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SYSTEMATIC REVIEW

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Effect of probiotic and prebiotics supplementation on hemoglobin levels and iron absorption among women of reproductive age and children: a systematic review and meta-analysis

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Abstract

Background This review aims to assess the effect of oral administration of probiotics and/or prebiotics in children and women of reproductive age (WRA) to improve intestinal iron absorption, hemoglobin, and ferritin levels.

Methods Randomized controlled trials from published literature on probiotics and or prebiotics for prevention or treatment of anemia as a supplement or fortification in children or WRA till Jan 31, 2023, were included. Studies on probiotics and prebiotics in patients with anemia due to other causes were excluded. Screening and data extraction was done using Distiller SR and meta-analysis was performed using Revman 5.4.1.

Results A total of 1925 records were identified from Pubmed, Embase, and Cochrane, of which 29 were included in the systematic review (14 supplementation and 15 fortification studies; 15 studies in children and 14 studies in WRA). The major interventions included galacto-oligosaccharide, inulin, heat-killed H61, *Lactobacillus plantarum* 299v, *Lactobacillus reuteri*, *Lactobacillus acidophilus*.

Meta-analysis of 5 studies in WRA showed that the use of prebiotics and/or probiotics with or without iron was associated with little or no effect on hemoglobin. However, there is low certainty of evidence that the intervention led to improvement in fractional absorption of iron as compared to placebo or iron [8 studies, $n=335$, mean increase 0.74%, 95%CI-0.11–1.38, $p=0.02$]. Meta-analysis of 6 studies in WRA using prebiotics and/or probiotics with or without iron led to a significant increase in ferritin levels in WRA (mean increase 2.45 ng/ml, 95% CI 0.61–4.3, $p=0.009$, $n=320$) [Moderate certainty of evidence].

In children, meta-analysis of up to 8 studies did not result in any significant change in hemoglobin, ferritin and fractional iron absorption [low or very low certainty of evidence].

Conclusion There is some evidence to show that the use of prebiotics or probiotics (especially *Lp299v* and GOS) with or without oral iron can improve iron absorption in women and lead to improvement in ferritin levels in women. However, the current evidence does not conclusively show the benefit of these interventions in improving hemoglobin levels in women and children.

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Keywords Anemia, Iron bioavailability, Iron deficiency, Ferritin

Introduction

Nutritional anemia is an important public health concern worldwide, especially among children and women of reproductive age (WRA). Globally, the anemia prevalence was reported as 29.9% in WRA and 39.8% amongst children aged 6–59 months in 2019 [1] with countries from South Asia and Sub-saharan Africa being particularly affected [2]. In India, the prevalence of anemia has been reported to be 67.1% in children aged 6–59 months, 59.1% amongst adolescent girls (aged 15–19 years), and 57% in women aged 15–49 years in National Family Health Survey-5 (NFHS-5) survey (2019–2021) [3]. The prevalence of anemia has increased in these populations as compared to NHFS-4 despite the implementation of a national program in the country for the last four decades [4].

About 30–50% of the anemia in these populations may be caused by iron deficiency [5, 6]. Timely correction of iron deficiency is crucial, as it significantly affects cognitive performance, behavior, and physical growth of infants, preschool, and school-age children. Furthermore, it adversely affects their immune status and increases susceptibility to infections [4, 5]. Iron deficiency anemia in women is associated with an increased risk of preterm delivery, low birth weight, and poor neurodevelopment in the baby [7, 8].

Rationale

Oral iron supplementation is associated with limited bioavailability which is further reduced due to barriers such as inflammation, and dietary inhibitors like phytates and oxalates [5, 9]. Further, the compliance to oral iron is poor due to gastrointestinal adverse effects [5, 9]. Hence, there is scope for exploring new interventions that can improve the effectiveness of oral iron in this vulnerable population.

Probiotics have been defined by the Food and Agricultural Organization (FAO)/World Health Organization (WHO) as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [10]. Prebiotics, a group of nutrients that are degraded by gut microbiota have undergone revisions in their definition with the acceptance of the following criteria (i) resistance to acidic pH of the stomach, non-hydrolyzability by mammalian enzymes, and lack of absorption in the gastrointestinal tract, (ii) fermentability by intestinal microbiota, and (iii) the capacity to selectively stimulate the growth and/or activity of the intestinal bacteria thereby enhancing the health of the host through this process [11]. These compounds when consumed by the intestinal microbiota, undergo degradation to produce short-chain fatty acids which can impact gastrointestinal and systemic effects.

There is increasing evidence of the use of probiotics and prebiotics in optimizing dietary iron bioavailability [12]. *Lactobacillus acidophilus*, *Bifidobacterium longum*, *and Lactobacillus plantarum* 299v are a few probiotic strains that have shown improvement in iron absorption in humans [12, 13]. Moreover, probiotics have been shown to play a role in the production of vitamins (B1, B2, B6, B12, K) [14, 15] and short-chain fatty acids. Some of the bacterial strains may have a beneficial role in iron absorption [13]. Galacto-oligosaccharides (GOS) have been suggested to improve iron absorption in the gastrointestinal tract probably by increasing the gastric residence time allowing more absorption, stimulating enterocyte gene expression of the proteins involved in iron absorption, stimulating enterocyte proliferation, providing a greater surface for iron absorption and anti-inflammatory effects in the colon reducing circulating hepcidin [16–18].

Despite this, there is no systematic review available on the effect of probiotic or prebiotic intervention on changes in hemoglobin levels or iron absorption in children and young women.

Objectives

This systematic review and meta-analysis was undertaken to systematically evaluate the evidence of the effect of prebiotics and probiotics on changes in hemoglobin levels, iron stores, and iron absorption in WRA and children.

Methods

The protocol for this systematic review was registered prospectively at PROSPERO [CRD42023399502].

Eligibility criteria

Original manuscripts on randomized controlled trials (RCTs) including parallel or cross-over design, quasi-experimental from published literature that used prebiotics and/or probiotics for prevention or treatment of anemia in children and WRA (15–45 years) were included. Studies related to probiotic, prebiotic or symbiotic interventions either provided as supplementation or as fortificant that assessed the impact of these interventions on change in the anemia status (using hemoglobin and/or ferritin) and absorption of iron using stable iron isotopes were included. The control groups could include placebo or regular iron supplementation or food that was not fortified with prebiotics or probiotics depending upon the study design. In addition, references from relevant articles were screened for eligibility. Studies on prebiotics and probiotics for anemia prevention in patients with underlying causes (e.g., anemia due to chronic renal disease, cancer, etc. were excluded from the review. Also, reviews, commentaries, opinion papers, and preclinical study papers relevant to the topic were not included.

Information sources

Medline, Cochrane Library, and Embase databases were used for the literature search. Literature related to the use of probiotics/prebiotics for prevention or treatment of anemia either in the form of a supplement or fortified food available from Jan 2005 till Jan 31, 2023, and written in English language was included.

Search strategy

A three-step search strategy as suggested by Joanna Briggs Institute was used [19]. As a first step, a limited search of Medline and Embase databases was done, following which analysis of the key terms used in the title or abstract, or index terms was done. In the second step, keywords extracted during step 1 were used to build up search in individual databases. The themes and key terms used for the literature search are displayed in Table 1. The full search strategy for the individual databases is attached as Supplementary Table 1. A uniform search strategy was used for searching all three databases and searches from all databases were pooled before the title and abstract screening. As the next step, reference lists of the identified articles were searched for relevant references.

Selection process

Screening of title/abstracts and data extraction was done using Distiller SR software. Citations from the individual databases (.ris file or .nbib file) were added to the Distiller SR project. Duplicates were removed before the screening of titles and abstracts.

Data collection process

For level 1 review (title and abstracts), the available search results were screened independently and simultaneously by two authors (AS and AP) based on the given eligibility criteria. Full texts were obtained for all the selected citations and the full texts were uploaded to the Distiller SR project. The full texts were independently screened by two reviewers against the eligibility (AS and AP). All the conflicts were resolved by the third author (AA) based on independent judgment.

