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*Review*

# Impact of Supplementation on Anemia, Cognition, and Growth in Children: A Scoping Review of Randomized Controlled Trials

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**ABSTRACT**

**Background:** Anemia in children is a global health problem that can affect their cognitive and physical development. Various supplementation interventions have been used to treat anemia, including iron, folic acid, vitamins, and other minerals. Although some studies have shown improvements in anemia status, challenges in adherence to treatment and side effects remain barriers. Objective: This scoping review aims to map the available scientific evidence related to interventions and supplementation in children with anemia. This study identifies the types of interventions used, the target population, and the outcomes reported in the studies. **Methods:** A literature search was conducted through PubMed and Google Scholar with the keywords "anemia," "intervention," "supplement," and "children." Included studies were publications from 2015 to 2024 involving children who received supplementation interventions to see the impact of supplementation on anemia, cognition, and growth in children. Data from relevant studies were collected and analyzed based on study design, type of intervention, and reported outcomes. **Results:** From the analysis of 10 studies, various interventions were found, including iron supplementation, combinations of iron and other micronutrients (folic acid, vitamin A, vitamin C), and food-based interventions. All interventions showed increased hemoglobin levels and improved anemia status, but adherence to treatment remains a challenge, especially in daily regimens. **Conclusion:** Appropriate supplementation interventions effectively reduce the prevalence of anemia in children. However, the management of side effects and the improvement of adherence are aspects that need further attention for long-term success.

**Keywords:** Anemia; supplementation; intervention; children

## 1. INTRODUCTION

Anemia is a major public health problem, particularly affecting young children, pregnant and postpartum women, adolescent girls, and menstruating women. Globally, Anemia is estimated to affect half a billion women aged 15–49 years and 269 million children aged 6–59 months worldwide. In 2019, 30% (539 million) of non-pregnant women and 37% (32 million) of pregnant women aged 15–49 years were anemic.[1] Iron deficiency anemia is the most common form of anemia and occurs frequently in early age groups. This condition impacts physical health and has long-term consequences for children's cognitive and social development.[2,3] Children with anemia are at high risk of growth retardation, attention deficit disorders, and learning difficulties2–4. Therefore, treating anemia in children is very important to ensure optimal development and a better quality of life in the future.

In Indonesia, adolescent anemia is also a serious concern. Basic Health Research 2018 recorded that 26.8% of children aged 5–14 years and 32% of adolescents aged 15–24 years were suffering from anemia.[5] Various factors contribute to this high figure, including inadequate diet, infection, and lack of access to nutritious food6478. In many rural areas, iron deficiency is often caused by a diet low in iron and high rates of worm infections, which can interfere with iron absorption in the body910. Therefore, appropriate interventions for anemia are needed, especially for the most vulnerable children.

Various strategies have been implemented to combat anemia in children, with supplementation of iron, folic acid, vitamin C, and other essential minerals being among the most common minerals1112. Iron supplementation, in particular, remains the primary approach due to its proven ability to boost hemoglobin levels in the blood significantly12,1314. However, this method is not without challenges, as low compliance with daily supplementation often arises from gastrointestinal side effects such as nausea and constipation1516. To address these issues, previous studies have explored alternative strategies, including weekly supplementation schedules1718 and combined micronutrient formulations12. These approaches have shown promise in enhancing adherence to treatment while also improving overall health outcomes in children, highlighting the need for flexible and tailored interventions in managing anemia. Other limitations include the lack of long-term data on the impact of interventions on children’s cognitive development and physical growth, as well as the paucity of studies that consider the influence of local social, economic, and cultural contexts on intervention effectiveness.

This article aims to bridge existing knowledge gaps by systematically mapping scientific evidence on various supplementation interventions, including innovative local food-based approaches and strategies to enhance adherence. It also provides a comprehensive analysis of the challenges encountered during intervention implementation and offers evidence-based recommendations for designing sustainable anemia programs at both local and global levels.

## 2. METHODS

The search was conducted through PubMed and Google Scholar with the keywords ("anemia"[All Fields]) AND ("intervention"[All Fields]) AND ("supplementation"[All Fields]) AND ("children"[All Fields]). Included studies were publications from 2015 to 2024 involving children under 19 years of age with anemia, in which various supplementation interventions were applied. This study is a scoping review to assess interventions and supplementation used to treat anemia in children by applying Tricco and colleagues' methodological framework. The flowchart illustrates the process of articles from search to final selection, following the preferred reporting items for systematic reviews and meta-analyses extended for scoping reviews (PRISMA-ScR).

### *2.1 Identifying the Questions*

The main questions to be answered in this review are: (1) What are the types of interventions implemented to address anemia and their impact on growth cognition in children? (2) What is the impact of these interventions on anemia status, cognitive function, and physical growth? (3) What are the challenges faced in implementing the interventions, especially related to side effects and compliance?

### *2.2 Identifying Relevant Study*

Literature search was conducted through PubMed and Google Scholar databases, using a combination of keywords: ("anemia"[All Fields]) AND ("intervention"[All Fields]) AND ("supplementation"[All Fields]) AND ("children"[All Fields]). A comprehensive search was conducted on full-text accessible academic journals using English language. Inclusion criteria included publications published between 2015 and 2024, involving children receiving interventions to treat anemia. In this search, all included study designs were Randomized Trial.

During study selection, two researchers independently performed the data extraction process, and consensus was obtained for all eligible studies. All reference lists of retrieved articles were manually searched for further eligible studies. Study titles were screened first, followed by abstracts. Key terms used to search for articles are listed in Table 1.

