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Effect of different Iron-Folic acid (IFA) formulations, doses, and frequencies on pregnancy and neonatal outcomes compared to multiple micronutrients (MMN) among pregnant women: a systematic review and meta-analysis

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Abstract

Background Iron-Folic Acid (IFA) supplementation during pregnancy is widely recommended to prevent maternal anemia and improve birth outcomes. However, the optimal formulation, dose, and frequency of IFA supplementation remain uncertain. This systematic review and meta-analysis aimed to evaluate the effect of different IFA formulations, doses, and frequencies on pregnancy and neonatal outcomes compared to Multiple Micronutrients (MMN) among pregnant women.

Methods A comprehensive literature search was conducted across PubMed, Google Scholar, Cochrane Library, Scopus, and TRIP databases to identify pertinent studies published up to December 31st, 2023. Outcome measures includes preterm birth (PTB), stillbirths, low birth weight (LBW), small for gestational age (SGA), miscarriage rate (MR), neonatal mortality, and perinatal mortality. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated, and the quality of evidence was assessed using GRADEpro.

Results Among 20 studies comparing IFA to MMN, our analysis showed a significant increased risk with LBW (RR: 1.07, 95% CI: 1.01 to 1.13, $p=0.02$, $I^2=24\%$) associated with IFA and MMN and elevated risk of stillbirth (RR: 1.08, 95% CI: 1.00 to 1.17, $p=0.05$, $I^2=19\%$), SGA (RR: 1.03, 95% CI: 0.99 to 1.06) compared to IFA with MMN. However, non-significant risk of PTB (RR: 0.84, 95% CI: 0.38 to 1.84) and MR (RR: 1.04, 95% CI: 0.92 to 1.16, $p=0.54$) was observed with IFA as compared to MMN. Neonatal mortality and perinatal mortality also did not significantly differ between the two groups. Certain formulations and doses showed trend of risk, particularly in relation to stillbirth and SGA.

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Conclusions Our findings emphasize the importance of carefully considering the potential risks and benefits of IFA supplementation in pregnancy, and suggest the need for further research to elucidate the underlying mechanisms driving these associations and to optimize supplementation strategies for maternal and neonatal health.

Keywords Iron-folic acid, Iron supplementation, Pregnancy outcomes, Neonatal outcomes, Multiple micronutrients, Systematic review, Meta-analysis

Introduction

Iron deficiency remains the most prevalent nutritional deficiency globally and is a primary etiological factor for anemia during pregnancy, significantly affecting pregnant women, infants, and children due to heightened iron requirements during critical developmental stages [1, 2]. This deficiency is associated with adverse pregnancy outcomes, including an increased risk of preterm birth (PTB), stillbirth, miscarriage (MR), low birth weight (LBW), small for gestational age (SGA) infants, and maternal mortality during childbirth [3–6].To mitigate iron deficiency anemia (IDA) in pregnancy, various public health interventions are implemented worldwide, including iron supplementation, nutrition education to promote dietary diversity, iron fortification of staple foods, and deworming programs, either individually or in combination [7, 8].

A systematic review evaluating the effects of iron-folic acid (IFA) supplementation during pregnancy demonstrated substantial benefits, including a 70% reduction in anemia at term, a 67% reduction in iron deficiency anemia, and a 19% reduction in the incidence of LBW [1, 9, 10]. Additionally, observational studies indicate lower neonatal mortality rates among infants born to mothers who adhered to antenatal IFA supplementation compared to those who did not [11]. Based on this evidence, the World Health Organization (WHO) recommends daily oral IFA supplementation for pregnant women, particularly in regions with a high prevalence of anemia [12]. WHO guidelines advocate a daily dose of 30–60 mg elemental iron with 400 µg folic acid throughout pregnancy to reduce the risk of maternal anemia, iron deficiency, and LBW [13]. However, there remains scientific uncertainty regarding the optimal IFA formulation, dosage, and frequency, necessitating further investigation.

Recent research has increasingly focused on evaluating the comparative effectiveness of different IFA formulations, dosages, and administration frequencies, particularly in relation to multiple micronutrient (MMN) supplementation [14–16]. A 2019 Cochrane review analyzing 19 randomized controlled trials (RCTs) conducted in low- and middle-income countries (LMICs) found that MMN supplementation reduced the incidence of LBW and SGA births and may also decrease PTB rates in women of reproductive age compared to IFA supplementation alone [17].

However, a critical knowledge gap remains, as this review did not assess outcomes among adolescent pregnancies, a population that has received limited research attention regarding the benefits of MMN supplementation [17].

MMN supplements provide a wider range of vitamins and minerals, potentially offering greater benefits beyond IFA alone [1, 18, 19]. Evaluating the relative efficacy and safety of various IFA formulations, dosages, and frequencies in comparison to MMN supplementation is crucial for enhancing evidence-based recommendations and improving maternal and neonatal health outcomes globally. Therefore, this systematic review and meta-analysis aim to synthesize the available evidence on the effects of different IFA formulations, dosages, and frequencies compared to MMN supplementation in pregnant women.

Methods

The Cochrane Handbook (version 5.1.0) was used to conduct a systematic review and meta-analysis [18]. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) were followed throughout the systematic review's creation [19].

Search strategy

A comprehensive literature search was performed across PubMed, Google Scholar, Cochrane Library, Scopus, and TRIP databases to identify relevant studies published up to December 31, 2023. The search focused on studies examining the effects of different IFA formulations, dosages, and frequencies on pregnancy outcomes and neonatal health in pregnant women. The search strategy included keywords and phrases such as ("iron-folic acid" OR "folic acid supplementation" AND "multiple micronutrients") AND ("pregnancy outcomes" OR "neonatal outcomes" OR "birth outcomes" OR "preterm birth" OR "low birth weight" OR "maternal anemia") AND ("different formulations" OR "diverse frequencies" OR "supplementation strategies"). The search was restricted to studies published in English and conducted on human participants. Additionally, a manual search of reference lists from selected articles was performed to identify any additional relevant studies. Full-text access to all relevant literature was obtained through our Institutional library resources.

Study selection

Inclusion Criteria:

Population (P): Pregnant women.

Intervention (I): Various IFA formulations, dosages, and frequencies.

Comparison (C): Multiple MMN supplementation.

Outcomes (O): Preterm birth (PTB), stillbirths, low birth weight (LBW), small for gestational age (SGA), miscarriage rate (MR), neonatal mortality, and perinatal mortality.

Study Design (S): Randomized controlled trials (RCTs).

Exclusion Criteria:

1. Animal studies, reviews, editorials, case reports, case series, and conference abstracts were excluded.
2. Studies without full-text availability were not considered.
3. Studies that did not report any of the primary outcomes—PTB, stillbirths, LBW, SGA, MR, neonatal mortality, or perinatal mortality—were excluded.
4. Studies involving participants receiving supplements other than IFA or MMN were not included.

Data extraction

Two independent reviewers (MS and AG) conducted the screening process and identified duplicate records by reviewing the titles and authors of the selected studies. Data extraction was performed using a predefined, standardized data extraction form to systematically collect relevant information from each included study. The publication with the most complete data set was used as the primary source.

The following data were recorded:

- Study characteristics: Author names, publication year, study design, country, and study duration.
- Participant characteristics: Sample size, maternal and neonatal outcomes.
- Outcome measures: PTB, stillbirth, LBW, SGA, MR, neonatal mortality, and perinatal mortality.

After data extraction, the two reviewers cross-checked their findings to identify any inconsistencies. Any discrepancies were resolved through discussion and consensus with the corresponding author (PK). Full-text access to all relevant literature was obtained through our Institutional library resources.

Quality assessment

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias (ROB) tool [20], considering random sequence generation, allocation concealment, blinding, incomplete data, selective reporting, and other biases. The certainty of the evidence for each outcome was evaluated using GRADEpro GDT [21], following GRADE guidelines [22]. Studies were classified as having low, unclear, or high risk of bias, while the certainty of evidence for each outcome was rated as high, moderate, or low.