Data items

Data charting for the selected articles was done by AA, AP and AS using data collection forms generated using Distiller SR. The following variables were extracted for all studies – author, year, country, type of population, age group, sample size, objectives, type of intervention (probiotic, prebiotic, with/without iron), and study outcomes (increase in iron absorption, change in hemoglobin). If required, the authors of the articles were contacted for further information. Data extraction done by one reviewer was crosschecked by another reviewer. Study characteristics of all included studies are uploaded as supplementary Table 2.

Study of risk of bias assessment

Risk of Bias assessment for the randomized controlled studies was done by AP and AS using the RoB 2.0 tool [33] for parallel design and cross-over design studies. For non-randomized studies, ROBIN-I was used [34]. Critical appraisal done by one reviewer was cross-checked by another. For each criterion, the studies were categorized as low risk of bias, some concerns, and high risk of bias.

Effect measures

The meta-analysis of selected studies was done for the outcomes of hemoglobin levels, ferritin levels, and iron absorption using mean and standard deviations. For studies where median and interquartile range (IQR) were available, median values were considered as mean, and standard deviations were calculated as IQR/1.35. For studies with before and after values, standard deviation of the difference was calculated using the following formula: SDchange = SQRT(SD^2baseline + SD^2final-(2XcorrelationXSDbaslineXSDfinal)) [35]. Where correlation is used as 0.5 independent of the study design.

Synthesis method

A random-effects or fixed-effects model was used to calculate the mean difference (MD). The test for overall effect size was assessed using Z-statistics for testing the null hypothesis of homogeneity. Heterogeneity was also assessed through I^2 and Chi-square test. I^2 values of 0–40%, 30–60%, 50–90%, and 75–100% were considered as not important, moderate, substantial, and considerable respectively. For heterogeneity values of more than 50%, random effect model was used

Table 1 Studies on prebiotic and/or probiotic for anemia in children

Author	Year	Country	Design	*N*	Age group	Intervention	Study outcomes
Manoppo [20]	2019	Indonesia	Parallel RCT	66	5–12 yrs	FeSO4 60 mg of elemental iron *2 + L. reuteri DSM 17,938 for 14 days	Change in mean Ret-He level Group 1–24.43 ± 1.64 to 28.21 ± 1.72 pg/ L ($P = 0.000$). Group 2–24.31 ± 1.42 to 27.03 ± 2.14 pg/L ($P = 0.000$).
Gerald MRosen [21]	2019	USA	Parallel RCT	52	5–18 yrs	3 mg/kg/day of elemental iron with or without 10 * 10 colony-forming units of the probiotic *LP299v* for 6 to 8 weeks.	Increase in S. ferritin level from 23.7 ng/mL to 45.4 ng/mL. No significant difference in the increase in serum ferritin in children taking the probiotic *LP299v* compared with controls (23.2 vs. 20.0 ng/mL, respectively)
Ferus [22]	2018	Poland	Parallel RCT	34	4–18 yrs	oligofructose-enriched inulin(10 g/day) for 3 months Placebo - maltodextrin for 3 months	In the Study group, serum hepcidin concentration was significantly decreased by 60.9% ($p = 0.046$). No significant difference was observed in the placebo group.
Daniela Paganini [17, 23]	2017	Kenya	Parallel RCT	155	6.5–9.5 mth	(1) MNP without iron (control), (2) the identical MNP with 5 mg iron (2.5 mg as sodium iron ethylenediaminetetraacetate and 2.5 mg as ferrous fumarate) (Fe group); or (3) the identical MNP as the Fe group with 7.5 g GOS (FeGOS group).	Hb and Ferritin were higher in the Fe and FeGOS groups ($p < 0.001$ for both); sTfR was lower in the Fe and FeGOS groups ($p < 0.001$ for both); and the prevalence of anemia and IDA was lower in the Fe and FeGOS group ($p < 0.001$ for both).
Daniela Paganini [17, 23]	2017	Kenya	Parallel RCT	50	6–14 mth	Maize porridge fortified with MNP containing Fefum [2.5 mg] + NaFeEDTA [2.5 mg] and 7.5 g galacto-oligosaccharides (GOSs) Control group - MNP without GOS	GOS consumption by infants increased iron absorption by 62% from an MNP containing FeFum + NaFeEDTA, thereby possibly reflecting greater colonic iron absorption.
Rina Augustina [24]	2013	Indonesia	Parallel RCT	494	1–6 yrs	180 ml milk fortified with *Lactobacillus casei CRL 431* or *Lactobacillus reuteri DSM 17,938* for 168 days. Control – Low calcium or regular calcium milk	During the intervention, Hb, Hct, other hematologic variables and serum ferritin significantly declined, and sTfR significantly increased in each of the groups (or all combined) ($P < 0.001$). However, none of the variables were significantly different amongst the study groups.
Sunil Sazawal [25]	2010	India	Parallel RCT	624	1–4 yrs	Milk fortified with *probiotic B lactis* HN019 and 2.4 g/day of prebiotic oligosaccharides milk Control – unfortified milk	As compared with nonfortified milk, consumption of probiotic- and prebiotic-fortified milk reduced the risk of being anemic and iron deficient by 45% (95% CI 11%, 66%; $P = 0.01$) and increased weight gain by 0.13 kg/year (95% CI 0.03, 0.23; $P = 0.02$).
Do Thi Kim Lien [26]	2009	Vietnam	Parallel RCT	444	7–8 yrs	Inulin and micronutrient fortified milk – Two servings of 250 ml milk every day for six months.	Change in Hb 9.1 ± 21.8 in the test vs. 4.2 ± 6.9 gm/dl in the control group ($p < 0.05$). Change in the ferritin 25.9 ± 60.4 ng/ml in the test vs. 6.3 ± 38.3 in the control group ($p < 0.01$).
Silva [27]	2008	Brazil	Nonrandomized trial	190	2–5 yrs	Fermented milk beverage fortified with iron amino acid chelate (3 mg iron per 80 mL) and supplemented With *Lactoba*cillus *acidophilus* (test) or not (control) for 101 days.	Change in Hb − 0.5 ± 0.6 gm/dl in the test group vs. − 0.7 ± 0.9 in the control. Change in ferritin of − 6.7 ± 18.9 ng/ml in the test group vs. 5.0 ± 26.1 in the control. Higher increase in Hb with intervention (38.2% vs. 30.2%).
Mohammad [28]	2006	Egypt	RCT	24	10–12 yrs	*Lactobacillus acidophilus* (La1) in yogurt matrix (1012 colony-forming units), for 42 days.	Hb changed from 121.29 ± 2.7 to 124.49 ± 1.8 gm/dl in the control group and 120.39 ± 3.1 to 131.79 ± 3.2 gm/dl in the test group.

Table 1 (continued)

