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Intermittent versus daily oral iron folic acid supplementation and pregnancy outcome in low- and middle-income countries: a systematic review and meta-analysis of experimental studies

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Abstract

Trials were inconsistent while reporting findings on the benefits of the intermittent regimen. Recent conclusive evidence to show overall effect was limited. This review compared intermittent and daily iron folic acid supplementation (IFAS) on pregnancy outcomes. Protocol is registered at Prospero with registration number CRD42023409161. The major data sources searched were PubMed/Medline, Hinari, and Google Scholar. The process was reported using a PRISMA flow diagram. The included studies were trials with English language reports. The population was pregnant women. The intervention was an intermittent oral iron folic acid regimen, and the control was a daily regimen. The outcome measures were blood hemoglobin level, side effects, and medication adherence. The GRADE approach and Cochrane collaboration tool were used in the quality evaluation. The selected trials were narrated for basic characteristics and major findings. The standardized mean difference was used for continuous outcomes and the relative risk for binary outcomes. A sensitivity analysis was performed to report the robustness of the estimate. Twenty-two trials were selected for analysis. The quality of the evidence ranges from high to very low. Maternal blood hemoglobin levels were different between the intermittent and daily groups (mean difference (MD), − 0.24 g/dl; 95%CI, − 0.35, − 0.12). However, either early initiation or frequently intermittent regimen in the subgroup analysis showed no difference in hemoglobin levels. Intermittent regimens had lower gastric side effects (relative risk (RR), 0.27; 95%CI, 0.11, 0.69) and better medication adherences (relative risk (RR), 1.6; 95%CI, 1.34, 1.91). There was no clear evidence of a difference in anaemia incidence between the groups (relative risk (RR), 1.09; 95%CI, 0.77, 1.54). The overall level of hemoglobin in pregnancy was different between the groups. However, anaemia incidence was similar. The combined results suggest the intermittent regimen had better benefits in pregnancy than daily.

Introduction

The American Congress of Obstetrics and Gynecology (ACOG) and the World Health Organization (W.H.O.) define anaemia as an insufficiency in the oxygen-carrying capacity of the blood to meet the physiologic needs of body tissues due to a reduction in erythrocytes and hemoglobin in the blood [1, 2]. The normal physiology of pregnancy is related to expansion in the red cell number

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and increased need of the fetus [3]. Clinically, it is diagnosed when hemoglobin level is < 110 g/L at sea level during pregnancy [3–5].

In pregnancy, anaemia is primarily caused by iron deficiency [2]. The occurrence is also associated with folate, vitamin B12, and vitamin A deficiency [6]. Other factors that possibly contribute to erythrocyte reduction in pregnancy are hookworm, malaria, schistosomiasis, TBC and HIV infections, and sickle cell diseases [1, 6].

World Health Assembly (W.H.A.) with resolution endorsement 65.6, a comprehensive implementation plan on maternal global nutrition target of 2025 targeting a 50% reduction of anaemia in global women of 15–49 years through an emphasis on investment, attention, and intervention on cost-effective interventions [7, 8]. Even if improvement in the global mean hemoglobin level of pregnant women was observed from 112 to 114 g/L, the target of 2025 is not on track [9].

The non-compliance rate was high among the iron-folic-acid users having side effects [10]. The majority of these were gastrointestinal episodes related to daily intake [10, 11]. Hence, the World Health Organization recommends context-specific use of intermittent weekly oral IFAS (IFAS) to apparently healthy, non-anaemic pregnant women as part of the ANC package to compensate for side effects and intolerability to improve blood hemoglobin concentration as an alternative option [6].

Why it is important to do this review

Studies reported intermittent iron folic acid (IFA) regimens had similar pregnancy outcomes as compared to daily regimens for risk of anaemia incidence and blood hemoglobin concentrations [12, 13]. The new regimen could be a feasible alternative to prevent gestational anaemia in pregnancy, but there were limitations with poor quality and only a few studies included in the former reviews [12, 13]. The World Health Organization needs a review with strong evidence to support alternative iron folic acid recommendations for pregnant women [6]. The conflicting results of maternal side effects with oral IFAS were observed, as several original studies reported low side effects in intermittent [10, 11, 14–16] and few others reported the existence of no significant difference between the regimens [17]. Therefore, an overall estimate needs to be done to get a pooled effect size that could convince all stakeholders, as recommended by former reviewers [12, 13]. The overall effect of women's oral iron folic acid adherence status in the intermittent versus daily group was not reported by the former reviews [12, 13], while several pocket studies observed better tolerance with an intermittent group [11, 14, 16, 18–21]. This systematic review and meta-analysis, therefore, compared intermittent and daily oral IFAS in pregnancy and its outcome on maternal blood hemoglobin concentrations, maternal side effects, maternal anaemia risk statuses, and medication adherence statuses.

Methods

Study locations and design

Selected studies were studies available in low and middle-income countries, as defined by the World Bank [22]. The study design was a systematic review and meta-analysis of interventional studies. The design of the selected studies was a randomized control trial and a quasi-experimental study.

Search strategy and study selection

The studies were selected using a search strategy to locate and select the studies. Several published and unpublished articles were searched electronically and manually. The electronic databases searched were PubMed, Google Scholar, Hinari, and Cochrane Library. Grey literature sources and others searched were Google, university repositories, clinicaltrials.gov, W.H.O. clinical trial registrations, and the Indian Pediatric Association repository. During searching, MeSH terms, Boolean operators, truncations, parenthesis, and quotations were used. The selection process is reported in the PRISMA flow diagram (Fig. 1). The search outputs that were used for screening and selection were exported into EndNote X7 as PDF documents for the selection process. The sample of search strategy is shown below (Table 1). Since the numbers of trials were few, all published articles from 1996 to 2021 were included in the study based on inclusion criteria. The dates of the search were May 8–22, 2023. Studies with abstracts only reports, duplicates, poor methodological quality, and languages (other than English) were excluded. Two reviewers participated in the selection independently (S.L and M.H) and mediated by the third author (E.M) in the case of inconsistency.

The eligibility criteria

The review included articles of randomized controlled trials either in cluster or individual and quasi-experimental, which were reported in English language. Participants of the intervention were non-anaemic (HGB ≥ 11 g/dl), mildly anaemic (HGB 10–10.9 g/dl), or moderately anaemic (HGB 70–99.9 g/dl), but apparently healthy pregnant women [23]. Types of intervention were oral IFAS (IFAS) either intermittently (as defined elsewhere [6, 13]) or control (IFAS daily).

Outcomes

The primary outcome was maternal blood HGB levels measured after 12 weeks of supplementation, between gestation ages of 25 and 40 weeks. Secondary outcomes

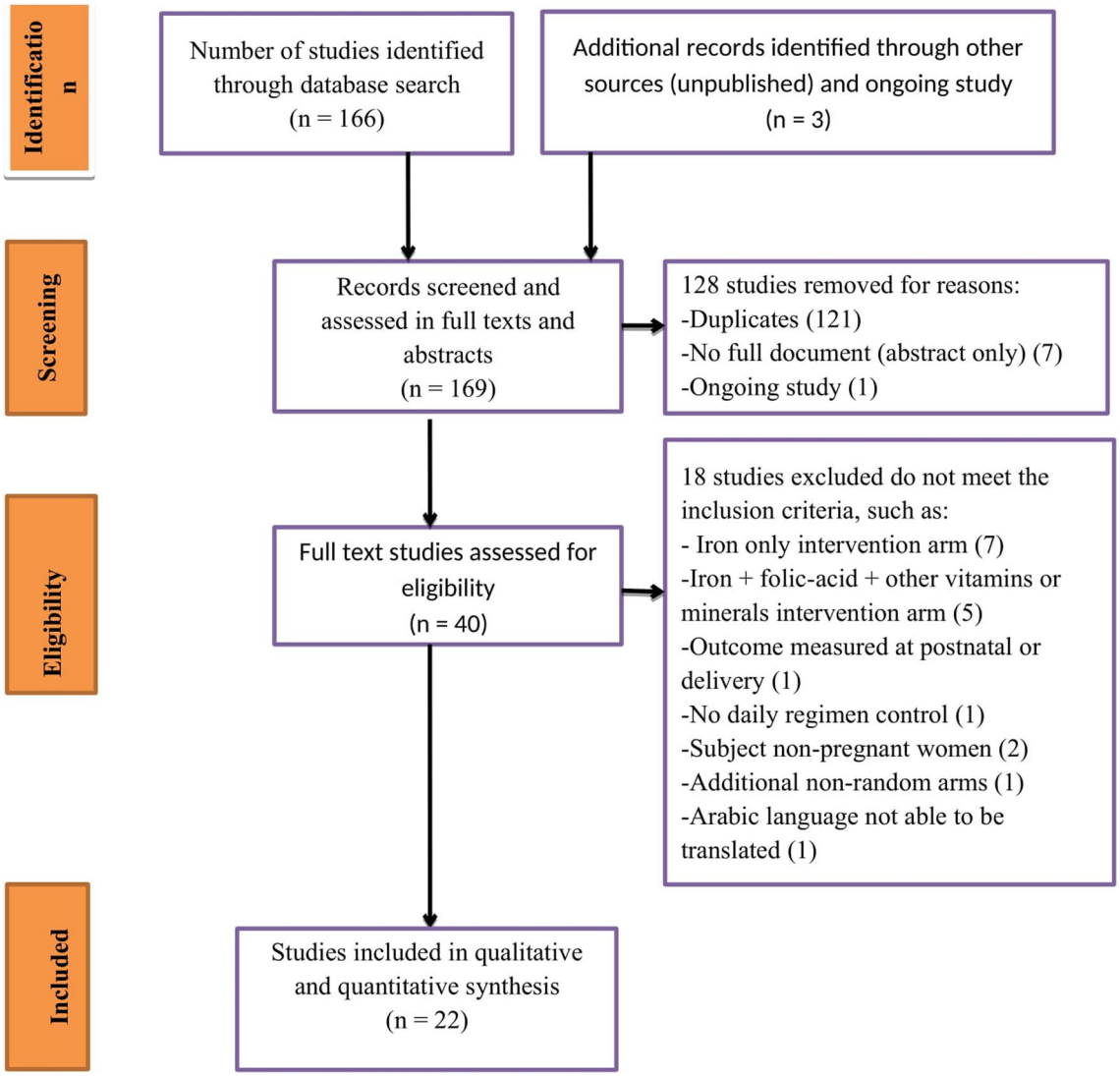

Fig. 1 PRISMA flow diagram of the review search results

Table 1 Sample search strategy used to select relevant studies in the database

Search strategy	Data base used	Number of articles
((((((("once a week" OR intermittent* OR weekly OR "thrice a week" OR "thrice-weekly"))) AND ((Iron OR Ferrous OR hematinic* OR "iron folic-acid" OR "iron folic acid"))) AND ((Supplementation* OR administration*))) AND ((Pregnant* OR Gestation* OR Conception*))) AND ((hematology* OR hemoglobin* OR hematocrit* OR anaemia* OR "maternal outcome" OR "side effect*" OR adherence*[tw] OR "pregnancy outcome*" OR "maternal outcome*")) Filters: Clinical Trial, Comparative Study, Controlled Clinical Trial, Government Publication, Observational Study, Randomized Controlled Trial, Humans, English, Female	PubMed	53