**Table 1.** Key search terms in scoping review

| Database | Search Terms | Filter | Initial records | Final records |
|---|---|---|---|---|
| Pubmed | ("anemia"[All Fields]) AND ("intervention"[All Fields]) AND ("supplementation"[All Fields]) AND ("children"[All Fields]). | Results by year: 2015-2024; Text availability: Free full text; Article type: Randomized controlled trials (RCTs) | 17 | 6 |
| Google Scholar | "anemia" AND "intervention" AND "supplementation" AND "children" | Results by year: 2015-2024; Text availability: Free full text; Article type: Randomized controlled trials (RCTs) | 21 | 4 |

The researchers deliberated and assessed disagreements that emerged throughout the process of selecting studies. The Flow chart of the scoping review is depicted in Figure 1.

### *2.3 Study Selection*

Two reviewers conducted the review in two stages. In the first stage, the literature was screened by title and abstract according to the inclusion and exclusion criteria (Table 2). In the second phase, articles that passed phase one will be reviewed.

The reviewed studies were selected with the information about: 1) Types of interventions used to address anemia and their impact on growth cognition in children; 2) Impact of these interventions on anemia status, cognitive function, and physical growth in children; 3) Challenges faced in implementing the interventions, primarily related to side effects and compliance.

**Table 2.** Inclusion and exclusion criteria form

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Studies involving children under 19 years of age | Studies involving adult populations |
| Studies using supplementation interventions | Studies not reporting supplementation interventions. |
| Study design randomized controlled trials (RCTs) | Observational or non-randomized studies |
| Articles published between 2015 and 2024 | Studies published before 2015 |
| Articles in English | Published in any language except English |
| Available full text | Articles not available in full text |

### *2.4 Charting the Data*

An electronic search utilizing PubMed and Google Scholar was conducted by accessing electronic databases. The articles were subsequently filtered to remove duplicates. The remaining full articles were evaluated for eligibility, using inclusion criteria: (1) Studies involving children under 19 years of age; (2) Studies using supplementation or dietary interventions; (3) Study design randomized controlled trials (RCTs); (4) Articles in English; and (5) Articles published between 2015 and 2024. Studies were excluded if (1) Studies involving adult populations; (2) Studies not reporting supplementation interventions; (3) Observational or non-randomized studies; (4) Articles not available in full text; and (5) Studies published before 2015. We didn't use any quality appraisal tools since the purpose of this review is to review existing evidence to notify future research.

## 3. RESULTS

From the 10 studies analyzed, various types of supplementation interventions and their impact on anemia, cognitive function, and physical growth in children were identified. All studies used randomized controlled trials (RCTs). The characteristics of the selected studies are represented in Table 3, and the study findings from these studies are presented in Table 4.

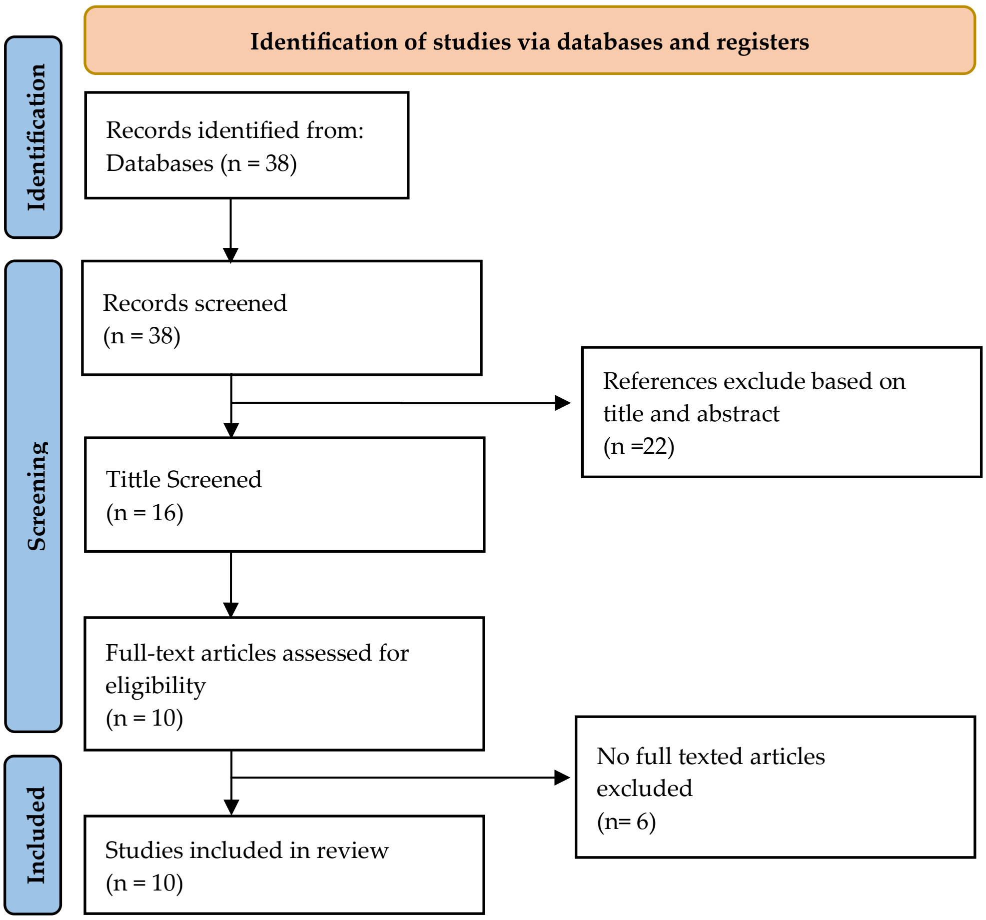


**Figure 1.** Flowchart of scoping review

### *3.1 Types of Interventions Applied to Address Anemia in Children*

The types of interventions used to address anemia problems usually concentrate on iron and other micronutrient supplementation. Micronutrient powder (MNP) containing iron, vitamins A, B1, B6, B12, folic acid, and other nutrients is a common treatment used19. In addition to MNP, oral iron supplementation, such as iron syrup, is given to children to increase hemoglobin levels and reduce the prevalence of anemia, especially in rural China where iron deficiency is high1920.