Author	Year	Country	Design	*N*	Age group	Intervention	Study outcomes
Owolabi [29]	2021	Nigeria	RCT	184	12–36 mth	Multi-nutrient fortified dairy-based drink (200, 400, or 600 mL, supplying 2.24, 4.48, and 6.72 mg of elemental iron, for 6 months. No control group.	All three dosages reduced anaemia prevalence, to 47%, 27% and 18%, respectively. ID and IDA prevalence was low and did not significantly decrease over time.
Nadja Mikulic [18]	2021	Kenya	Cross over RCT	23	6–14 mth	4 stable iron isotope–labeled maize porridge meals fortified with MNPs containing 5 mg iron as FeFum + NaFeEDTA, or FeSO4, either without or with 7.5 g GOS.	Given with GOS, FIA from FeSO4 was 40% higher than from FeFum + NaFeEDTA ($P < 0.001$); given without GOS, it was 51% higher ($P < 0.01$).
Nadja Mikulic [30]	2020	Kenya	Cross over RCT	25	3 to 6 mth	1) labeled ferrous sulfate (FeSO4) alone; 2) labeled FeSO4 given with bovine apo-Lf; and 3) intrinsically labeled bovine holo-Lf.	The FIA from the meal containing apo-Lf + FeSO4 (geometric mean, 9.8%; −SD and + SD, 5.4% and 17.5%) was higher than from the meals containing FeSO4 (geometric mean, 6.3%; −SD and + SD, 3.2% and 12.6%; $P = 0.002$) or holo-Lf (geometric mean, 5.0%; −SD and + SD, 2.8% and 8.9%; $P < 0.0001$).
Siti Helmyati [31]	2020	Indonesia	RCT	59	8–12 mth	ISFM group - iron supplementation in syrup with fermented milk (containing synbiotic *Lactobacillus plantarum* and fructo Oligosaccharide) for 3 months. IS group - iron supplementation in syrups. A dose of syrup contains FeSO4 which equals 10 mg iron/day.	The hemoglobin and serum ferritin levels in IS and ISFM groups improved significantly ($p < 0.05$) although the difference between the two groups was not significant ($p > 0.05$).
Ambra Giorgetti [32]	2022	Kenya	Cross-over RCT	55	8–12 mth	Meals fortified with 1 of the following: (1) 5.0 mg iron as 54Fe-labeled ferrous fumarate (FeFum); (2) 5.0 mg iron as 58FeFum and 3.0 g GOS FeFumþGOS); and (3) 5.0 mg iron as 57FeFum and 2.0 g 2′-FL and 1.0 g LNnT (FeFumþHMO)	FIA from the FeFum + GOS group [median (IQR) 22.2% (16.5–25.9%)] was higher than that from the FeFum group [12.5% (9.5–20.9%)] (P ¼ 0.005). FIA from the FeFum + HMO group was 13.3% (7.1–24.4%) and did not differ from the FeFum group (P ¼ 0.923)

for analysis. For sensitivity analysis, studies with a high risk of bias were included and removed from the analyses, this was repeated for both fixed and random effects. Also, the analysis was repeated after including and excluding studies using supplementation and fortification Separate analyses were conducted for women and children. All analyses were done using Revman 5.4.1. version and p-values less than 0.05 were considered statistically significant.

Reporting bias assessment

The assessment of reporting bias was done through grading and by visual inspection of the funnel plots for each meta-analysis if it involves 10 or more studies.

Certainty of evidence

Summary of finding tables were prepared for both comparisons using GRADEpro GDT software. The certainty of evidence for each outcome was assessed while examining the risk of bias within studies the directness

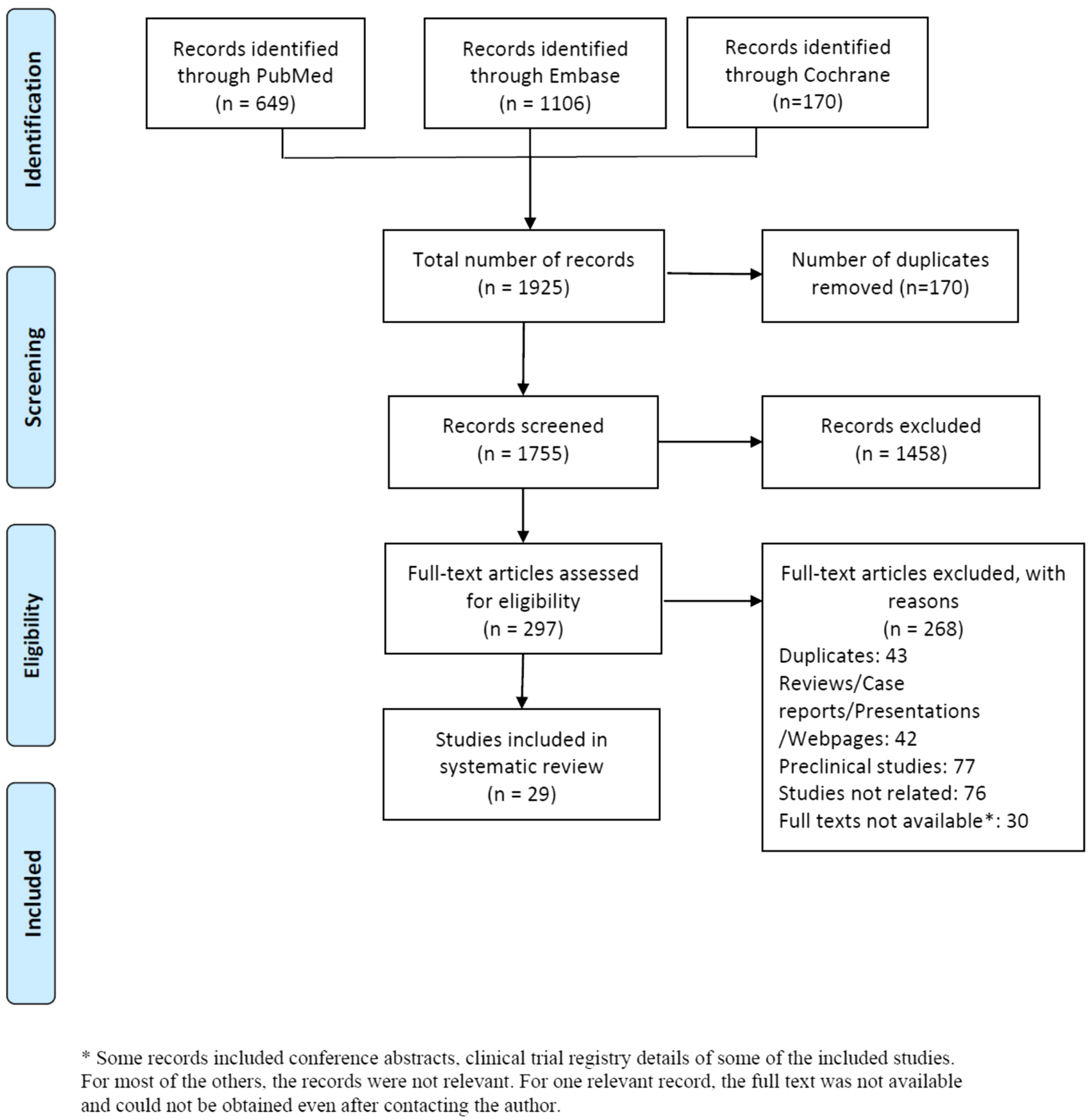

Fig. 1 PRISMA flow chart

Table 2 Studies on prebiotic and/or probiotic for anemia in women of reproductive age

Author	Year	Country	Design	*n*	Age	Intervention	Outcome
Takaragawa [37]	2022	Japan	Randomized controlled trial	50	18–25 years	H61 (60 mg/day) or placebo daily for 4 weeks. which contained heat-killed H61 (One tablet contained 30.0 mg of heat-killed H61, 167.5 mg dextrin, 50.0 mg crystalline cellulose, and 2.5 mg calcium stearate. The placebo tablet contained 197.5 mg dextrin, 50.0 mg crystalline cellulose, and 2.5 mg calcium stearate	Four-week consumption of heat-killed Lactococcus lactis subsp. cremoris H61 was demonstrated to increase serum iron, TSAT, and ferritin levels and decrease UIBC
Ambra Giorgetti [32]	2022	Switzerland	Randomized cross-over study	30	18–45 y	100 mg Fe tablet labeled with 4 mg 57Fe or 58Fe, given with either *1*) 15 g GOS; *2*) 15 g FOS; *3*) 15 g acacia gum; or *4*) 6.1 g lactose and 1.5 g sucrose (control; matching the amounts of sucrose and lactose present in the GOS powder providing 15 g GOS), dissolved in water.	FIA from FeFum given with GOS and FOS was significantly higher (+45% and +51%, respectively; $P<0.001$ for both) than control; median [IQR] total iron absorption was 34.6 mg [28.4–49.1 mg], 36.1 mg [29.0–46.2 mg], and 23.9 mg [20.5–34.0 mg], respectively. Acacia gum did not significantly affect FIA from FeFum ($P=0.688$).
Husmann [38]	2022	Switzerland	Randomized cross-over study	12	18–45	2 supplemental iron doses of 14 mg iron (as FeFum), containing a 6-mg isotopic tracer (57Fe or 58Fe). The iron doses were administered in parallel to the GOS (58Fe) or control (57Fe) formulations. The 2 tests (58Fe/GOS or 57Fe/control) were randomly allocated.	FIA (20.3% (8.6–38.7%) with GOS, and 15.6% (10.6–24.8% f) or control) were not different with compared to without GOS ($P=0.064$; $P=0.080$).
Sandroni [39]	2022	USA	Randomized controlled trial	20	18 years onwards	Synbiotic supplement or placebo, each single-serve packet of synbiotic supplement consisted of 5 g prebiotic fiber + 8 billion CFU probiotic B. lactis). The placebo packet consisted of 5 g maltodextrin powder along with Fe supplementation (140 mg ferrous sulfate, FeSO4/d) for 8 weeks.	Fe supplementation in both groups, log sFer increased ($p<0.03$), but significantly more so in the Synbiotic supplement group compared to the Placebo group ($p<0.15$ for the time-by-group interaction).In the Placebo group, sFer (log sFer) was 122% (107%) & in Synbiotic supplementation group, values were 209% (121%) of the baseline values.
Ulrika Axling [40]	2021	Sweden	Randomized controlled trial	326	18–42 years	Lp ($n=161$) or placebo ($n=165$) twice daily from gestational weeks 10–12 until end of pregnancy or until the potential start of iron therapy. The Lp capsule contained freeze-dried *Lactiplantibacillus plantarum* 299v® (1010 colony forming units), 4.2 mg iron (ferrous fumarate), 12 mg ascorbic acid, and 30 µg folic acid per capsule.	Intake of Lp attenuated the decrease in serum ferritin from baseline to week 28 ($p=0.003$) and week 35 ($p<0.001$), resulted in reduced prevalence of iron deficiency (59% vs. 78%, $p=0.017$) and iron deficiency anemia (7.4% vs. 21%, $p=0.023$).

