Systematic review on supplementation, fortification, and food-based interventions for prevention of iron deficiency anemia in low- and middle-income countries

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ABSTRACT

Background and Objectives: Prioritizing key preventive and therapeutic interventions are the one of the actions to accelerate the reduction of anemia. This study aimed to examine interventions intended for preventing anemia. **Methods and Study Design:** The systematic search was conducted in PubMed, Web of Science, Scopus, and Cochrane Library. Analysis of publication bias was done using The Joanna-Briggs Institute critical appraisal tool. Data collected from articles included author, year of publication, setting and location of the study, study type, participant of the study, intervention and control given, main outcome, main findings, and risk of bias. **Results:** Three nutrition-specific interventions aimed at preventing iron deficiency anemia in low- and middle-income countries utilized diverse types and dosages of iron. While most studies showed success, some indicated a worsening trend in anemia, even with standard dosages and the same form of iron. Determining effective interventions requires consideration of factors such as other micronutrient composition, compliance rate, availability of educational intervention, and dietary backgrounds in those countries. **Conclusions:** Supplementation, fortification, and food-based interventions generally result in higher hemoglobin levels and lower prevalence of anemia. It is important to consider several factors before deciding on an approach.

Key Words: Iron deficiency anemia, iron, vitamin C, supplementation, fortification

INTRODUCTION

Anemia remains a global public health problem impacting developed and developing countries. Particularly in low- and middle-income countries, iron deficiency anemia (IDA) is the most common anemia.[1,2] Anemia leads to decreased labor productivity in adults and poor cognitive and motor development in children, which impacts the country's economic progress. Many factors contribute to anemia, including inadequate dietary intake, low nutrient absorption, increased needs during growth and pregnancy, inflammation, and infection.[2-6] Anemia can negatively impact infant development and work productivity of women of reproductive age, including pregnant women.[5,7] Anemia during pregnancy is associated with poor pregnancy and birth outcomes, including preterm birth, low birth weight, and maternal mortality.

In 2019, anemia affected 37% of pregnant women, 30% of women aged 15 to 49 years, and 40% of children aged between 6 months and 5 years. At least 1.92 billion people worldwide were anemic in 2021 with western and central sub-Saharan Africa and South Asia having the

most cases.[8] Therefore, various efforts must be made to reduce anemia rates worldwide to achieve the target of reducing anemia in women of childbearing age by 50% by 2025.[4,9]

The World Health Organization (WHO) recommends five action areas to accelerate the reduction of anemia, one of which is prioritizing key preventive and therapeutic interventions. Increasing consumption of certain micronutrients, particularly iron, folate, vitamin B12, vitamin A, and riboflavin, as well as other micronutrients, through food diversification, food fortification, and supplementation is one way to reduce the prevalence of anemia. It is estimated that for every US$1 invested in interventions aimed at reducing anemia in women, such as iron and folic acid (IFA) supplementation for both pregnant and non-pregnant women, preventive treatment for malaria in pregnancy, and iron fortification of cereals, there is an economic return of US$12.[10,11]

Iron and folic acid supplementation greatly benefits iron-deficient women,[12] and is increasingly combined in various micronutrient formulations.[13] Several studies have shown the positive impact of iron supplementation and fortification on iron status.[14] Some studies have also reported adverse events such as increased risk of illness (e.g. diarrhea or inflammation of the gastrointestinal tract), reduced growth, or effects on child development.[15,16] Food-based approaches have the potential to be a simple and sustainable method to prevent and treat not only IDA, but also malnutrition. However, improving food quality and promoting behavior change may take long time.[17]

Iron enhancers and inhibitors influence the success of interventions to prevent iron deficiency anemia. Therefore, it is necessary to pay attention to what micronutrients need to be added or consumed together to increase iron absorption, for example by adding vitamin C.[18] Health educators must also understand micronutrient content, dietary differences, cultural practices, food processing and preparation methods and economic constraints when educating the public.[17,19] In this systematic review, some interventions intended for preventing anemia are discussed.

MATERIALS AND METHODS

Study design and research sample

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and has been registered on the Prospective Register of Systematic Reviews (PROSPERO) database with registered number CRD42023479171. This review included articles published from 2018-2023, which were carried out from four databases: PubMed, Scopus, Web of Science, and Cochrane. The

research is focused on studies about preventing anemia in pregnant women and children using supplementation and fortification of iron and vitamin C.

Research query

We searched on the databases with the following query “children under 5” OR “children under 2” OR “pregnant*” AND “fortification” OR “supplementation” OR “vitamin C” OR “deworming” OR “digital screening” AND “anaemia” OR “anemia” OR “anaemic” OR “anemic” OR “low haemoglobin” OR “iron status”.

Data collection procedures

Article was selected based on population-intervention-comparison-outcome-study design (PICOS): (1) Population: pregnant women and children under 5 in low- and middle-income countries; (2) Intervention: iron and vitamin C fortification or supplementation; (3) Comparison/control: government recommendation or active placebo; (4) Outcomes: anemia prevalence and/or incidence, hemoglobin (Hb) level, and ferritin; (5) Study design: the studies must be experimental studies with RCTs or quasi-experimental studies.

The studies also had to be published between 2018-2023 to obtain research novelties. To meet the study objective and research strategy, we only included articles that investigated the effect of iron and vitamin C supplementation, fortification, or food-based prevention of anemia in pregnant women and/or children under five. It also looks at the amount of iron content of what is given. Table 1 presents iron recommendations and its form for pregnant women and children.

On the other hand, studies were excluded if they were articles reviewed, proceedings, or protocols. Studies with subjects that had comorbidities (except for tuberculosis and worming) were conducted in high-income countries were also excluded. In addition, articles that had no full text and non-English language were excluded as well. The data collection process can be seen in Figure 1.

Data extraction

Articles that meet the requirements were then extracted based on a predetermined table to obtain the following information: identity, countries, setting, study type, participant (sample size and criteria), intervention (intervention type, frequency, and duration), intervention specifics, comparison, main outcomes (outcomes and measurement), main findings, and risk

of bias. SH, AS, MH, GR, YNR, and MA separately carried out this process by reading the articles' full text. The data extraction can be seen in Table 2.

Data management

The article titles and abstract were screened by SH, AS, MH, GR, YNR, and MA by searching to determine suitability with the predetermined inclusion criteria and excluding duplicated and unrelated articles. This process used EndNote software to manage the articles. The review process was expanded to articles with titles and abstracts that matched the inclusion criteria to view the full text of the article. The entire article selection process was shown in the PRISMA flow chart for systematic review.[24] The data that met the criteria was displayed in a matrix to identify the effect of iron or vitamin C supplementation or fortification on pregnant women and children under five.

Quality assessment

The risk of bias from the article was evaluated by GR, YNR, and MA using The Joanna Briggs Institute (JBI) critical appraisal tools for RCTs,[25] and for Quasi-Experimental Studies,[26] and any discrepancy was addressed through discussion. Articles were classified into three categories: (1) low risk of bias (the RCT article had 10-13 "Yes" answers or 7-9 in quasi-experimental studies); (2) medium risk of bias (the RCT article had 7-9 "Yes" answers or 5-6 in quasi-experimental studies); (3) high risk of bias (the RCT article had 0-6 "Yes" answers or 0-4 in quasi-experimental studies).

RESULTS

Characteristics of studies

This study retrieved 3961, with 859 from PubMed, 849 from Web of Science, 1530 from Scopus, and 723 from Cochrane Library. After deletion of the duplicates in EndNote, 2302 articles were screened by title and abstract, which resulted in 183 articles screened for full-text review. The 156 articles were assessed according to the inclusion and exclusion criteria. Finally, 17 studies were eligible for inclusion in this review. A detailed description of the selected articles is reported in Table 2.

All studies included were conducted across low- and middle-income countries. Three studies were conducted on India,[33,38,43] two studies on Ghana,[35,42] and one study each in Gambia,[27] Thailand,[29] Uganda,[30] Malawi,[31] Bangladesh,[32] Tanzania,[34] Republic of Congo,[28] Palestine,[36] Mexico,[39] Brazil,[40] Mali,[41] and Guinea-Bissau.[37] This systematic review included

sixteen RCTs,[27,29-43] and one quasi-experimental study.[28] A total of six studies had pregnant women as their subjects,[27,30-33] nine studies had children under five as their subjects,[28,36-43] and two studies observed pregnant women and continued to track their children until they reached the age of 6-18 months as its subject.[34,35]

Three types of interventions were identified based on the approaches: supplementation intervention in eleven studies,[27-36] fortification intervention in five studies,[38-42] and food-based intervention in one study.[43] Meanwhile, no experimental research was found that discussed preventive interventions for anemia using screening. The results of the articles' quality assessment using JBI critical appraisal tools in this review (Table 3) showed that seven had a low risk of bias[32,36-38,40,42] and ten had a medium risk of bias.[27-30,32-35,39,43]

Outcomes measurement

Among all seventeen studies, there were various identified outcomes. Identified biochemical markers of iron status outcomes include Hb level,[28-43] serum ferritin level,[27,29,32,33,39,40,42,43] serum transferrin level,[29,43] and soluble transferrin receptor level.[31,32,40,43] Other observed outcomes were the prevalence of anemia,[27,36,38,39] and compliance with the intervention.[27-30,33,38]

Supplementation intervention

A Total of eleven studies examined the effect of supplementation intervention. The types of supplementations provided for pregnant women include IFA; multi-micronutrient supplementation (MMN) and lipid-based nutrition supplementation (LNS). The iron in these supplements comes in several forms, including ferrous sulfate, ferrous fumarate, and ferrous bisglycinate.