were maternal side effects; maternal anaemia incidences (anaemia as defined elsewhere [3, 4]); and medication adherence status.

Data extraction and quality assessment

Data from databases were screened and extracted independently and exported to a Microsoft Excel sheet by the two authors (S.L and M.H). Authors discussed inconsistencies

and made final approval. Any disagreements were managed through mediation by a third author (E.M). Basic characteristics of selected studies include authors with years of publication, study design, study country, participant gestation age at recruitment, and outcome measurement. Characteristics of exposure variables include: type of supplementation, frequency of supplementation intake, dose of supplementation, and sample size. Characteristics of outcome variables include mean HGB levels, proportion of anaemia, proportion of side effects, and medication adherences. The GRADE approach was used to assess evidence certainty, with findings reported as high, moderate, low, or very low in the summary of findings table.

Summary of findings for the main comparison

Intermittent Oral Iron Folic Acid Supplementation (IFAS) vs. Daily

Participant: pregnant women
Settings: all settings
Intervention: intermittent oral IFAS
Control: daily oral IFAS

Outcomes	Number of participants (#studies)	Relative effects/SMD (95%CI)	certainty of evidence (GRADE)	Comments
Maternal blood HGB level at the end of IFA supplementation during pregnancy	2231 (15)	SMD − 0.24 g/dl (− 0.35 to − 0.12)	⊕⊕⊕⊕ High	Downgraded 1 level for risk of bias, but upgraded 1 level for large magnitude effect
Maternal side effects during pregnancy	686 (5)	RR 0.27 (0.11, 0.69)	⊕⊕⊖⊖ Low	Downgraded 1 level for risk of bias, 1 level for inconsistency, 1 level for publication bias, but upgraded 1 level for large effect
Incidence of anaemia during pregnancy	1497 (7)	RR 1.09 (0.77, 1.54)	⊕⊕⊕⊖ Moderate	Downgraded 1 level for publication bias
Medication adherence status of the participant	1584 (7)	RR 1.6 (1.34, 1.91)	⊕⊖⊖⊖ Very Low	Downgraded 1 level for risk of bias, 1 level for inconsistency, 1 level for publication bias

CI: Confidence Interval; IFA: Iron Folic Acid; GRADE: Grades of Recommendation, Assessment, Development, and Evaluation; HGB: hemoglobin; SMD: Standardized Mean Difference; RR: risk ratio; #: number
GRADE Working Group grades of evidence
High quality: New further study is very unlikely to alter our confidence in the effect size
Moderate quality: New further study is likely to influence on our confidence in the effect size and could alter the estimate
Low quality: Further study is very likely to influence on our confidence in the estimate and likely to alter the effect size
Very low quality: We authors are very uncertain about the effect size

Risk of bias assessment for selected studies

Two authors assessed the risk of bias independently among the included study reports. Some disagreements were solved through discussions by mediation with the third author. The summary of the risk of bias was reported in Figs. 2, 3. The assessment process in general was implemented using the Cochrane Collaboration Tool (CCT) [24]. For cluster RCT, we used a revised Cochrane risk of bias framework that included additional considerations in the assessment of risk of bias using an algorithm for judgment [25]. It was performed as follows:

Random sequence generation bias

Low risk of bias: if randomly allocated, for example: TRN or computer generated; high risk of bias: if non-random allocation, for example: even or odd ID number used or others; unclear risk of bias: if there is no information about allocation sequence generation.

Random allocation concealment bias

Low risk of bias: if central or telephone randomization is used or a sealed envelope is used (for on-site randomization); high risk of bias: if randomization is open/known, which groups receive treatment and control, or an open/unsealed envelope is used; or unclear: if there is no information.

Blinding (performance and outcome detection)

Low risk of bias (for HGB data): if blinded women AND personnel; high: if not blinded both or either women or personnel; or unclear: if there is no information. Low risk of bias: if physician blinded for groups in outcome detection (for side effects data); high if not blinded; or unclear if there is no information. Low risk of bias: if (laboratory worker) blinded outcome detection (for HGB level laboratory test); high if not blinded; or unclear if there is no information.

Bias due to missing outcome data (attrition bias)

Low risk of bias: if the missing outcome data is likely not to affect the result (< 20%), or the proportion of missing data is similar in the intervention and control data, or a similar proportion of the difference between missing and existing data; high risk of bias: if > 20% of the data is missed and likely to affect the result; and unclear risk of bias: no possible to obtain appropriate information of missing.

Selective outcome reporting bias

Low risk of bias: if all pre-specified outcomes are reported; high risk of bias: if not completely reporting

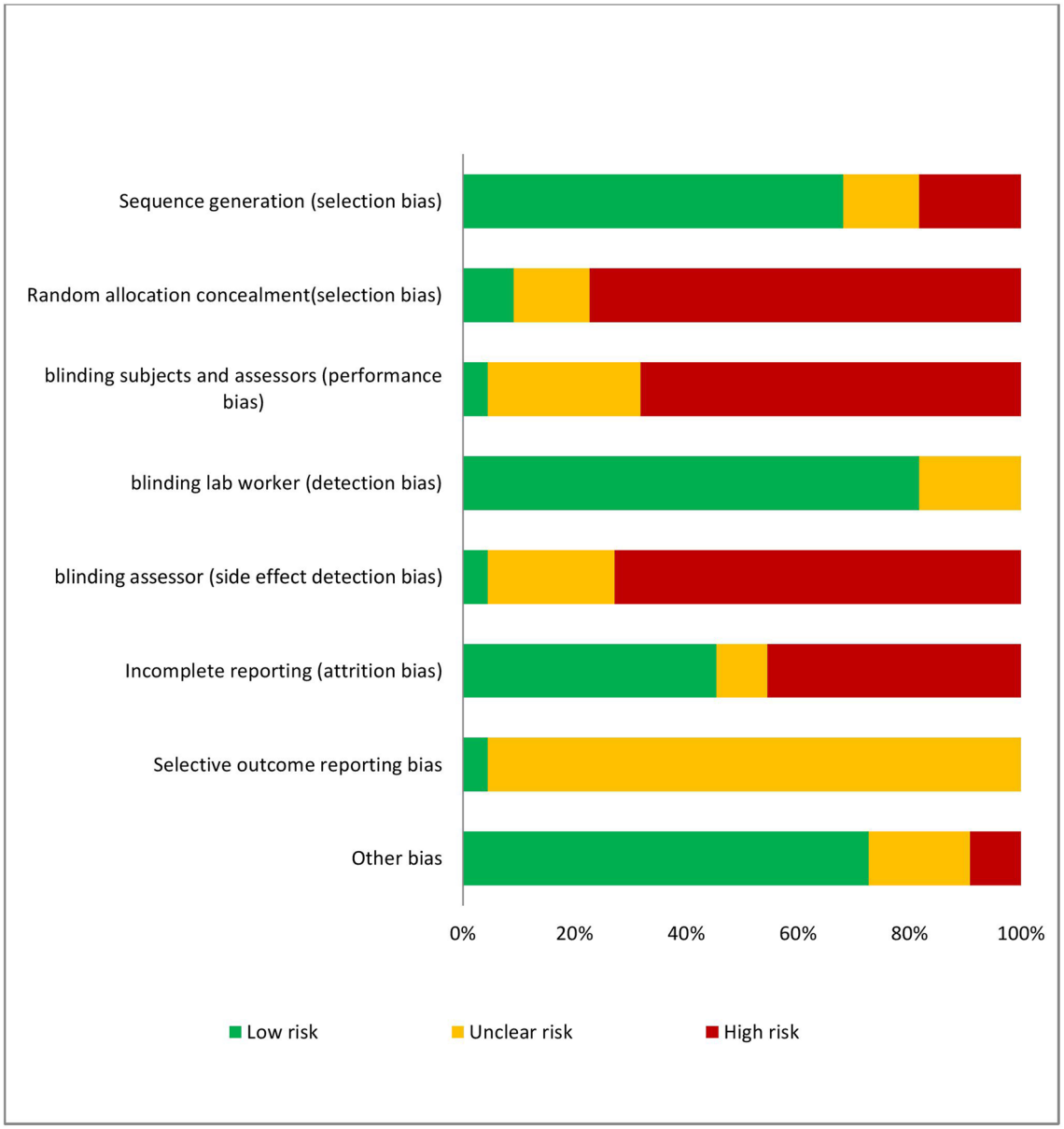

Fig. 2 Risk of bias by key domains

pre-specified outcome variables; and unclear risk of bias: if not specified/not available.