Publication bias

A funnel plot analysis was used to assess publication bias [23]. Egger's regression test was used to determine the asymmetry of funnel plots [24].

Statistical analysis

The pooled Risk Ratio (RR) with a 95% confidence interval (CI) was computed using either a fixed or random-effect model. Heterogeneity was assessed using the I^2 statistic, with values greater than 50% indicating significant heterogeneity, prompting the use of a random-effects model; otherwise, a fixed-effect model was applied [25, 26]. Statistical significance for all the investigated outcomes was determined at a p-value of less than 0.05. Data analysis was performed using RevMan, version 5.4.1 and STATA, version 16.0 (Stata Statistical Software, Release 16; StataCorp LP, College Station, TX). We conducted Trial Sequential Analysis (TSA) using TSA software (Copenhagen Trial Unit, Denmark) to assess sample size adequacy, control for random errors, and estimate the Required Information Size (RIS) [27]. A random-effects model (DerSimonian and Laird) was used with relative risk (RR) as the effect measure. The analysis incorporated alpha-spending boundaries (Type I error: 5%), 80–100% power, and model variance-based heterogeneity correction. The Z-curve was plotted against TSA monitoring boundaries to determine whether findings were conclusive, required further trials, or suggested futility. Sensitivity analysis was performed by sequentially omitting a single study in each turn, to validate the pooled observed effect.

Results

Literature selection

Figure 1 presents the PRISMA flow diagram outlining the literature selection process. The initial search yielded 596 records, with duplicate entries removed, leaving 213 full-text articles for assessment. Following systematic screening, 82 articles were excluded for not meeting inclusion criteria. Ultimately, 20 studies [28–46] were included, analyzing the impact of different IFA formulations, doses, and frequencies on pregnancy and neonatal outcomes compared to MMN.

Characteristics of included studies

Our systematic review and meta-analysis included a total of 20 RCTs [28–46], showcasing a diverse range of

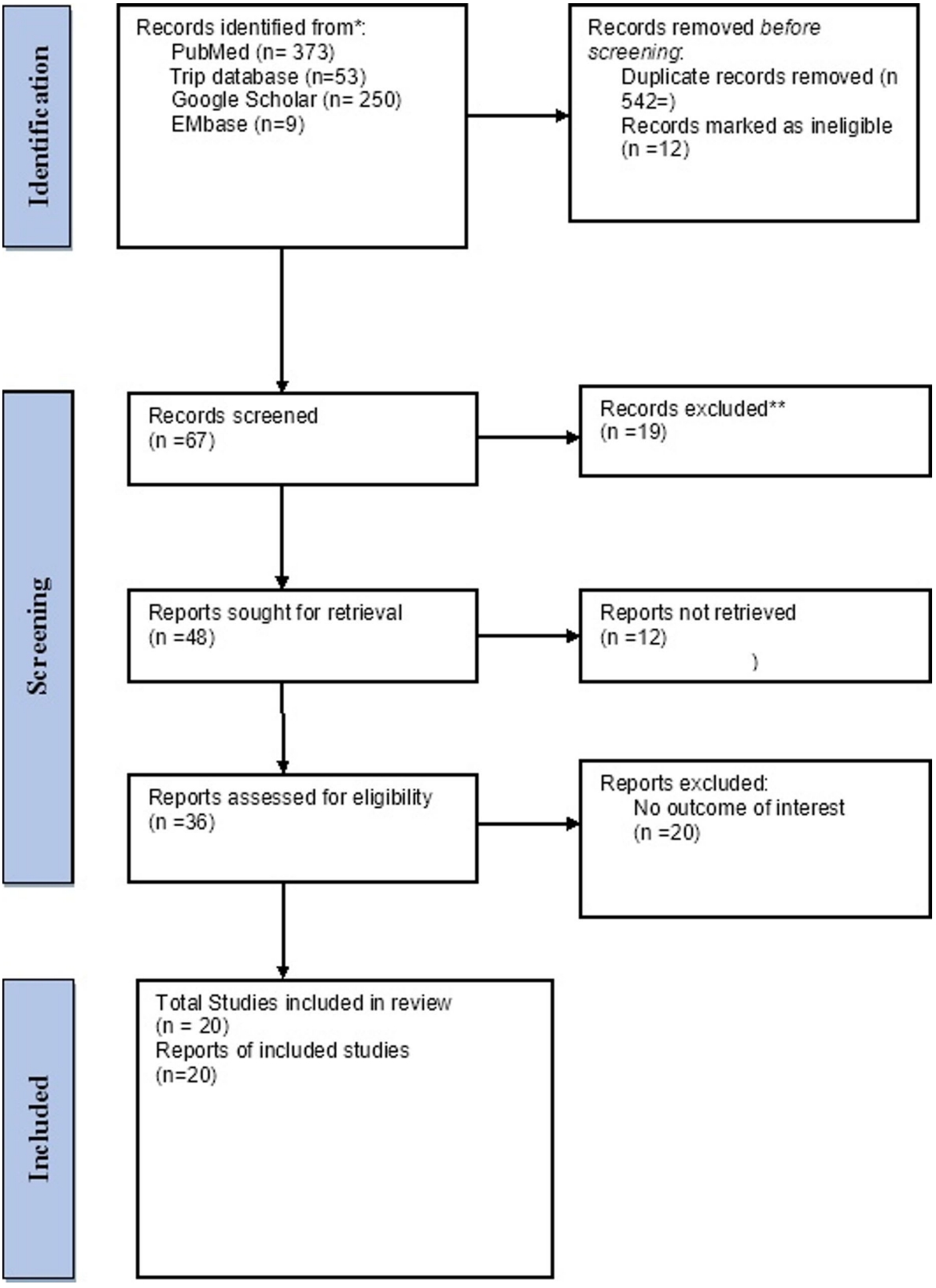

Fig. 1 Forest plot for the risk of still birth in Iron-Folic Acid (IFA) vs. multiple micronutrients (MMN) group

baseline characteristics as represented in Table 1. These studies, were conducted between 2003 and 2019, provided valuable insights into the effects of various IFA formulations, dosages, and frequencies on pregnancy and neonatal outcomes among pregnant women. The sample size was varied from 219 to 15,804 with follow-up duration ranging from 28 days to 52 weeks. Geographically, 13 studies were conducted in Asian regions, with the remaining 7 studies conducted in Caucasian populations. The IFA interventions across the studies encompassed different formulations (tablet, capsule, caplets), doses were as follows: 60 mg of iron combined with 0.25–0.4 mg of FA, 30 mg of iron combined with 0.4 mg of FA, and 60 mg of iron combined with 1.5–3.0.5.0 mg of FA and frequencies (daily and weekly), while comparing IFA supplementation with MMN.

Main findings

Preterm birth (PTB)

Our analysis showed a non-significant reduction in PTB risk with IFA supplementation compared to MMN (RR: 0.84, 95% CI: 0.38 to 1.84), $p = 0.66$, $I^2 = 99\%$) [Table S1]. Subgroup analysis by formulation indicated a non-significant risk with tablets (RR: 0.68, 95% CI: 0.20 to 2.27), $p = 0.53$, $I^2 = 99$ and capsules (RR: 1.13, 95% CI: 0.97 to 1.33), $p = 0.12$, $I^2 = 3\%$, while the combined formulation showed a comparable risk (RR: 0.85, 95% CI: 0.62 to1.16), $p = 0.30$.

Dose-wise analysis found no significant difference with 60 mg iron + 0.25–0.4 mg FA (RR: 1.01, 95% CI: 0.83 to 1.23), $p = 0.95$, $I^2 = 19\%$, whereas a lower dose (30 mg iron + 0.4 mg FA) was linked to a slightly increased risk (RR: 0.60, 95% CI: 0.15 to 2.50), $p = 0.49$, $I^2 = 99\%$, though this effect was not statistically significant.