Srivastava et al.[33] conducted a study comparing the effects of an IFA fumarate capsule and an IFA sulfate tablet, both containing 100 mg elemental iron and 500 mcg folic acid. Pregnant women receiving daily IFA fumarate capsules for three months had a greater change in Hb than those who received IFA sulfate tablets (0.79 vs 0.44 mg/dL, respectively) (Figure 2). The proportion of women with good compliance (>90%) at the end of 3 months was 16.8% in the IFA sulfate group and 22.0% in the IFA fumarate group.

A study by Byamugisha, et al.30 compared IFA with two types of packaging: blister and loose package. The proportion of women with 100% adherence was higher in the blister package group compared with the loose package group. After two months, pregnant women

who received daily IFA in blister packaging showed a higher change in Hb than those who received IFA in loose packaging (0.6 vs 0.2 g/dL, respectively) (Figure 2).

Matias et al.32 compared the effect of daily Lipid-based Nutrient Supplements for Pregnant and Lactating women (LNS-PL) containing 20 mg of iron to daily IFA containing 60 mg of iron and 400 mcg of folic acid in pregnant women. Both groups had a decrease in Hb, but the decrease was smaller in pregnant women who received IFA. A study by Jorgensen et al.[31] compared the effects of MMN, LNS, and IFA on Hb levels in pregnant women. IFA contained 60 mg of elemental iron and folic acid, while MMN and LNS contained 20 mg of elemental iron and 17 other micronutrients. The results showed that after 5 months of intervention, the groups receiving MMN and LNS had a decrease in Hb, while the group given IFA had a slight increase in Hb (0.14 g/dL) (Figure 2).

A study by Bumrungpert et al.[29] compared iron supplementation in the form of ferrous fumarate (containing 66 mg elemental iron and multivitamin) vs ferrous bisglycinate (containing 24 mg elemental iron with folinic acid and multivitamins) for pregnant women. After 6 months of intervention, the ferrous bisglycinate group showed a higher change in Hb compared with the ferrous fumarate group (2.78 vs 1.92 g/dL) (Figure 2).

Bah et al.[27] conducted experimental research on pregnant women aged 14-22 weeks. The intervention consisted of administering multiple micronutrient capsules daily for 12 weeks, given in three ways: (1) according to WHO standards (60 mg ferrous fumarate); (2) using a 60 mg iron hepcidin-guided screen-and-treat approach; (3) using a 30 mg iron hepcidin-guided screen-and-treat approach. The results showed that after 12 weeks of intervention, a reduction in anemia prevalence occurred only in the group receiving the WHO standard intervention (from 58% to 45%). Meanwhile, a decrease in the prevalence of IDA was found in the group that received the WHO standard intervention (from 39% to 17%) and in the 60 mg iron with screen-and-treat approach group (from 40% to 29%).

The study of Adu-Afarwuah et al.[35] compared the Hb and iron status of children born to women enrolled in the International Lipid-based Nutrient Supplements (iLiNS) Project. Supplementation provided to pregnant women was IFA, MMN, or small-quantity lipid-based nutrient supplements (SQ LNS) during pregnancy until six months postpartum. From 6-18 months of age, infants born to women in the IFA and MMN groups didn't receive any micronutrient supplementation. Meanwhile, women in the LNS group were asked to consume SQ LNS designed for infants. At 6 and 18 months of age, the Hb concentration of infants was measured. The results showed that in the IFA group, the Hb concentration decreased from 11.4 g/dL at six months of age to 11.2 g/dL at 18 months of age. In the LNS group, the Hb

concentration also decreased from 11.4 g/dL at 6 months of age to 11.3 at 18 months of age. While in the MMN group, the Hb concentration remained at 11.2 g/dL at both 6 and 18 months of age. Meanwhile, at 6 to 18 months of age, the IFA, MMN, and LNS groups showed an increase in anemia prevalence of 10.5%, 7.1%, and 5.2%, respectively. In the IDA indicator, the IFA and MMN groups showed an increase in IDA prevalence of 5.4% and 1.8%, respectively, while the LNS group showed a decrease of 1.6%.

A similar study was conducted by Wang et al.[34] This study provided multiple-micronutrient supplements as an intervention or placebo as a control to pregnant women from 12-27 weeks of gestation until 6 weeks postpartum. At 6 weeks to 18 months postpartum, participants were randomized again to receive multiple-micronutrient supplementation (MMS) or placebo. From birth to less than 18 months of age, the Hb concentration of the children was measured. Prenatal MMS led to a decrease in Hb at 6 months of age but slightly increased at 12 months of age. Meanwhile, postnatal MMS showed a slightly greater increase than prenatal MMS at 12 months of age.

Several studies gave standard micronutrient supplements (NMS) combined with multi-micronutrient powder (MNP)[36] or SQ LNS28 for children in the intervention group. Some studies also used supplementation as an intervention for control groups. The types used include NMS only,[36] multi-micronutrient syrup,[39] and iron-folic acid supplementation.[28,40]

Addo et al.[28] compared the use of SQ LNS with IFA in children aged 6–12 months. The control group received standard care, including IFA supplementation, antimalarial medication, and counseling, while the intervention group received an enhanced program, which included three additional components: daily SQ LNS, a nutrition education campaign, and reinforcement of the community health worker's role. After ≥3 months, the results showed a decrease in Hb and an increase in the prevalence of anemia in both the intervention and control groups. However, there was an increase in ferritin and a decrease in the prevalence of iron deficiency (serum ferritin ≤12 mcgl/L) in both groups after intervention.

The study by Albelbeisi et al.[36] compared the effectiveness of MNP + NMS with NMS only in 6-month-old children.[36] The NMS was a component of the national nutrition supplementation program in the Gaza Strip that contained 2 mg/kg/day of iron sulfate, 2 drops annually for children aged 6 months and above. This program also administered one capsule containing 200-600 µg of vitamin A every 6 months, and two drops containing 10 µg of vitamin D daily for 30 days every 3 months for children aged 9 months and above, meanwhile MNP was multi-micronutrient powder containing 400 mcg of vitamin A, 30 mg vitamin C, 5 µg vitamin D, 90 µg folic acid, 10 mg iron and other micronutrient such as vitamin B1,

vitamin B2, vitamin B6, vitamin B12, vitamin E, niacin, zinc, copper, selenium, and iodine. The intervention group received 3 sachets of MNP every week for 12 months. The results showed that both groups experienced a decrease in average Hb at the end of the study. However, the decrease was smaller in the MNP + NMS group compared to the NMS-only group (Figure 3). The MNP + NMS group was able to maintain its average Hb level within normal limits (11.92 g/dL), whereas the NMS-only group observed a drop in Hb below normal (10.92 g/dL) (Figure 3).

Fortification intervention

Total five studies examined the effect of fortification intervention on children. Study of Black et al.,[38] Garcia-Guerra et al.,[39] Machado et al.,40 and Somassè et al.[41] showed Hb gain in groups with MNP intervention. These studies also reported a decrease in the prevalence of anemia in the group that used MNP as an intervention. Meanwhile, a study of Tchum et al.[42] showed that MNP intervention using either iron or no iron both reduce Hb concentration. However, the reduction in the iron group was slightly lower than in the non-iron group.

The the highest increase in Hb was found in Black et al.[38] at 1.2 g/dL within eight months after MNP intervention containing iron (encapsulated ferrous fumarate), zinc, folic acid, vitamin A, vitamin C, vitamin B12, and riboflavin (Figure 3). Black et al.[38] study also found that MNP intervention resulted in the greatest reduction in anemia prevalence, at 36% (Figure 4). In the study of Machado et al.,[40] the MNP intervention (contained retinol acetate, cholecalciferol, alpha-tocopherol acetate, ascorbic acid, thiamine nitrate, riboflavin, and pyridoxine hydrochloride, niacinamide, cyanocobalamin, folic acid, encapsulated ferrous fumarate, zinc gluconate, copper gluconate, sodium selenium and potassium iodide) also showed a considerable increase in Hb in a shorter period of time which was 0.86 g/dL within four months. Further, the study of Garcia-Guerra et al.,[39] Machado et al.,[40] and Black et al.[38] revealed success in achieving normal Hb levels (reference value = 11 g/dL) at the endline with intervention using MNP, micronutrient syrup, Ferrous Sulfate Folic Acid, and Placebo Riboflavin. The highest Hb value was found in the fortification using Ferrous Sulfate Folic Acid in the study of Machado et al.[40] (Figure 3).

Furthermore, in the case of Ferritin values as one of the indicators in IDA, study of Garcia-Guerra et al.,[39] Machado et al.,[40] Tchum et al.,[42] and Black et al.[38] showed the increase of Ferritin in groups with MNP intervention (Figure 3). Furthermore, the greatest change in Ferritin was found in fortification using MNP in the study of Tchum et al.[42] at 102.75 µg/L.

Food-based intervention

One study examined the effect of food-based intervention. The intervention provided included vitamin C-rich fruit along with a cereal and pulse-based SNP (Supplementary Nutrition Program) meal. Roy Choudhury, et al.[43] showed that a cereal and pulse-based SNP meal with guava increased Hb levels and serum ferritin after 140 days of intervention.