Other bias

Other bias was evaluated as low, high, or unclear after careful evaluation of the whole document for any possible bias not mentioned in the list.

Data synthesis

Qualitative Synthesis was analyzed by description of selected studies for study types, year of publication, country of study, frequency of supplementation, weekly IFA doses, sample sizes, mean ± SD of HGB levels after supplementation, proportion of side effects, anaemia incidences, and adherence statuses. Quantitative synthesis was performed to estimate the overall standardized mean difference (SMD) of blood HGB levels. The STATA 14 statistical software package was used in the meta-analysis. An overall relative risk (RR) was used in binary outcomes, such as side effects, incidence of anaemia, and adherence status. In all the analyses, we reported the result of random effect modeling

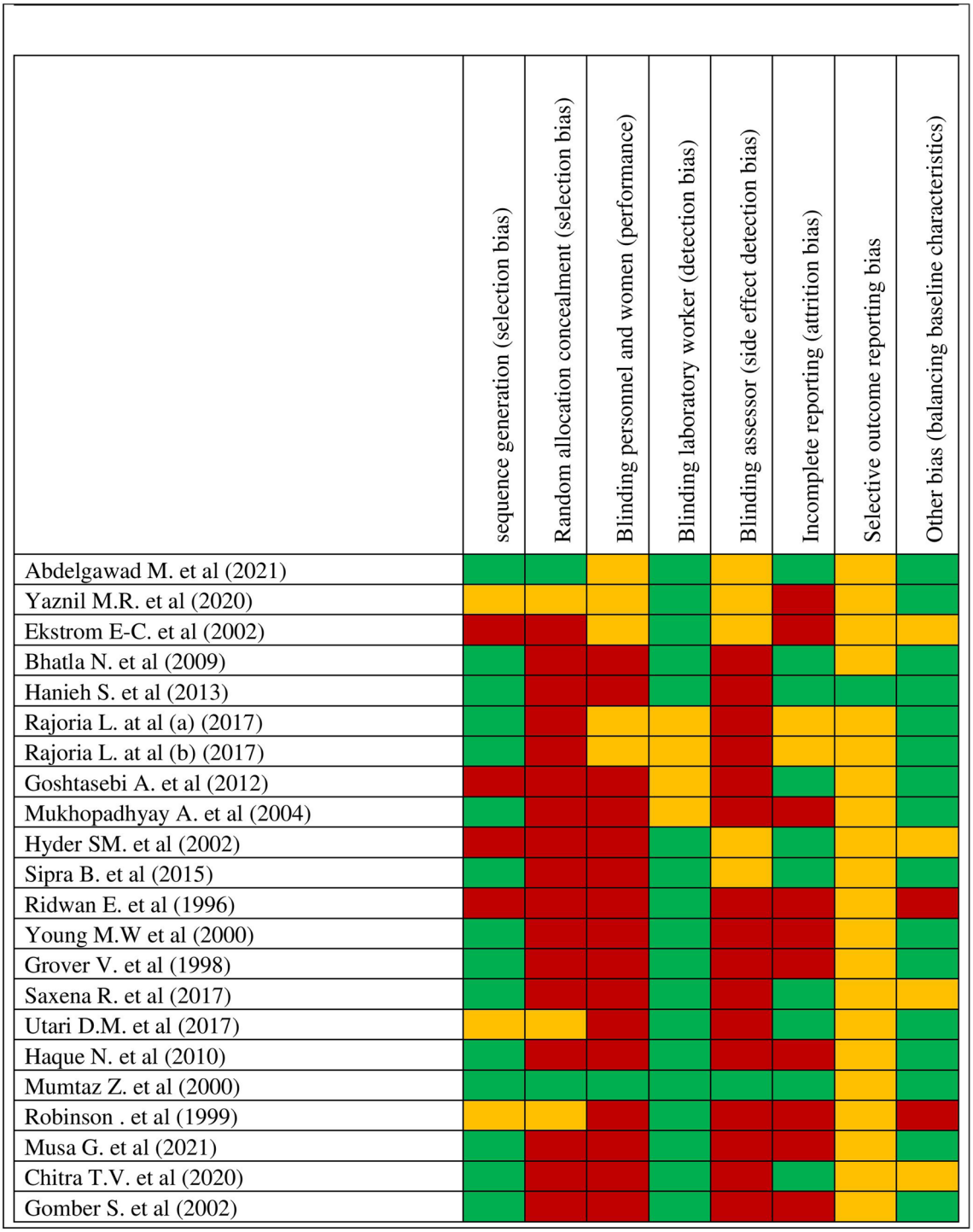

Fig. 3 Summary risk of bias by review authors' judgments about risk of bias items for each of selected studies

where the sample weight was balanced between studies. Results of influence analysis, subgroup analysis, and funnel plot were reported by figures. The I^2, Tau^2, Q test with P-value were reported with the forest plot result. Statistical heterogeneity was analyzed using the Q test ($P > 0.1$ for statistical significance) and I^2 statistics ($I^2 > 50\%$ for substantial heterogeneity). The

PRISMA checklist and the flow diagram were used for reporting.

Sensitivity and missing data analysis

Sensitivity analysis was performed to report the robustness of the estimate using various assumptions [26]. Initially, we checked for similarities or differences in the overall results of the estimate after the inclusion or exclusion of a given study among included studies for meta-analysis. Subgroup analysis was applied to check any change in the overall effect and subgroup effect. We applied fixed and random effects in the modeling to check the similarity of the overall estimate. The attrition rate of the included studies was evaluated to note missing data levels. The balance between missing and completed was evaluated.

Publication bias and heterogeneity

To check heterogeneity, visual observation of the forest plots was used to see the size or direction of the treatment effect of the studies. The I^2, Tau^2, and P value (of chi^2) tests were used to describe heterogeneity in quantity in fixed (I^2) and random (Tau^2) effect modeling. For heterogeneity, if the I^2 was more than 50% in the output, it was considered substantial [27] after applying random effect modeling. Subgroup analysis was employed for HGB-level data since it had sufficient studies (more than 10). Sensitivity analysis was also employed to identify influences of missing a given data in the data set, and that also showed robustness in the result where there was no difference in the overall outcome of HGB level data, side effects, anaemia incidences, and adherence status. Publication bias was visually assessed using a funnel plot and an additional Egger's asymmetry test.

Subgroup analysis

Subgroup analysis was performed for outcome of HGB-level by frequency of IFA administration (once weekly versus twice or more times weekly), by gestational age at the start of supplementation (≤ 20 weeks or mixed (overall < 30 weeks)), and by anaemia status at the start of supplementation.

Quality of evidences using grade

Quality of evidence is defined as the extent to which we are confident that an estimate of the effect is correct [28]. The Grading of Recommendations, Assessment, Development, and Evaluation (the GRADE approach) was used to categorize it into high, moderate, low, or very low [28]. High quality of evidence states that authors are very confident in the results that the true effect lies close to the statistical estimate; moderate quality: we are moderately confident in the effect estimate that the true effect is likely to be close to the statistical estimate, but there is a possibility of substantial difference; low quality: our confidence in the effect estimate is limited that the true effect may be substantially different from the statistical estimate; very low quality: we have very little confidence in the effect estimate that the true effect is likely to be substantially different from the statistical estimate [29]. GRADE was rated using the rating the grade up and down technique. For rating down by one level: five factors used for serious limitations were overall risk of bias (across studies); heterogeneity (substantial, if $\geq 50\%$); indirectness of evidence (does the data answer research question, external validity); imprecision (small sample size, or wide CI), serious if $> 20\%$ attrition rate from estimated sample size; and publication bias, serious if forest plot is non-symmetrical [28, 29]. We rated down two levels for very serious limitations. For rating up, a large magnitude of effect (1 upgrade if overall RR > 2 or < 0.5, or 2 upgrades if RR > 5 or < 0.2) was used [28, 29]. Moreover, sensitivity analysis was employed to support the 'risk of bias' decisions.

Results

Study selection

This systematic review and meta-analysis included published clinical trials that exist in low- and middle-income countries. In the process, a total of 166 published and three unpublished and ongoing studies were found. Of these, a total of 145 studies were rejected due to duplications, not being in line with inclusion criteria, and having no full document. A total of 22 studies were included in the final qualitative and quantitative synthesis. The selection process is described in the PRISMA flow diagram (Fig. 1).

Characteristics of included studies

All the included studies were randomized controlled trials and quasi-experimental studies that had either supervised or non-supervised controls. The review had the smallest sample size of 56 (27 treatment, 29 control) in India [30] and the largest, 705 (361 treatment, 344 control) in Vietnam [31]. The total sample size of the included studies was 3605 pregnant women. Inclusion and exclusion criteria in the selected studies fit with the criteria set by the review authors in the protocol registration. Of the included studies, 9 (41%) were conducted in India [10, 14, 17, 20, 30, 32–35] and 7 (32%) in Indonesia [21, 36–38] and Bangladesh

[18, 19, 39]. The remaining 6 (23%) studies were conducted in Africa [11, 16, 40], Vietnam [31], Iran [15], and Pakistan [41]. All these selected studies were done in the last three decades and found in low- and middle-income countries, as categorized by the World Bank [42] (Tables 2 and 3).

Participants

Women included in the trial were all pregnant and were found in the first, second, and third trimesters of gestation age. Only 3 trials out of 22 extended inclusion into the third trimester [16, 36, 38]. Nine trials initially recruited and started the supplementation at a gestation age of ≤ 20 weeks [10, 11, 14, 15, 17, 31, 32, 34, 35]. Others (13 studies) were either mixed or have no clear report of the gestational age [16, 18–21, 30, 33, 36–41].