Food-based interventions, such as providing fortified snacks or iron-rich foods, are available in addition to MNP and iron syrup. The use of the Indian "Sesame Jaggery Ball" is one example21. By using nutrient-rich snacks to provide additional iron intake22, this method is expected to increase iron levels in the body and improve anemia status. Several studies have also looked at a combination of interventions, such as iron supplementation and nutrition education, to improve eating habits at home.

### *3.2 Impact of Intervention on Anemia Status*

Interaction using Micronutrient Powder (MNP) effectively reduces the prevalence of anemia in children. In a study in China, MNP administration reduced the prevalence of anemia by 8% and significantly increased hemoglobin, especially in children who previously had moderate anemia. Increased dietary diversity was also observed in the intervention group; this suggests that the intervention affects children's diets in the medium term19. In addition, consistent iron supplementation improves hemoglobin rate, especially in children with moderate to severe anemia.

Oral iron supplementation has also shown positive effects in addition to MNP. For example, in India, iron-rich foods such as sesame jaggery ball (SJB) increase hemoglobin levels higher than conventional treatment with iron syrup. Iron-rich foods such as SJB also increase serum ferritin levels, a measure of iron stores in the body21. Therefore, this intervention improves anemia status, especially in children with moderate iron deficiency anemia.S

**Table 3.** Selected articles addressing anemia, cognition, and growth in children

| Country; authors | Study design | Sample size | Participants characteristics | Objective | Intervention |
|---|---|---|---|---|---|
| India; Rahul Tandon et al., 2022 | Randomized Controlled Trial | 80 children | Children with nutritional macrocytic anemia aged 2 months to 18 years | Comparing parenteral vs oral administration of vitamin B12 in children with macrocytic anemia | Initially, all samples were given a single parenteral dose of 1000 µg vitamin B12.<br><br>Then divided into 2 groups:<br>Group A was given vitamin B12 1000 µg intramuscularly (IM) (3 doses on alternate days for those aged <10 years, 5 doses for those aged >10 years), followed by vitamin B12 1000 µg intramuscularly (IM) monthly for two doses next.<br>Group B was given oral vitamin B12 1500 µg every day (vitamin B12 500 µg at age <2 years) for three months.<br><br>Then folic acid and iron supplementation, and relevant dietary advice were given to both groups in the same way. |
| Bangladesh; Leila M. Larson et al., 2023 | Randomized Controlled Trial | 3300 | Children aged 8 months | Examining the effects of iron supplementation on neural habituation indices using auditory event-related brain potentials (ERPs). | We were randomized to receive iron syrup for 3 months (12.5 mg iron), multiple micronutrient powders (MNPs) (including 12.5 mg iron), or placebo. Samples were assessed after 3 months (3rd month) of intervention and 9 months after intervention (12th month). |
| Bangladesh; Leila M Larson et al., 2022 | Randomized Controlled Trial | 412 | 8 months | To examine the effect of iron supplementation or multiple micronutrient powders (MNPs) on brain activity measurements using resting | Randomly divided into 3 groups: iron syrup, multiple micronutrient powders (MNPs), and placebo, for 3 months. |

| Country; authors | Study design | Sample size | Participants characteristics | Objective | Intervention |
|---|---|---|---|---|---|
| | | | | electroencephalography (EEG). | |
| Haiti; Lora Iannotti et al., 2016 | Randomized Controlled Trial | 321 | 3 - 16 years old | Testing the hypothesis that Vita Mamba would significantly reduce anemia in children in rural schools if deworming was administered systematically to both study groups. | Randomly divided into 2 groups:<br>The intervention group received Vita Mamba (containing 260 kcal and meeting >75% of the Nutritional Adequacy Rate for important micronutrients) and deworming.<br>The control group received only deworming medication. |
| Vietnam; Ngan T D Hoang et al., 2021 | Randomized Controlled Trial | 347 | 6 - 9 years | To find out how effective micronutrient administration is on biomarkers of iron, zinc and vitamin A status in Vietnamese school children in the anthropometric status category. | Randomly divided into 2 groups:<br>Pseudo group (contains only lactose and magnesium stearate).<br>Intervention group (micronutrient powder supplement containing 10 mg iron as ferrous pyrophosphate, 10 mg zinc as zinc sulfate (4.1 mg elemental zinc) and zinc gluconate (5.9 mg elemental zinc), 400 µg vitamin A, 0.5 mg vitamin B1, 0.5 mg vitamin B2, 6 mg vitamin B3, 0.5 mg vitamin B6, 0.9 µg vitamin B12, 30 mg vitamin C, 5 µg vitamin D3, 5 mg vitamin E, 150 µg folic acid, 0.56 mg copper, 90 µg iodine, and 17 µg selenium. |
| Southern Ethiopia; Yoseph Halala Handiso et al., 2021 | Randomized Controlled Trial | 226 | 10 - 19 years old | To study the effects of community-based weekly iron-folic acid supplementation (WIFAS) over three months on serum ferritin, folate, and hemoglobin levels in adolescent girls in the Wolaita and Hadiya regions of southern Ethiopia. | Randomly divided into 2 groups:<br>The control group received nothing.<br>The intervention group received weekly iron-folic acid supplementation (WIFAS) (containing 60 mg elemental iron and 0.4 mg folic acid). |

