, preconception nutrition supplements (iron and or folic did, multiple micronutrients, Vitamin A or beta carotene supplement, multivitamins, and a lipid-based nutrient supplement) had no significant effect on preterm birth (RR: 0.93 (95% CIs 0.69, 1.25); $n=12$) as shown in Supplemental Figure S2. Moderate heterogeneity was observed for the analysis of preterm birth $I^2=57\%$, $Q=25.47$; $p<0.01$) as illustrated in Supplemental Figure S2.

Meta-regression findings

For maternal hemoglobin, the meta-regression analysis of nine studies revealed that none of the examined factors, including publication year, intervention type, control arm, risk of bias, mean age, or mean BMI, were statistically significant contributors to the observed mean difference in hemoglobin levels (Supplemental Table S2). The regression coefficients were generally close to zero with wide confidence intervals, such as for the comparison between multiple micronutrients (MMN) and iron-folic

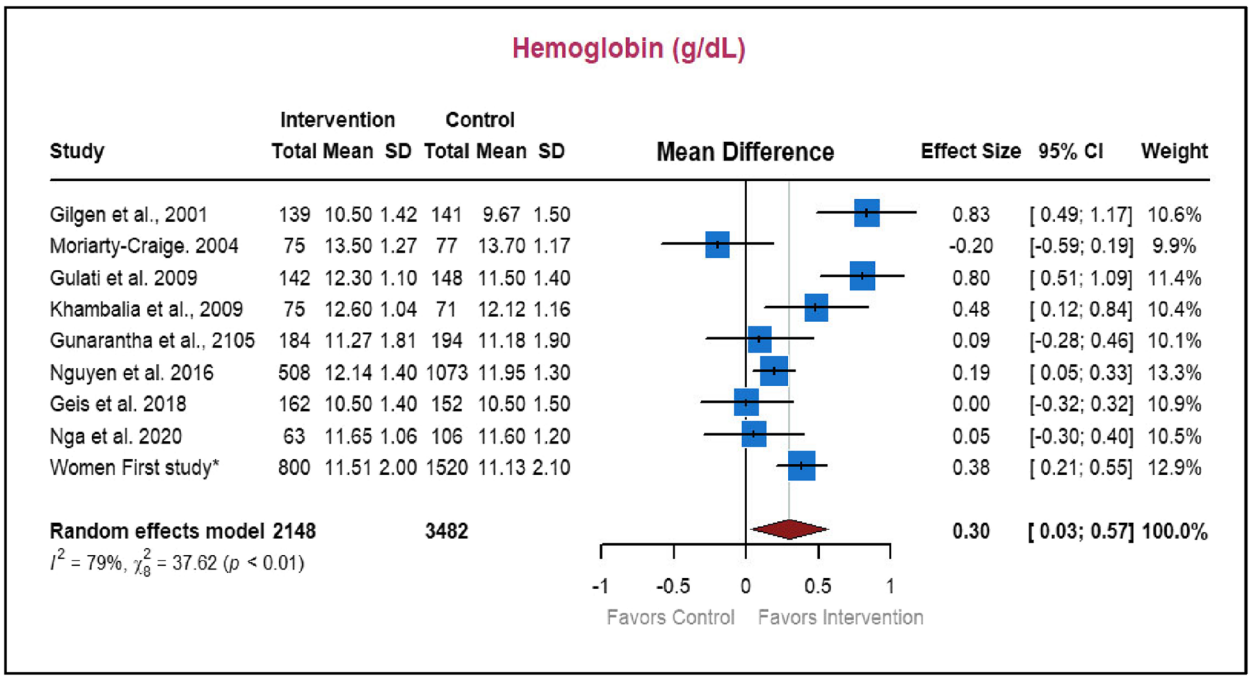


Fig. 2 Effect of preconception nutrition supplements (iron and foilc acid, multiple micronutrients, and a lipidbased nutrient supplement) on maternal hemoglobin (g/dL). Forest plot depicting the overall pooled effect of preconception nutrition supplements (iron and folic acid, multiple micronutrients, and a lipid-based nutrient supplement) on maternal hemoglobin (g/dL). The blue squares represent individual RCT's mean difference in maternal hemoglobin (g/dL) between intervention and control groups and horizontal black lines indicate corresponding 95% CIs. The maroon diamond represents pooled mean difference in hemoglobin (g/dL) between intervention and control arms and corresponding 95% CIs. * The hemoglobin data from Women First study, conducted in Pakistan, India, DRC, and Pakistan, is not published. The Principal Investigator of the Women First study granted permission to publish the data