Table 2 (continued)

Author	Year	Country	Design	*n*	Age	Intervention	Outcome
Ulrika Axling [41]	2020	Sweden	Randomized controlled trial	39	16–40 years old	Lp299v product or control for 12 weeks. The *Lp299v* product (LpFe) contained freeze-dried probiotic *Lactobacillus plantarum299v* at a concentration of 1010 CFU/capsule, 20 mg of iron (ferrous-fumarate). The control product (CtrlFe) contained all ingredients except *Lp299v*.	Intake of *Lp299v* with iron for increased ferritin levels more than iron alone (13.6 vs. 8.2 _g/L), but the difference between the groups was not significant ($p=0.056$). The mean reticulocyte hemoglobin content increased after intake of *Lp299v* compared to control (1.5 vs. 0.82 pg) but the difference between the group was not significant ($p=0.083$)
Nandyala. Bhargavi [42]	2020	India	Non-randomised comparative study	80	18–25 Years	Probiotic capsules (Lpv)- every alternative day after lunch along with iron and folic acid 1 tab/week after breakfast for 3 months.	There was significant difference in the increase in serum iron taking the probiotic LP299V compared with controls {Control: 80.6 mg/dl to 79.99 mg/dl, Diet: 50.05 mg/dl to 51.1 mg/dl, Folic acid + Diet: 45.15 mg/dl to 48.35 mg/dl, Probiotic + Folic acid + Diet: 64.6 mg/dl to 74.1 mg/dl}
Nicolai Petry [43]	2012	Switzerland	Randomized cross-over study	32	18 to 40 years	Inulin or placebo 3 times/d (;20 g/d) for 4 wk, separated by a 2-wk washout period. After the washout period, each subject received the alternative treatment for 4 wk.	Mean fractional iron absorption in the inulin (15.2%; 95%CI: 8.0%, 28.9%) and placebo (13.3%; 95% CI: 8.1%, 24.3%) periods did not differ significantly ($P=0.10$).
Jeroense [16]	2019	Switzerland	Randomized cross-over study	34	18–45 years	I 14 mg iron labeled with stable isotopes – *1*) ferrous fumarate (FeFum) in water, with and without 15 g GOS; *2*) FeFum in a test meal given with and without 15 g GOS; *3*) ferrous sulfate (FeSO4) in a test meal given without 15 g GOS. All subjects then consumed ~15 g GOS daily for 4 wk.	GOS significantly increased FIA from FeFum when given with water (+61%; $P<0.001$) and the meal (+28%; $P=0.002$). After GOS consumption, it significantly increased FIA from FeFum in the meal (+29%; $P=0.044$). Compared with baseline, consumption of GOS did not significantly enhance absorption from FeFum in the meal given without GOS. FIA from FeSO4 given with GOS in a meal after 4 wk of GOS consumption was not significantly greater than FIA from FeSO4 in a meal without GOS at baseline.
Jeroense [44]	2020	Switzerland	Randomized cross-over study	43	18–45 yrs	FIA was measured from 14 mg iron labeled with stable isotopes in the following conditions: *1*) FIA from FeFum given with 3.5 g, 7 g GOS, and without GOS; *2*) FIA from FeSO4 and FePP given with and without 15 g GOS; and *3*) FIA from FeFum given with 7 g GOS with and without 93 mg AA	7 g of GOS significantly increased FIA from FeFum (+26%; $P=0.039$), whereas 3.5 g GOS did not ($P=0.130$). GOS did not significantly increase FIA from FeSO4 ($P=0.998$) or FePP ($P=0.059$). FIA from FeFum given with GOS and AA was significantly higher compared with FeFum given with GOS alone (+30%; $P<0.001$).

Table 2 (continued)

Author	Year	Country	Design	*n*	Age	Intervention	Outcome
Michael Hoppe [45]	2015	Sweden	Randomized cross-over study	22	20 to 40 years	Trial 1, iron absorption from a fruit drink containing 109 colony-forming units (CFU) Lp299v compared with that from a control drink without Lp299v. Trial 2 had the same design but 1010 CFU were used. The test and control drinks contained approximately 5 mg of iron as ferrous lactate and were labeled with 59Fe (B) and 55Fe (A), respectively, and consumed on 4 consecutive days in the order AABB	Mean iron absorption from the drink containing 109 CFU Lp299v (28·6 (SD 12·5) %) was significantly higher than from the control drink (18·5 (SD 5·8) %), n 10, $P<0·028$). The fruit drink with 1010 CFU Lp299v gave a mean iron absorption of 29·1 (SD 17·0) %, whereas the control drink gave an absorption of (20·1 (SD 6·4) %) (n 11, $P<0·080$). The difference in iron absorption between the 109 CFU *Lp299v* and the 1010 CFU *Lp299v* drinks was not significant ($P=0·941$)
Iqbal [46]	2022	Pakistan	Randomized controlled trial	75	18–25 yrs	5 groups (4 treatment groups and 1 control group). Four different types of fortified wheat flour were prepared using two iron fortificants (NaFeEDTA and FeSO4) and two prebiotics [inulin and galacto oligosaccharides (GOS)], while the control group was treated with iron-fortified flour without any prebiotics.	Improvement in all iron biomarkers as well as hematological indices among the treatment groups (*P*-value < 0.05), as compared to the control group. A maximum Hb (11.86 _ 0.24 mg/dL) and hematocrit value (35.06 _ 1.32%), were reported in group G3 which was treated with fortified wheat flour at a dose of 963 mg/kg GOS + 15 ppm FeSO4., highest mean values for RBC Count (4.73 _ 0.41 mil/mm3), MCV (81.41 _ 3.21 fL), serum iron (75.62 _ 2.79 mg/dL), serum transferrin (16.82 _ 0.30 mg/dL), and TIBC (403.68 _ 7.27 mg/dL) were observed in G4 group receiving the fortified wheat flour at a dose of 963 mg/kg GOS + 30 ppm FeSO4 level.
Bering [47]	2007	Denmark	Randomized cross-over study	18	22 +/- 3 years	Two test gruels, extrinsically labeled with 59Fe and served with two enter-coated capsules containing 55Fe (II) and 55Fe (III), respectively). The meals were consumed on two consecutive days, e.g. in the order AA followed by BB in a second period.	The non-haem Fe absorption in the present study was 1·4 and 1·3% from the heat-activated fermented oat gruels with and without viable L. plantarum 299v, respectively.
Bering [48]	2005	Denmark	Randomized cross-over study	24	25+/- 4 years	(A) fermented gruel, (B) pasteurized fermented gruel, (C) pH-adjusted non-fermented gruel, and (D) non-fermented gruel with added organic acids. The meals were extrinsically labelled with 55Fe or 59Fe and consumed on 4 consecutive days.	The fermented gruel with live L. plantarum 299v increased Fe absorption significantly (P,0·0001). The lactic acid concentration in the fermented gruel was 19% higher than in the pasteurized gruel, but the Fe absorption was increased by 50%.

of evidence, heterogeneity, precision of effect estimates, and risk of publication bias. The quality of evidence was graded as 'high', 'moderate', 'low', or 'very low' [36].