DISCUSSION

The World Health Organization suggests that there are effective interventions to prevent and treat IDA. These interventions focus on addressing causal and risk factors by increasing consumption of specific micronutrients such as iron, folate, vitamin B12, vitamin A, and riboflavin as well as other micronutrients that can be obtained from food diversification, fortification, and supplementation.[2]

The types of iron used in the studies reviewed were ferrous sulfate, ferrous fumarate, and ferrous bisglycinate. Among the three types of iron, ferrous bisglycinate is one type of iron that has good efficacy.[29] It has lower gastrointestinal side effects and higher bioavailability than conventional iron salts such as ferrous sulfate and ferrous fumarate, and the absorption is not affected by phytate.[44,45] However, ferrous bisglycinate is the most expensive type of iron salt when compared to ferrous fumarate.[44]

Ferrous fumarate is the most cost-effective type of iron salts. In addition, this type of iron salt has equivalent efficacy to ferrous bisglycinate in increasing Hb. Ferrous fumarate is also known to produce a more significant increase in ferritin than ferrous bisglycinate. However, side effects are more common in ferrous fumarate[44] so it needs to be considered when given as an anemia-prevention intervention in pregnant women and children.

The studies examined in this review used different doses. All intervention groups that used the standard IFA showed better outcomes than the comparison. In research conducted by Bumrungpert and colleagues in 2022, the intervention group was administered ferrous bisglycinate with 24 mg of iron and ferrous fumarate with 66 mg of iron to the control group. On the contrary, the study group that received the lower dose had an increase in Hb.[29] This may be due to iron bisglycinate, which has advantages, as explained previously.

In children, the dose of iron given depended on the child's age. In this review, the doses used vary but are still within the recommended range for both iron supplementation and fortification in MNP. Another study also showed that fortification with 10 mg iron in MNP significantly affected Hb values and reduced the prevalence of anemia.[46]

However, in this systematic review, only some interventions were effective in raising Hb levels or decreasing the prevalence of anemia in this systematic review. Based on these results, it is crucial to consider several factors to determine an effective intervention to address iron-deficiency anemia.

First is the presence of substances inhibiting or enhancing iron absorption in the supplementation or fortification composition. Most multivitamin formulations contain insufficient iron to treat anemia and may contain other minerals that inhibit iron absorption.[47] Most studies involving children provide MNP with added zinc for growth-related benefits. However, iron and zinc have antagonistic interactions. Zinc competes with iron in obtaining the same receptor sites on intestinal mucosal cells, which can inhibit iron absorption during metabolism.[48] In addition to zinc, calcium is also known to have competitive interactions with iron through the regulation of enterocyte iron transporter proteins, which then reduce iron bioavailability.[18]

On the other hand, there are iron absorption enhancers such as vitamin C and protein.[18] Some of the studies in this review used multi-micronutrient supplements or powders containing around 30-50 mg of vitamin C. Ascorbic acid or vitamin C is known to increase the absorption of iron, especially nonheme iron and also increases the mobilization of iron from storage.[17,49] Vitamin C can create a more acidic environment in the stomach and prevent oxidation of ferrous iron to ferric iron.[50,51] A study by Lauryn et al.[52] showed a better change in Hb levels in women who were given 65 grams of iron with 75 grams of vitamin C than those given iron alone.

Second, compliance can support the effectiveness of the provided intervention. Compliance rates found in articles in this systematic review ranged from 16.8-97%.[27-30,33,38] Adherence to the given intervention is influenced by various factors, including the side effects caused, forgetfulness,[53-55] boredom,[54] an education level,[30] socioeconomic status, ethnicity, occupation, parity,[56] improper storage, low motivation and lack of awareness,[20,54] dietary habits, and improper method of taking supplements.[20] The side effects of taking iron supplements are often in the form of gastrointestinal disorders. Gastrointestinal disorders appear when the dose of ferrous iron given reaches 180-200 mg/day.[45] Therefore, the iron dose should be reduced if gastrointestinal disorders occur.[20]

Third, educational interventions were found to contribute to the effectiveness of intervention programs. The study by Somassè, et al.[41] showed that home fortification of foods (HFF) and group education resulted in increased Hb and reduced anemia prevalence. This finding is in line with the study of Beinner and Lamounier,[57] which stated that education

resulted in behavior change and greater awareness of the importance of fighting iron-deficiency anemia. This study also showed that iron fortification of drinking water and education improved Hb concentrations and reduced the prevalence of iron deficiency and anemia. Besides fortification, education is also known to affect the effectiveness of supplementation programs. Shet et al.[58] stated that children receiving supplements and parental education or counseling from health workers showed Hb increase and adherence to supplement consumption compared to the group that only received standard care. This suggested maternal/caregiver education and counseling increase maternal awareness of a child's anemia, which can optimize adherence and or the effectiveness of iron prescribed for anemia treatment.[59]

Fourth, the background diet of the population. One of the etiologies for IDA is dietary patterns. Therefore, interventions to address anemia need to be concerned about the dietary background of the intended group. None of the 17 articles reviewed examined the subjects' dietary background during the intervention. However, some studies described the possible role of diet in the success of the intervention. For example, Albelbeisi et al.[36] found a decrease in Hb after a 12-month intervention of ferrous fumarate fortification in MNP + NMS. The study explained that infants and children are usually introduced to cereal and plant-based fortified foods. These foods are often low in energy and lack micronutrients with high bioavailability due to phytates.

WHO recommends fortifying vitamins and minerals such as iodine, iron, vitamin A, and folic acid in maize flour, cornmeal, wheat flour, and rice.[60] Besides those already mentioned, one type of food vehicle that can be used for iron fortification to overcome anemia is milk and its products. A review study by Vohra et al.[61] found that iron fortification in milk and milk products can improve iron status in all ages. This will help in reducing the prevalence of anemia. Sazawal et al.[62] provided milk fortified with zinc, iron, selenium, copper, vitamin A, vitamin C, and vitamin E to children 1-4 years old. After 1 year of intervention, the result showed that children who received the fortified milk had an 88% lower risk of IDA. El Menchawy et al.[63] studied schoolchildren by providing iron fortified milk. This intervention resulted in 27% reduction of iron deficiency prevalence. In the last five years, the number of studies examining iron-fortified milk is limited, so none were included in this review. Therefore, if the following study wants to review the effectiveness of iron-fortified milk in preventing anemia, it is recommended that the range of publication years in the inclusion criteria be extended.

Finally, it is essential to consider the consumption patterns of iron in the community before supplementing or fortifying. Public consumption surveys tend to focus on macro nutrition rather than micronutrition, which means that data on whether or not we have IDA is still based on assumptions. Currently, data on iron consumption in communities is limited and is usually only conducted by university researchers. For example, systematic review by Helmyati et al.[64] showed that the coverage of the IFA supplementation program in five provinces in Indonesia was still below 50% with the acceptance of the IFA supplementation program that was in accordance with the standard only ranged from 0-25.2%. This situation is one of the reasons why anemia is still a problem in Indonesia. Therefore, in 2023 the Indonesian government introduced anemia screening regulations as one of the primary health care services for adolescent girls aged 12 and 15 who have not been screened, and for brides-to-be.[65]

Anemia screening is essential for both children and pregnant women. In pregnant women, identifying iron deficiency early before anemia occurs is essential to correct the condition immediately and prevent long-term effects on fetal development.[66] Since majority of all anemia cases are attributable to iron deficiency, screening for IDA in children should be considered, especially nowadays, several instruments for non-invasive and easy-to-use anemia screening have been developed.[59,67]

Unfortunately, in certain area it was thought there is insufficient evidence on the benefits and harms of universal routine screening for both children and pregnant women.[68] This has led to different recommendations regarding anemia screening, as in certain areas worldwide, anemia may not be a public health issue. Some organizations, such as the PrevInfad workgroup, the United Kingdom National Screening Committee, and the United States Preventive Services Task Force, do not recommend universal screening. Instead, PrevInfad and the United States Preventive Services Task Force recommend targeted screening for anemia in specific high-risk populations such as children born prematurely, LBW, those living in low middle income countries in relation to poor sanitation facilities, and those with risky consumption patterns.[69]

Anemia screening aims to determine IDA status which can be measured using Hb, Mean Corpural Volume (MCV), Mean Corpusal Hemoglobin (MCH), and Mean Corpusal Hemoglobin Concentration (MCHC) indicators. Hb indicators can be used to determine the status of IDA in high-prevalence populations. However, Hb cannot be a specific biomarker because its presence is affected by vitamin B12 or folic acid deficiency, genetic disorders, and other chronic diseases. Therefore, it needs to be combined with other biomarker

measurements to be more specific. Serum transferrin receptor and serum ferritin biomarkers represent 85% of iron in the body, so the combination of Hb and serum ferritin measurements can be an alternative to improve sensitivity and specificity in measuring the severity of iron deficiency.[70]

The strengths of the present systematic review include the use of a comprehensive search strategy, the PRISMA in reporting this review, and then the use of JBI as a critical appraisal tool. Another strength of this systematic review is the inclusion of two crucial groups at risk of anemia: pregnant women and children. The review successfully captured a broad range of outcomes, not only Hb levels and anemia prevalence but also serum ferritin levels and birth outcomes in interventions for pregnant women.

Conclusions

This review discusses three types of interventions for the prevention of anemia. Supplementation, fortification, and food-based interventions generally increase Hb levels and reduce anemia prevalence. However, it is not only the type of iron and the dose used that is important in determining the appropriate intervention. This review suggests that the effectiveness of intervention programs can be enhanced by incorporating the existence of enhancers such as animal protein and vitamin C for better iron absorption and ensuring better compliance, appropriate diet, and educational intervention. Future studies are recommended to consider these factors in their intervention for optimal Hb improvement.

The findings of this review must be interpreted carefully since this review has several limitations. For feasibility, it is limited to English language studies, yet studies published in other languages could provide additional insights. Furthermore, because of the heterogeneity of interventions and outcome measurements, meta-analyses were not possible, and all studies were given equal weighting in the narrative synthesis. Several limitations were also identified in the research area. Data regarding the use of food-based intervention and the role of screening in preventing anemia were limited. Most studies on anemia screening were cross-sectional, thus failing to meet the inclusion criteria. Not all studies reported the dietary background of the study population, so the effect on the intervention is unknown.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors report no conflict of interest.