Still birth

Our analysis identified a significant increase in stillbirth risk with IFA supplementation compared to MMN (RR: 1.08, 95% CI: 1.00–1.17, p = 0.05, I^2=19%) [Figure 2]. Subgroup analysis by formulation revealed a statistically significant risk with tablets (RR: 1.11, 95% CI: 1.02 to 1.21, p = 0.02), indicating a higher stillbirth risk compared to other formulations. In contrast, capsules showed no significant association with stillbirth (RR: 0.92, 95% CI: 0.75 to 1.14, p = 0.46, I^2=47%), suggesting no substantial risk difference from MMN. Further subgroup analysis based on ethnicity showed significant increase in stillbirth risk with IFA supplementation compared to MMN in Asian Population (RR: 1.09, 95% CI: 1.01–1.18, p = 0.03) [Table-S8].

Dose-wise analysis demonstrated a significant correlation between 30 mg iron + 0.4 mg FA and stillbirth (RR: 1.13, 95% CI: 1.02 to 1.24, $p = 0.02$), indicating an increased risk compared to other dosage combinations. However, other dosage regimens did not exhibit statistically significant associations with stillbirth [Table S2].

Miscarriage rate (MR)

Our analysis found no significant overall risk of miscarriage (MR) with IFA supplementation compared to MMN (RR: 1.04, 95% CI: 0.92 to 1.16, $p = 0.54$) [Table S3]. Subgroup analysis by formulation showed a non-significant association for tablets (4 studies, RR: 1.07, 95% CI: 0.94 to 1.22, $p = 0.29$). Moreover, a non-significant effect was observed with capsules (3 studies, RR: 0.90, 95% CI: 0.69 to 1.17, $p = 0.43$), suggesting a lower miscarriage risk in the IFA group compared to MMN. Dose wise analysis revealed the non-significant association with 60 mg iron + 0.25–0.4 mg FA (RR: 1.06, 95% CI: 0.94 to 1.19), $p = 0.37$, and also another dose with 60 mg iron + 1.5–3.0.5.0 mg FA (RR: 0.82, 95% CI: 0.54 to 1.26), $p = 0.37$, $I^2 = 99\%$.

Low birth weight (LBW)

Our analysis of 10 studies indicated a significant risk of LBW with IFA supplementation compared to MMN (RR: 1.07, 95% CI: 1.01 to 1.13, $p = 0.02$, $I^2 = 24\%$) [Figure 3]. Subgroup analysis by formulation showed a significant LBW risk with tablets (6 studies, RR: 1.13, 95% CI: 1.02 to 1.26, $p = 0.02$), while capsules (2 studies) demonstrated a non-significant risk (RR: 1.17, 95% CI: 0.95 to 1.46, $p = 0.14$). Similarly, combined formulation (Tablet & Capsule) (RR: 1.02, 95% CI: 0.52 to 1.98, $p = 0.96$) and Caplets (RR: 0.99, 95% CI: 0.94 to 1.06, $p = 0.86$) were showed a non-significant association. Dose-wise analysis found that 60 mg Fe + 0.25–0.4 mg FA (8 studies) (RR: 1.06, 95% CI: 1.00–1.12, $p = 0.06$, $I^2 = 29\%$) and two studies using 30 mg Fe + 0.4 mg FA reported a non-significant associated with a LBW risk. [Table-S4].

Small for gestational age (SGA)

The pooled analysis of five studies showed a significant risk of SGA with IFA supplementation compared to MMN (RR = 1.03, 95% CI: 0.99 to 1.06, $p = 0.15$, $I^2 = 15\%$) [Figure 4]. Subgroup analysis by formulation indicated a significant risk of SGA with tablets (2 studies, RR = 1.02, 95% CI: 1.00–1.05, $p = 0.09$) as well as with capsules (2 studies, RR = 1.15, 95% CI: 1.0 to 1.31, $p = 0.04$). Dose-wise analysis revealed that supplementation with 60 mg Fe + 0.25–0.4 mg FA (4 studies) was not significantly associated with SGA risk (RR = 1.06, 95% CI: 0.97–1.17, $p = 0.19$, $I^2 = 46\%$) [Table-S5].

Neonatal mortality

The overall analysis showed no significant association between IFA supplementation and neonatal mortality compared to MMN (RR = 1.02, 95% CI: 0.94 to 1.11, $p = 0.61$, $I^2 = 19\%$) [Table-S6]. Subgroup analysis by

Table 1 Baseline characteristics for the included studies investigating for effect of different Iron-Folic acid (IFA) formulations versus multiple micronutrients (MMN) Doses, and frequencies on pregnancy and neonatal outcomes among pregnant women

S.N. no.	Author, Year	Country	Ethnicity	Study design	Study Duration	Enrollment time	Group investigated (*n*)	Doses	Formulation	Frequency	Duration of Intervention	PTB gestation duration	Outcome Investigated	Follow Up
1	Christian et al. 2003[29]	Nepal	Asian	Double blind cluster randomized controlled trial	Dec. 1998 to Apr. 2001	12 wk	IFA (940)	60 mg $FeSO_4$, 0.4 mg FA	Caplets	Daily	12 wk to 12 wk postpartum	< 37 wk	Birth weight, birth length, HC/CC, LBW	NR
							MMN (1038)	FA 0.4 mg, IFA (60 mg ferrous fumarate), IFA-zinc (30 mg zinc sulphate), or multiple IFA-Zn plus vit. D 10 g, vit. E 10 mg, vit. B_1 1.6 mg, vit. B_2 1.8 mg, Vit. B_3 20 mg, vit. B_6 2.2 mg, vit. B_{12} 2.6 g, vit. C 100 mg, vit. K 65 g, Cu 2.0 mg, Mg 100 mg) all with vit. A						
							Control (1037)	Vit. A 1 mg						
							FA (929)	0.4 mg						
							IFA Zn. (982)	60 mg $FeSO_4$,0.4 mg FA, 30 mg Zn. sulphate						
2	Friis et al. 2004 [30]	Zimbabwe	Caucasian	Randomized, placebo-controlled, double blind effectiveness trial	1996 to 1997	22–35 wk	IFA (832)	30 mg Fe, 0.4 mg FA	Tablet	Daily	22 wk to 35 wk	< 37 wk	GA and birth size	NR
							MMN (837)	Vit.- A 3000 (g RE), β -Carotene 3.5 mg, Vit.B_1 1.5 mg, Vit.B_2 1.6 mg, B_6 2.2 mg, Vit.B_{12} 4.0 µg, B_3 17 mg, C 80 mg, D 10 µg, E 10 mg. Minerals- Zn 15 mg, Cu 1.2 µg, Se 65 ug						

Table 1 (continued)

S.N. no.	Author, Year	Country	Ethnicity	Study design	Study Duration	Enrollment time	Group investigated (*n*)	Doses	Formulation	Frequency	Duration of Intervention	PTB gestation duration	Outcome Investigated	Follow Up
3	Kaestel et al. 2005[31]	Guinea-Bissau	Caucasian	Randomized, controlled, double masked trial	Jan. 2001 to Oct. 2002	22 wk	IFA (366)	60 mg Fe + 0.4 mg FA	Tablet	Daily	16.6 wk to delivery	< 37 wk	Birth weight, PM, NM, MR	NR
							MMN-1 (360)	Vit. A (mg RE) 0.8 mg, Vit. D (IU) 0.2 mg, Vit. E 10 mg, Vit. B_1 mg, 1.4 mg, Vit. B_2 1.4 mg, Vit.B_3 18 mg, FA 0.4 mg, Vit. B_6 1.9 mg, Vit. B_{12} 2.6 mg, Vit. C 70 mg, Zn 15 mg, Fe 30 mg, Fe 30 mg, Cu 2.0 mg, Se 0.065 mg, I 0.15 mg.						
							MMN-2 (374)	Vit. A 1.6 mg RE, Vit. D 0.4 mg, Vit. E 20 mg, Vit. B_1 2.8, Vit. B_2 2.8 mg, Vit.B_3 36 mg, FA 0.8 mg, Vit. B_6 3.8 mg, Vit. B_{12} 5.2 mg, Vit. C 140 mg, Zn 30 mg, Fe 30 mg, Fe 30 mg, Cu 4 mg, Se 0.13 mg, I 0.3 mg						
4	Osrin et al. 2005[32]	Nepal	Asian	Double-blind, randomized controlled trial	Aug. 2002 to Oct. 2003	20 wk	IFA (600)	60 mg Fe, 0.4 mg FA	Tablet	Daily	12 wk to delivery	NR	Birth weight, GA, and infant length and HC	3 month
							MMN (600)	Vit. A 0.8 mg, vit.E 10 mg, vit. D 5 mg, vit.B_1 1·4 mg, vit. B_2 1·4 mg, vit.B_3 18 mg, vit. B_6 1·9 mg, vit. B_{12} 2·6 mg, FA 0.4 mg, vit. C 70 mg, Fe 30 mg, zinc 15 mg, Cu 2 mg, Se 0.065 mg, and I 0.15 mg						
5	Zagré et al. 2007[28]	Niger	Caucasian	Cluster-randomized, double-blinded controlled supplementation trial	Jan. 2004 to Mar. 2005	12 wk	IFA (1328)	60 mg Fe, 0.4 mg FA	Capsule	Daily	12 wk to delivery	NR	LBW	NR
							MMN (1222)	Vit. A 0.8 mg, Vit. D 200 UI, Vit. E 10 mg, Vit. C 70 mg, Vit. B_1 1.4 mg, Vit. B_2 1.4 mg, Vit. B_3 18 mg, Vit. B_6 1.9 mg, Vit. B_{12} 2.6 mg, FA 0.4 mg, Fe 30 mg, Zn 15 mg, Cu 2 mg, Se 0.065 mg, I_2 0.15 mg						