acid (IFA) supplementation (β = −0.09, 95% CI −0.68, 0.50, p = 0.72). Notably, heterogeneity (τ^2 = 0.11, I^2 = 85.9%) was high, and the R^2 values indicated that the explored factors explained little to no heterogeneity (e.g., R^2 = 0 for most factors). The highest R^2 was 37% for the type of control arm, indicating it explained some heterogeneity, although not statistically significant (Supplemental Table S2). For birth weight, a meta-regression of 10 studies similarly found no significant association with the factors examined (Supplemental Table S2). For example, the LMICs vs. HICs comparison yielded a β of −41.61 (95% CI −128.98, 45.75, p = 0.30), indicating a small, non-significant mean difference between low- and middle-income countries and high-income countries. High heterogeneity was again evident (τ^2 = 1517.85, I^2 = 64.1%), with R^2 values of 0 for most variables, highlighting limited explanatory power (Supplemental Table S2).

Multiple meta-regression analysis was not performed for hemoglobin and birth weight because none of the variables assessed in univariate meta-regression analyses were statistically significant at p-value < 0.05. Attempting to include these non-significant variables in a multiple regression model would lack a sound statistical basis and likely result in overfitting, especially given the small number of studies available (9 for hemoglobin and 10 for birth weight). Additionally, the high heterogeneity observed (e.g., τ^2 = 0.11, I^2 > 80% for hemoglobin) and low explanatory power of individual variables (R^2 values close to 0) indicated that the included covariates were not meaningful contributors to heterogeneity. As such, a multiple regression approach was deemed unnecessary and inappropriate under these conditions.

Publication bias

The symmetrical shape of funnel plots for the outcomes (i.e., hemoglobin, birth weight, small for gestational age, and preterm birth) suggests that evidence of publication bias was unlikely, which was confirmed by Egger's regression test (Supplemental Figures S3 and S4). The results of Egger's regression test showed that the intercept of the regression model was < 0 and the p-value was > 0.05 (Supplemental Figures S3 and S4), indicating a funnel plot symmetry with less likely evidence of publication bias. Due to the small number of RCTs on birth length (n = 5) and head circumference (n = 4), we did not assess publication bias for these two outcomes.