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Table 1. Iron recommendations for pregnant women and children

Subject	Recommendations
Pregnant women as part of antenatal care	30-60 mg/day of elemental iron (equivalent to 150-300 mg ferrous sulfate heptahydrate, 250-500 mg ferrous gluconate, and 90-180 mg ferrous fumarate)[20]
Pregnant women in countries where the prevalence of anemia exceeds 40%	60 mg/day along with 400 µg of folic acid[21]
Children aged 6-23 months	Supplementation 10 – 12.5 mg of elemental iron (equals with 50 – 62.5 mg of ferrous sulfate heptahydrate, 30 – 37.5 mg of ferrous fumarate or 83.3 – 104.2 mg of ferrous gluconate) per day[22]
Children aged 24 – 59 months	Supplementation 30 mg of elemental iron (equals with 150 mg of ferrous sulfate heptahydrate, 90 mg of ferrous fumarate or 250 mg of ferrous gluconate) per day[22]
Children aged 6-23 months and 2 – 4 years	Fortification in MNP 10 – 12.5 elemental iron (12.5 mg elemental iron equals to 37.5 mg ferrous fumarate or 62.5 mg ferrous sulfate)[23]
Children aged 5-12 years	Fortification in MNP 12.5 – 30 mg elemental iron[23]

MNP, Micronutrient Powder

Table 2. General characteristics of studies

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
1. Bah et al.[27] 2019	Community-based (rural areas) in Gambia (Africa)	Three-arm, randomized, double-blind, non-inferiority trial	n = 498 Pregnant women 18-45 years between 14 and 22 weeks of gestation	Multiple micronutrient capsules including iron with hepcidin- guided screen-and- treat approach (1) 60 mg iron screen-and- treat approach. (2) 30 mg iron screen-and- treat approach Duration: 84 days; Frequency: daily
2. Addo et al.[28] 2020	Community-based (intervention group: rural areas, control group: urban areas) in Democratic Republic of Congo (Africa)	Quasi experimental study	n = 2995 Children aged 6-18 months and their mothers or caregivers in two health zones	Small-quantity lipid-based nutrient supplements (SQ LNS) for infants 6-12 months Duration: ≥3 months; Frequency: daily

Control	Main Outcomes (and anemic indicators measurement tools)	Main Findings	Risk of bias
(1) WHO's recommended 60 mg ferrous fumarate regimen (no screen-and- treat approach)	Hemoglobin at Outcomes: Hb at day 84, prevalence of anemia (Hb), iron deficiency (plasma ferritin, CRP), iron-deficiency anemia (Hb, plasma ferritin, CRP). Hemoglobin measurement: Rapid (HemoCue Hb301 analyser, cobas integra)	1. The mean difference in the amount of Hb at day 84 was –2.2 g/L with the 60 mg screen-and-treat approach and –2.7 g/L with the 30 mg screen-and-treat approach. 2. Anemia prevalence: (a)WHO 60 mg ferrous fumarate: dropped from 58% to 45% (b) 60 mg iron screen-and-treat: increased from 52% to 57% (c) 30 mg iron screen-and-treat: increased from 53% to 59% 2. Iron-deficiency anemia prevalence: (a) WHO 60 mg ferrous fumarate: dropped from 39% to 17% (b) 60 mg iron screen-and-treat: dropped from 40% to 29% (c) 30 mg iron screen-and-treat: increased from 37% to 40% 3. Adherence at 3 groups: 86%	Medium
Standard infant young children feeding package	Outcomes: Anemia, iron and vitamin A deficiencies, stunting, wasting, and underweight Hemoglobin measurement: Rapid (HemoCue® 301 hemoglobin system)	1. There was a reduction in anemia prevalence by 11.0% point (95% CI: −18.1, −3.8; $p<0.01$) an increase in hemoglobin by mean +0.26-g/dL (95% CI: 0.04, 0.48; $p=0.02$), but no effect on anthropometry or iron or vitamin A deficiencies. Children who received ≥ 3 months of SQ-LNS had higher Hb (+0.65 g/dL, $p=0.007$). 2. Hemoglobin change (a) SQ LNS: changed from 10.13 to 9.83 g/dL (-0.3 g/dL) (b) Standard package: changed from 11.31 to 10.83 g/dL (-0.48 g/dL) 3. Anemia prevalence (a) SQ-LNS: changed from 64.8% to 72.2 % (+7.4%) (b) Standard package: changed from 32.1% to 48.7% (+16.6%) 4. Compliance rate 74.7%	Medium

BG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
3. Bumrungpert et al.[29] 2022	Hospital-based (antenatal care clinic) in Thailand (Asia)	Simple randomized controlled trial	n = 120 Pregnant women with iron deficiency (20-40 years)	Oral iron as ferrous bisglycinate (equiv. iron 24 mg) in supplement form with folinic acid and multivitamins Duration: 6 months; Frequency: daily
4. Byamugisha et al.[30] 2022	Hospital-based (antenatal clinics) in Uganda (Africa)	Randomized controlled open-label/non blinded trial	n = 952 Pregnant women who receive IFA supplementation in their second trimester up to 28 weeks	Blister packaged iron-folic acid supplementation Duration: 60 days; Frequency: daily

Control	Main Outcomes (and anemic indicators measurement tools)	Main Findings	Risk of bias
Oral iron as ferrous fumarate (equiv. iron 66 mg iron) + multivitamin.	Outcomes: Blood chemistry (hematological, iron status, and inflammatory status). Hemoglobin measurement: Non-rapid (laboratory analysis).	1. Ferrous bisglycinate with folinic acid as a multivitamin nutraceutical format comparatively had better absorption, tolerability, and efficacy and with a lower elemental iron dosage (equiv. iron 24 mg) than standard ferrous fumarate. 2. Hemoglobin change: (a) Ferrous bisglycinate with folinic acid. - Baseline: 10.04 ± 0.83 g/dL. - After 3 months: 12.40 ± 0.68 g/dL (mean change 2.356 ± 0.69). - After 6 months: 12.82 ± 0.66 g/dL (mean change 2.78 ± 0.822). (b) Ferrous fumarate. - Baseline: 10.17 ± 0.77 g/dL. - After 3 months: 11.78 ± 0.72 g/dL (mean change 1.61 ± 0.838). - After 6 months: 12.09 ± 0.60 g/dL (mean change 1.92 ± 0.89). 3. Compliance at intervention vs control: 97% vs 92%.	Medium
Loose packaged iron-folic acid supplementation	Outcomes: Hemoglobin level and adherence Hemoglobin measurement: Non-rapid. CBC analyzer machine model MEK-6500K	1. The mean Hb level at 4 weeks was higher in the blister than in the loose packaging arms (11.9 + 1.1 g/dL and 11.8 ± 1.3 g/dL, respectively; p=0.02), however, similar at week 8 (12.1 ± 1.2 and 12.0 ± 1.3, respectively; p=0.23). 2. Over the 8-week period blister packaging arm had a higher change in hemoglobin level compared to loose package (0.6 ± 1.0 vs 0.2 ± 1.1; difference: 0.4 g/dL (95% CI: 0.24–0.51 g/dL); p=0.001. 3. Adherence at 8 weeks: 51.9% vs 46.8%	Medium

BG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
5. Jorgensen et al.[31] 2018	Mangochi District of rural Malawi (Africa)	Randomized, controlled, outcome assessor-blinded supplementation trial	n = 1391 Mean age 25 years, gestational age <20 week.	1) 20 mg iron plus 17 micronutrients in a capsule (MMN) 2) lipid-based nutrient supplement (LNS) contain the same 18 micronutrients as the MMN + as well as four additional minerals, protein, and fat, and also provided 118 kcal of energy. Duration: from enrollment to delivery. Frequency: daily.

Control	Main Outcomes (and anemic indicators measurement tools)	Main Findings	Risk of bias
1) 60 mg iron and folic acid (IFA);	Outcomes: Hemoglobin, iron status (zinc protoporphyrin (ZPP) and transferrin receptor (sTfR)). Hemoglobin measurement: Rapid (Hb = Hemocue 201+ system).	1. Women in the IFA group had higher Hb at 36 gestational weeks than women in the LNS group and higher iron status than women in both the LNS and MMN. 2. Hb change (a) IFA: increased from 111.3 to 112.7 g/L (b) MMN: decreased from 111.4 to 110.3 g/L (c) LNS: decreased from 111.7 to 110.0 g/L 3. Prevalence of iron deficiency anemia (a) IFA: cut-off 100g/L decreased from 10.7% to 10.0%; cut-off =110 g/L increased from 10.7% to 20.5% (b) MMN: cut-off 100g/L increased from 12.6% to 14.6%; cut-off =110 g/L increased from 12.6% to 28.3% (c) LNS: cut-off 100g/L increased from 12.2% to 15.7%; cut-off =110 g/L increased from 12.2% to 30.1%	Medium

BG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.