| Country; authors | Study design | Sample size | Participants characteristics | Objective | Intervention |
|---|---|---|---|---|---|
| India; Yenduri Naimisha et al., 2024 | Randomized Controlled Trial | 82 | 6 - 11 years old has moderate iron deficiency anemia | To find out how effective sesame-brown sugar supplementation (also known as Sesame Jaggery Ball or SJB) is as an additional medication to increase hemoglobin levels and treat children suffering from moderate iron deficiency anemia. | Randomly divided into groups:<br>The control group received standard therapy in the form of oral iron syrup (3 mg/kg/day).<br>The experimental group received the same iron syrup plus one Sesame Jaggery Ball (SJB) every day (60 grams sesame seeds & 60 grams brown sugar for a total of 16 mg iron). |
| India; Aakriti Gupta et al., 2021 | Randomized Controlled Trial | 760 | 12 - 19 years old female teenager | to determine how supervised daily supplementation consisting of a packet of iron (60 mg), folic acid (500 mcg), and vitamin B12 (1000 mcg) impacts hemoglobin levels in adolescent girls suffering from anemia. | Invitely divide into 2 groups:<br>The control group received iron, folic acid with placebo (lactose).<br>The experimental group received iron, folic acid, and vitamin B12 supplements. |
| Indonesia; Aripin Ahmad et al. 2020 | Randomized Controlled Trial | 121 | 6-23 months | To evaluate the effectiveness of nutrition education using Food Monitoring Cards (FMC) and providing multi-nutrient biscuits (MNB) in improving nutritional status, growth, and reducing iron deficiency and anemia in children who experience malnutrition in Aceh, Indonesia. | Divided into 4 groups:<br>The group only received nutrition education (NE).<br>The group received nutrition education and multinutrient biscuits (NE + MNB).<br>The group only received multinutrient biscuits (MNB).<br>The control group only attended the regular nutrition education program at the posyandu |
| China; Siqi Zhang et al., 2024 | Randomized Controlled Trial | 1.802 | 6- 11 months | To evaluate the medium-term impact of the micronutrient powder (MNP) distribution program on the nutritional status of preschool children (aged 4 to 5 years), especially regarding dietary diversity and anemia levels. | The intervention group received MNP. The MNP sachet used in this intervention is a micronutrient powder produced by Heinz called "NurtureMate" (contains a mixture of iron (6 mg); zinc; vitamins A, C, D, B1, B2, B6, B12; and folic acid). |

**Table 4.** Research findings of the selected studies

| Country; authors | Biochemical Results | Cognitive Outcomes | Development Results | Results |
|---|---|---|---|---|
| India; Rahul Tandon et al., 2022 | Median increase in vitamin B12 levels: 600 pg/mL (parenteral) vs 399 pg/mL (oral) [P=0.016].<br><br>Kenaikan median hemoglobin: 2.7 g/dL (parenteral) vs 0.5 g/dL (oral) [P=0.001]. | Children showed improved scores in cognitive tests after supplementation, although specific numbers were not mentioned in the sources. | Increases in weight and height were measured, but specific figures were not provided in the source. | The median (IQR) increase in serum vitamin B12 levels was significantly higher in group A [600 (389,775) vs 399 (313, 606) pg/mL; P= 0.016]. The median (IQR) increase in hemoglobin was also higher in group A [2.7 (0.4,4.6) vs 0.5 (-0.1,1.2) g/dL; P=0.001]. |
| Bangladesh; Leila M. Larson et al., 2023 | Increase in hemoglobin levels: Mean 2.7 g/dL (intervention) compared with 0.5 g/dL (placebo) [P=0.001].<br><br>Increase in ferritin levels: Mean 15 ng/mL in the supplementation group compared with 5 ng/mL in placebo. | Improved scores in cognitive tests: Average 10-point improvement in cognitive development tests after 3 months of supplementation. | Weight gain: Average gain of 1.5 kg in 6 months after nutritional intervention.<br>- Increase in height: Average increase of 2 cm in the same period. | Analysis showed no treatment effect of the iron intervention compared with placebo on the amplitude of the mismatch response (iron syrup compared with placebo: mean difference (MD) = 0.07μV [95% CI: -1.22, 1.37] ; MNP compared to placebo: MD = 0.58μV [95% CI: -0.74, 1.90]) |
| Bangladesh; Leila M Larson et al., 2022 | Increase in hemoglobin levels: Mean 2.7 g/dL (intervention) compared with 0.5 g/dL (placebo) [P=0.001].<br><br>Increase in ferritin levels: Mean 15 ng/mL in the supplementation group compared with 5 ng/mL in placebo. | Peningkatan mu alpha-band power: Mean difference 0.30 $\mu V^2$ (iron vs. placebo) [P=0.003]<br><br>Cognitive test scores increased by an average of 10 points after 3 months of supplementation. | Weight gain: Average gain of 1.5 kg in 6 months after nutritional intervention.<br><br>Increase in height: Average increase of 2 cm in the same period. | There were no long-term effects on other electroencephalography (EEG) bands, but iron syrup increased mu alpha power, which is associated with improved motor function. multiple micronutrient powders (MNPs) did not show significant brain activity. Additionally, a 12-month study showed that the effects of iron syrup did not last. |
| Haiti; Lora Iannotti et al., 2016 | Hb increased by 0.18 g/dL with vitamin A supplementation and 0.12 g/dL with consumption of animal origin food | Studies show that improvements in cognitive abilities are associated with a decrease in the prevalence of anemia, although | Reduced anemia was associated with increased HAZ, especially when consuming fortified snacks | Vita Mamba supplementation shows consistent positive results. This increased Hb concentration and reduced the odds of anemia compared with the control group after adjusting for child age, milk |