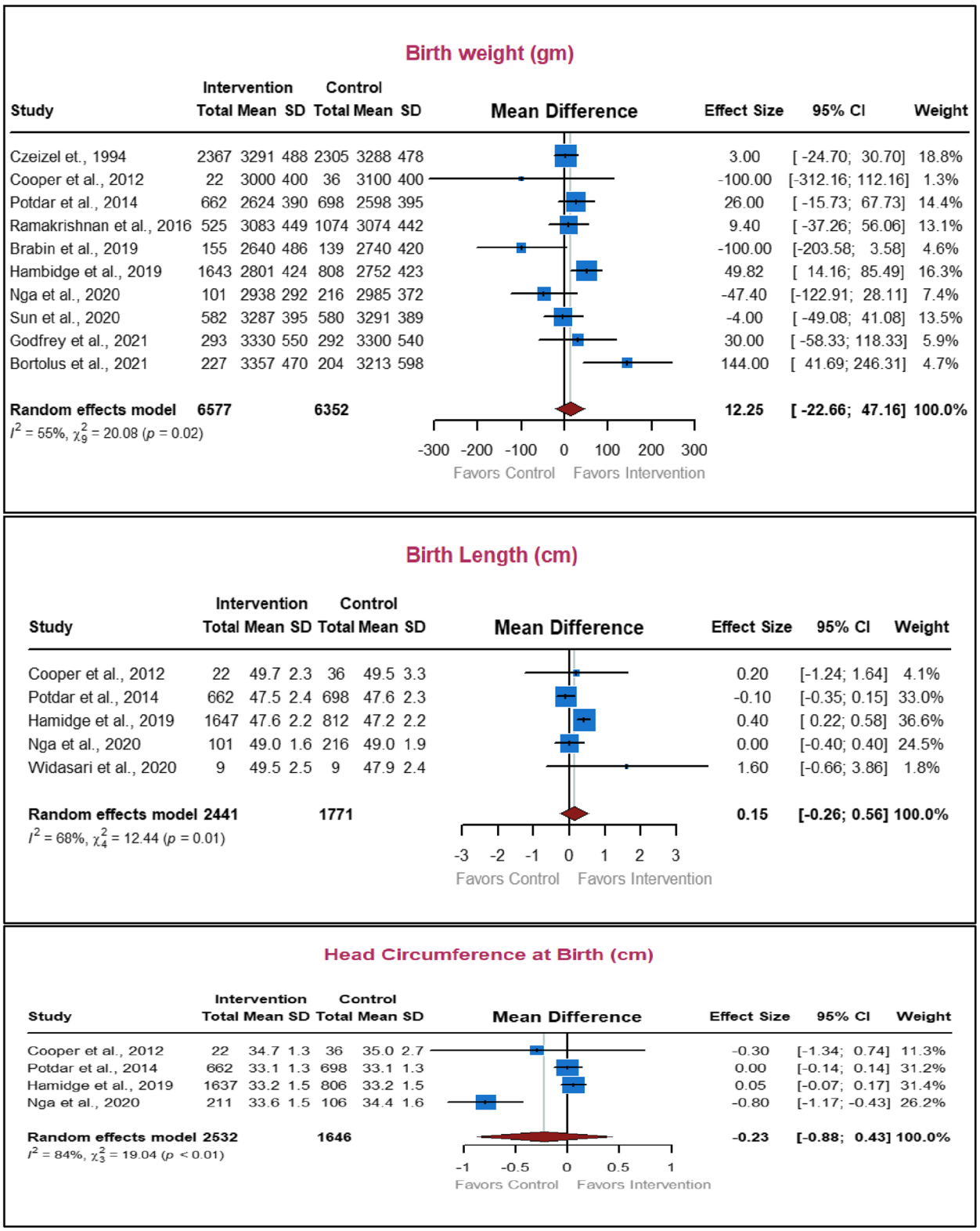


Fig. 3 Effect of preconception nutrition supplements (iron and folic acid, multiple micronutrients, and a lipid based nutrient supplement) on birth weight, birth length, and birth head circumference. Forest plots depicting the effect of preconception nutrition supplements (iron and folic acid or folic acid alone, multiple micronutrients, and a lipid based nutrient supplement) on birth weight (gm), birth length (cm), and birth head circumference (cm). Blue square represents individual study's mean difference in the markers of intrauterine growth and horizontal black lines indicate 95% CIs. The maroon diamond represents pooled mean difference and 95% CIs

Risk of bias findings

Overall, the risk of bias assessments for the included unique studies ($n=20$) revealed that 45% (9/20) of the studies were rated as having an overall low risk of bias, while 30% (6/20) were classified as high risk, and 25% (5/20) showed some concerns (Supplemental Table S3). Most studies demonstrated low risk in domains such as the randomization process (15/20; 75%), deviations from intended interventions (18/20; 90%), and measurement of outcomes (18/20; 90%). For example, studies like the MRC Vitamin Study [28], Khambalia et al. [35], Hambidge et al. [45], and Godfrey et al. [52] consistently scored low risk across all domains. However, studies such as Czeizel et al. [29], Rolschau et al. [30], and Sun et al. [49], had high risks in specific domains, including "measurement of the outcome", "randomization process", or "selection of the reported result", respectively affecting their overall assessments. Several studies exhibited "some concerns" in specific domains, particularly in missing outcome data (e.g., Widasari et al. [50]) and deviations from intended interventions (e.g., Sumarmi et al. [44]). While a majority of studies had low risk in multiple domains, consistent methodological gaps in specific studies highlight areas for cautious interpretation of results (Supplemental Table S3).