Table 1 (continued)

S.N. no.	Author, Year	Country	Ethnicity	Study design	Study Duration	Enrollment time	Group investigated (*n*)	Doses	Formulation	Frequency	Duration of Intervention	PTB gestation duration	Outcome Investigated	Follow Up
6	Roberfroid et al. 2008[33]	Burkina Faso	Caucasian	Double-blind, randomized controlled trial	Mar. 2004 to Oct. 2006	20 wk	IFA (712) MMN (714)	60 mg Fe + 0.4 mg FA Vit. A 0.8 mg, Vit. D 200 UI, Vit. E 10 mg, Vit. C 70 mg, Vit. B_1 1.4 mg, Vit. B_2 1.4 mg, Vit. B_3 18 mg, Vit. B_6 1.9 mg, Vit. B_{12} 2.6 mg, FA 0.4 mg, Fe 30 mg, Zn 15 mg, Cu 2 mg, Se 0.065 mg, I_2 0.15 mg	Tablet	Daily	< 20 wk to 12 wk postpartum	< 37 wk	GA, birth weight, birth length, LBW & SGA	NR
7	Shankar et al. 2008[34]	Indonesia	Asian	Double-blind cluster-randomized trial	July 2001 to April 2004	37 wk	IFA (15486) MMN (15804)	60 mg Fe + 0.25 mg FA 30 mg Fe (ferrous fumarate) and 0.4 mg FA along with 0.8 mg vit.A_1 (retinyl acetate), 200 IU vit. D 10 mg vit. E (alpha tocopherol acetate), 70 mg ascorbic acid, 1·4 mg vit. B_1 (thiamine mononitrate), 18 mg (niacinanide), 1·9 mg vit. B_6, 2·6 mg vit. B_{12}, 15 mg zinc (zinc gluconate), 2 mg Cu, 65 µg Se 0.065 mg, I_2 0.15 mg	Tablet	Daily	12 wk to 12 wk postpartum	< 37 wk	Early NM, fetal loss (abortions & still birth) & LBW	12 weeks
8.	Tofail et al. 2008[35]	Bangladesh	Asian	Randomized, controlled trial	May 2002 to Dec. 2003	17 wk	IFA (473/488) MMN (469/469)	60 mg Fe, 0.4 mg FA/30 mg Fe, 0.4 mg FA 150 µg I (potassium iodide), 15 mg Zn (sulfate), 65 µg Se (sodium selenite), 2 mg Cu (sulfate), 800 µg RE vit. A, 1.4 mg thiamine mononitrate, 1.4 mg vit.B_2, 18 mg vit. B_3, 1.9 mg vit. B_6 (pyridoxine hydrochloride), 2.6 µg vit. B_{12}, 70 mg vit. C, 200 IU vit. D (vit. D3), and 10 µg vit. E (tocopherol acetate), 30 mg Fe (fumarate) and 400 µg folate.	Tablet	Daily	14 wk to delivery	NR	Infant development	NR

Table 1 (continued)

S.N. no.	Author, Year	Country	Ethnicity	Study design	Study Duration	Enrollment time	Group investigated (*n*)	Doses	Formulation	Frequency	Duration of Intervention	PTB gestation duration	Outcome Investigated	Follow Up
9	Zeng et al. 2008[36]	China	Asian	Cluster randomized double blind controlled trial	Aug. 2002 to Jan. 2006	0.23 wk	IFA (1912) FA (178) MMN (1899)	60 mg Fe + 0.4 mg FA 0.4 mg FA 30 mg iron, 400 µg folate, 15.0 mg Zn, 2.0 mg Cu, 65.0 µg Se, 0.15 mg I, 0.8 mg vit. A, 1.4 mg vit. B_1, 1.4 mg vit. B_2, 1.9 mg vit. B_6, 2.6 mg vit. B_{12}, 5.0 µg vit. D, 70.0 mg vit. C, 10.0 mg vit. E, and 18.0 mg B_3	Capsule	Daily	12 wk to delivery	< 37 wk	Birth weight, birth length, and HC	6 weeks
10	Bhutta et al. 2009[37]	Pakistan	Asian	Cluster-randomized, controlled trial	NR	12.2 wk	IFA (1230) MMN (1148)	60 mg Fe, 0.4 mg FA 30 mg of Fe (ferrous fumarate) and 0.4 mg of FA along with 0.8 mg of retinol (retinyl acetate), 200 IU of vit. D, 10 mg of vit. E (α-tocopherol acetate), 70 mg of ascorbic acid, 1.4 mg of vit. B_1 (thiamine mononitrate), 18 mg of vit.B_3, 1.4 mg of vit.B_2,1.9 mg of vit. B_6, 2.6 mg of vit. B_{12}, 15 mg of Zn (zinc gluconate), 2 mg of Cu, 0.065 mg of Se, and 0.15 mg of I	Tablet	Daily	< 16 wk gestation to delivery	NR	Birth weight, NM	28 Days
11	Sunawang et al. 2009[38]	Indonesia	Asian	Randomized community trial	May 2001 to Sep. 2003	20 wk	IFA (411) MMN (432)	60 mg FeSO4 + 0.25 mg FA Vit. A 0.8 mg, vit.E 10 mg, vit. D 5 mg, vit.B_1 1·4 mg, vit. B_2 1·4 mg, vit.B_3 18 mg, vit. B_6 1·9 mg, vit. B_{12} 2·6 mg, FA 0.4 mg, vit. C 70 mg, Fe 30 mg, zinc 15 mg, Cu 2 mg, Se 0.065 mg, and I 0.15 mg, 30 mg of ferrous fumarate	Tablet	Daily	12 wk to 1 wk postpartum	NR	Birth weight, birth length	30 days

Table 1 (continued)