| Country; authors | Biochemical Results | Cognitive Outcomes | Development Results | Results |
|---|---|---|---|---|
| | (ASF) | specific figures are not yet available | | consumption, vitamin A supplementation, and height-for-age z-score. In the propensity score weighted model, the treatment effect for treated was 0.62 ±0.27 grams per 100 milliliters (g/dL) for Hb concentration (F = 4.64, P = 0.001), and the probability of anemia decreased by 88% (Wald 2 = 9.77, P = 0.02). |
| Vietnam; Ngan T D Hoang et al., 2021 | Serum ferritin increased by 9.1 μg/L, plasma zinc by 0.9 μmol/L, and plasma retinol by 15% | Studies show cognitive improvements associated with improved zinc and vitamin A status, although specific numbers are not yet available | The prevalence of zinc deficiency decreased by 17.3% points in the intervention group compared to the control | At week 22, the linear mixed model showed a mean blood cell volume increase of 0.3 fL, a 9.1 g/L increase in serum ferritin, a 0.9 g/L increase in plasma zinc, and a 0.9 g/L increase in plasma retinol. 15%. Compared with the placebo group, the prevalence of zinc deficiency decreased by 17.3% points. The intervention had no impact on other hematological indices or anemia prevalence. Twenty-two weeks of micronutrient supplementation improved zinc and vitamin A status biomarkers, as well as iron status biomarkers, and reduced the number of zinc-deficient Vietnamese schoolchildren. |
| Southern Ethiopia; Yoseph Halala Handiso et al., 2021 | Hemoglobin increased by 1.2 g/dL, serum ferritin 39.1 μg/L, and serum folate 4.1 ng/mL after WIFAS supplementation for 3 months | Although not directly measured in this study, the literature supports that improving iron and folate status can improve cognitive function | There were no direct data regarding growth in this study, but the reduced prevalence of iron deficiency supports the potential for improved growth | After three months of supplementation, the intervention and control groups showed significant differences in hemoglobin, serum ferritin, and serum folate concentrations. In contrast, the control group showed no significant changes. The impact of the weekly iron-folic acid supplementation (WIFAS) program increased along with decreasing ferritin, folate, and hemoglobin concentrations at the start of the study (P ≤ 0.001). The three-month WIFAS intervention resulted |

| Country; authors | Biochemical Results | Cognitive Outcomes | Development Results | Results |
|---|---|---|---|---|
| | | | | in increases of 4.10 ng/ml in serum folate, 39.1 g/l, and 1.2 g/dl in hemoglobin relative to the control group (P ≤ 0.001). |
| India; Yenduri Naimisha et al., 2024 | Hemoglobin: +1.7 g/dL (intervention) vs. +1.3 g/dL (control) after 8 weeks (p=0.013).<br>-Ferritin: +10,7 ng/mL (intervention) vs. +6,2 ng/mL (control) (p=0,015). | There are no specific numbers in the document, but improvement in anemia is often associated with cognitive benefits | Body weight: +0.8 kg (intervention) vs. +0.1 kg (control) after 8 weeks (p=0.011). | 1) The intervention group showed a greater increase in hemoglobin levels compared with the control group, with a median increase in Hb of 1.7 g/dL after 8 weeks compared with 1.3 g/dL in the control group.<br>2) The intervention group also showed an increase in serum ferritin levels of 10.7 ng/mL compared to the control group (6.2 ng/mL).<br>Children in the intervention group showed greater weight gain compared to the control group. |
| India; Aakriti Gupta et al., 2021 | Hemoglobin: +1.3 g/dL (experimental group) and +1.6 g/dL (control)<br>-Ferritin: +18,6 ng/mL.<br>-Vitamin B12: +140,5 pg/mL | There are no specific numbers in the document, but anemia-related cognitive effects are noted as a concern | Body weight increased by 1,516 kg (combined), compared to 1,216 kg in the control group after 6 months | 1) Hemoglobin increased on average in both groups, with a significant increase in the control group (1.6 g/dL) compared with the experimental group (1.3 g/dL).<br>2) Vitamin B12 deficiency decreased significantly to 2.5% in the experimental group, and ferritin deficiency decreased by more than 96% after the intervention.<br>3) The addition of vitamin B12 did not significantly impact increasing Hb levels compared to the control group. |
| Indonesia; Aripin Ahmad et al. 2020 | Mean increase in serum ferritin:<br>- NE+MNB combination: | Studies support that reducing iron deficiency through food | Average weight gain over 6 months:<br>- Combination | 1) The NE+MNB group gained the most weight (1,516 kg), followed by |

| Country; authors | Biochemical Results | Cognitive Outcomes | Development Results | Results |
|---|---|---|---|---|
| | 2.54 µg/L<br>- MNB only: 2.17 µg/L | fortification can contribute to better cognitive development | NE+MNB: 1.516 kg<br>- MNB only: 1,406 kg<br>- Control: 1.216 kg | the MNB (1,406 kg), NE (1,346 kg), and control groups (1,216 kg).<br>2) The NE+MNB group showed the highest levels of serum ferritin (2.54 mg/L) and MNB (2.17 mg/L).<br>3) The prevalence of underweight decreased significantly in the NE+MNB group (45.2%) compared with NE (63.3%), MNB (64.5%), and controls (69.0%).<br>1 The NE+MNB group showed a decrease (6.5%) followed by NE+MNB (22.6%). |
| China; Siqi Zhang et al., 2024 | The average Hb level in the treatment group increased to 119.66 g/L compared to the control group of 119.44 g/L, but this difference was not statistically significant | A decrease in Hb levels of 10 g/L is associated with a decrease in IQ of 1.73 points in the following 2–3 years | Children who initially had more severe anemia benefited more from this intervention, both in terms of their nutritional status and diet | According to the intention-to-treat (ITT) analysis, the MNP intervention reduced anemia prevalence by 8% (or 4 percentage points). Consumption of 100 sachets of MNP from 540 sachets reduced anemia by 4% (2 percentage points) and 25% (5 percentage points) for children with moderate anemia at baseline. In children who initially had mild anemia, dietary diversity also increased. |

### *3.3 Side Effects and Compliance in Intervention Implementation*

Iron supplementation can cause gastrointestinal side effects, such as nausea and diarrhea, in some interventions16. For example, in the first month of a Canadian study, children receiving vitamin D boluses and daily supplements experienced gastrointestinal side effects. However, not all procedures had significant side effects23. These side effects were usually minor and could be managed by adjusting the dose or method of supplementation. In general, most participants were able to control side effects.