Quality and certainty of the evidence

Table 2 summarizes the findings of the GRADE assessment for outcomes including maternal hemoglobin, birth weight, length, head circumference, small for gestational age, and preterm birth. Overall, the quality of RCTs studying maternal hemoglobin and small for gestational age was found to be moderate. However, the quality of RCTs examining birth weight, length, head circumference, and preterm birth was found to be very low (Table 2). For each outcome, Supplemental Table S4 presents the details of the quality assessment against each of the five GRADE tool domains (risk of bias, inconsistent findings, indirectness of evidence, imprecision of the impact measurements, and publication bias). The very low-quality evidence was mainly due to substantial heterogeneity in the type of nutrient supplement, high risk of bias, and imprecision of the estimate due to the small number of RCTs assessing birth length and birth head circumference (Supplemental Table S4).

Discussion

In the current meta-analysis of RCTs, all types of preconception nutrition supplements studied, namely iron and folic acid, multiple micronutrients, and a lipid-based nutrient supplement were associated with improved maternal hemoglobin. In contrast, no improvements in birth weight, length, head circumference, small for gestational age, or preterm birth are observed if preconception nutrition supplements are considered overall.

Our findings on the beneficial effect of preconception nutrition supplements (i.e., iron and folic acid, multiple micronutrients, and a lipid-based nutrient supplement) on maternal hemoglobin are consistent with prior reviews [13, 14]. However, investigators in the prior reviews did not consider the preconception window; rather, the researchers only examined the studies that offered supplements to women after they became pregnant [13, 14]. A sole focus on pregnancy is necessary but may not be sufficient for rectifying nutrient deficits and improving iron stores, especially for women residing in LMICs [15]. Addressing nutrition deficiencies before conception may be relevant for LMICs, where women may hide their pregnancies owing to cultural and societal beliefs or may remain unaware of their pregnancies [59]. Consequently, women seek antenatal care late in the second or third trimester [60], which may hinder women's ability to commence nutrition supplements in a timely manner [61]. As a result, women might not be exposed to the supplements for enough duration to raise their iron and hemoglobin levels. To address these challenges, the supplements can be offered to women during the preconception period, a window of opportunity to improve women's nutrition status, iron stores, and hemoglobin before planning for pregnancy [62].

The findings regarding the beneficial effect of preconception nutrition supplements on maternal hemoglobin are biologically plausible [63]. Animal and human studies suggest that depletion of iron and other nutrient stores increases the capacity of the small intestine to absorb iron and other nutrients [64]. Bone marrow erythropoiesis is an additional regulator that controls intestinal absorption of iron in response to increased erythropoietic demands subsequent to low iron and hemoglobin levels [65]. In LMICs, due to food insecurity and poor diet quality, women may enter pregnancies with inadequate micronutrients, poor iron stores, and increased nutrition demands [21]. Increased demand and subsequent intestinal absorption of iron and other micronutrients may result in a better hematological response with a subsequent rise in hemoglobin levels and better iron stores [63].

We found that the preconception nutrition supplements (iron and folic acid, multiple micronutrients, and a lipid-based nutrient supplement) did not improve birth weight, length, and head circumference. Also, the supplements did not reduce the risk of being small for gestational age or preterm birth, findings consistent with prior reviews [23, 66]. The null effect of the preconception nutrition supplements on markers of fetal growth might be explained by various factors. First, nearly all