S.N. no.	Author, Year	Country	Ethnicity	Study design	Study Duration	Enrollment time	Group investigated (*n*)	Doses	Formulation	Frequency	Duration of Intervention	PTB gestation duration	Outcome Investigated	Follow Up
12.	Persson et al. 2012[39]	Bangladesh	Asian	Randomized factorial trial	Nov. 2001 to Oct. 2003	20 wk	IFA (741/738) MMN (740)	30 mg Fe, 0.4 mg FA/60 mg Fe, 400 ug FA 30 mg of Fe [fumarate], 400 µg of FA, 800 µg of RE vit. A [retinyl acetate], 200 IU of vit. D [D3], 10 mg of vit. E [α-tocopherol acetate], 70 mg of vit. C, 1.4 mg of vit. B_1 [thiamine mononitrate], 1.4 mg of vit. B_2, 18 mg of vit. B_3, 1.9 mg of vit. B_6 [pyridoxine hydrochloride], 2.6 µg of vit. B_{12}, 2.6 µg of vit.B_{12}, 15 mg of Zn [sufphate], 2 mg of Cu [sulfate], 65 µg of Se [sodium selenite], and 150 µg of I [potassium iodide]	Capsule	Daily	20 wk to delivery	NR	Maternal Hb. Level, GA, birth weight, and NM, PM birth length and HC, GA	30 weeks
13.	Hanieh et al. 2013[40]	Viet Nam	Asian	Cluster randomized trial	Sep. 2010 to Nov. 2010	16 wk	IFA (426/425) MMN (407)	60 mg Fe,0.4 mg FA/60 mg Fe, 1.5 mg FA Twice Weekly (capsule) = Elemental Fe 60 mg, Zn 20 mg, I 300 mg, Cu 4 mg, Se 130 mg, Vit A 1.6 mg, Vit.B_1 2.8 mg, Vit.B_2 2.8 mg, vit.B_3 36 mg, Vit. B_6 3.8 mg, Vit. B_{12} 5.2 mg, FA 1.5 mg, Vit. C 140 mg, Vit. D 400 IU, Vit. E 20 mg, Elemental Fe 30 mg, Zn 15 mg, I 150 mg, Cu 2 mg, Se 65 mg, Vit. A 0.8 mg, vit.B_1 1.4 mg, vit.B_2 1.4 mg, vit.B_3 18 mg, Vit. B_6 1.9 mg, Vit.B_{12} 2.6 mg, FA 0.4 mg, Vit. C 70 mg, Vit. D 200 IU, Vit. E 10 mg	Tablet, Capsule	Daily,	< 16 wk to 12 wk postpartum	< 37 wk	Birth weight, maternal Hb.	32 weeks of gestation

Table 1 (continued)

S.N. no.	Author, Year	Country	Ethnicity	Study design	Study Duration	Enrollment time	Group investigated (*n*)	Doses	Formulation	Frequency	Duration of Intervention	PTB gestation duration	Outcome Investigated	Follow Up
14	Liu et al. 2013[41]	China	Asian	Randomized double-blind controlled trial	May 2006 to Apr. 2009	20 wk	IFA (6252) FA (6261) MMN (6262)	30 mg Fe, 0.4 mg FA 0.4 mg FA 0.4 mg, Fe (ferrous fumarate, 30 mg), vit. A 0.8 mg, vit. E 10 mg, vit. D 5 µg, vit. C 70 mg, Vit.B_1 1.4 mg, Vit.B_2 1.4 mg, vit. B_6 1.9 mg, vit. B_{12} 2.6 µg, Vit. B_3 18 mg, Zn 15 mg, Cu 2 mg, I 0.15 mg, and Se 0.065 mg	Capsule	Daily	20 wk to delivery	NR	PM, NM, PTB, birth weight, GA and maternal Hb. conc. & anemia	1 year
15	West et al. 2014[42]	Bangladesh	Asian	Cluster randomized, double-masked trial	Jan. 2008 to Aug. 2012	9 wk	IFA (22162) MMN (22405)	27 mg Fe + 0.6 mg FA Vit. A (770-µg retinol activity equivalents), D (5 µg, or 200 IU), E 15 mg, $B_1$1.4 mg, B_2 1.4 mg, $B_3$18 mg, B_6 1.9 mg, B_9 0.6 mg, B12 2.6 µg, and C 85 mg, Fe 27 mg; Zn 12 mg, Cu 1 mg, Se 0.06 mg and I 220 µg.	Tablet	Daily	9 wk to 12 wk postpartum	< 37 wk	All-cause NM, still birth, PTB, and LBW	6 month
16	Adu-Afarwuah et al. 2015[43]	Ghana	Caucasian	Community-based, partially double-blind, individually randomized controlled trial	Dec. 2009 to Dec. 2011	20 wk	IFA (349) MMN (354)	60 mg Fe + 0.4 mg FA Vit. A 0.8 mg RE, Vit. C 100 mg, Vit. B-1 2.8 mg, Vit. B_2, 2.8 mg, B_3 36 mg, FA 400 mg, Vit. B_5 7 mg, Vit. B-6 3.8 mg, Vit. B-12 5.2 mg, Vitamin D 400 IU, Vitamin E 20 mg, Vit. K 45 mg, Fe 20 mg, Zn 30 mg, Cu 4 mg, Se 0.13 mg, I 0.25 mg, Manganese 2.6 mg	Capsule	Daily	< 20 wk to delivery	< 37 wk	Birth weight, birth length, HC, PTB, LBW, GA, SGA	36 weeks

Table 1 (continued)

S.N. no.	Author, Year	Country	Ethnicity	Study design	Study Duration	Enrollment time	Group investigated (*n*)	Doses	Formulation	Frequency	Duration of Intervention	PTB gestation duration	Outcome Investigated	Follow Up
17	Ashorn et al. 2015[44]	France	Caucasian	Randomized, controlled, outcome assessor-blinded trial	Feb. 2011 to Aug. 2012	24 wk	IFA (288) MMN (290)	60 mg Fe + 0.4 mg FA Vit. A 0.8 mg RE, Vit. C 100 mg, Vit. B-1 2.8 mg, Vit. B_2 2.8 mg, Vit.B_3 36 mg, FA 400 mg, Vit.B_5 7 mg, Vit. B-6 3.8 mg, Vit. B_{12} 5.2 mg, Vit. D 400 IU, Vit. E 20 mg, Vit. K 45 mg, I 20 mg, Zn 30 mg, Cu 4 mg, Se 130 mg, I 250 mg, Manganese 2.6 mg	Capsule	Daily	24 wk to 24 wk postpartum	NR	Infant length, birth weight, HC and MUAC	6 month
18	Ramakrishnan et al. 2016[45]	Vietnam	Asian	Double-blind, randomized controlled trial	NR	26 wk	IFA (1671) FA (1672) MMN (1668)	60 mg Fe + 2.8 mg FA 2.8 mg Vit. A-0.8 mg, Vit. D- 600 IU, Vit. E- 10 mg, Vit. C-70 mg, Vit.B_1—1.4 mg, Vit. B_2-—1.4 mg, Vit.B_3,—18 mg Vit. B_6- 1.9 mg, Vit. B_{12}- 2.6 µg, FA-2.8 mg, Fe (ferrous sulfate)—60 mg, Zn (sulfate)—15 mg, Cu- 2 mg, Se-0.065 mg and I-0.15 mg	Capsule	Daily	> 26 wk to 12 wk postpartum	< 37 wk	Birth weight, GA, PTB & SGA	6 month
19	Wang et al. 2016[46]	China	Asian	Double-blind randomized controlled trial	May 2006 to Apr. 2009	20 wk	IFA (5909) MMN (5904)	30 mg Fe, 0.4 mg FA FA 0.4 mg, Fe (ferrous fumarate, 30 mg), vit. A 0.8 mg, vita. E10 mg, vit. D 5 µg, vit. C 70 mg, vit.B_1 1·4 mg, vit.B_2 1·4 mg, vit. B_6 1·9 mg, vit B_{12} 2·6 µg, vit. B_3 18 mg, Zn 15 mg, Cu 2 mg, I 0.15 mg and Se 0.065 mg.	Capsule	Daily	20 wk to delivery	NR	Birth weight	NR

Table 1 (continued)