Results

Study selection

A total of 1925 records were identified from the three databases, PubMed (649), Cochrane (170), and Embase (1106) of which 1755 titles/abstracts were screened after removing 170 duplicate records. Of these, a total of 1458 was not found to be relevant and the remaining 297 were included for level 2 full-text review. Of these, 29 records were included based on the predefined inclusion criteria. Figure 1 illustrates the PRISMA flow chart with each stage of the selection process with the reasons for exclusion.

Study characteristics

We included a total of 29 studies in the systematic review of which 16 were parallel randomized control studies, 11 were cross-over design randomized control studies and 2 were non-randomized controlled studies. Fifteen out of 29 studies were from low- and middle-income countries (Kenya −5, Egypt −1, India −2, Indonesia – 3, Brazil, Nigeria, Pakistan, Vietnam – 1 each), and 14 studies were from high-income countries (Switzerland −5, Sweden −3, USA-2, Denmark-2, Japan-1, Poland −1). There were 15 studies in children and 14 studies in women of reproductive age. The brief study characteristics are provided in Tables 1 and 2.

Risk of bias in studies

Of 29 studies, 4 studies were not included in the meta-analysis due to the following reasons – very high risk of bias [42], study in patients with coeliac disease [22], probiotic formulation not specified [29] study in mixed population including women [49].

Overall, In studies where random sequence generation was conducted, less bias was observed [16–18, 20–26, 29–32, 37–41, 43–48, 50]. Key sources of bias in the studies included absence of blinding for outcome assessment (detection bias) [17, 18, 20, 27, 28, 30, 32, 38, 42, 44, 45, 50], blinding of participants and personnel (performance bias) [17, 18, 29, 30, 45], selective reporting (reporting bias) [27, 28], incomplete outcome data (attrition bias) [16, 17, 25, 27, 29, 37] and where attrition data was not reported Figs. 2 and 3.

Results of individual studies

Out of 29, 14 studies involved probiotics and/or prebiotics in the form of supplementation; whereas 15 studies used prebiotics and/or probiotics as fortificants to food items. Six studies assessed the use of probiotics and/or prebiotics alone for prevention or treatment of anemia, whereas in 23 studies these interventions were combined with oral iron supplementation. Twelve studies were conducted in healthy population, and 17 were conducted in population with iron deficiency or iron deficiency anemia. Eleven studies assessed the effect of probiotics and/or prebiotics on iron absorption and 14 studies assessed the effect of probiotics and/or prebiotics on an increase in hemoglobin or a change in the prevalence of anemia (Table 3).

The prebiotics included in the studies are galacto-oligosaccharide (5 studies), fructo-oligosaccharide (2 studies), and inulin (1 study). The probiotics included in the studies were: H61 60(1 study), *Lp299v* (3 studies), *L. reuteri DSM* 17,938 (1 study), and *B. lactis* (1 study).

Results of syntheses

Change in hemoglobin

Using the random effects model, a meta-analysis of 5 studies in WRA [37, 39–41, 46] (n = 256) using prebiotics and/or probiotics with or without iron compared to iron or placebo alone did not show significant improvement in hemoglobin levels. The I^2 value was 87% indicating high heterogeneity (Fig. 4A).

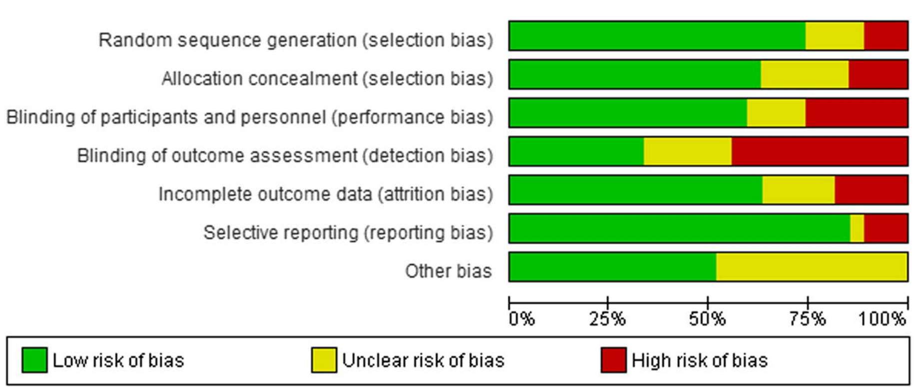

Fig. 2 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

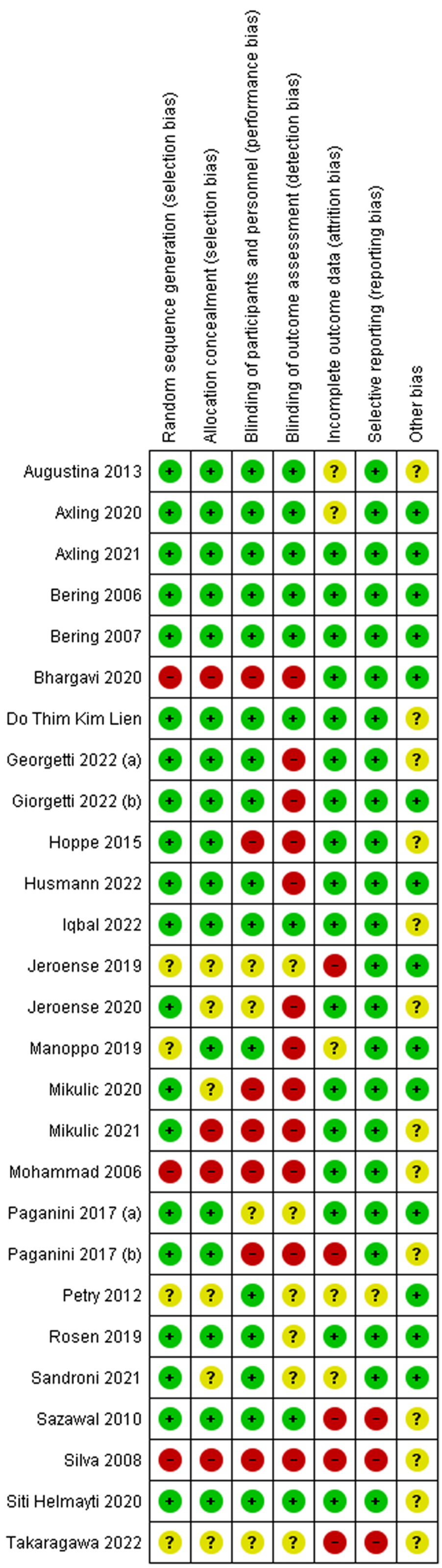

Fig. 3 Risk of bias summary: review authors' judgments about each risk of bias item for each included study

Meta-analysis of 8 studies in children [17, 20, 23–25, 27, 28, 31] using prebiotics and/or probiotics with or without iron as compared to placebo or iron did not lead to any significant change in the hemoglobin levels using the random effects model. Using the fixed effects model, these 8 studies showed a 0.21 gm/dl increase in hemoglobin (95% CI 0.1–0.31) [$p<0.0001$; $n=1361$] as compared to placebo or iron. The I^2 value was 83% indicating considerable heterogeneity in the studies (Fig. 4B).