Table 2. General characteristics of studies

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
6. Matias et al.[32] 2018	Community-based, in the poorest region of Bangladesh (Asia)	Cluster, randomized effectiveness trial	n = 4011 Pregnant women, gestational age ≤20 weeks	Lipid-based nutrient supplements (LNS) containing 20 mg of iron Duration: during pregnancy and the first month postpartum Frequency: daily during pregnancy and every other day during the first 3 mo postpartum
7. Srivastava et al.[33] 2019	Antenatal clinic of hospital in Faridabad, India (Asia)	Single-blinded, active comparator, simple randomized controlled trial	n = 204 Pregnant women aged ≥18 years with gestational age >12 weeks.	Iron supplementation in capsule formulation (100 mg iron, ferrous fumarate) Duration: 3 months; Frequency: daily

Control	Main Outcomes (and anemic indicators measurement tools)	Main Findings	Risk of bias
Iron and folic acid (IFA) containing 60 mg of iron	Outcomes: Anemia (Hb), iron status (ferritin and serum transferrin), iron deficiency (low ferritin or high serum transferrin), iron deficiency anemia (anemia and iron deficiency) Hemoglobin measurement: Rapid (HemoCue Hb 301 System)	1. Women in the LNS-PL group had lower ferritin (–6.2 µg/L) and higher sTfR concentrations (+0.5 mg/L), and higher risk of ID (OR=1.93) at 36 weeks of gestation but not at 6 mo postpartum. Among infants at 6 mo, there were no group differences except for a lower risk of elevated sTfR (OR=0.61) in the LNS-PL group than in the IFA group. 2. Hb change (a) LNS-PL Mother: changed from 116.2 ± 12.7 to 114.1 (36 weeks gestation) to 122.5 g/L (6mo postpartum). Child: decreased from 116.1 ± 13.0 to 106.9 g/L (6mo of age). (b) IFA Mother: changed from 116.0 ± 13.0 to 115.6 (36 weeks gestation) to 122.2 g/L (6mo postpartum). Child: changed from 115.5 ± 13.0 to 105.6 g/L (6mo of age).	Medium
Iron supplementation in tablet formulation (100 mg iron, ferrous sulfate)	Outcomes: Compliance to oral iron supplementation, change in mean Hb and serum ferritin level Hemoglobin measurement: Rapid (HemoCue Hb 301)	1. Proportion of women with good compliance (>90%) at the end of 3 months was 16% in control and 22% in the intervention arm, the difference was statistically not significant. 2. Mean change in Hb levels for the intervention arm was 0.79 (±1.21) g/dL while the control arm was 0.44 (±1.50) g/dL, which was statistically not significant (p=0.11). 3. The mean serum ferritin level decreased by 0.80 (19.2) ng/mL in the intervention arm and 1.14 (30.8) ng/mL in the control arm, among pregnant women who completed the trial. The difference between the two arms was not statistically significant (p=0.93).	Medium

BG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
8. Wang et al.[34] 2022	Antenatal clinics in Dares Salaam, Tanzania (Africa)	Randomized, double-blind, Placebo-controlled trial	n= 8428 Mean age= 25 years. Gestational age= 12-27 weeks.	Multiple-micronutrient supplementation (20mg of vitamin B-1 (thiamine), 20mg of vitamin B-2 (riboflavin), 100mg of vitamin B-3 (niacin), 25mg of vitamin B-6 (pyridoxine), 0.8mg of folic acid, 50lg of vitamin B12 (cobalamin), 500mg of vitamin C and 30mg of vitamin E) Frequency: daily

Control	Main Outcomes (and anemic indicators measurement tools)	Main Findings	Risk of bias
Placebo (IFA)	Outcomes: Child-growth and nutrition outcomes (weight, length, head circumference, arm-circumference, and hemoglobin concentrations) and child-morbidity outcomes (diarrhea, cough, fever, and common cold) Hemoglobin measurement: Non rapid (laboratory analysis)	1. Prenatal MMS slightly increases WAZ and LAZ during the first six months of life. 2. There's no effect of prenatal and postnatal MMS on Hb concentration. 3. Hb concentration: (a) MMS Prenatal: - At birth: 13.9 g/dL - 6 months of age: 10.1 g/dL - 12 months of age: 10.3 g/dL Postnatal: - At birth: 14.1 g/dL - 6 months of age: 10.5 g/dL - 12 months of age: 11.3 g/dL (b) IFA Prenatal - At birth: 14 g/dL - 6 months of age: 10.2 g/dL - 12 months of age: 10.2 g/dL Postnatal: - At birth: 14.1 g/dL - 6 months of age: 10.5 g/dL - 12 months of age: 11.4 g/dL	Low

BG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
9. Adu-Afarwuah et al.[35] 2019	Community-based (semi-urban areas) in Ghana (Africa)	Partially double-blind, individually randomized controlled trial	n = 1057. Women ≥18 years from ≤20 week pregnancy until their children aged 6-18 months	Intervention: (1) 18 micronutrients including 20-mg Fe (MMN) one capsul/d during pregnancy until 6 months postpartum (2) Small-quantity lipid-based nutrient supplements (SQ LNS, 118 kcal/d) with the same micronutrient levels as in MMN daily during pregnancy until 6 months postpartum + SQ LNS for infants Duration: during pregnancy until delivery or 6 months post-partum for mothers, and from 6-18 months for infants Frequency: daily

Control	Main Outcomes (and anemic indicators measurement tools)	Main Findings	Risk of bias
60mg Fe+400-μgfolic acid (IFA) one capsule/d during pregnancy	Outcomes: Hemoglobin (Hb, g/L) and iron status (zinc protoporphyrin, ZPP, μmol/mol heme) Hemoglobin measurement: Rapid (HemoCue Hb301; Hemocue AG)	1. At 18 months of age, ZPP was lower in the SQLNS group than the IFA, but not the MMN group. Further, the SQLNS group had a lower prevalence of elevated ZPP compared to IFA and MMN combined, and marginally lower prevalence of anemia (38.7% compared with 44.9%; p=0.06). 2. Hb change (a) IFA - At 6 mo of age: 114 g/L - At 18 mo of age: 112 g/L (b) MMN - At 6 mo of age: 112 g/L - At 18 mo of age: 112 g/L (c) LNS - At 6 mo of age: 114 g/L - At 18 mo of age: 113 g/L 3. Anemia prevalence (a) IFA - At 6 mo of age: 33.4% - At 18 mo of age: 43.9% (b) MMN - At 6 mo of age: 38.8% - At 18 mo of age: 45.9% (c) LNS - At 6 mo of age: 33.5% - At 18 mo of age: 38.7%	Medium

BG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Supplementation				
10. Albelbeisi et al.[36] 2020	Community setting in Gaza Strip, Palestine (Asia)	Two-arm parallel-group randomized controlled trial	n = 200 6 months-old infants	Micronutrient Powder Supplementation (MNP) + National Micronutrient Supplement (NMS) Duration: 12 months, 15 months
11. Roberts et al.[37] 2020	Community-based (villages) in Guinea-Bissau (Africa)	Cluster randomized controlled trial	n = 433 Children younger than 4 years of age	(1) NEWSUP: Supervised isocaloric servings of food supplement high in plant polyphenols and omega 3 fatty acids and protein Duration: 23 weeks, five mornings each week

Control	Main Outcomes (and anemic indicators measurement tools)	Main Findings	Risk of bias
National Micronutrient Supplement (NMS) only	Outcomes: Change in weight, Hb concentration, and anemia Hemoglobin measurement: Non rapid (spectrophotometer)	1. Home Fortification of Foods (HFF) with MNP showed a modest change on Hb concentration and significantly reduced the rate of severe anemia 2. Hb change: (a) MNP + NMS From 11.42 ± 0.35 to 11.13 ± 0.52 to 11.24 ± 0.44 g/dL (b) NMS From 11.44 ± 0.37 to 10.92 ± 0.61 to 10.81 ± 0.59 g/dL	Low
FBF: fortified blended food (corn soy cooked as porridge with fortified vegetable oil, sugar, and salt) Control: traditional rice breakfast (white rice cooked with water, soybean oil and salt)	Outcomes: Hemoglobin (g/dL) Hemoglobin measurement: non rapid (Sysmex KN21)	1. Children in the treatment group had increased hemoglobin concentration compared to those in the control group (0.65 g/dL, 95%CI 0.23-1.07). 2. Hb concentration: - NEWSUP: increased from 10.2 to 10.8 g/dL (mean 10.5) - FBF: increased from 10.1 to 10.7 (mean 10.4) Control: increased from 10.1 to 10.7 (mean 10.4)	Low

BG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Fortification				
1. Black et al.[38] 2021	Community setting in India (Asia)	Cluster-randomized, double-masked, controlled trial	n = 22. Children 29-49 months	Multiple micronutrient powder (MNP) including 13 mg iron (encapsulated ferrous fumarate), 5 mg zinc, 20 µg folic acid, 150 µg vitamin A, 20 mg vitamin C, 0.5 µg vitamin B-12, and 0.5 mg riboflavin Duration: 8 months; Frequency: 6 days per week
2. Garcia-Guerra et al.[39] 2022	Urban areas of southern Mexico from 54 communities assigned to a national program	Cluster randomized trial	n = 988. Children 6-12 months	(1) Micronutrient powder (MNP); or (2) Micronutrient syrup Duration: 4 months, Frequency: 6 days per week.