Anaemia status and hemoglobin cut-point of participants at recruitment vary among studies. Anaemia status at initial recruitment included non-anaemic women [10, 11, 15], mildly/moderately anaemic participants [33, 38, 39, 41], mixed [14, 16–20, 30, 31, 34, 37, 40], or having no report of the status [21, 32, 35, 36]. Severely anaemic women were not included in any of the included trials. Anaemia status and hemoglobin cut-points to categorize anaemia status were used from the W.H.O. vitamins and minerals nutrition information system [5].

Interventions

Out of 22 selected studies, 14 studies were supplemented once every week. Once weekly regimen also varies between studies where it was administered a double dose (administered as a divided dose) a day, one in the morning and the other in the afternoon [10, 11, 14, 18, 19, 37]. In 4 trials, it was administered as a double dose received at once [16, 17, 21, 33]. In 4 studies, it was administered as a single dose (the same as the control or routine dose) that was received once on any one of the days in the week [30, 32, 38, 39]. 5 studies administered the same routine dose but twice a week [15, 31, 36, 40, 41]. One trial supplemented a single routine dose thrice a week [35] and two trials supplemented on the alternative days [20, 34].

The total sum of oral weekly dosages of elemental iron received by intervention arms ranged from 60 to 400 mg. A single weekly dose of 60 mg [32, 38], 100 mg [30], and 120 mg [39] were administered once a week. A double weekly regimen (twice daily comparator) of 120 mg

Table 2 Summarized basic characteristics of included studies, July 2023

Authors, year published	Study design	Country	Gestation at recruitment (weeks)	Gestation at outcome measurement (weeks)	Frequency of supplementation in the week	Iron dose (weekly/daily) (in mg)	Sample size
Abdelgawad M. et al. 2021	RCT	Egypt	13–20	25–32	Once weekly	200/100	125
Yaznil M.R. et al. 2020	RCT	Indonesia	13–28	26–40	Twice-weekly	120/60	62
Ekstrom E-C. et al. 2002	RCT	Bangladesh	14–22	26–34	Once weekly	120/60	140
Bhatla N. et al. 2009	RCT	India	14–18	30–34	Once weekly	200/100	60
Hanieh S. et al. 2013	RCT	Vietnam	< 16	32	Twice-weekly	120/60	705
Rajoria L. et al. (a), 2018	RCT	India	14–16	34	Thrice-weekly	180/60	57
Rajoria L. et al. (b), 2018	RCT	India	14–16	34	Once weekly	60/60	66
Goshtasebi A. et al. 2012	Quasi-RCT	Iran	14–20	37–40	Twice-weekly	100/50	360
Mukhopadhyay A. et al. 2004	RCT	India	14–20	32–34	Once weekly	200/100	80
Hyder SM. et al. 2002	RCT	Bangladesh	18–24	22–28	Once weekly	120/60	172
Sipra B. et al. 2015	RCT	India	16–22	28–34	Once weekly	200/100	89
Ridwan E. et al. 1996	RCT	Indonesia	8–24	28–32	Once weekly	120/60	139
Young et al. 2000	RCT	Malawi	≤ 30	36	Once weekly	120/60	216
Grover V. et al. 1998	RCT	India	16–24	37–40	Alternate day	400/100	120
Saxena R. et al. 2017	RCT	India	14–20	18–24	Once weekly	200/100	200
Utari D.M. et al. 2017	RCT	Indonesia	≤ 27	≤ 35	Once weekly	60/60	104
Haque N. et al. 2010	RCT	Bangladesh	18–22	28	Once weekly	120/120	57
Mumtaz Z. et al. 2000	RCT	Pakistan	20–22	32–34	Twice-weekly	120/60	105
Robinson. et al. 1999	RCT	Indonesia	No report	No report	Once weekly	120/60	399
Musa G. et al. 2021	RCT	Nigeria	16–24	30–38	Twice-weekly	130/65	120
Chitra TV. et al. 2020	RCT	India	10–14	32–34	Alternate day	400/100	173
Gomber S. et al. 2002	RCT	India	16–24	30–38	Once weekly	100/100	56

Table 3 Summarized characteristics of outcome variables, July 2023

Author, year published	Participant category											
	Daily arm						Weekly arm					
	Mean (HGB)	SD	n	Side effect (%)	Anaemia (%)	Adherence (%)	Mean	SD	n	Side effect (%)	Anaemia (%)	Adherences (%)
Abdelgawad M. et al. 202*	11.1	0.8	58	56.7	1.7	27.14	10.8	1	67	3.4	10.4	85.7
Yaznil M.R. et al. 2020	11.33	0.74	29	–	–	–	11.27	0.95	33	–	–	–
Ekstrom E-C. et al. 2002	12.48	1.61	66	–	–	42.3	12.26	1.61	74	–	–	70.5
Bhatla N. et al. 2009	11.79	0.84	30	43.3	–	–	11.25	0.9	30	10	–	–
Hanieh S. et al. 2013^{+}	12.49	1.22	344	–	10.2	–	12.38	1.17	361	–	9.1	–
Rajoria L. et al. (a), 2018^{+}	–	–	31	–	16	–	–	–	26	–	7.7	–
Rajoria L. et al. (b), 2018^{+}	–	–	31	–	16	–	–	–	35	–	37	–
Goshtasebi A. et al. 2012^{+}	12.2	1.03	168	–	8.3	–	12.1	1.17	192		12.3	–
Mukhopadhyay A. et al. 2004^{+}	11.3	0.8	40	50	25	28.57	11.2	0.9	40	10	42.5	61.81
Hyder SM. et al. 2002	–	–	86	–	–	60.46	–	–	86	–	–	93
Sipra B. et al., 2015	11.04	0.45	45	–	–	–	10.8	0.69	44	–	–	–
Ridwan E. et al. 1996	11	0.7	68	–	–	–	10.8	0.8	71	–	–	–
Young et al. 2000	10.6	1.4	112	17	–	59.72	10.4	1.5	104	6	–	76.2
Grover V. et al. 1998	–	–	64	–	–	75	–	–	56	–	–	89.3
Saxena R. et al. 2017	–	–	100	27	–	–	–	–	100	23	–	–
Utari D.M. et al. 2017	10.6	0.99	52	–	61.5	–	10.4	1.02	52	–	67.3	–
Haque N. et al. 2010	8.94	0.55	25	–	–	–	8.8	0.72	32	–	–	–
Mumtaz Z. et al. 2000	11.36	1.83	55	–	–	–	10.09	1.23	50	–	–	–
Robinson. et al. 1999^{+}	–	–	200	–	–	69.5	–	–	199	–	–	96
Musa G. et al. 2021	10.9	1.4	60	–	–	–	10.4	0.9	60	–	–	–
Chitra TV. et al. 2020	11.31	1.15	80	–	–	–	11.38	1.12	93	–	–	–
Gomber S. et al. 2002	11.7	0.9	29	–	–	–	11.2	0.9	27	–	–	–

a: the reported was Median; SD: standard deviation; n: sample size, (-): not assessed.; *:anaemia defined HGB < 10 g/dl; $^{+}$:anaemia defined HGB < 11 g/dl;

[16, 18, 19, 21, 37] and 200 mg [10, 11, 14, 17, 33] were administered once a week and received at once orally or in divided doses, one in the morning and the other in the afternoon. Another 400 mg of elemental iron was given weekly, as every other day (divided into four per week) [20, 34], and 180 mg was given weekly as a thrice-weekly dose (divided into three per week) [35]. A single regimen of 100 mg [15], 120 mg [31, 36, 41], and 130 mg [40] elemental iron were administered weekly as twice a week (divided into two).

Folic-acid regimen on a weekly dose ranges throughout the studies from 0.5 to 10 mg. In 14 trials, 1 mg [10, 14, 17], 3 mg [33], 0.5 mg [16, 18, 19, 21, 37], and 4 mg [11] folic acid were given (as divided or once double dose), and 0.25 mg [38], 0.5 mg [30, 39], and 1 mg [32] (as a single dose equals to daily comparator) were given once a week. In the alternate-day regimen, two trials were given a weekly sum dose of 2 mg of folic acid every other day [20, 34]. In the other trials, 0.4 mg [31, 36], 1 mg [15, 41], and 5 mg [40] folic acid were given twice a week as a single dose as a comparator daily dose. A single trial woman received 1 mg of folic acid per week (similar to a daily dose) but administered thrice weekly [35].

A comparator dose of iron in the trials ranges from 50 to 120 mg, where they were all given as a daily routine with or without supervision. More specifically, 50 mg [15], 60 mg [16, 18, 19, 21, 31, 32, 35–38, 41], 65 mg [40], 100 mg [10, 11, 14, 17, 20, 30, 33, 34], and 120 mg [39] elemental iron were administered on a daily basis. These daily regimens were routine interventions in each of the study countries as one of the antenatal care packages for a pregnant woman during pregnancy or the postpartum period. Most of these regimens depend on W.H.O. recommendations for antenatal care for women during pregnancy and the postnatal period.

A comparator dose of folic acid in the trial ranges from 0.25 to 5 mg, as it was given daily. Each trial was supplemented with 0.25 mg [16, 18, 19, 21, 37, 38], 0.4 mg [31, 36], 0.5 mg [10, 14, 17, 20, 30, 34, 39], 1 mg [15, 32, 35, 41], 1.5 mg [33], 2 mg [11], and 5 mg [40] folic acid in a daily manner. Most of them were administered 30 min or more before a meal and not received with milk, tea, or coffee. This folic acid preparation was not separate. It was manufactured and administered as a fixed-dose combination therapy with elemental.

Comparisons

All the selected trials compared weekly (once, twice, thrice, or alternative day) oral iron with folic acid supplementation by daily oral iron with folic acid intake by pregnant women. The outcomes of the comparison were hematologic markers, side effects, and adherence status while using the regimen. All of them assessed pregnancy outcomes at the midway and/or after the end of supplementation in the arms.