Change in ferritin

Using the random effects model, meta-analysis of 6 studies in WRA [37, 39–41, 43, 46] ($n=320$) showed improvement of 2.45 ng/ml in ferritin levels [95% CI 0.61–4.30, $p=0.009$] with prebiotics and/or probiotics with or without iron as compared to placebo or iron. The I^2 value was 80% indicating high heterogeneity in the studies (Fig. 5A). With fixed effect model, the effect size was reduced to 1.39 ng/ml.

On the other hand, using the fixed effect model, meta-analysis of 4 studies in children [17, 23, 24, 31] using prebiotics and/or probiotics with or without iron in comparison with placebo or iron did not show significant change in ferritin levels (Fig. 5B). The heterogeneity increased to 71% after including the study by Silva et al. [27] which has high risk of bias in several domains, the analysis showed significant reduction of −3.78 ng/ml in ferritin levels [95% CI=−7.45- −0.12, $n=640$].

Fractional iron absorption

In women, the use of prebiotics and/or probiotics with or without iron was associated with a mean increase in iron absorption of 0.74% [95% CI 0.11–1.38] ($p=0.02$, $n=234$) as compared to use of placebo or iron. Use of pro/prebiotics with iron was associated with 8.15% [2.17–14.12] increase in the iron absorption ($p=0.008$, $n=334$) as compared to ingestion of iron only in WRA. Use of pre/probiotics was associated with mean 0.48% [0.09–0.87] iron absorption as compared to placebo ($p=0.01$, $n=53$) in WRA. In children, change in iron absorption was not found to be significant. Both the analyses were associated with high heterogeneity (Fig. 6).

Sensitivity analysis

There was no difference in the statistical significance on repeating the analysis after separating the studies using supplementation and fortification. Also, no significant change was observed after removing the studies with high risk of bias.

Reporting of bias

Based on the risk of bias assessment, two studies were found to have selective reporting [27, 28]. Based on

Table 3 Description of studies included in the review

Type of intervention	Probiotic and/or prebiotic as supplementation – 14 studies	Probiotic and/or prebiotic as fortification – 15 studies
	Probiotic and/or prebiotic alone – 6 studies	Probiotic and/or prebiotic combined with oral iron – 23 studies
Type of Population	Healthy population – 12 studies	Population with iron deficiency or iron deficiency anemia – 17 studies
Type of outcome	Iron absorption – 11 studies	Change in hemoglobin or change in prevalence of anemia – 14 studies

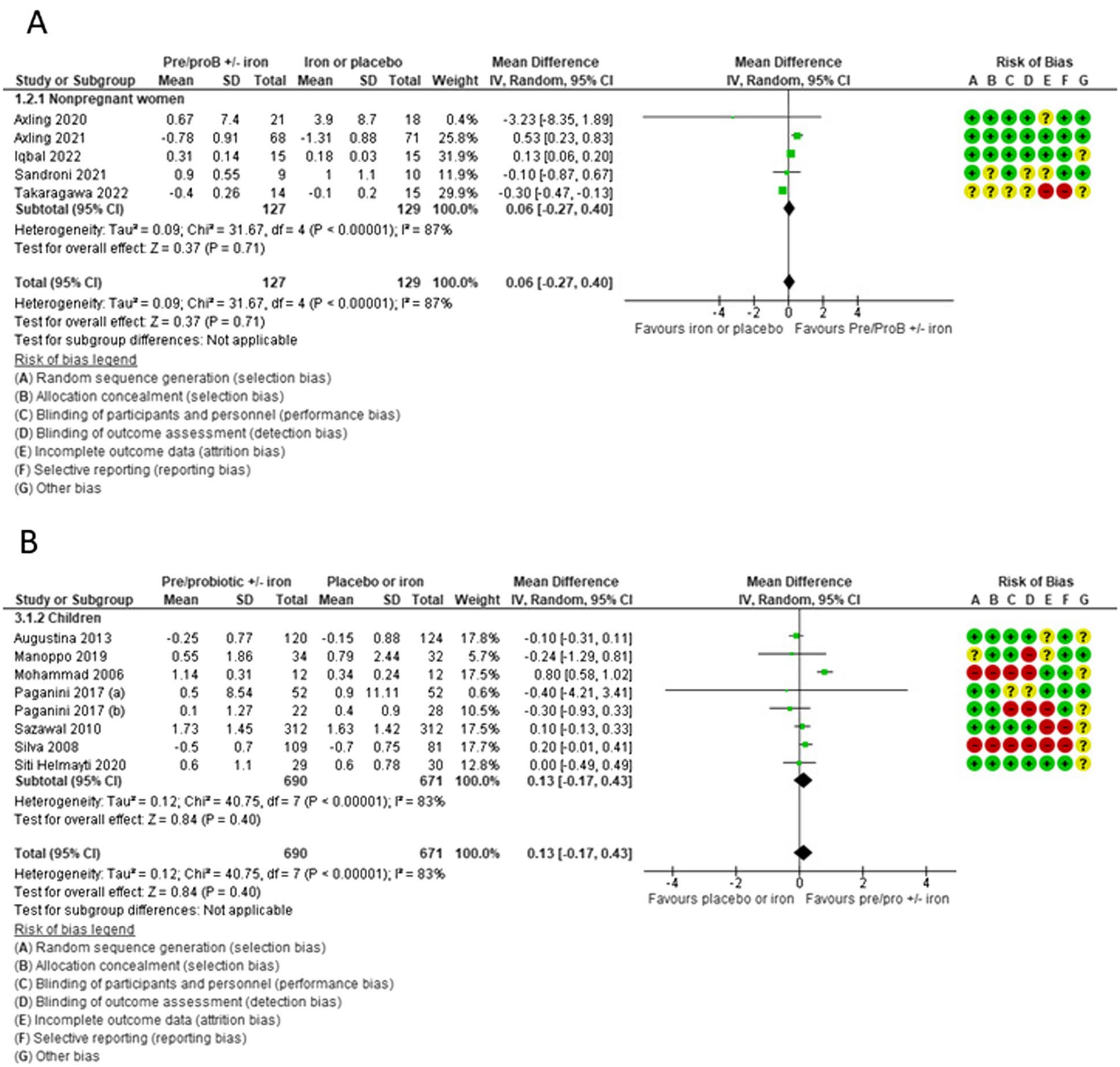

Fig. 4 Forest plot of comparison: Probiotic or prebiotic with or without iron vs. placebo or iron in (**A**) women of reproductive age (**B**) Children: Change in hemoglobin levels (gm/dl)

visual inspection of the funnel plots, asymmetry was seen especially in studies amongst WRA. However, the asymmetry could be attributed to the heterogeneity of the studies. No objective assessment of the reporting bias could be done due to less than 10 studies per analysis.