Control	Main Outcomes (and anemic indicators measurement tools)	Main Findings	Risk of bias
Placebo fortification containing 0.5 mg riboflavin	Outcomes: Child development and anemia biomarker Hemoglobin measurement: Rapid (HemoCor-D)	1. MNP had greater reduction of anemia and iron deficiency compared with placebo (a) MNP Hb: changed from 10.9 ± 0.1 to 12.1 ± 0.1 g/dL Anemia prevalence: changed from 46.7% to 10.1% (b) Placebo riboflavin Hb: changed from 10.9 ± 0.1 to 11.2 ± 0.1 g/dL Anemia prevalence: changed from 49% to 35.5% Adherence: 74.5% (MNP), 73.4% (Placebo)	Low
Fortified food (fortified pap, Nutrisano) containing energy, protein, carbohydrates, lipids, and micronutrients;	Outcomes: Changes in serum zinc, ferritin, soluble transferrin receptor, hemoglobin concentration and their deficiencies. Hemoglobin measurement: rapid (HemoCue B-Hemoglobin device)	1. Zinc concentration increased significantly in all groups with the largest change in the syrup group (+4.4 µmol/L; 95%CI:3.2, 5.5), followed by micronutrient powder (+2.9 µmol/L; 95%CI:2.1, 3.6) and fortified food (+0.9 µmol/L;95%CI:0.3, 1.6). 2. Hemoglobin concentration significantly increased (+5.5 g/L; 2.5, 8.4) Significant reduction in anemia prevalence (44.2% to 26.8%, p<0.01) only in the micronutrient powder group.	Medium

BG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Fortification				
3. Machado et al.[40] 2021	School-setting in Brazil (America)	Open in parallel, cluster-randomized controlled trial	n = 169 Children 6 - 42 months	Group A: Anemia and receiving MNP (60 sachets) + 3.2 mg/kg/day of elemental iron (EI) Ferrous sulfate Group B: Non anemia and receiving MNP Duration: 15 weeks; Frequency: every lunch Monday-Friday
4. Somassè et al.[41] 2018	Community-based (villages in municipalities) in Mali (Africa)	Cluster-randomized controlled trial	n = 722 Children age 6-23 months	Multiple-micronutrient powder Group education on child complementary feeding + Home fortification of foods (HFF) with MNP (containing vitamin A, folic acid, cholecalciferol, iodine, Se, vitamin B12, niacin, Fe, Zn, Cu, thiamin, riboflavin, vitamin C, vitamin B6, vitamin E) Duration: 3 months; Frequency: daily

Control	Main Outcomes (and anemic indicators measurement tools)	Main Findings	Risk of bias
Group C: Anemia and receiving 4.2 mg/kg/day of EI + 50 µg folic acid (FA) Group D: Non anemia and receiving EI (1.4 mg/kg/day) + 50 µg FA.	Outcomes: Hemoglobin, serum ferritin and soluble transferrin Hemoglobin Measurement: Non-rapid (electronic count Syesmex XE-2100)	Iron deficiency and anemia prevention was effective by MNP fortification (a) MNP - Hb: changed from 11.68 ± 0.13 to 12.90 ± 0.11 g/dL - Anemia prevalence: changed from 15.09% to 1.30% (b) Ferrous sulfate + Folic acid - Hb: changed from 11.64 ± 0.14 to 12.53 ± 0.12 g/dL - Anemia prevalence: changed from 11.89% to 1.34%	Low
Group education on child complementary feeding only	Outcomes: Hb change, anemia and children weight Hemoglobin measurement: Rapid (Hemocue Hb301)	1. Intervention group (group education + HFF) provided a modest but statistically significant Hb change vs control group (0.50 vs 0.09 g/dL, p=0.023). 2. Prevalence of anemia changed: 91.3–85.8% (p=0.04) in the intervention group vs 88.1–87.5% (p=0.86) in the control group. Proportion of severe anemia was reduced by 84% (from 9.8 to 1.6%) in the intervention group, but increased in the control group (from 8.5 to 10.8%).	Medium

BG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Fortification				
5. Tchum et al.[42] 2021	Community-based (households in compounds) in Ghana (Africa)	Population-based randomized cluster-trial	n = 1958 Children aged 6-35 months	Multiple micronutrient powder (MNP) containing 12.5 mg elemental iron (as ferrous fumarate), vitamin A (400 µg), ascorbic acid (30 mg) and zinc (5 mg), mixed with semi-solid meals Duration: 5 months; Frequency: daily

Control	Main Outcomes (and anemic indicators measurement tools)	Main Findings	Risk of bias
MNP without iron	Outcomes: Hemoglobin, serum ferritin, and soluble transferrin receptor levels; anemia status Hemoglobin measurement: Rapid (HemoCue Hb 201+ analyzer)	1. Intervention group had significantly higher hemoglobin and serum ferritin levels than the placebo group. 2. STfR levels were more saturated among children from the intervention group compared to the control group. 3. Anemia status in the iron group improved compared to the placebo group. 4. Hb change (a) MNP + iron From 10.29 ± 1.26 to 9.65 ± 1.70 g/dL (b) MNP From 10.29 ± 1.27 to 9.31 ± 1.52 g/dL 5. Anemia status (a) MNP + Iron Increased from 36.84% to 55.52% (b) MNP Increased from 35.66% to 62.63%	Low

BG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.

Table 2. General characteristics of studies (cont.)

Author, year	Setting	Study type	Participant (n, inclusion criteria)	Intervention
Food-based intervention				
1. Roy Choudhury et al.[43] 2021	Community-based (pre-schools in villages) in India (Asia)	Three-arm, non blinded, cluster-randomized controlled trial	n = 261 Healthy children of 24-48 months	1) GG: cereal/pulse– based supplementary meal containing 500 kcal and 12–15 g protein + 25 gram of Guava (vitamin-C rich fruit) 2) BG: cereal/pulse– based supplementary meal containing 500 kcal and 12–15 g protein + 25 gram Banana (low vitamin C fruit) Duration: 140 days; Frequency: 6 days per week

Control	Main Outcomes (and anemic indicators measurement tools)	Main Findings	Risk of bias
CG: cereal/pulse– based supplementary meal containing 500 kcal and 12–15 g protein + 25 g Cucumber	Outcomes: Iron status (Hb, serum ferritin, soluble transferrin receptor) and cognitive development Hemoglobin measurement: Non rapid (cyanmethemoglobin31 methods)	1. A cereal/pulse-based meal with guava increased vitamin C content, thereby reducing Iron Deficiency (higher Hb, serum ferritin, vitamin C, and lower soluble TfR) and Acute Respiratory Infection-related morbidity. 2. Hb concentration (a) GG - Baseline: 10.0 ± 0.16 g/dL - Endline: 10.3 ± 0.20 g/dL - Mean change: 0.3 ± 0.11 (b) BG - Baseline: 10.4 ± 0.16 g/dL - Endline: 9.9 ± 0.20 g/dL - Mean change: -0.6 ± 0.11 (c) CG - Baseline: 10.3 ± 0.16 g/dL - Endline:10.0 ± 0.21 g/dL Mean change: -0.4 ± 0.11	Medium

BG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.

Table 3. Critical appraisal summary using the JBI approach

	Bah et al.[27]	Bumrungpert et al.[29]	Byamugisha et al.[30]	Jorgensen et al.[31]	Matias et al.[32]	Srivastava et al.[33]	Wang et al.[34]	Adu-Afarwuah et al.[35]	Albelbeisi et al.[36]
Was true randomization used for assignment of participants to treatment groups?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was allocation to treatment groups concealed?	✓	?	✓	✓	✓	✓	✓	✓	✓
Were treatment groups similar at the baseline?	✓	✓	✓	X	✓	✓	✓	✓	✓
Were participants blind to treatment assignment?	✓	✓	X	X	X	?	✓	X	X
Were those delivering treatment blind to treatment assignment?	✓	?	?	X	?	?	✓	X	?
Were outcomes assessors blind to treatment assignment?	X	✓	?	✓	✓	?	✓	X	?
Were treatment groups treated identically other than the intervention of interest?	X	✓	?	✓	✓	?	✓	X	✓

	Roberts et al.[37]	Black et al.[38]	Garcia-Guerra et al.[39]	Machado et al.[40]	Somasse et al.[41]	Tchumet al.[42]	Roy Choudhury et al.[43]	Addo et al.[28†]
Was true randomization used for assignment of participants to treatment groups?	✓	✓	?	✓	✓	✓	✓	
Was allocation to treatment groups concealed?	✓	✓	X	X	X	✓	X	
Were treatment groups similar at the baseline?	✓	✓	✓	✓	✓	✓	✓	✓
Were participants blind to treatment assignment?	✓	✓	X	X	X	✓	X	
Were those delivering treatment blind to treatment assignment?	✓	✓	X	X	X	✓	X	
Were outcomes assessors blind to treatment assignment?	✓	?	✓	✓	X	?	✓	
Were treatment groups treated identically other than the intervention of interest?	✓	✓	✓	✓	X	✓	✓	

[†]Quasi-Experimental Studies; [‡]Critical Appraisal Using JBI for Quasi-Experimental Studies.

Table 3. Critical appraisal summary using the JBI approach (cont.)

	Bah et al.[27]	Bumrungpert et al.[29]	Byamugisha et al.[30]	Jorgensen et al.[31]	Matias et al.[32]	Srivastava et al.[33]	Wang et al.[34]	Adu-Afarwuah et al.[35]	Albelbeisi et al.[36]
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	✓	X	✓	✓	✓	✓	?	✓	✓
Were participants analyzed in the groups to which they were randomized?	X	✓	✓	X	✓	?	✓	✓	✓
Were outcomes measured in the same way for treatment groups?	✓	✓	✓	✓	✓	?	✓	✓	✓
Were outcomes measured in a reliable way?	?	?	✓	✓	✓	✓	✓	✓	✓
Was appropriate statistical analysis used?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	?	✓	✓	✓	✓	✓	?	✓	✓

	Roberts et al.[37]	Black et al.[38]	Garcia-Guerra et al.[39]	Machado et al.[40]	Somasse et al.[41]	Tchumet al.[42]	Roy Choudhury et al.[43]	Addo et al.[28†]
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	X	✓	?	✓	✓	✓	?	?
Were participants analyzed in the groups to which they were randomized?	✓	✓	✓	✓	✓	✓	✓	
Were outcomes measured in the same way for treatment groups?	✓	✓	✓	✓	✓	✓	✓	✓
Were outcomes measured in a reliable way?	✓	✓	✓	✓	✓	✓	✓	✓
Was appropriate statistical analysis used?	✓	✓	✓	✓	✓	✓	✓	✓
Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	✓	✓	✓	✓	✓	✓	✓	

†Quasi-Experimental Studies; ‡Critical Appraisal Using JBI for Quasi-Experimental Studies.