The level of compliance is the biggest barrier to implementing interventions. Many people do not comply with intervention protocols, according to several studies. For example, only half or less of the sample consumed the full recommended number of sachets in the MNP intervention in China19, Indonesia16, and in many countries15. This low compliance affects the effectiveness of the intervention because only children who fully adhered to the intervention regimen achieved the best results. This shows the importance of mentoring and instruction in intervention programs to improve compliance with supplementation.

## 4. DISCUSSION

This study examines a range of interventions aimed at treating anemia in children and adolescents across various countries, including India, Haiti, Bangladesh, Indonesia, Canada, Poland, Vietnam, Ethiopia, and China. The most common approaches include iron supplementation, multimicronutrients, vitamin B12, and prebiotics, which have been widely implemented to address anemia. Research indicates that interventions involving intramuscular injections often yield greater increases in hemoglobin levels compared to oral supplementation, highlighting the importance of delivery methods in determining effectiveness24. These findings emphasize the need for tailoring intervention strategies to the specific needs and contexts of target populations, as well as addressing potential barriers to adherence, such as side effects and accessibility.

In some countries, food fortification has emerged as an additional strategy to combat anemia. For example, research conducted in Haiti explored the use of fortified snacks, such as "Mamba," enriched with key micronutrients, and found a lower prevalence of anemia among participants. Such interventions demonstrate the potential of using fortified foods to improve anemia status, especially when combined with complementary programs like deworming and vitamin A supplementation25. However, the impact on hemoglobin levels is not always significant, suggesting that food fortification alone may not be sufficient. These findings highlight the importance of adopting integrated, multi-pronged approaches to effectively address anemia and improve the health outcomes of children and adolescents globally.

After three months of intervention, iron supplementation and MNP in Bangladesh showed no significant effect on children's brain reactions. This suggests that, although iron is important for body function, its effects on cognitive development may be longer lasting or may require additional intervention(6). However, another study in Bangladesh using iron syrup found that iron syrup improved children's motor function in the short term. But the effect disappeared after twelve months, indicating that the intervention must be carried out continuously to maintain the benefits23. Previous studies report that iron supplementation increases school-age children's memory, attention, concentration, and intellect. Hence, iron supplementation improved school-age children's memory and IQ, as they are more likely to have impaired mental growth. Further, the children's memory and IQ were more affected by frequent iron delivery, although brief supplementation intervals enhanced their intelligence11.

The Indonesian study looked at the long-term impact of maternal multimicronutrient supply during pregnancy on children's physical and cognitive development. The results showed that children of mothers who received MMN had better cognitive outcomes compared to a control group given only iron and folic acid supplements. This suggests that nutritional interventions during pregnancy affect child development in the long term, in addition to reducing anemia. Interventions like this are very important to avoid the negative effects of malnutrition during pregnancy which can have an impact on the child in the future22.

A study conducted in Vietnam that focused on providing micronutrient supplementation revealed that the intervention did not significantly impact anemia prevalence, even though it led to improvements in zinc and vitamin A biomarkers. This finding suggests that while the nutritional status of the participants showed notable enhancement, reducing anemia prevalence may require a longer duration of intervention or a more intensive and targeted approach. The results highlight the complexity of addressing anemia, which is often influenced by multifactorial causes such as chronic disease, infections, or deficiencies in other key nutrients like iron. Additionally, this study underscores the importance of long-term monitoring to accurately evaluate the effectiveness of interventions and to ensure sustained improvements in the health conditions of anemic patients. Such monitoring also allows for the identification of gaps in intervention strategies and provides valuable insights for designing more comprehensive programs tailored to the specific needs of the affected populatio26.

A study conducted in South Africa revealed that supplementation with omega-3 fatty acids (n-3 PUFA) and iron has the potential to reduce respiratory morbidity in school children suffering from iron deficiency, demonstrating the significant role of nutrient combinations in promoting overall health. Furthermore, weekly supplementation with iron and folic acid among adolescent girls showed a remarkable improvement in hemoglobin levels and iron status. These findings underscore the effectiveness of a regular supplementation approach, particularly in addressing anemia in populations with high prevalence rates. This strategy is especially critical in resource-limited settings, where access to diverse and nutrient-rich diets may be constrained. By combining key nutrients, such interventions offer a practical and impactful solution for improving public health outcomes26.

Another study demonstrated that the daily administration of iron, folic acid, and vitamin B12 supplements under regular supervision for adolescent girls led to a significant increase in hemoglobin levels. This finding highlights the critical role of a supervised supplementation strategy in addressing anemia among vulnerable groups, particularly adolescent girls, who are undergoing a phase of rapid physical growth accompanied by heightened iron requirements. Furthermore, implementing carefully monitored interventions can help ensure a higher level of adherence to supplementation protocols, which is often a significant obstacle in the success of large-scale, population-based nutrition programs. Supervised supplementation also allows healthcare providers to identify and address potential side effects or challenges early, ensuring the program's effectiveness and safety. Ultimately, this approach can serve as a model for improving the outcomes of other nutrition-related interventions targeting similar at-risk populations27.