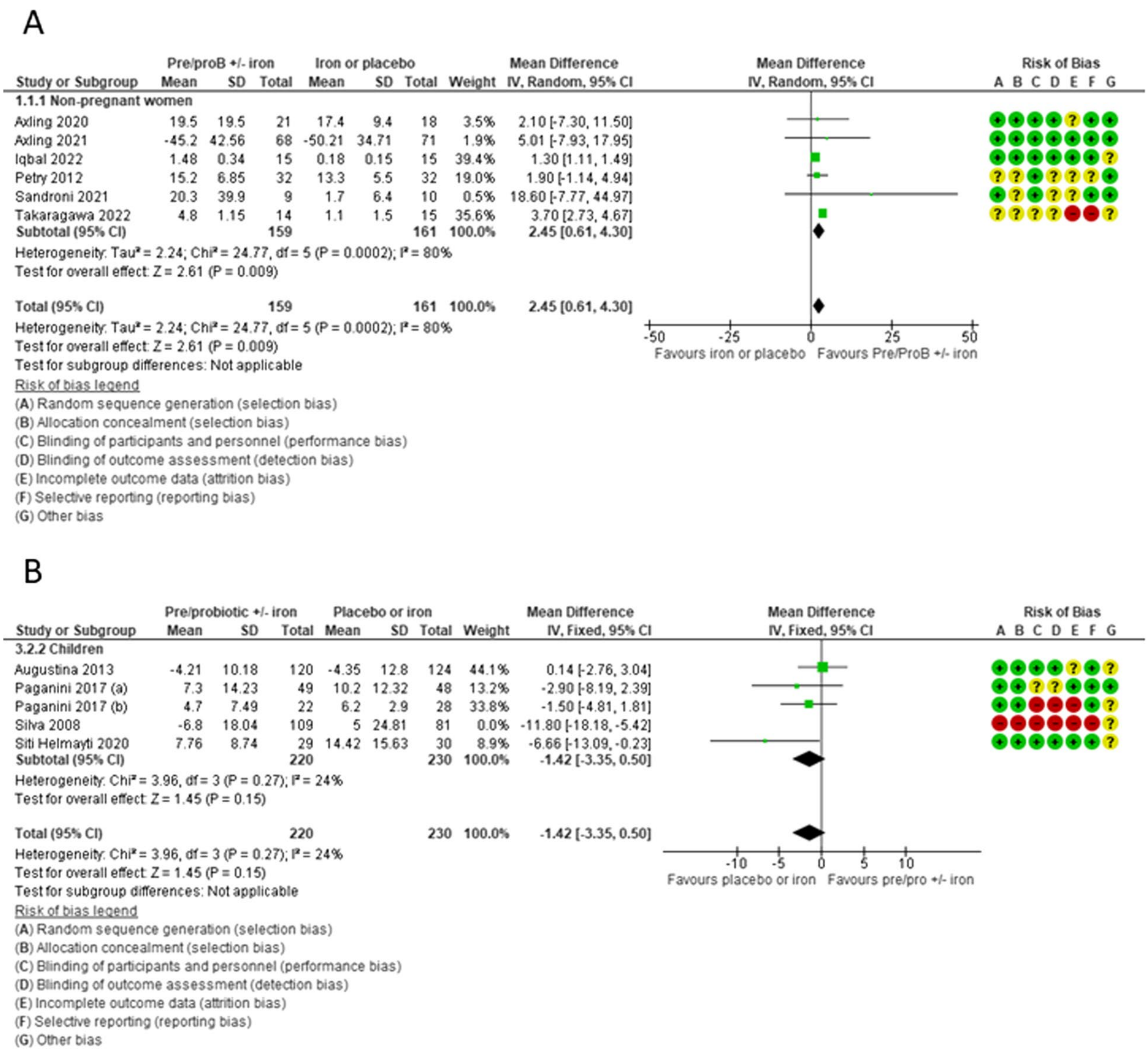

Fig. 5 Forest plot of comparison: Prebiotic and/or probiotic with or without iron vs. Iron or placebo in (**A**) women of reproductive age (**B**) children, Outcome: Change in ferritin levels (ng/ml)

Certainty of evidence using GRADE

The analyses in WRA show that there is low certainty of evidence that supplementation of prebiotics and/or probiotics with or without iron can increase iron absorption and moderate certainty of evidence that these interventions can improve ferritin levels. However, the evidence is not enough to demonstrate improvement in hemoglobin levels in WRA (Table 4). The analyses in children show that there is low-quality evidence that prebiotics or probiotics may not result in significant changes in the ferritin levels. The evidence is very uncertain about the effect of these interventions on hemoglobin levels and fractional iron absorption (Table 5).

Discussion

Poor gastrointestinal absorption of iron is one of the major limitations of iron supplementations and probiotics as well as prebiotics are potential interventions that can improve iron absorption and mitigate the adverse gastrointestinal effects associated with unabsorbed iron. This is the first systematic review and a meta-analysis to our knowledge that provides systematic evidence on the effect of prebiotic and probiotic interventions on iron parameters including changes in hemoglobin, ferritin, and iron absorption in women and children. Considering that about 50% of the studies were conducted in low and middle-income countries (LMIC), this analysis has

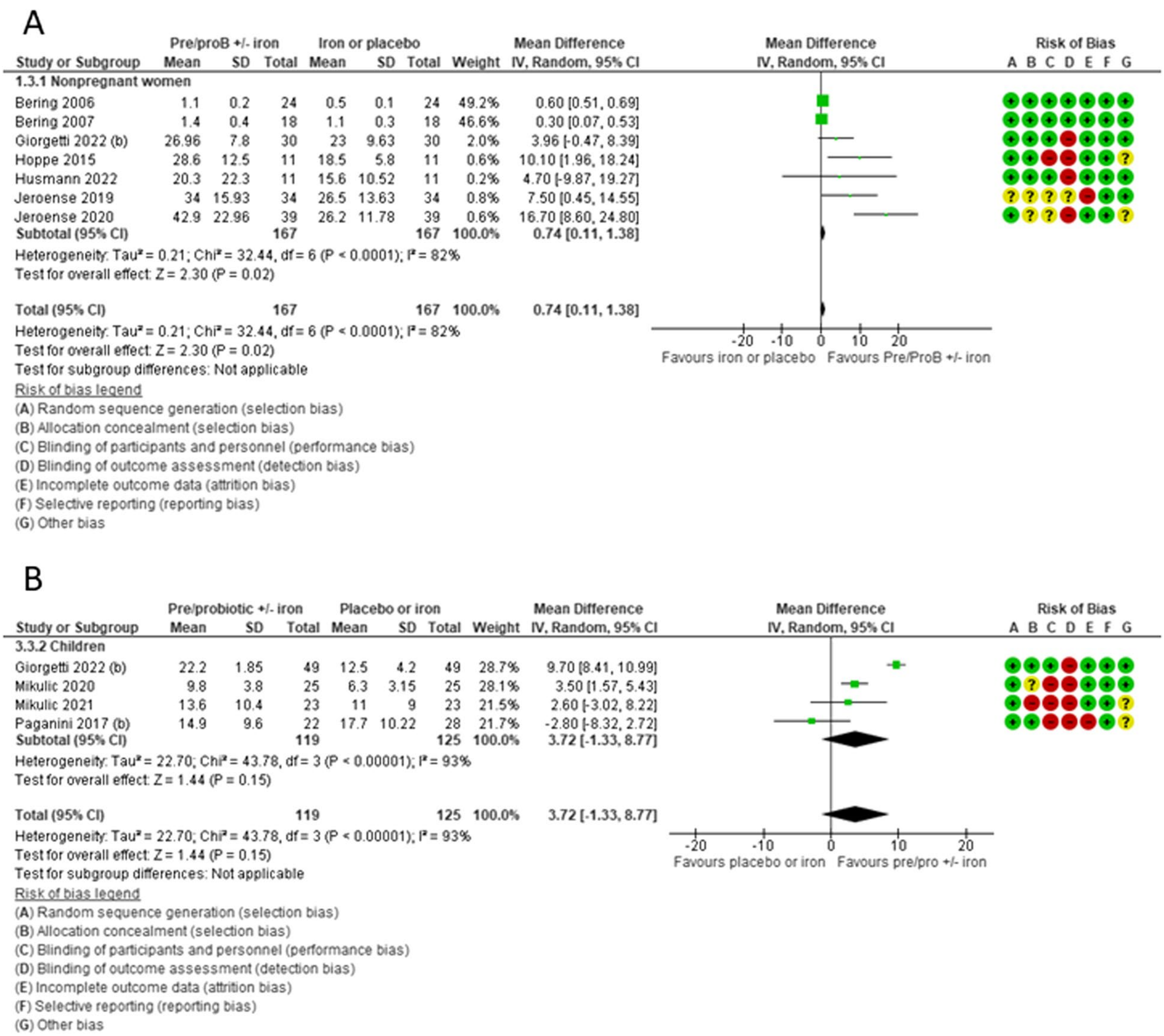

Fig. 6 Forest plot of comparison: Prebiotic and/or probiotic with or without iron vs. Iron or placebo in (**A**) women of reproductive age (**B**) children, Outcome: Fractional iron absorption (%)

a good representation of the LMICs. The commonest prebiotic intervention included GOS whereas *Lp299v* and other species probiotics like *Bacillus Lacti*, *lactobacillus acidophilus*, and *lactobacillus reuteri*, and prebiotic species of fructo-oligosaccharide, inulin, and lactoferrin were found to be used in the studies. We have combined studies that used probiotics or prebiotics as fortificants with studies that used them as supplements. The studies included a spectrum of interventions ranging from food fortified with prebiotic or probiotic or both to isolated probiotic or prebiotic formulation given with iron formulation.