Table 3. Critical appraisal summary using the JBI approach (cont.)

	Bah et al.[27]	Bumrungpert et al.[29]	Byamugisha et al.[30]	Jorgensen et al.[31]	Matias et al.[32]	Srivastava et al.[33]	Wang et al.[34]	Adu-Afarwuah et al.[35]	Albelbeisi et al.[36]
Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?‡									
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?‡									
Was there a control group?‡									
Were there multiple measurements of the outcome both pre and post the intervention/exposure?‡									

	Roberts et al.[37]	Black et al.[38]	Garcia-Guerra et al.[39]	Machado et al.[40]	Somasse et al.[41]	Tchumet al.[42]	Roy Choudhury et al.[43]	Addo et al.[28†]
Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?‡								✓
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?‡								✓
Was there a control group?‡								✓
Were there multiple measurements of the outcome both pre and post the intervention/exposure?‡								✓

†Quasi-Experimental Studies; ‡Critical Appraisal Using JBI for Quasi-Experimental Studies.

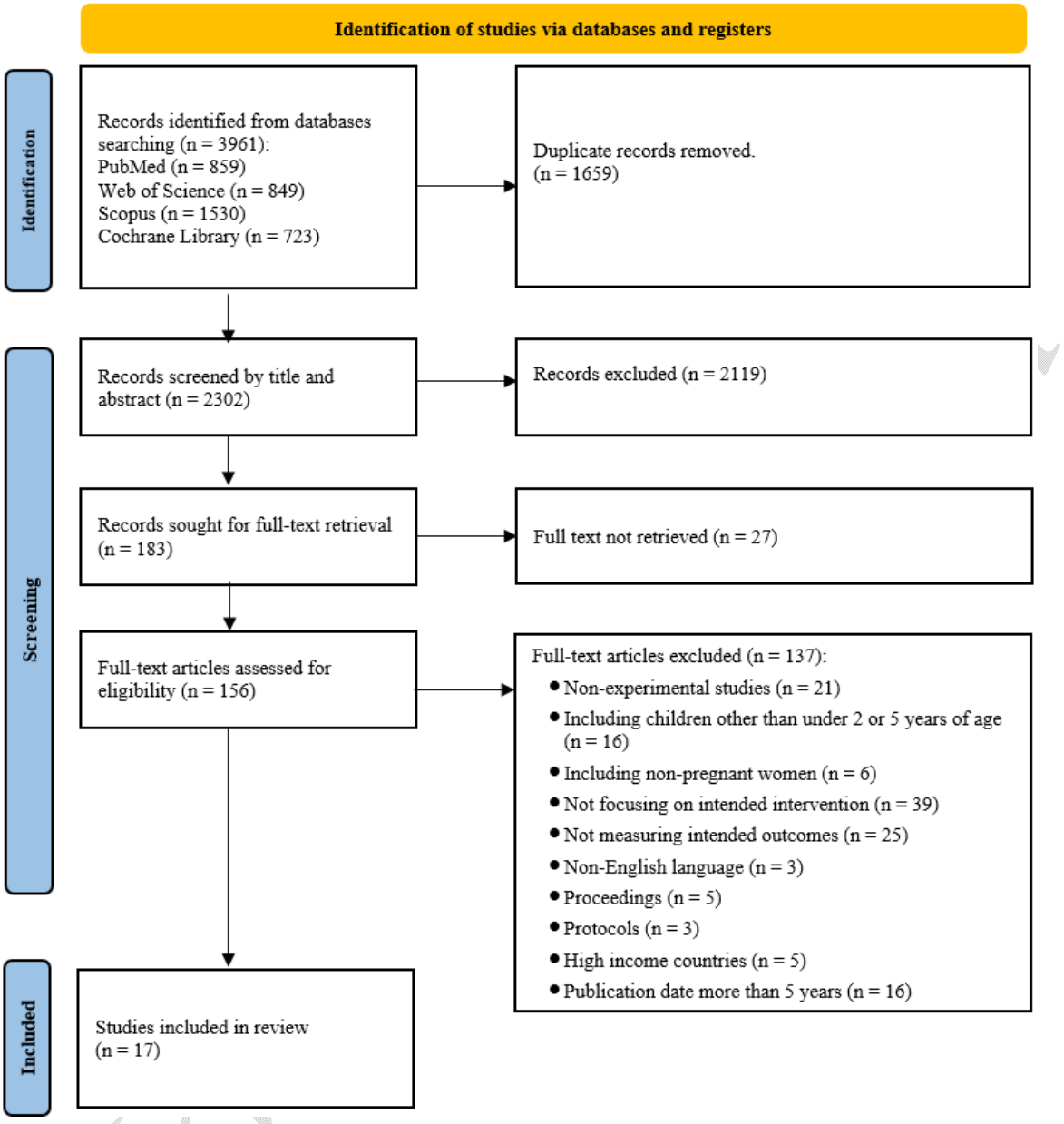


Figure 1. PRISMA systematic review flow diagramBG, Banana Group; CG, Cucumber Group; FBF, Fortified Blended Food; FF, Food Fortification; FS_FA, Ferrous Sulfate Folic Acid; GG, Guava Group; HFF, Home Fortification of Foods; IFA, iron-folic acid; LNS, Lipid based nutrient supplement; LNS-PL, Lipid-based Nutrient Supplements for Pregnant and Lactating women; MMN, Multi Micronutrient; MNP, Micronutrient Powder; NMS, National Micronutrient Supplement; Syrup, Micronutrient syrup; SQLNS, Small-quantity lipid-based nutrient supplements.
aSupplementation
bFortification
cFood-based intervention
*Control group
**Intervention 1 group
***Intervention 2 group

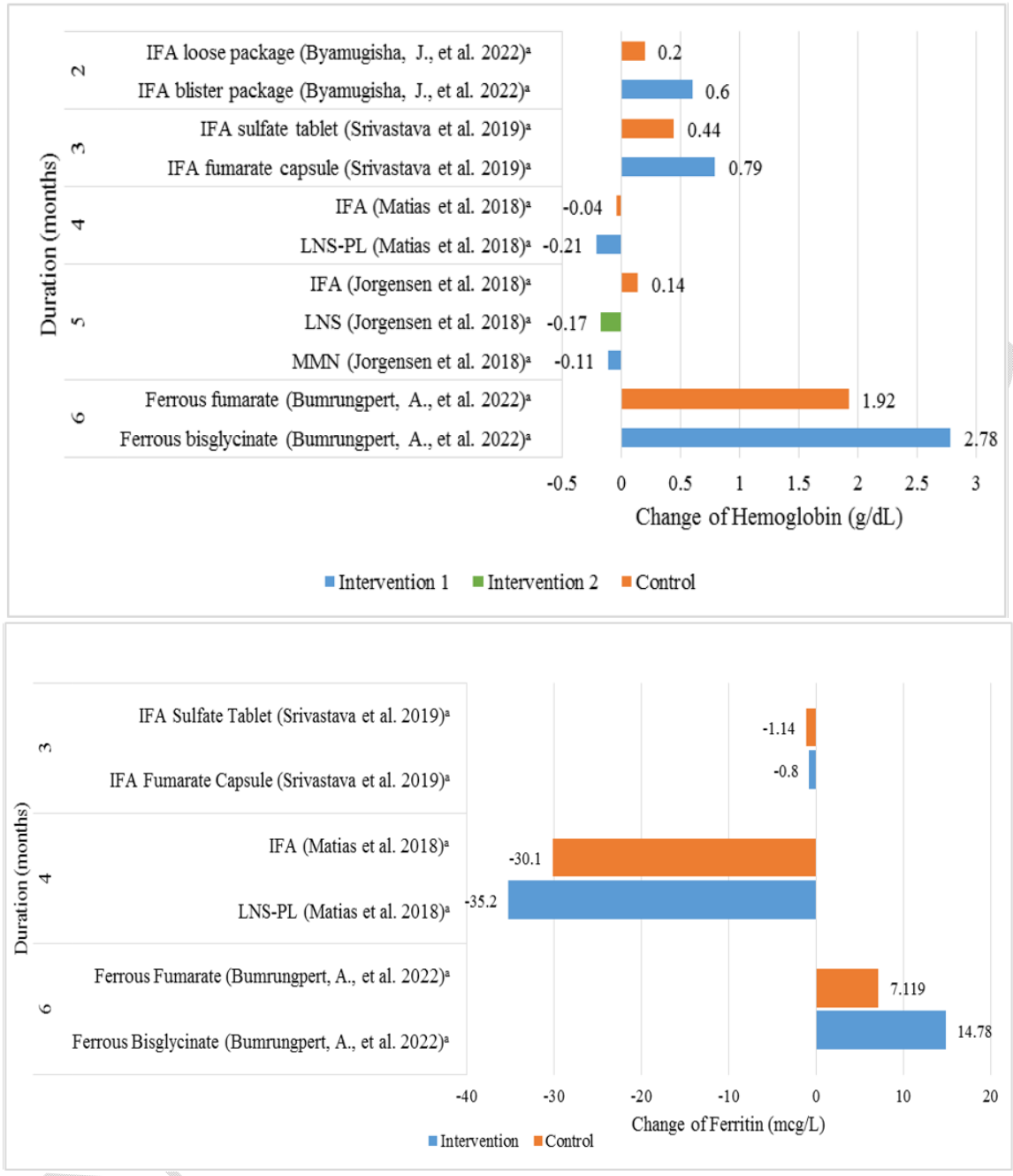
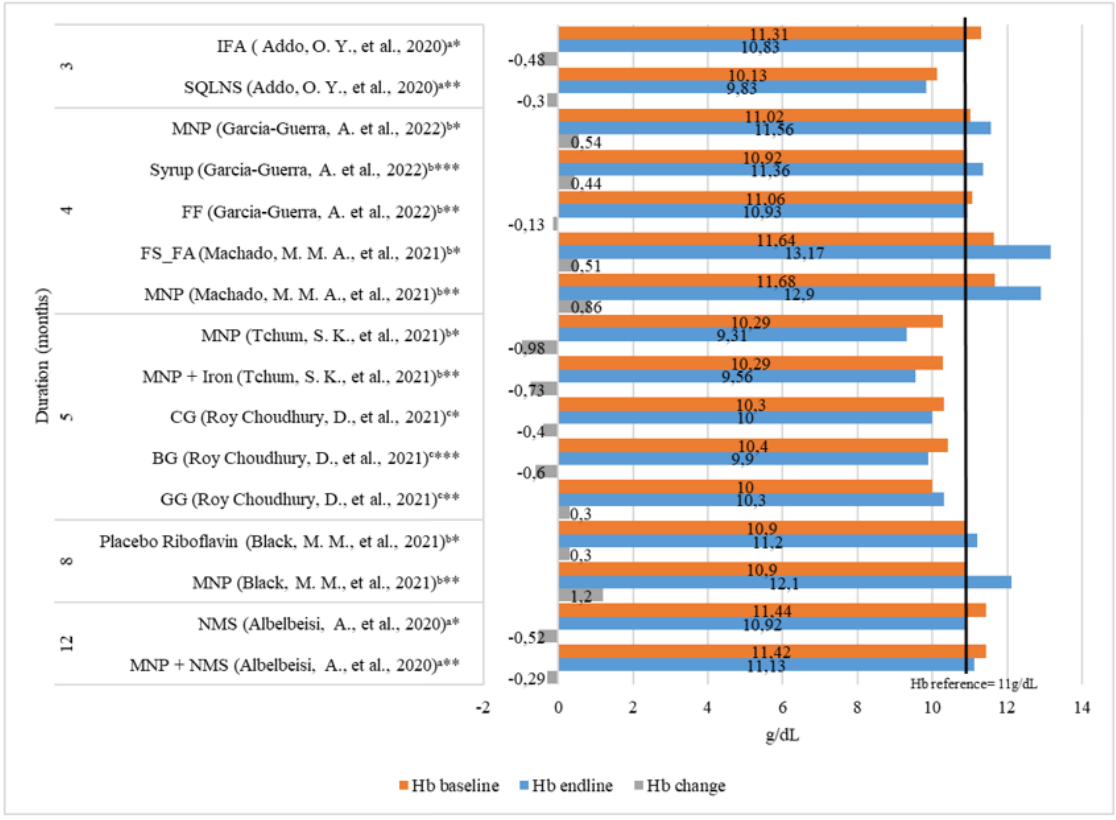