RCTs included in the review provided women with either iron and folic acid, multivitamins, or micronutrients rather than offering both macro and micronutrients. A sole focus on iron and folic acid or micronutrients; rather than providing both micro and macronutrients, may have constrained the supplements from showing any favorable effects on fetal growth. A single nutrient intervention may only be beneficial in the absence of other nutrient deficits [67]. Without having enough macronutrients, undernourished women may not utilize the nutrients supplied by the micronutrient supplements [67]. Enough macronutrient supply is necessary to meet the energy needs of both the mother and the fetus [8]. Energy, obtained from macronutrients, is essential for transporting micronutrients, cellular motility, and synthesis of the placenta, fetal tissues, and amniotic fluid [8]. Proteins and fatty acids are necessary for the growth of the eyes and brain, and their inadequate intake may lead to suboptimal fetal development [68]. Without having energy provided by macronutrients, micronutrients may not be metabolized or transferred across the placenta for fetal growth [67]. The importance of providing a more comprehensive package of nutrition supplements that incorporates both micro- and macronutrients is supported by a large multi-country RCT, Women First Preconception Nutrition Trial [45]. In contrast to the other RCTs, this trial offered a lipid-based nutrient supplement that included both micro and macro nutrients including vitamins, minerals, iron and folic acid, proteins, energy, and fatty acids, and was the only large trial to report a positive effect of a nutrition supplement on fetal growth.

Second, the interval between commencing the preconception nutrition supplements and conception must be sufficient to ensure the favorable effects of the supplements on fetal growth [69]. The exact timing of starting the supplements before conception is a topic of debate [70]. However, women probably should start consuming the supplements at least 3 months before pregnancy for optimal gamete function and placental development [69]. In RCTs with null findings [29, 32, 41], women were perhaps not exposed to the supplements for a sufficient duration of at least 3 months before pregnancy. Insufficient exposure to nutrition supplements before pregnancy may have diluted the effect of the preconception supplements on markers of intrauterine growth in the current review. The multi-country trial which observed the benefit of the lipid-based nutrient supplement provided the supplement for ≥ 3 months before pregnancy supporting the importance of consuming the supplements for a sufficient duration [45]. Two additional trials conducted in Vietnam and India while not reporting benefits overall observed an increase of ~ 60 and 48 g in birth weight when women consumed multiple micronutrients for ≥ 26 weeks and ≥ 3 months before pregnancy, respectively [36, 41].

Lastly, nutrition supplements may not work universally for everyone; rather specific maternal characteristics may be necessary for the supplements to influence fetal growth [71]. For example, young, nulliparous, underweight, and anemic women may benefit more from the supplements than multiparous and non-anemic women [71, 72]. While not all RCTs conducted stratified analyses, the few that did suggest that women with specific characteristics may benefit most from supplements. Again within the multi-country study of the lipid-based intervention, greater effects on birth weight and length were observed in anemic and nulliparous women than in non-anemic and multiparous women [72]. Other trials have observed greater benefits of supplements on birth weight for women with a BMI of > 18.6 kg/m^2 than women with a BMI of ≤ 18.6 kg/m^2 [36] or a BMI of 24.9–29.9 kg/m^2 [49]. Collectively, these findings suggest that these supplements do not benefit all, and hence effects are diluted when viewed overall. Rather benefits of the supplements accrue only to women with specific characteristics.

In addition to the potential reasons mentioned above, the null effects of preconception nutrition supplements on birth weight, length, and head circumference may also be attributed to several biological mechanisms. First, maternal nutrient status and placental transfer play critical roles; even with supplementation, variations in baseline nutrient levels, nutrient absorption, and placental regulation can limit nutrient availability to the fetus, affecting growth outcomes [9]. In addition, nutrient interactions and bioavailability are complex; for instance, high iron intake can reduce zinc absorption, while genetic differences in folate metabolism influence nutrient utilization [9]. Besides, fetal adaptive responses in nutrient-limited environments often prioritize brain growth over other growth outcomes, potentially leading to no observable improvement in birth markers [73]. Lastly, genetic and epigenetic factors significantly influence fetal growth, and supplementation may not overcome genetic predispositions or epigenetic changes that affect growth potential, especially in diverse populations [74]. These mechanisms, combined with study design variability and population-specific differences, could account for the limited effects of preconception nutrient supplements on birth outcomes.