Results from the meta-analysis show that iron absorption was significantly improved in women with very low certainty of evidence especially GOS (4 studies in 114 women) [16, 32, 38, 44] and *Lp299v* (3 studies in 53 women) [45, 47, 48]. This is similar to the results reported by Vonderheid et al. on Lp299v on iron absorption [mean difference of 0.55 (95% CI 0.22–0.88, $p = 0.001$)] [51]. The outcomes of ferritin showed significant improvement with probiotic and/or prebiotic interventions (which included *Lp299v*, GOS, and inulin) with moderate certainty of evidence. Despite this, it did not show significant improvement in hemoglobin. On the other hand, in children none of the outcomes were significantly improved with prebiotic and/or probiotic interventions. There was a trend toward reduction in ferritin levels amongst children. This could probably be due to higher

Table 4 Summary of findings: prebiotic and/or probiotics with or without iron compared to Iron or placebo for prevention and treatment of iron deficiency anemia (Hb, ferritin and FIA) in women of reproductive age

Patient or population: prevention and treatment of iron deficiency anemia (Hb, ferritin and FIA) in women of reproductive age
Setting: Hospital or community
Intervention: prebiotic and/or probiotics with or without iron
Comparison: Iron or placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Iron or placebo	Risk with prebiotic and/or probiotics with or without iron				
Change in ferritin levels	The mean change in Ferritin levels ranged from **−50.2–17.4** ng/ml	MD **2.45 ng/ml higher** (0.61 higher to 4.3 higher)	-	320 (6 RCTs)	⨁⨁⨁◯ Moderate[a, b,c]	Prebiotic and/or probiotics with or without iron probably increases ferritin levels slightly.
Change in hemoglobin	The mean change in Hemoglobin ranged from **−0.78–0.9** gm/dl	MD **0.06 gm/dl higher** (0.27 lower to 0.4 higher)	-	256 (5 RCTs)	⨁⨁◯◯ Low[b, c,d, e]	The evidence suggests that pro/probiotics with iron results in little to no difference in change in hemoglobin.
Fractional absorption of iron	The mean fractional absorption of iron ranged from **1.1–42.9**%	MD **0.74% higher** (0.11 higher to 1.38 higher)	-	334 (8 RCTs)	⨁⨁◯◯ Low[b, c,d, f,g]	Prebiotic and/or probiotics with or without iron may increase fractional absorption of iron .

***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).
CI: confidence interval; **MD**: mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate 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 different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very 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.

Explanations

[a] Some concern with selection bias for randomisation but not rated down for risk of bias

[b] Large variations in the effect sizes amongst different studies

[c] Significant hererogeneity

[d] High risk of attrition bias

[e] High risk of reporting bias

[f] High risk of detection bias

[g] High risk of performance bias

iron requirements during growing periods of childhood especially infancy which results in fast depletion of iron stores [52].

A major reason for no change in hemoglobin despite the increase in ferritin and iron absorption could be the fact that nutritional anemia has diverse etiologies like deficiency of other micronutrients especially B12, and the status of background inflammation that decides the availability of iron for hemoglobin synthesis. Also, in this review, we included studies from healthy population as well as population with iron deficiency or iron deficiency anemia, this could have masked the real effect of the intervention present in anemic population. One of the reasons for the lack of change in hemoglobin levels could be the wide scope of the studies included in the meta-analyses and wide range of doses of interventions included in the studies. Amongst the interventions, *Lp299v* [40, 41] and *lactoba*cillus *acidophilus* [28] did show improvement in hemoglobin but the effects were not statistically significant. The intervention of GOS showed improvement in hemoglobin in the women [46], but it was not found to improve hemoglobin in the pediatric studies conducted by Paganini et al. [17, 23]. The probable reason for this could be suboptimal

Table 5 Summary of findings: Prebiotics and/or probiotics with or without iron compared to placebo or iron for prevention and treatment of iron deficiency anemia (Hb, ferritin, FIA) in children

Patient or population: prevention and treatment of iron deficiency anemia (Hb, ferritin, FIA) in children
Setting: Hospital or community
Intervention: Prebiotics and probiotics with or without iron
Comparison: Placebo or iron

Outcomes	**Anticipated absolute effects**[*] (95% CI)		**Relative effect (95% CI)**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with Placebo or iron	**Risk with Prebiotics and probiotics with or without iron**				
Change in ferritin	The mean change in ferritin ranged from **−6.8–7.76** ng/ml	MD **1.68 ng/ml lower** (4 lower to 0.64 higher)	-	450 (4 RCTs)	⊕⊕◯◯ Low[a, b]	Prebiotics and/or probiotics with or without iron may result in little to no difference in change in ferritin
Change in hemoglobin	The mean change in hemoglobin was **−0.5–1.73** gm/dl	MD **0.13 gm/dl higher** (0.17 lower to 0.43 higher)	-	1361 (8 RCTs)	⊕◯◯◯ Very low[a, b,c, d]	The evidence is very uncertain about the effect of prebiotics and probiotics with or without iron on change in hemoglobin
Fractional iron absorption	The mean fractional iron absorption was **9.8–22.2**%	MD **3.72% higher** (1.33 lower to 8.77 higher)	-	244 (4 RCTs)	⊕◯◯◯ Very low[c, d,e]	The evidence is very uncertain about the effect of prebiotics and probiotics with or without iron on fractional iron absorption.

*__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).
CI: confidence interval; **MD**: mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate 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 different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very 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.

Explanations

[a] High risk of attrition and reporting bias

[b] Wide confidence intervals

[c] High risk of detection bias

[d] High heterogeneity

[e] High risk of performance bias

improvement in the iron absorption and iron stores which did lead to some improvement in hemoglobin levels that was not significant. Also, the studies included two studies in non-anemic women [39, 40] and of the two studies in children, only one by Manoppo et al. [20] had iron deficiency anemia as eligibility. This indicates that the intervention may have differential effects in anemic and non-anemic populations as well as in women and children due to differential physiology, pharmacokinetics, and background inflammatory status. Therefore, there is a need for large-scale studies in iron-deficient women and children to assess the effectiveness of prebiotic and probiotic interventions.

Thus, overall GOS and *Lp299v* appear to be promising interventions for improving iron bioavailability in women. However, there is no substantial evidence to show that these interventions consistently improve ferritin or hemoglobin levels. There is a dearth of large-scale studies assessing the effectiveness of these interventions either alone or with oral iron in the prevention and treatment of anemia in women. Also, studies demonstrating the smallest effective dose of probiotic/prebiotic to offset the adverse effects of iron are needed. In children, the current evidence does not substantiate any benefit of using prebiotics or probiotics either alone or with oral iron to improve iron parameters.

The review had some limitations. It combines all probiotic and prebiotic interventions that have been evaluated in women and children, however, it does not focus on one intervention. This led to significant heterogeneity in meta-analysis results. Also, few studies had a moderate risk of bias. Nonetheless, this provides comprehensive present evidence on the benefits provided by prebiotics and/or probiotics for outcomes related to anemia that can be useful to design future studies in this area. The evidence provided necessitates high-quality large-scale research studies in women of reproductive age where potential benefit of using prebiotics and probiotics has been seen.

Conclusion

There is low to very low certainty of evidence that the use of prebiotics or probiotics (especially *Lp299v* and GOS) can improve iron absorption and lead to some improvement in ferritin levels in women. The current evidence does not conclusively show the benefit of these interventions in improving hemoglobin levels in women and children. Well-designed RCTs with adequate power should be conducted to assess the role of probiotics and prebiotics in the improvement of iron biomarkers in an anemic population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40795-025-01015-3.

Supplementary Material 1.

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Not applicable.

Authors' contributions
AA and AS conceived and designed the analysis. AA, AP, and AS collected the data. AA, AP, RN, and AS contributed data and/or analysis tools. AA and RN performed the analysis. All authors contributed to the writing of the paper.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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