Risk of biases

In general, we authors challenged while assessing the risk of bias since study methods of some trials were not reported transparently. Each study was evaluated individually and independently by two authors. It was mediated by the third author when inconsistencies were faced. Results were reported in Figs. 2 and 3.

Allocation

Fifteen trials had a low risk of bias as they generated random sequences to select participants into the arms [10, 11, 14, 16–18, 30–35, 37, 40, 41]. The remaining 7 trials had either a high risk of bias or unclear evidence [15, 19–21, 36, 38, 39].

Only one trial had reported concealment, though we authors doubt whether the weekly supplement was aware of by experienced health workers and/or women since it had no placebo and an identical color code of regimen reported [11]. The remaining 21 trials were evaluated as either high risk of bias (9 trials) or had no clear evidence for judgment (12 trials) as reviewed using trialists' reports [10, 14–21, 30–41].

Blinding

Nine trials had unclear evidence to judge whether they had blinded participants and physicians to eliminate performance bias [11, 17, 32, 33, 35–39]. Four studies had a low risk of bias [30, 34, 40, 41]. Nine trials had a high risk of performance bias [10, 14, 15, 18–21, 31, 43]. The review authors' judgment was based on the trialist report of methodology.

Outcome detection bias (laboratory report) was seen as a low risk of bias in all 22 selected trials, as it was less likely to be biased as far as instrument functionality was promising.

Twelve trials were considered to have a low risk of side effect detection bias, whether side effect was their primary objective or not (not applicable) [11, 30, 32–41]. Four trials had unclear evidence [14, 16, 17, 19], and the rest of the 6 trials had a high risk of bias [10, 15, 18, 20, 21, 31].

Incomplete outcome data

We judged that 11 trials had acceptable levels of attrition (missing data less than 20% and balanced basic characteristics with completed data) [10, 11, 15, 17, 19, 31, 33, 34, 36, 38, 39]. The remaining 11 trials had either unclear

evidence to justify the risk of attrition bias [30, 32, 35, 40] or a high risk of bias [14, 16, 18, 20, 21, 37, 41].

Selective outcome reporting bias

Studies reported registration numbers and links were evaluated for similarity of reporting for outcomes evaluated. Based on this evidence, only two studies reported and observed a low risk of bias [15, 31]. The remaining 20 trials had no clear information to evaluate outcome similarity [10, 11, 14, 16–21, 30, 32–41].

Other risk of bias

We focused on the similarity of participant characteristics at initial recruitment to evaluate other risks of bias. A single trial had a high risk of bias as trialists reported baseline hemoglobin level and/or basic characteristics not similar at initial recruitment [21]. Five trials had unclear risk of bias, where they never reported characteristics status before supplementation started [17, 19, 20, 34, 37]. The remaining 16 trials had a low risk of bias, where similarity between the arms was reported [11, 14–16, 18, 21, 30–33, 35, 36, 38–41].

Overall risk of bias

Among 22 studies reviewed, the overall risk of bias was assessed within and across studies. Eleven trials reported a high risk of bias within the studies [10, 14, 16, 18–21, 31, 37, 39, 41], and the remaining 11 trials reported an unclear risk of bias [11, 15, 17, 30, 32–36, 38, 40]. When the overall risk of bias was evaluated across the studies for each of the outcomes, the risk of bias was high in maternal blood hemoglobin level, side effects, and adherence status. Across studies, the overall risk of bias was low in the incidence of anaemia reports, as it was judged through careful evaluation and using additional sensitivity (influence) analysis support.

Primary outcome

Maternal blood hemoglobin level

Among selected studies, most 16 trials reported maternal blood hemoglobin levels as an outcome variable after supplementations of iron with folic acid [10, 11, 14–16, 18, 30, 31, 33, 34, 36–41]. Among the trials selected, one trial reported the hemoglobin outcome variable using the median level of maternal hemoglobin difference [15]. Ten trials reported having no statistical difference between administering IFA either intermittently or daily. Five trials reported having a statistical difference, where women on the intermittent regimen had lower concentrations of hemoglobin than in the daily regimen. The pooled standardized mean difference (SMD) showed the existence of a statistical difference between the arms (SMD − 0.24 g/dl; 95%CI − 0.35 to − 0.12; 15 studies; 2231 women), where intermittently supplemented women had lower maternal blood hemoglobin level differences than daily groups (Fig. 4).

Secondary outcomes

Maternal side effects

Six trials reported maternal side effects after administration of IFA [10, 11, 14, 16, 17, 44]. Except one trial [17], five trials reported significant differences between the arms in that the intermittent group had lower side effects than daily groups. One trial did not report the proportion of side effects as one variable (such as yes/no response), but reported the proportion of each side effect that women reported. The side effects of iron that most women complained about and reported were nausea, vomiting, heartburn, constipation, and a metallic taste. The overall estimate showed intermittent regimens were at lower risk of side effects than daily (RR 0.27; 95%CI 0.11, 0.69; five studies; 686 women). The result has to be interpreted cautiously as a result of substantial heterogeneity. (Heterogeneity: I^2 81.4%, tau^2 0.89, chi^2 test P-value > 0.001) (Fig. 5).

Incidence of anaemia

Seven trials reported the incidence of anaemia after supplementation of IFA during pregnancy [11, 14, 15, 31, 32, 35, 38]. As can be seen in Fig. 5, all the trials reported having no difference in anaemia incidence between the intermittent and daily IFA supplementation groups. The overall effect size also showed anaemia incidence was similar between the arms (RR 1.09; 95%CI 0.77, 1.54; 7 studies, 1497 women) (Fig. 6).

Medication adherences

As we tried to see women's medication adherence status, seven trials reported the outcome [11, 14, 16, 18–21]. In each of the studies, intermittent supplementations had better adherence than daily groups. The overall effect showed a woman in the intermittent arm was 1.6 times more likely to adhere than those in the control (daily) supplementation arm (RR 1.6; 95%CI 1.34, 1.91; 7 studies; 1584 women). The result should be used cautiously due to substantial heterogeneity. (Heterogeneity: I^2 83.8%, tau^2 0.04, chi^2 test P-value < 0.001) (Fig. 7).

Subgroup analysis for maternal blood HGB concentrations

Subgroup analysis was done on frequency of weekly intermittent regimen, gestation age, and anaemia status

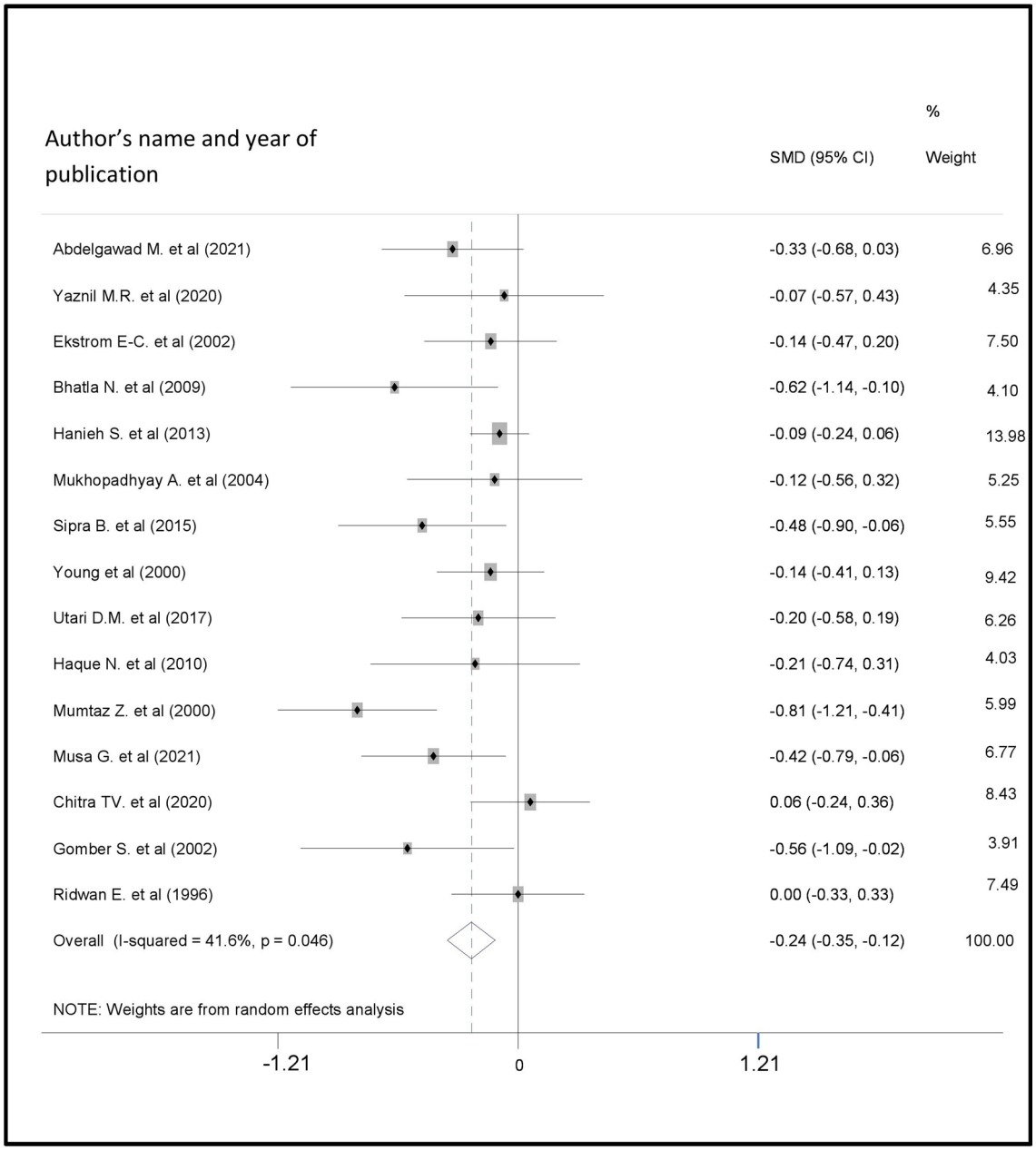

Fig. 4 comparison of standardized mean differences of maternal blood HGB concentration after oral supplementation of iron with folic-acid between intermittent and daily arms, May 2023

at recruitment. Pregnant women who were on a 'twice or more weekly frequency' intermittent regimen had similar HGB levels between the arms (SMD − 0.25; 95%CI − 0.52, 0.03; 5 trials; 1165 women, quality: high). However, low HGB concentration was seen in the once weekly intermittent arm (SMD, − 0.23; 95%CI, − 0.35, 0.11; 10 trials; 1066 women). Figure 8. Women who started the intermittent regimen ≤ 20 weeks gestation had similar blood HGB levels between the arms (SMD − 0.15; 95%CI − 0.33, 0.02; 5 studies, 1143 women). Conversely, those who started the intermittent regimen at any week of gestation (mixed groups study report) had lower blood HGB levels (SMD − 0.28; 95%CI − 0.44, − 0.13; 10 trials; 1088 women) (Fig. 9). Subgroup analysis based on anaemia status at recruitment (such as: not-anaemic, mixed (anaemic or non-anaemic), and anaemic only), the blood HGB levels were lower in the intermittent arm (Fig. 10).