S.N. no.	Author, Year	Country	Ethnicity	Study design	Study Duration	Enrollment time	Group investigated (*n*)	Doses	Formulation	Frequency	Duration of Intervention	PTB gestation duration	Outcome Investigated	Follow Up
20	Moore et al. 2019[47]	The Gambia	Caucasian	Randomized factorial, partially blinded trial	NR	13.6 wk	IFA (219) MMN (219)	60 mg Fe + 0.4 mg FA FA 0.4 mg, Fe (ferrous fumarate, 30 mg), vit. A 0.8 mg, vit. E 10 mg, vit. D 5 µg, vit. C 70 mg, Vit.B_1 1.4 mg, Vit.B_2 1.4 mg, vit. B_6 1.9 mg, vit. B_{12} 2.6 µg, Vit. B_3 18 mg, Zn 15 mg, Cu 2 mg, I 0.15 mg, and Se 0.065 mg	Tablet	Daily	13.6 wk to delivery	NR	Infant thymic size	52 weeks

formulation indicated non-significant findings for tablets (6 studies, RR = 1.03, 95% CI: 0.95 to 1.12, $p = 0.51$, $I^2 = 43\%$) and capsules (4 studies, RR = 0.90, 95% CI: 0.64 to 1.26, $p = 0.54$, $I^2 = 7\%$). Studies combining both tablet and capsule formulations (1 study) also reported no significant association (RR = 1.91, 95% CI: 0.17 to 20.99, $p = 0{,}60$). Dose-wise analysis revealed no significant association for 60 mg Fe + 0.25–0.4 mg FA (8 studies, RR = 1.05, 95% CI: 0.92 to 1.20, $p = 0.45$, $I^2 = 21\%$) or 30 mg Fe + 0.4 mg FA (3 studies, RR = 1.00, 95% CI: 0.90 to 1.11, $p = 0.96$, $I^2 = 37\%$).

Perinatal mortality

The overall analysis, incorporating 5 studies across all formulation types, found no significant association between IFA supplementation and perinatal mortality compared to MMN (RR = 1.02, 95% CI: 0.91 to 1.14, $p = 0.75$) [Table-S7]. Subgroup analysis by formulation and dose revealed non-significant associations for tablets (3 studies, RR = 1.02, 95% CI: 0.91 to 1.14, $p = 0.74$), capsules (2 studies, RR = 1.0, 95% CI: 0.71 to 1.42, $p = 0.98$).

Dose wise analysis demonstrated that 60 mg Fe + 0.25–0.4 mg FA (4 studies, RR = 1.02, 95% CI: 0.91 to 1.14, $p = 0.74$), and 30 mg Fe + 0.4 mg FA (RR = 1.0, 95% CI: 0.68 to 1.47, $p = 0.99$).

The subgroup analysis based on ethnicity of all the outcomes has been included in table S8.

Publication bias

Funnel plot analysis showed no clear signs of asymmetry, indicating an even distribution of studies around the estimated effect. This suggests the absence of significant publication bias that could influence the results. The funnel plots for stillbirth ($p = 0.69$), LBW ($p = 0.32$) and neonatal mortality ($p = 0.56$) are presented in Supplementary Figure S1 (a–c). For outcomes reported in fewer than 10 studies, funnel plots were not generated due to the limited number of data points, which could affect the reliability of asymmetry assessment.

Trial sequence analysis (TSA)

Figure 5 illustrates the graphical representation of the TSA findings. With a total sample size of 1,20,775 participants from the included studies on IFA and MMN, the analysis achieved 100% power, ensuring the robustness of the results. The cumulative Z-curve surpassed the trial sequential monitoring boundary before attaining the required sample size, further strengthening the validity of our conclusions.

Quality assessment

The risk of bias assessment for individual studies is presented in Figure S2 (risk of bias graph) and Figure S3 (risk of bias summary), which display the evaluation across all

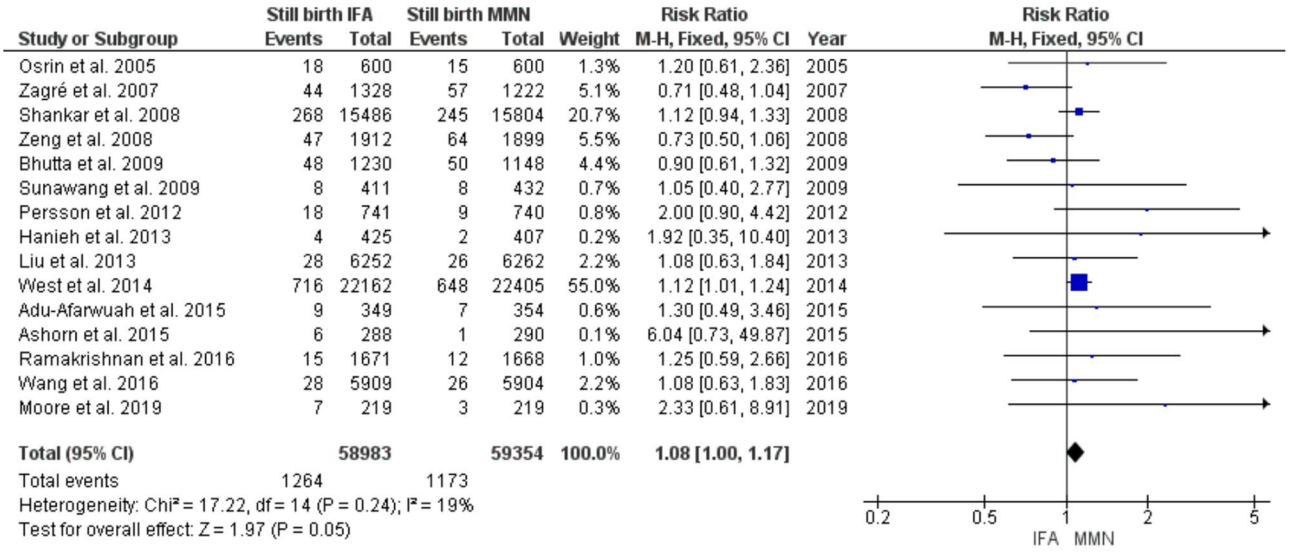

Fig. 2 Forest plot for the risk of still birth in Iron-Folic Acid (IFA) vs. multiple micronutrients (MMN) group

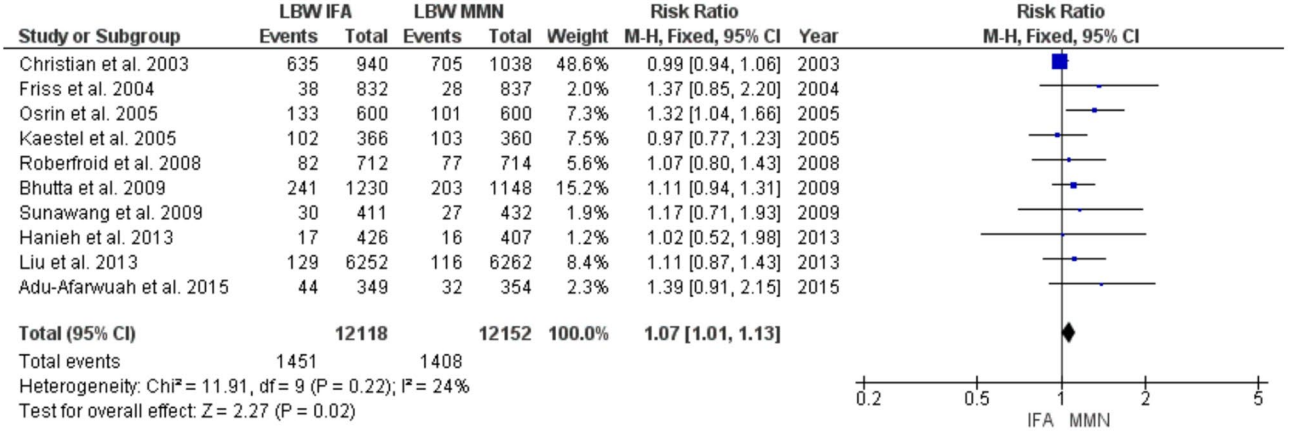

Fig. 3 Forest plot for the risk of LBW in Iron-Folic Acid (IFA) vs. multiple micronutrients (MMN) group