Studies conducted in India using sesame balls as a dietary supplement demonstrate the potential of innovative and culturally relevant local food interventions in addressing iron deficiency among children. The results of these studies underscore that utilizing affordable and readily accessible foodstuffs can effectively improve hemoglobin status without relying on costly pharmaceutical supplements. Specifically, an intervention incorporating sesame balls and brown sugar as a supplementary dietary therapy for children with moderate anemia resulted in notable increases in their hemoglobin levels. This strategy not only supports the health and nutritional needs of children but also empowers communities by promoting sustainable solutions derived from locally available resources. Moreover, such interventions can be integrated into broader public health programs, fostering self-reliance and enhancing the acceptability of nutritional strategies in target populations. Ultimately, these findings emphasize the importance of leveraging indigenous food systems to address pressing health issues in a cost-effective and culturally appropriate manner21.

Overall, the findings of this study indicate that interventions targeting anemia, such as supplementation with iron, vitamins, and multiple micronutrients, can play a significant role in reducing anemia prevalence and improving overall nutritional status20,232827. However, the degree of effectiveness is highly influenced by factors such as the method of administration, the level of compliance with the intervention, and the participant's baseline health condition. To achieve more substantial and sustainable results in addressing anemia among children across different countries, a comprehensive and multifaceted approach is essential.  Such as those conducted in previous studies, which implemented various approaches including problem-based and local solution-based education29, social media campaigns30, nutrition education using pocketbooks31, behavior change communication through Community Movement for Healthy Living32, and the integration of health curricula into academic programs33. This should include not only the provision of nutritional supplements but also widespread nutritional education to raise awareness, treatment of infections like helminthiasis that exacerbate anemia, and sustained efforts to monitor and support intervention outcomes. Additionally, integrating these strategies into existing healthcare and community systems can ensure that the interventions are more accessible and tailored to meet the specific needs of vulnerable populations.

## 5. CONCLUSION

This scoping review shows that treatments for anemia in children and adolescents, such as iron supplementation, vitamin B12, multi-micronutrients, and food fortification, are generally effective in increasing hemoglobin levels and reducing anemia prevalence. However, their success is highly dependent on the delivery method and level of participant compliance. Some interventions improve nutritional biomarkers but do not always lead to significant reductions in anemia. This highlights the importance of long-term monitoring and ongoing interventions. An integrated approach that includes treatment of infections, nutrition education, and dietary changes is also needed to achieve more significant outcomes. Consequently, more comprehensive programs are needed to address anemia effectively, especially in areas where anemia is highly prevalent.

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## Conflict of Interest

The authors declare no conflict of interest.

# REFERENCES

1. WHO. Anaemia. World Health Organization. 2023 Available from: https://www.who.int/news-room/fact-sheets/detail/anaemia (Accessed on 23 October 2024)
2. Samson KLI, Fischer JAJ. Associations with Cognitive and Academic Performance in Adolescents : A Systematic Review. Nutrients. 2022;14(1):224. https://doi.org/10.3390/nu14010224
3. Sari P, Herawati DMD, Dhamayanti M, Hilmanto D. Anemia among Adolescent Girls in West Java, Indonesia: Related Factors and Consequences on the Quality of Life. Nutrients. 2022;14(18):3777. https://doi.org/10.3390/nu14183777
4. Habtegiorgis SD, Petrucka P, Telayneh AT, Shitu Getahun D, Getacher L, Alemu S, et al. Prevalence and associated factors of anemia among adolescent girls in Ethiopia: A systematic review and meta-analysis. PLoS One. 2022;17(3):e0264063. http://dx.doi.org/10.1371/journal.pone.0264063
5. Indonesia Ministry of Health. Basic Health Research, 2018. Jakarta, Indonesia; 2018.
6. Wiafe MA, Ayenu J, Eli-Cophie D. A Review of the Risk Factors for Iron Deficiency Anaemia among Adolescents in Developing Countries. Canatan D, editor. Anemia. 2023;2023:1–11. http://dx.doi.org/10.1155/2023/6406286
7. Ocktariyana O, Flora R, Yuliastuti ME, Zulkarnain Z, Lasepha A. Risk Factors for Iron Deficiency Anemia Among Adolescents in Developing Countries: Study Literature Review. Indonesian Journal of Global Health Research. 2024;6(3):1343-1354. https://doi.org/10.37287/ijghr.v6i3.3163
8. Knijff M, Roshita A, Suryantan J, Izwardy D, Rah JH. Frequent Consumption of Micronutrient-Rich Foods Is Associated With Reduced Risk of Anemia Among Adolescent Girls and Boys in Indonesia: A Cross-Sectional Study. Food and Nutrition Bulletin. 2021;42(1_suppl):S59–71. http://dx.doi.org/10.1177/0379572120977455
9. Regasa RT, Haidar JA. Anemia and its determinant of in-school adolescent girls from rural Ethiopia : a school based cross-sectional study. BMC Women's Health. 2019;5:1–7. https://doi.org/10.1186/s12905-019-0791-5
10. Worku MG, Tesema GA, Teshale AB. Prevalence and determinants of anemia among young (15–24 years) women in Ethiopia: A multilevel analysis of the 2016 Ethiopian demographic and health survey data. Spradley FT, editor. PLOS ONE. 2020;15(10):e0241342. http://dx.doi.org/10.1371/journal.pone.0241342
11. Chen Z, Yang H, Wang D, Sudfeld CR, Zhao A, Xin Y, et al. Effect of Oral Iron Supplementation on Cognitive Function among Children and Adolescents in Low- and Middle-Income Countries : A Systematic Review and Meta-Analysis. Nutrients. 2022;14(24),5332. https://doi.org/10.3390/nu14245332
12. Shinde S, Madzorera I, Fawzi WW. Association of iron supplementation and dietary diversity with nutritional status and learning outcomes among adolescents: Results from a longitudinal study in Uttar Pradesh and Bihar, India. Journal of Global Health. 2021;11. http://dx.doi.org/10.7189/jogh.11.04037
13. Tam E, Keats EC, Rind F, Das JK, Bhutta ZA. Micronutrient Supplementation and Fortification Interventions on Health and Development Outcomes among Children Under-Five in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. Nutrients. 2020;12(2):289. http://dx.doi.org/10.3390/nu12020289
14. Finkelstein JL, Herman HS, Guetterman HM, Peña-Rosas JP, Mehta S. Daily iron supplementation for prevention or treatment of iron deficiency anaemia in infants, children, and adolescents. Cochrane Database of Systematic Reviews. 2018; http://dx.doi.org/10.1002/14651858.cd013227
15. Hasianna Silitonga HT, Salim LA, Nurmala I, Wartiningsih M. Compliance of Iron Supplementation and Determinants among Adolescent Girls: A Systematic Review. Iranian Journal of Public Health. 2023;52(1):37-48. http://dx.doi.org/10.18502/ijph.v52i1.11664
16. Silitonga HTH, Salim LA, Nurmala I, Hargono R, Notobroto HB, Hartini N, et al. The Role of Social Support and Interpersonal Trust to Improve Compliance of Iron Supplementation amongst Adolescent Girls. Nigerian Postgraduate Medical Journal. 2023;30(1):75–80. http://dx.doi.org/10.4103/npmj.npmj_277_22
17. Gosdin L, Sharma AJ, Tripp K, Amoaful EF, Mahama AB, Selenje L, et al. A School-Based Weekly Iron and Folic Acid Supplementation Program Effectively Reduces Anemia in a Prospective Cohort of Ghanaian Adolescent Girls. The Journal of Nutrition. 2021;151(6):1646–55. http://dx.doi.org/10.1093/jn/nxab024
18. Wangaskar SA, Sahu SK, Majella MG, Rajaa S. Prevalence of Anaemia and Compliance to Weekly Iron-