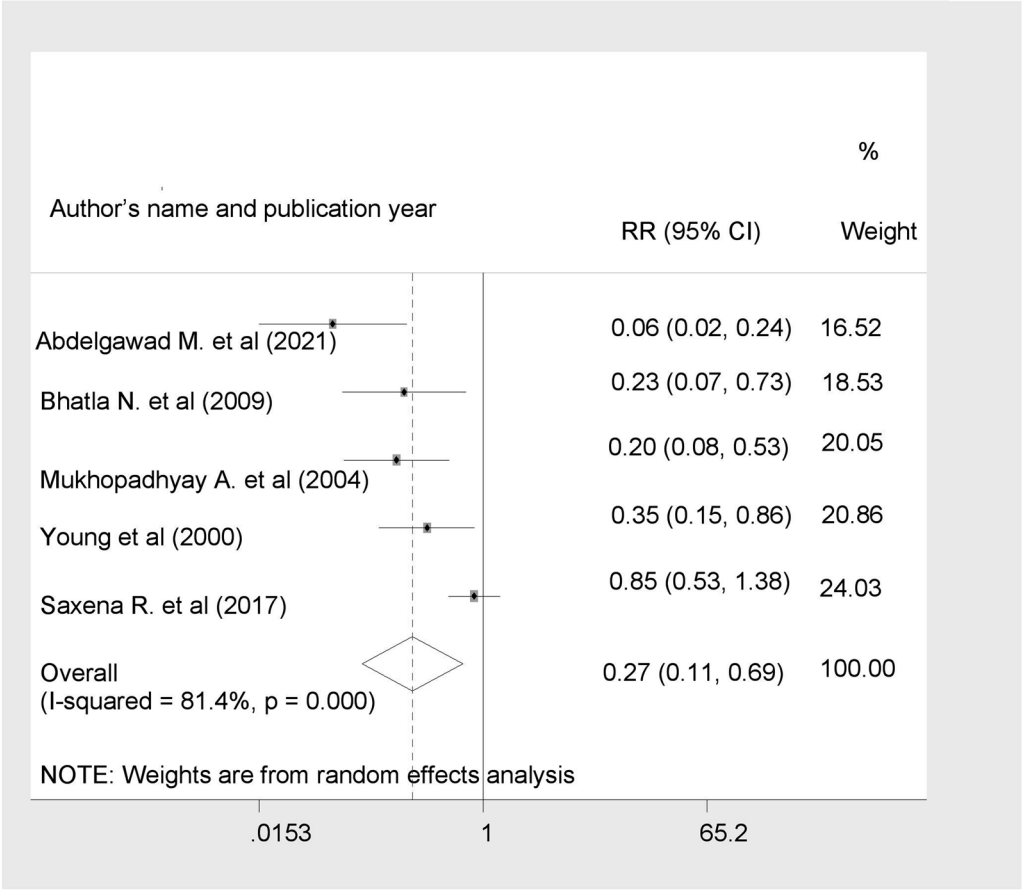

Fig. 5 The pooled estimate of maternal side effects between the intermittent and daily arms after oral IFASs in pregnancy

Sensitivity analysis

A comparison of overall estimates of fixed and random effect modeling was done for statistical analysis. The comparison showed similar results for the outcomes of maternal blood hemoglobin level, side effects, anaemia incidences, and adherence. Influence analysis was employed to determine the effects of overall estimates through the inclusions or exclusions of a particular study. For the given outcomes, there was no change in overall effect size (annexes 1, 2, 3, and 4). Subgroup analysis results that compared the groups by the anaemia status of pregnant women at recruitment and before the initiation of supplementation showed similar overall mean differences in blood hemoglobin concentrations (Fig. 10). Results differed by subgroup analysis as compared to overall estimates for gestation age at recruitment (Fig. 9) and frequency of weekly supplementation subgroups (Fig. 8). Subgroup analysis was not done due to the minimum number of studies identified for maternal side effects, maternal anaemia incidences, or regimen adherence.

Discussion

Summary of main results

Findings of this study showed that the overall maternal blood hemoglobin concentrations, maternal side effects, and regimen adherences were influenced by either intermittent or daily IFA supplementations. However, anaemia incidence was not influenced by either of the regimen approaches. Moreover, there was no influence on blood HGB levels between the arms when IFA supplementation was initiated early in pregnancy (≤ 20 weeks) and with more frequent regimens (≥ 2 times per week).

Certainty of the evidence

Overall certainty of evidence was summarized based on the outcomes of interest. Inconsistency, risk of bias, and publication bias were common factors to downgrade the quality of evidence GRADE by one level. The large magnitude of effect has been commonly observed to upgrade the quality of evidence in some outcomes. For maternal blood HGB level, we downgraded the score by 1 level for risk of bias but upgraded to 1 level for large magnitude effect (which is RR below 0.5). Maternal side effects after

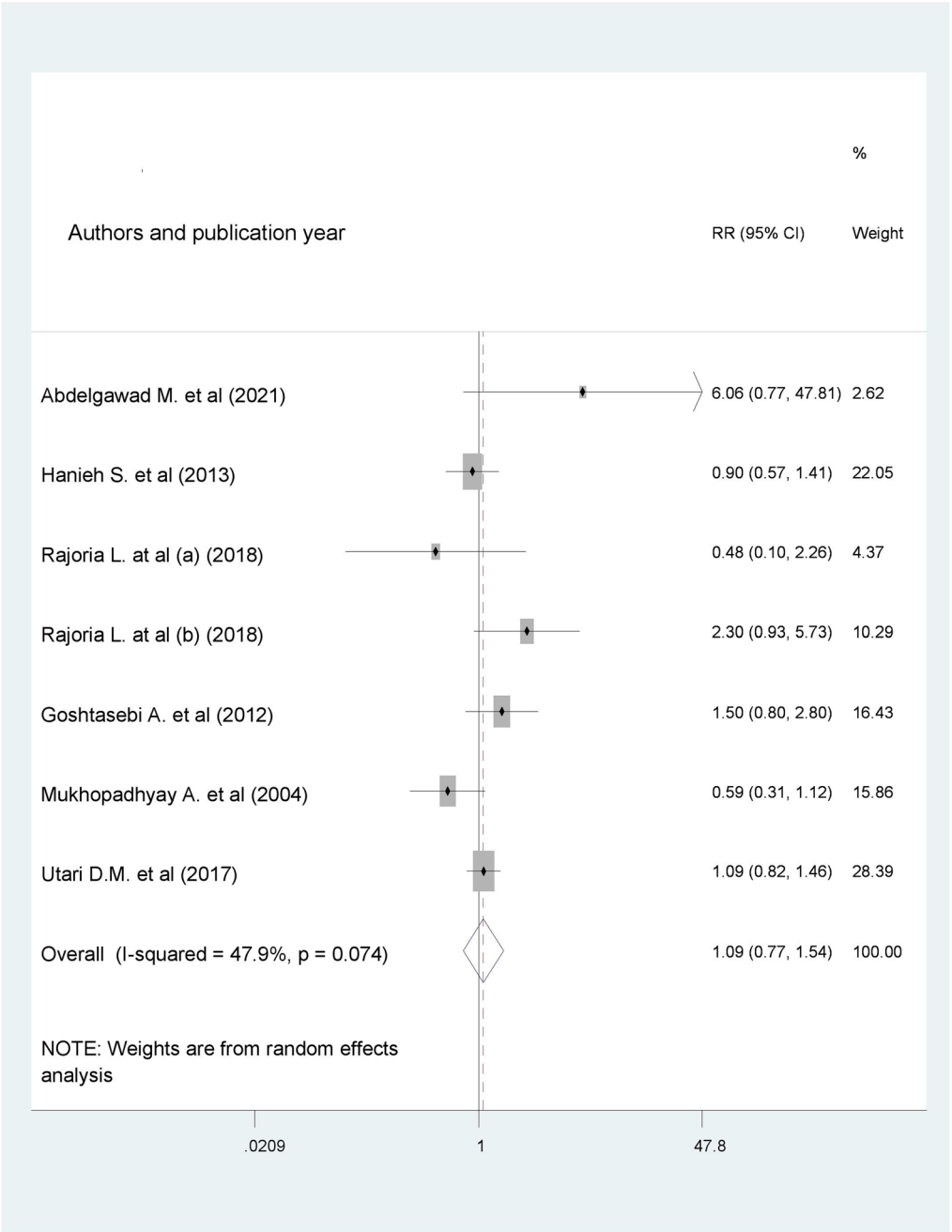

Fig. 6 The pooled estimate of anaemia between the intermittent and daily arms after oral IFASs in pregnancy

supplementation were downgraded to 1 level for risk of bias, 1 level for inconsistency, and 1 level for publication bias, but upgraded to 1 level for large magnitude effect. The incidence of anaemia was downgraded to 1 level for publication bias. Medication adherence was downgraded to 1 level in each of risk of bias, inconsistency, and publication bias. Overall certainty of evidence was found to be high in maternal blood HGB level outcome, moderate in maternal anaemia incidence outcome, low in maternal side effects outcome, and very low in maternal supplement adherence status outcome.