Figure 2. Change of hemoglobin and ferritin in pregnant women



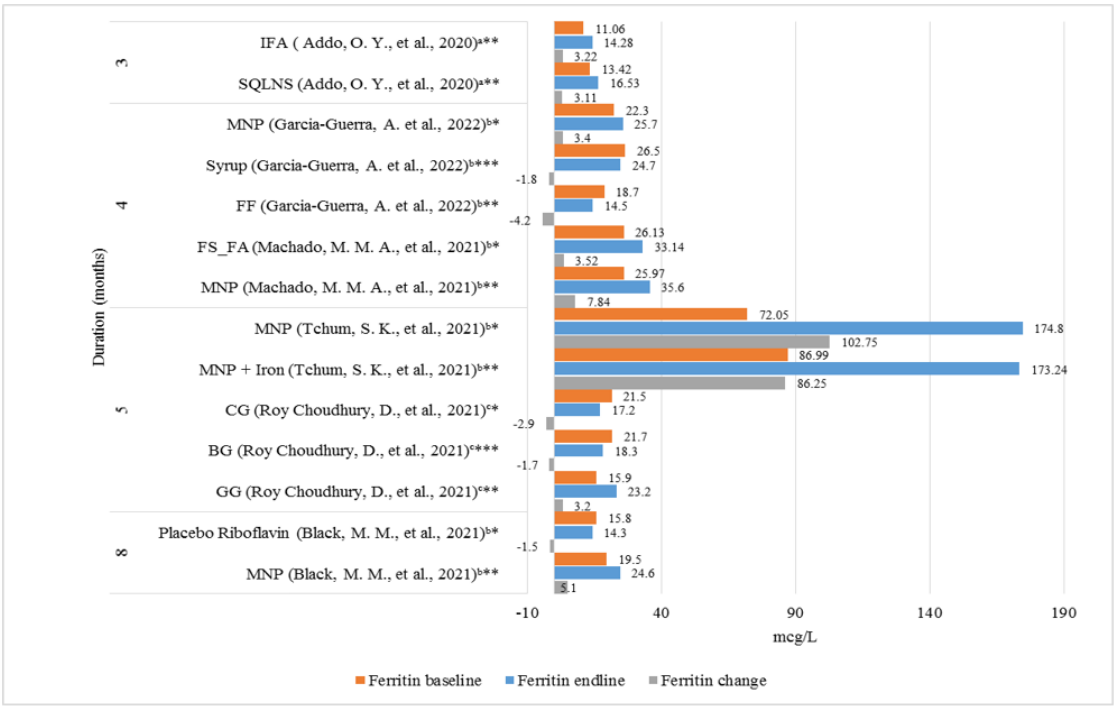


Figure 3. Change of hemoglobin and ferritin in children

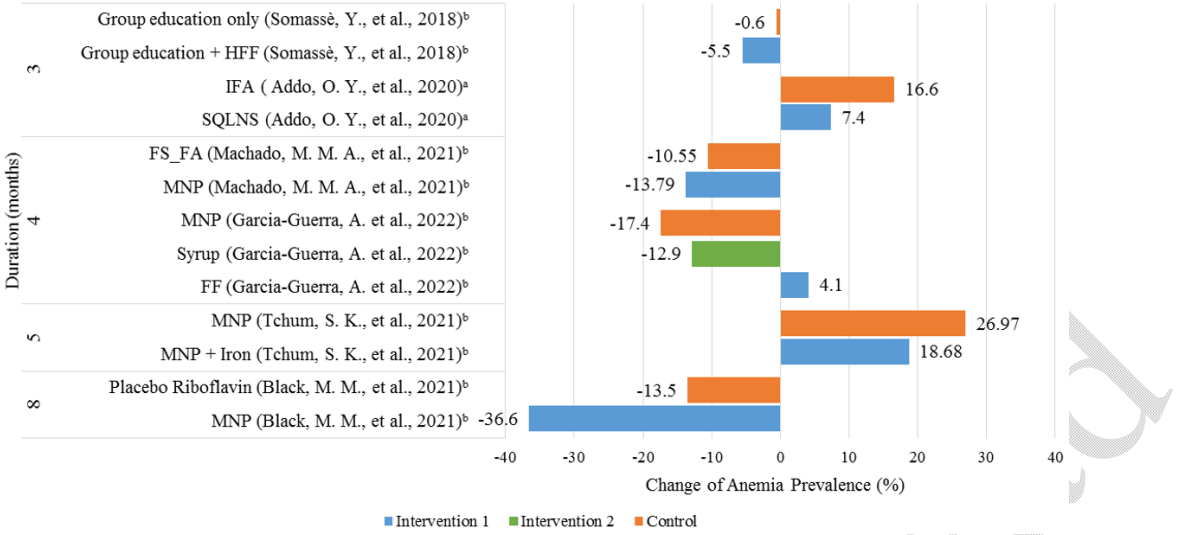
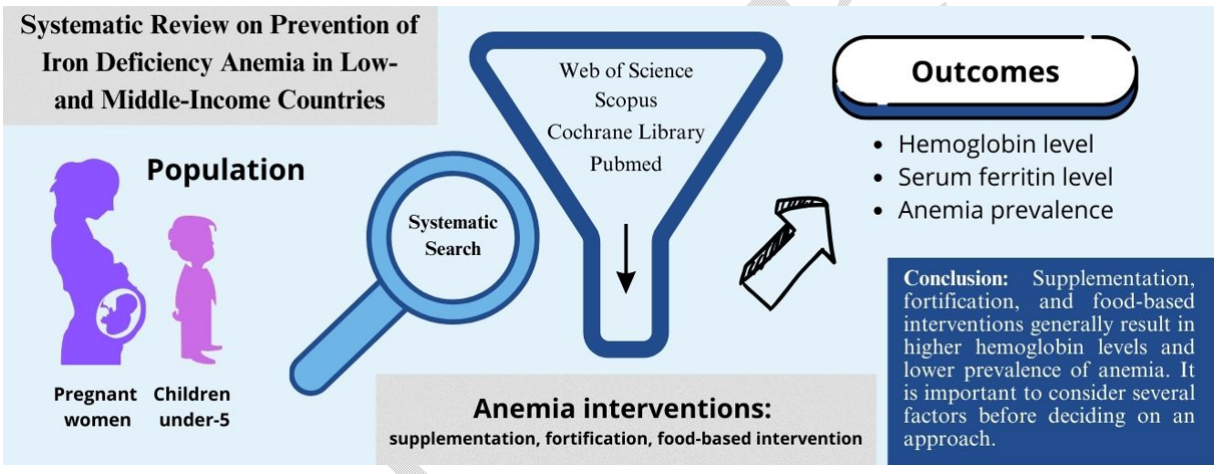


Figure 4. Change of anemia prevalence in children



Graphical abstract.