Strengths and limitations

Null findings of preconception nutrition supplements on markers of fetal growth should be cautiously interpreted due to the following limitations. First, overall, the quality of evidence was low for outcomes including birth weight, length, and head circumference primarily due to

substantial heterogeneity and a high risk of bias. Second, most of the included RCTs in the current review measured birth weight, and only five RCTs measured birth length and head circumference. A dearth of RCTs on birth length and head circumference limited our ability to draw conclusions regarding all markers of intrauterine growth. In the future, researchers should also ascertain birth length and head circumference as important outcomes in RCTs. Third, only one RCT, a multi-country trial by Hambidge et al. [45], in the current review assessed the effect of a comprehensive lipid-based nutrient supplement on all markers of intrauterine growth. While the RCT was adequately powered, well-designed, and gained the highest weight in the meta-analysis, limited inferences can be drawn from a single trial. Further trials of the more comprehensive and longer-duration intervention studied in this RCT are warranted. Fourth, while we employed Egger's regression test to evaluate for publication bias, due to insufficient RCTs ($n < 10$) we may not have enough power to confirm funnel plot symmetry for all outcomes except for preterm birth ($n = 12$) and birth weight ($n = 10$). Fifth, we did not perform a meta-regression analysis for outcomes, including birth length and head circumference (4–5 studies). Meta-regression requires a sufficient number of studies to produce robust estimates, as including more covariates than studies leads to overfitting and unreliable results. In these cases, statistical power is severely reduced, confidence intervals are wide, and the ability to detect meaningful associations or heterogeneity sources is limited. Additionally, omitting subgroup analyses for binary outcomes (preterm birth and small for gestational age) further restricts the interpretability of findings in outcomes with small study numbers. The number of studies required for subgroup analysis depends on the complexity of the subgroups and the desired statistical power [24]. Typically, at least 5–10 studies per subgroup are recommended to ensure reliable and interpretable results [24]. This threshold helps avoid overfitting and provides sufficient data to detect meaningful differences between subgroups. When fewer studies are available, the risk of spurious findings increases, and results may lack generalizability. In the context of binary outcomes like preterm birth and small for gestational age, the limited number of studies in each subgroup further restricts the ability to conduct meaningful subgroup analyses, emphasizing the need for caution in interpreting findings derived from small datasets. Lastly, regional and socio-economic factors can play a crucial role in shaping the outcomes of studies on preconception nutrition supplements. For instance, access to healthcare, dietary patterns, and cultural practices may vary widely across different settings, influencing the effectiveness of nutritional interventions. Socioeconomic status can affect the ability to afford supplements, access to prenatal care, and overall health, all of which may contribute to variations in fetal growth markers. Therefore, these factors must be considered when interpreting study results, as they may limit the generalizability of findings to broader populations.

There are several strengths of this review. We did not apply restrictions on publication year and geographic location, which enabled us to examine relevant published RCTs to provide useful insights into the role of preconception nutrition supplements on maternal hemoglobin and markers of fetal growth. Despite substantial heterogeneity, the results of the current meta-analysis provide results consistent with prior reviews that had investigated the effect of nutrition supplements during pregnancy on maternal hemoglobin, birth weight, small for gestational age, and preterm birth [23, 66]. While the prior reviews have primarily focused on birth weight, we examined two additional markers of fetal growth including birth length and birth head circumference.