Comparison with other reviews

Two systematic review and meta-analysis reports done by Peña-Rosas and colleagues in 2012 (four trials) and 2015 (five trials) observed that there was no evidence

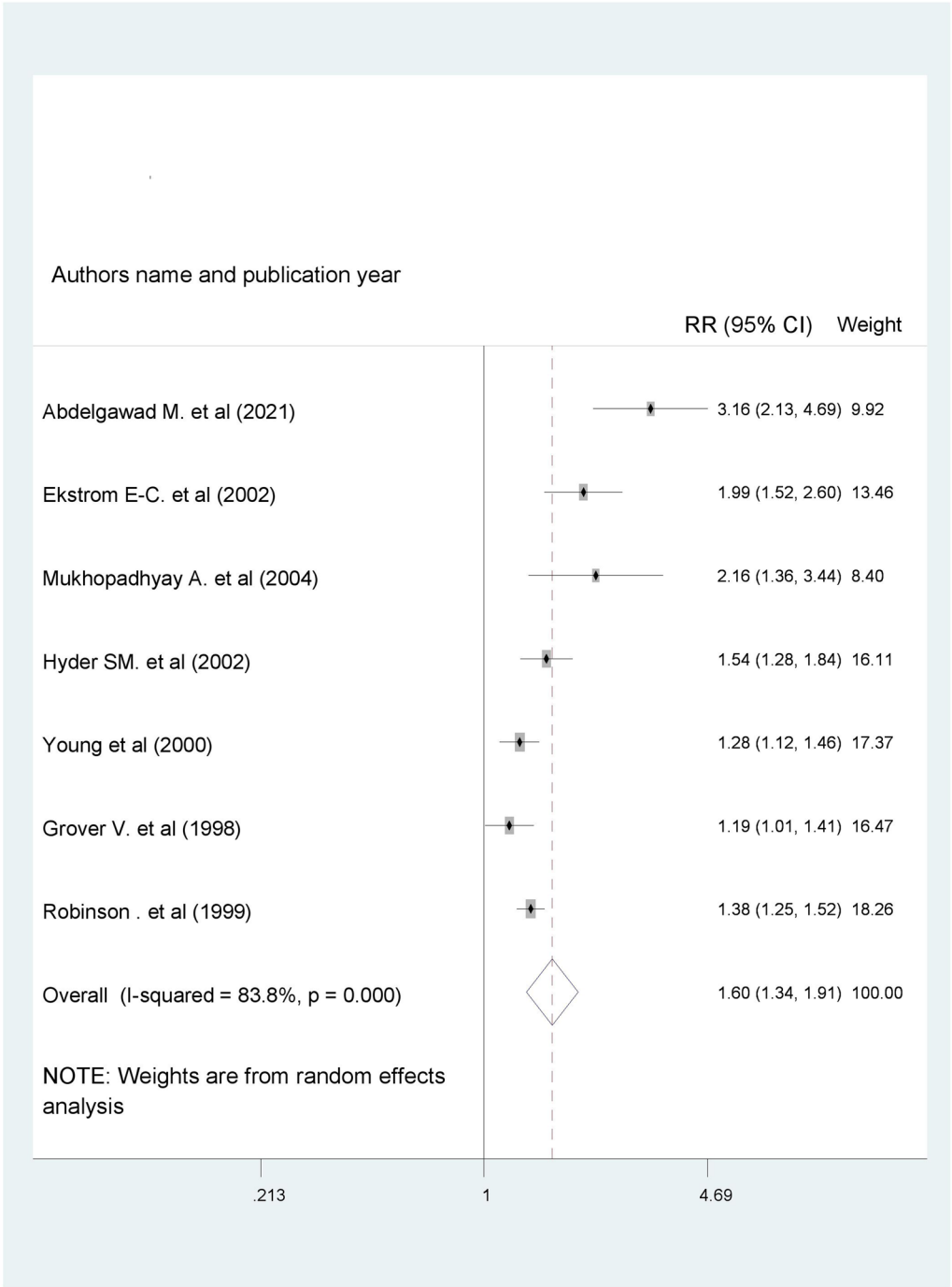

Fig. 7 The pooled estimate of medication adherences between the intermittent and daily arms after oral IFASs in pregnancy

of significant difference in maternal blood HGB levels between the arms [8, 9]. They were in contrast with the current review results. The addition of 10 more trials in the updated current review (4/5 vs. 15 trials) might have changed the results. Anaemia incidence, however, was in agreement with former reviews [8, 9].

Even though former reviewers have not reported subgroup influences due to the minimum number of trials identified after search [8, 9], the current review observed a non-influential effect on blood HGB levels when the intermittent regimen was received either more frequently or early in gestation. The result notifies stakeholders still

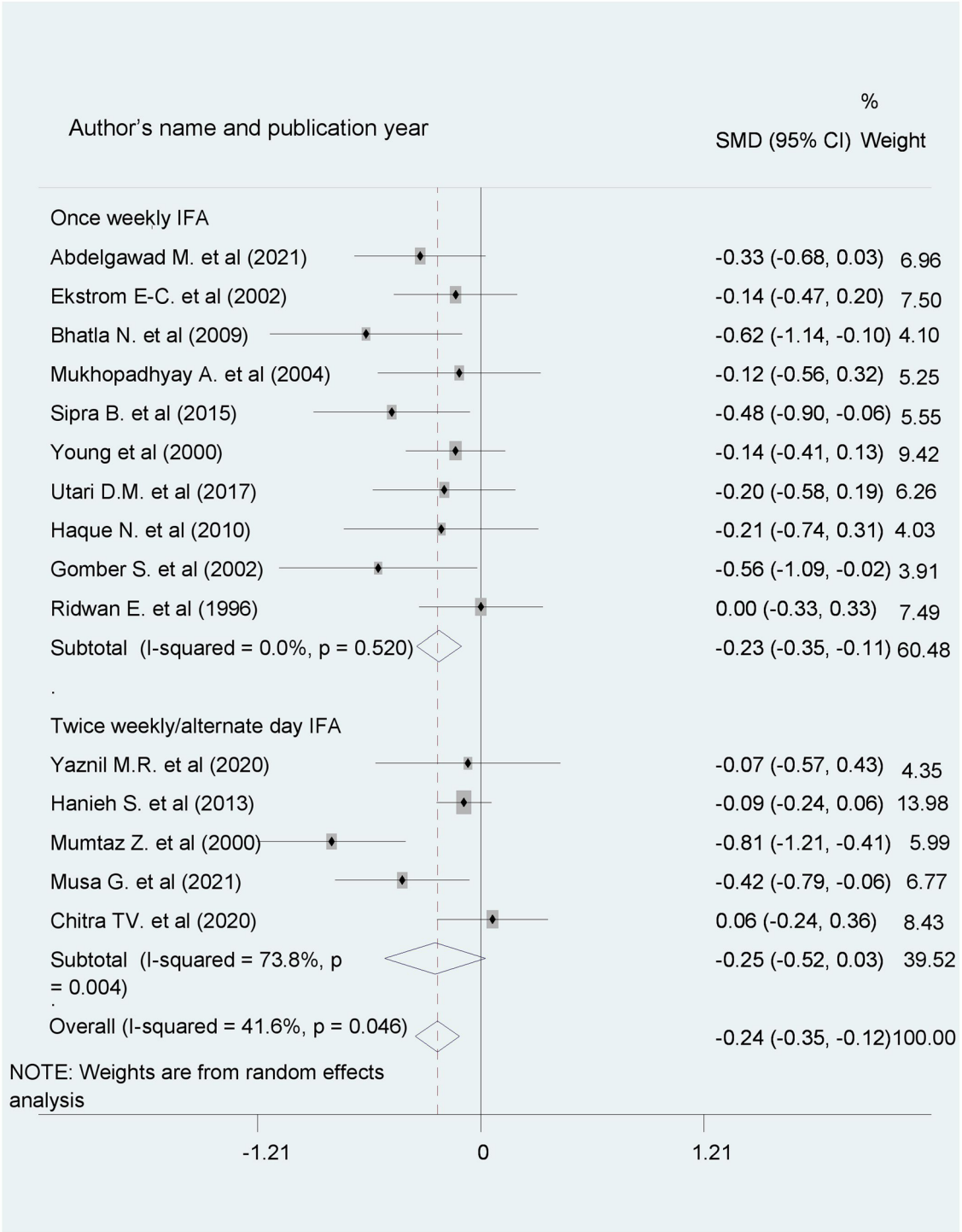

Fig. 8 Subgroup analysis compared SMD of maternal blood HGB level, once weekly IFA and twice weekly/alternate day IFA supplementations among the intermittent and daily groups