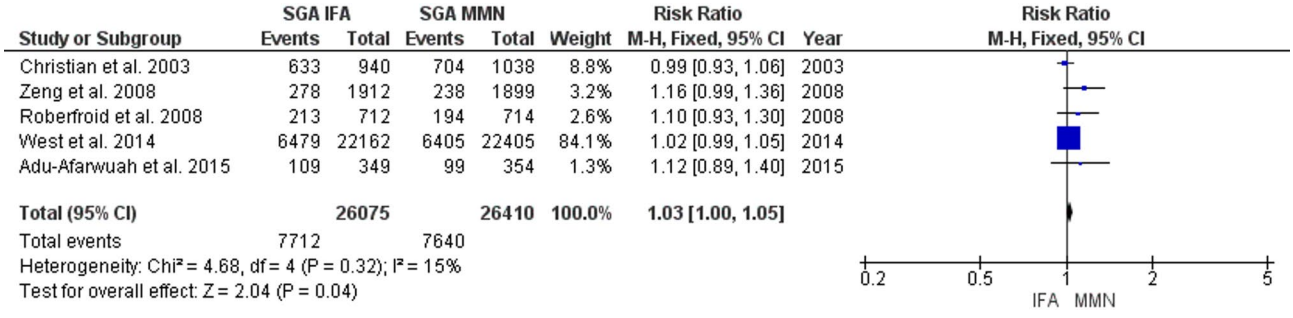

Fig. 4 Forest plot for the risk of SGA in Iron-Folic Acid (IFA) vs. multiple micronutrients (MMN) group

domains of the Cochrane Risk of Bias tool and the distribution of low, unclear, and high risk of bias among the included studies. The certainty of evidence for each outcome was assessed using the GRADEpro GDT software and was generally rated as moderate. While the findings suggest potential benefits of IFA over MMN in reducing preterm birth (PTB) and no significant differences in most other outcomes, moderate uncertainty remains, warranting cautious interpretation of the results (Table 2). The overall moderate risk of bias identified across the included studies further highlights the need for

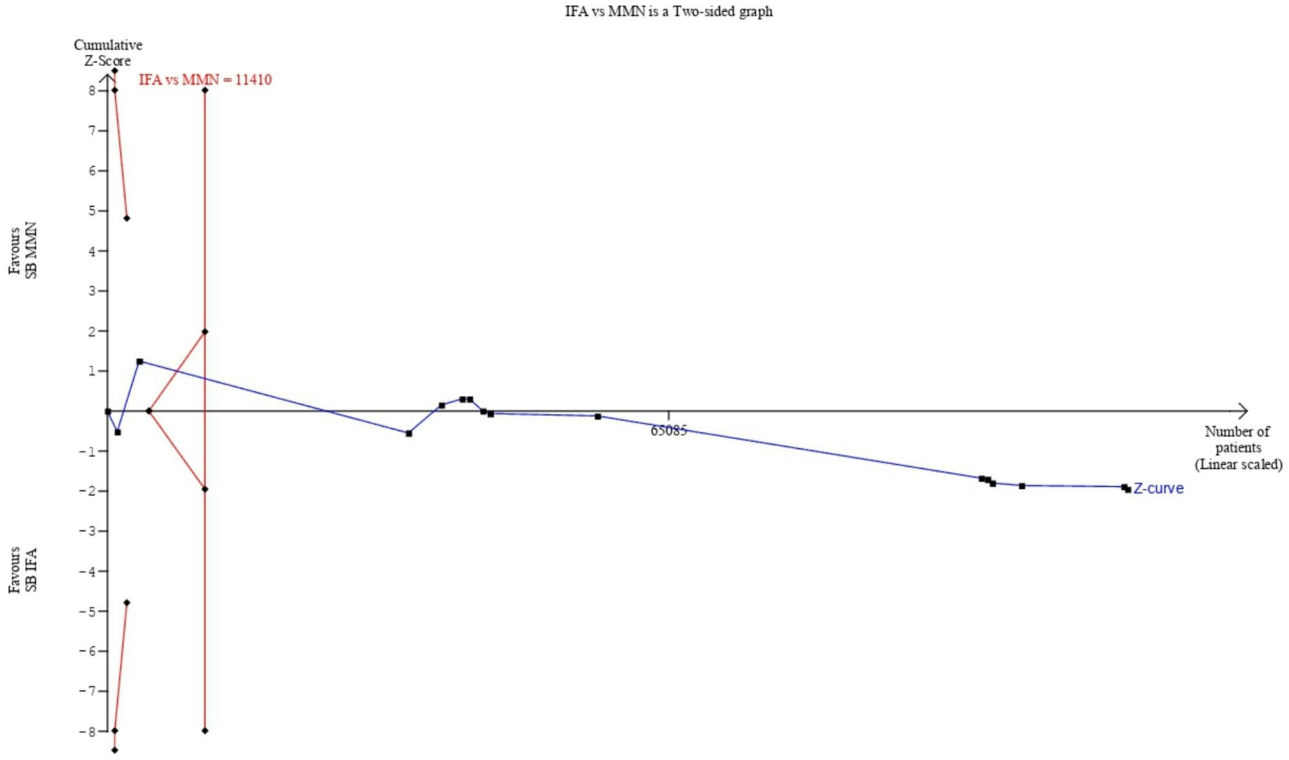

Fig. 5 Trial Sequential Analysis (TSA) for the sample size in Iron-Folic Acid (IFA) Formulations versus multiple micronutrients (MMN) Doses for Still birth

careful consideration when drawing conclusions from this analysis.

Sensitivity analysis

Our sensitivity analysis demonstrated that overall pooled estimates were not significantly influenced by the removal of any individual study but one or two studies of all the investigated outcomes were slightly deranged form the point estimates as inspected during the sensitivity analysis. However, these findings indicate the robustness of our meta-analysis results, reassuring that they are not driven by any single study, enhancing confidence in the validity of our findings Figure-S4 (a-g).

Discussion

The results of our comprehensive meta-analysis, which encompassed 20 studies contrasting IFA with MMN, offer valuable insights into the potential impact of these supplements on pregnancy outcomes. Our examination unveiled a notable increase in the risk of stillbirth, LBW, and SGA associated with IFA supplementation compared to MMN. Conversely, we observed a non-significant reduction in the risk of PTB, MR, as well as neonatal and perinatal mortality with IFA supplementation compared to MMN. The initiation of maternal IFA supplementation relatively early in pregnancy, preferably no later than the second trimester, suggests that a dosage of 60 mg of iron may not confer greater efficacy in improving hemoglobin or iron status compared to 30 mg [47]. It's worth noting that MMN are commonly employed for preventing anemia and other adverse pregnancy outcomes, with 30 mg of iron per day likely providing a sufficient dosage [48].

In cases where Iron Deficiency Anemia (IDA) is detected at the commencement of antenatal care or develops during pregnancy, it might be advisable to incorporate additional iron supplementation alongside continued MMN usage [49]. Nonetheless, clinical and laboratory evaluations should be conducted to ascertain whether anemia primarily stems from iron deficiency or other factors such as micronutrient deficiencies (e.g., vitamins A, folic acid, B12), genetic hemoglobin disorders, inflammation, or infectious diseases (e.g., tuberculosis, HIV, parasitic infections) [50, 51]. If iron deficiency does not emerge as the primary cause of anemia, administering more iron might not alleviate anemia and could entail an unnecessary intervention with potential risks of adverse effects [52]. Caution must be exercised when comparing the studies reviewed in this analysis due to variations in the composition of MMN supplements, supplementation frequency and duration, and initial rates of pregnancy. However, some overarching conclusions can be drawn [16, 53].