Potential future directions

Evidence regarding the beneficial effects of preconception nutrition supplements on maternal hemoglobin, largely from RCTs of moderate quality, underscores the potential to enhance hematological health and guide policy decisions. The role of preconception nutrition supplements in improving maternal hemoglobin can guide policymakers in efforts to improve hematological indices among women prior to conception. Focusing on the preconception period may offer an opportunity to prepare women with adequate iron stores before planning their pregnancy. The findings may be pertinent to LMICs, where women may not obtain antenatal care on time. To improve iron stores and to meet the increased nutrition demands of pregnancy, women in LMICs may need to start nutrient supplements before conception and continue the supplements throughout pregnancy. In addition, integrating modern technologies, such as "Chatbot" could amplify these benefits [75], offering real-time support and personalized guidance to encourage timely adoption of preconception supplements. Chatbots can deliver targeted reminders and health information, helping women in LMICs better understand and adhere to supplement regimens, potentially increasing the effectiveness of preconception interventions. The favorable effect of the preconception lipid-based nutrient supplement on fetal growth from the large multi-country RCT suggests the significance of commencing a comprehensive nutrition supplement during the preconception window. The positive findings from the multi-country RCT warrant conducting more robust RCTs in the future to ascertain the benefits of comprehensive preconception

nutrient supplements, incorporating both micro and macronutrients, on all markers of fetal growth including birth weight, length, and head circumference.

Conclusion

Preconception lipid-based nutrient supplements, multiple micronutrients, and iron and folic acid can be used as a preventive measure to reduce maternal anemia, especially in LMICs with limited access to timely antenatal care. However, the favorable effects of preconception nutrition supplements, when all types of supplements are lumped together, on birth weight, length, head circumference, small for gestational age, and preterm birth are unclear due to low-quality evidence. More well-designed and robust RCTs are warranted to ascertain the benefits of comprehensive preconception nutrient supplements on all markers of intrauterine growth and other important perinatal outcomes.

Abbreviations

BMI	Body mass index
CIs	Confidence intervals
Cm	Centimeter
Gm	Gram
GRADE	Grading of recommendations, assessment, development, and evaluation
HICs	High-income countries
IFA	Iron and folic acid
LBW	Low birth weight
LMICs	Low-middle-income countries
LNS	Lipid-based nutrient supplement
MMN	Multiple micronutrient
PICO	Population, Intervention, Comparison, and Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
ROB	Risk of bias
RR	Risk ratio
WF	Women First
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02726-7.

Supplementary Material 1. Supplemental Figure S1. Effect of preconception nutrition supplements (iron and folic acid, multiple micronutrients, and a lipid based nutrient supplement) on small for gestational age. Supplemental Figure S2. Effect of preconception nutrition supplements (iron and folic acid, multiple micronutrients, and a lipid based nutrient supplement) on preterm birth. Supplemental Figure S3. Funnel plot and Egger's regression test results for meta-analysis of RCTs included in the review (maternal hemoglobin and birth weight). Supplemental Figure S4. Funnel plot and Egger regression test results for meta-analysis of RCTs included in the review (Small for gestational age and preterm birth). Supplemental Table S1. Search terms used to search electronic databases for systematic review and meta-analysis of RCTs investigating the role of preconception nutrient supplements on maternal anemia and three markers of intrauterine growth. Supplemental Table S2. Findings of meta-regression analysis for hemoglobin and birth weight. Supplemental Table S3. Risk of bias assessments for each domain for studies included in the review. Supplemental Table S4. Quality of evidence of RCTs assessing the effect of preconception nutrition supplements on maternal hemoglobin, birth weight, length, head circumference, small for gestational age, and pre-term birth: GRADE assessment tool findings.

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None.

Authors' contributions

The study was conceptualized by SAA. SAA and NK screened all articles independently, compiled all data, and assessed the quality of eligible RCTs after extracting relevant data from the RCTs. SAA prepared the first draft of the manuscript and LK edited the draft and provided constant supervision to carry out the review. JG, KK, LV, and NFK reviewed the manuscript and provided feedback to improve the quality of the manuscript. All authors have reviewed and approved the final version of the paper.

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Data availability

The results of the current review and meta-analysis were synthesized after retrieving data from RCTs and references to those RCTs are listed in the reference list. The authors of specific research can be contacted individually by anyone in need of the raw data from those studies, or the data can be obtained from the published articles. The RCTs can be accessed online via a reference list, and each RCT is correctly referenced in the provided bibliography.

Declarations

Ethics approval and consent to participate

Not applicable as this was a systematic review and meta-analysis of published RCTs.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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