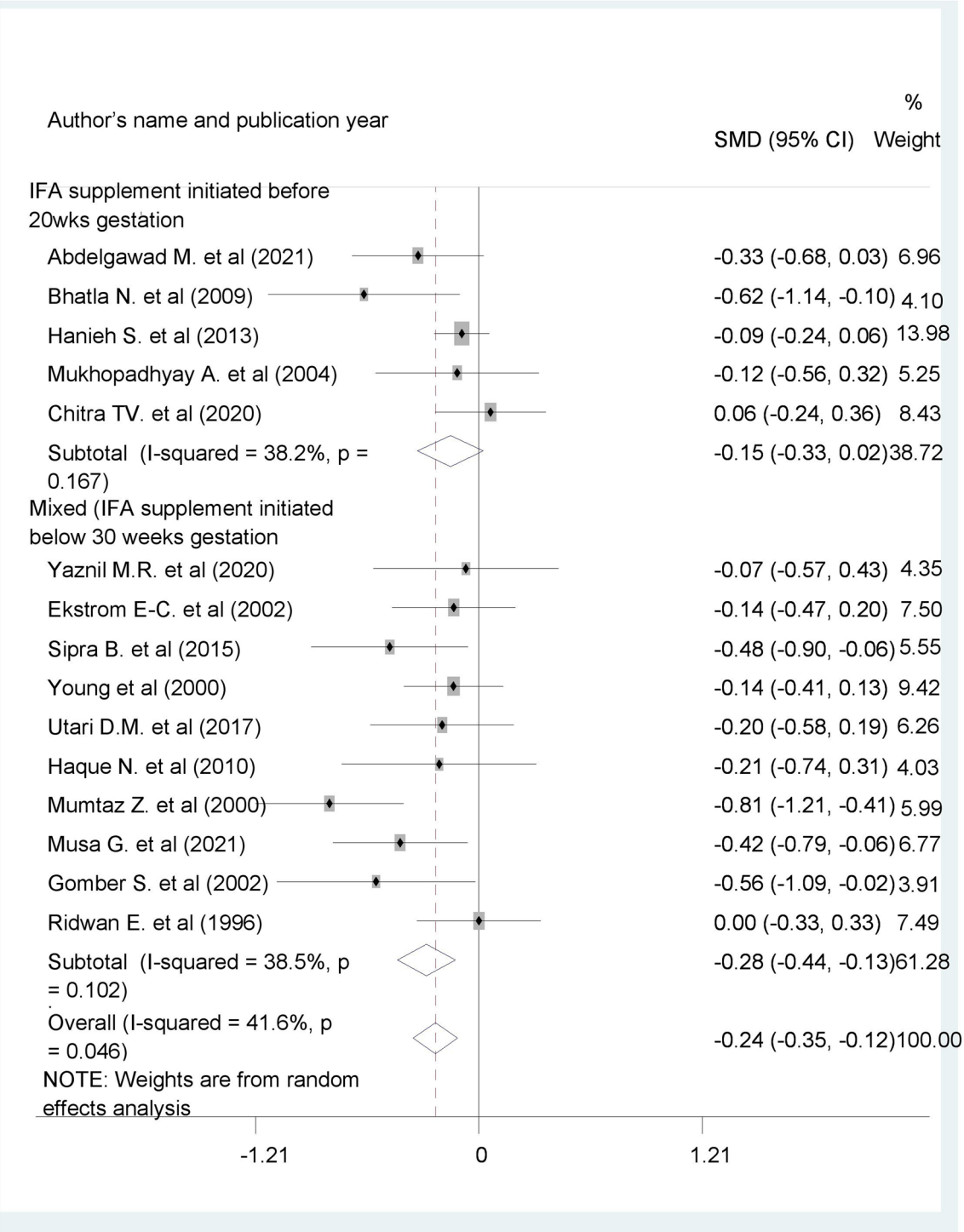

Fig. 9 Subgroup analysis compared the arms by gestation age at recruitment and initiation of supplementation

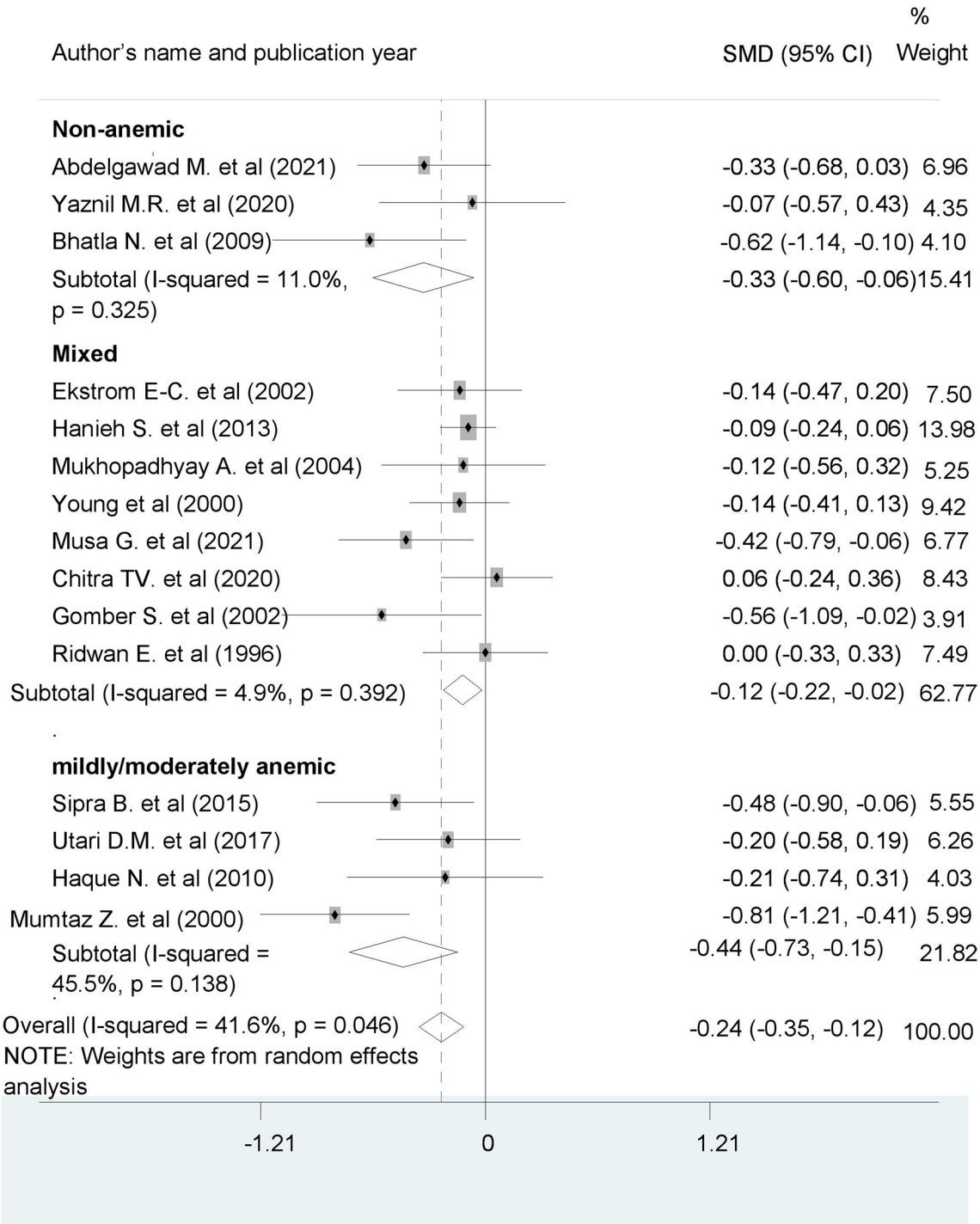

Fig. 10 Subgroup analysis compared the two arms by anaemia status at recruitment and before initiation of supplementation

to consider the intermittent supplementations, as recommended by W.H.O. second option [1], starting from early pregnancy follow-up (≤20 weeks gestation) and more than two times frequency per week.

Women in the daily arm were comparatively less tolerant of the regimen's side effects and were poorly adhered to. This was in agreement with the former review reports for side effects [8, 9]. Former reviews never assessed adherence. Repeated intake of the regimen in the daily arm could have facilitated more side effects and poor adherence. However, review results should be used cautiously, as the heterogeneity was substantial.

Strengths and limitations

We performed subgroup analysis to further observe subgroup influences on the primary outcome variable. Given the limited number of studies, subgroup analysis was not performed for secondary outcome variables. Due to the availability and accessibility of a few numbers of trials in the search, we authors were indebted to include studies in the last three decades. We acknowledge potential biases in the review process due to personal judgments, but we strived to minimize them. We treated a single study of three arms as two separate studies where the two intervention arms were able to fulfill the selection criteria of the intermittent group [35]. While scoring risk of bias assessment, we relied on trialists' reported documents for reporting bias assessment, though it was not apparent in most reports.

Conclusions and implications

Review findings generally suggest that the overall HGB level between the two arms was different. The incidence of anaemia in pregnancy showed no significant difference between the groups. IFA supplementations with an early and more frequent regimen could be a feasible alternative in pregnancy if gastric side effects are intolerable. Due to substantial heterogeneity and publication bias among existing evidence, the alternative option should be used cautiously in that the woman should be under supervision in the cohort of antenatal visits. Interpretations, recommendations, and guideline preparations based on this review report must take into consideration the quality of the evidence status summary report. As all of the selected studies in the current review were done in the developing world, where multiple additional causes of anaemia (such as malaria, low nutritional iron intake, hookworm infections, and other micronutrient deficiencies and infectious diseases) exist, future reviews must include the updated trials throughout the world so that improved conclusions will be developed. Moreover, emphasis has to be given to the harmful effects of high maternal HGB concentrations related to the daily IFA regimen.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12978-024-01917-8.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.
Supplementary Material 6.
Supplementary Material 7.

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Author contributions
The contributions of the authors were substantial in the review process and development of the manuscript. Serawit Lakew: Developed and performed the concept, reviewed the literature, designed, searched, and extracted data, data analysis, quality analysis, report writing, sequencing, and manuscript drafting. Mesay Hailu: Reviewed the literature, participated in designing and performing searching, extracting data, participated in data analysis, performed quality analysis, report writing, sequencing, and drafting the manuscript. Endrias Markos. Searched the literature and participated in extracting data, data analysis and quality analysis, report writing, sequencing, and manuscript drafting. All the authors approved the final manuscript.

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Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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in preventing anaemia during pregnancy. J Obstetr Gynaecol Res. 2018;44(3):417–24.

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