Our review confirms several findings from earlier meta-analyses conducted by Shah et al. [54] and by

Table 2 Summary for Quality of Evidences based on GRADEpro

Iron Folic Acid Formulation compared to Multiple Micronutrients for Pregnancy and Neonatal Outcome

Patient or population: Pregnancy and Neonatal Outcome
Setting: RCTs
Intervention: Iron Folic Acid Formulation
Comparison: Multiple Micronutrients

Outcomes	№ of participants(studies)Follow-up	Certainty of the evidence(GRADE)	Relative effect(95% CI)	Anticipated absolute effects	
				Risk with Multiple Micronutrients	Risk difference with Iron Folic Acid Formulation
IFA Vs MMN for PTB	25990(8 RCTs)	⨁⨁⨁◯Moderate	RR 0.83(0.41 to 1.69)	95 per 1,000	16 fewer per 1,000(56 fewer to 65 more)
SGA IFA Vs SGA MMN	52485(5 RCTs)	⨁⨁⨁◯Moderate	RR 1.03(1.00 to 1.05)	289 per 1,000	9 more per 1,000(0 fewer to 14 more)
Perinatal mortality IFA Vs Perinatal mortality MMN	50244(6 RCTs)	⨁⨁⨁◯Moderate	RR 0.99(0.89 to 1.09)	50 per 1,000	0 fewer per 1,000(5 fewer to 4 more)
Neonatal mortality IFA Vs Neonatal mortality MMN	102656(13 RCTs)	⨁⨁⨁◯Moderate	RR 1.02(0.94 to 1.11)	32 per 1,000	1 more per 1,000(2 fewer to 4 more)
Miscarriage rate IFA Vs Miscarriage rate MMN	44500(9 RCTs)	⨁⨁⨁◯Moderate	RR 0.98(0.88 to 1.09)	29 per 1,000	1 fewer per 1,000(3 fewer to 3 more)
Still birth IFA Vs Still birth MMN	120648(17 RCTs)	⨁⨁⨁◯Moderate	RR 1.08(1.00 to 1.17)	20 per 1,000	2 more per 1,000(0 fewer to 3 more)
LBW IFA Vs LBW MMN	25102(11 RCTs)	⨁⨁⨁◯Moderate	RR 1.06(1.00 to 1.12)	113 per 1,000	7 more per 1,000(0 fewer to 14 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

GRADE Working Group grades of evidenceHigh certainty: we are very confident that the true effect lies close to that of the estimate of the effectModerate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effectVery low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

CI Confidence interval, *RR* Risk ratio

Haider et al. [1] regarding the benefits of MMN supplementation during pregnancy. Additionally, our review adds new insights by comparing the effects of IFA as compared to MMN supplementation based on different maternal and neonatal outcomes. We found that MMN supplementation during pregnancy was more effective than IFA supplements alone in reducing the incidence of LBW and SGA. This contrasts with earlier findings, such as those by Haider [1] and Bhutta [55], which only found a beneficial effect compared to placebo or supplementation of two or fewer micronutrients in nine trials, but is consistent with recent reviews by the same authors. Shah and colleagues [54] reported similar observations regarding LBW risk and increases in mean birth weight when comparing MMN supplementation with IFA alone, although they did not find a significant effect on the risk of delivering SGA infants. Our review included findings from additional trials that were not present in the review by Shah et al. [54].

However, our finding of a non-significant risk of neonatal and perinatal mortality with MMN supplementation in trials that began intervention after the first trimester is novel and presents a major concern, particularly in settings where women do not receive prenatal care in the first trimester. Although these findings may have occurred by chance, they cannot be disregarded and have important policy implications. Our findings align with earlier versions of the Cochrane review and other systematic reviews by Haider (2011) [56], Ronsmans (2009) [57] and Christian (2018) [58] also reported comparable findings regarding neonatal mortality. Concerns previously raised about potential harmful effects of MMN supplements, such as increased risk of perinatal and neonatal mortality through elevated birth asphyxia in heavier babies, have not been consistently supported by research. While initial trials in Nepal suggested a non-significant increase in neonatal and perinatal mortality, subsequent studies have not replicated these findings. Notably, recent trials, such as SUMMIT (2008) [59] and West (2014) [41], did not indicate an increase in neonatal or early infant mortality risk in the MMN supplementation group compared to iron and folic acid supplementation.

Variations in iron formulation significantly influence absorption, efficacy, and tolerability. Conventional salts like ferrous sulfate and fumarate, though widely used, often cause gastrointestinal side effects, reducing

adherence, whereas newer forms like liposomal iron offer better bioavailability with fewer adverse effects [60]. Higher doses may enhance efficacy but are linked to increased side effects, leading to poor compliance and diminished benefits [61, 62]. Moreover, baseline iron status plays a crucial role; individuals with iron deficiency benefit more from supplementation, while iron-replete individuals may face risks such as oxidative stress or gut dysbiosis [63, 64]. These factors likely contribute to the heterogeneity observed across subgroups.

Biological and clinical interpretation of subgroup findings

The subgroup findings suggest that differences in iron-folic acid formulation, dose, and population characteristics may underlie the observed variability in outcomes. Capsule formulations generally showed more favorable or neutral effects compared to tablets, possibly due to better tolerability and absorption. Lower or higher iron doses yielded inconsistent results, with some indications of increased risk for stillbirth and low birth weight, particularly with tablets. Variability in baseline nutritional status and ethnicity, especially among Asian populations, also appeared to influence outcomes such as stillbirth. These patterns highlight the biological and clinical relevance of tailoring supplementation strategies based on formulation, dosing, and population context to optimize maternal and neonatal outcomes.

The majority of studies included in our analysis were conducted in low- and middle-income countries (LMICs), where micronutrient deficiencies are more prevalent and baseline nutritional status is often suboptimal. As such, the observed effects of iron-folic acid supplementation in these settings may be more pronounced due to higher baseline risk. In high-income countries, where dietary iron intake is generally adequate and antenatal care is more accessible, the benefits of routine supplementation may be less marked, and the risk-benefit profile could differ. Therefore, while our findings provide valuable insights for global maternal and neonatal health strategies, their direct applicability to high-income settings should be interpreted with caution. Further research in diverse populations, particularly in high-resource contexts, is needed to assess the generalizability and contextual relevance of these results.

The variation in iron dosages (30 mg vs. 60 mg) across studies included in the meta-analysis reflects differences in national guidelines, baseline population needs, and trial-specific protocols. While our dose-wise subgroup analysis showed that outcome differences between 30 mg and 60 mg doses were often subtle or statistically non-significant, these findings likely reflect the complex interplay between iron absorption, baseline iron status, and adherence. Evidence suggests that lower doses may be better tolerated and sufficient for preventing deficiency in iron-replete populations, whereas higher doses may be more appropriate in settings with widespread anemia. However, the absence of consistent differential effects in our analysis underscores the need for individualized, context-specific dosing rather than a one-size-fits-all approach.

Despite the robustness of our analysis, certain limitations must be acknowledged. The included trials varied considerably in sample sizes, which may introduce bias, especially where larger studies disproportionately influence the pooled estimates. Additionally, substantial heterogeneity was observed in outcomes such as perinatal mortality, limiting the precision of our conclusions. This variability likely stems from differences in maternal nutritional status, reproductive history, and the timing, type, and duration of iron supplementation. A key limitation of this review is that none of the included studies reported preterm birth data stratified by gestational age, reducing the clinical applicability of the findings.Furthermore, while we assessed risk of bias using standardized tools, a more detailed examination of potential methodological limitations—such as lack of allocation concealment, inadequate blinding, and incomplete outcome data in some randomized controlled trials—highlights the need for cautious interpretation. Lastly, variations in study populations, settings, and healthcare systems may affect the external validity of our findings and limit their generalizability to broader contexts.

In conclusion, our findings highlight the need for a nuanced approach when considering IFA supplementation during pregnancy. While MMN supplementation appears to offer superior benefits in reducing adverse pregnancy outcomes, further research is essential to clarify the underlying biological mechanisms and optimize supplementation strategies for maternal and neonatal health. Policymakers should consider these findings when developing nutritional guidelines to ensure the most effective interventions for pregnant women worldwide.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-025-08292-7.

Supplementary Material 1.

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None.

Authors' contributions

"MS contributed to data searching, data extraction, quality assessment and analysis, writing the original draft, and methodology. AG helped in data extraction, and quality assessment. ADU, KKP, MJS and AS helped in drafting and writing the manuscript. AS assisted in the funding support and conceptualization. PK drafted the full protocol, conceptualized, executed the study and finalized the draft version of the manuscript."

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Data availability
Our data includes the supporting analysis, which is provided as supplementary figures and tables.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
Ethical Approval was obtained from Institutional Ethics Committee, AIIMS, New Delhi, India (IEC-359/15.06.2023).

Consent for publication
Not applicable.

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