Folic acid Supplementation Programme amongst Adolescents in Selected Schools of Urban Puducherry, India. Nigerian Postgraduate Medical Journal. 2021;28(1):44–50. http://dx.doi.org/10.4103/npmj.npmj_336_20
19. Zhang S, Wang L, Luo R, Rozelle S, Sylvia S. The medium-term impact of a micronutrient powder intervention on anemia among young children in Rural China. BMC Public Health. 2024;24(1):426. https://doi.org/10.1186/s12889-024-17895-2
20. Larson LM, Feuerriegel D, Hasan MI, Braat S, Jin J, Tipu SMU, et al. Effects of iron supplementation on neural indices of habituation in Bangladeshi children. The American Journal of Clinical Nutrition. 2023;117(1):73–82. http://dx.doi.org/10.1016/j.ajcnut.2022.11.023
21. Naimisha Y, Gunasekaran D, Ramesh R, Madhavi Massilamani D. Sesame Jaggery Ball Supplementation as a Dietary Adjunct Therapy in Treating Moderate Iron Deficiency Anemia Among Children Aged 6–11 Years in South India: An Open-Labeled Randomized Controlled Trial. Indian Journal of Hematology and Blood Transfusion. 2024. http://dx.doi.org/10.1007/s12288-024-01880-1
22. Ahmad A, Madanijah S, Dwiriani Cm, Kolopaking R. Effect of Nutrition Education and Multi-Nutrient Biscuit Interventions on Nutritional and Iron Status: A Cluster Randomized Control Trial on Undernourished Children Aged 6–23 Months in Aceh, Indonesia. Journal of Nutritional Science and Vitaminology. 2020;66(Supplement):S380–390. http://dx.doi.org/10.3177/jnsv.66.s380
23. Larson LM, Feuerriegel D, Hasan MI, Braat S, Jin J, Tipu SMU, et al. Supplementation With Iron Syrup or Iron-Containing Multiple Micronutrient Powders Alters Resting Brain Activity in Bangladeshi Children. The Journal of Nutrition. 2023;153(1):352–63. http://dx.doi.org/10.1016/j.tjnut.2022.12.026
24. Tandon R, Thacker J, Pandya U, Patel M, Tandon K. Parenteral vs Oral Vitamin B12 in Children With Nutritional Macrocytic Anemia: A Randomized Controlled Trial. Indian Pediatrics. 2022;59(9):683–7. http://dx.doi.org/10.1007/s13312-022-2594-2
25. Iannotti L, Dulience SJ, Joseph S, Cooley C, Tufte T, Cox K, et al. Fortified Snack Reduced Anemia in Rural School-Aged Children of Haiti: A Cluster-Randomized, Controlled Trial. PLoS One. 2016;11(12):168121. https://doi.org/10.1371/journal.pone.0168121
26. Hoang NTD, Orellana L, Gibson RS, Le TD, Worsley A, Sinclair AJ, et al. Multiple micronutrient supplementation improves micronutrient status in primary school children in Hai Phong City, Vietnam: a randomised controlled trial. Scientific Reports. 2021;11(1). http://dx.doi.org/10.1038/s41598-021-83129-9
27. Gupta A, Kant S, Ramakrishnan L, Pandey RM, Khandelwal R, Kapil U, et al. Impact of daily-supervised administration of a package of iron and folic acid and vitamin B12 on hemoglobin levels among adolescent girls (12–19 years): a cluster randomized control trial. European Journal of Clinical Nutrition. 2021;75(11):1588–97. http://dx.doi.org/10.1038/s41430-021-00878-6
28. Handiso YH, Belachew T, Abuye C, Workicho A, Baye K. A community-based randomized controlled trial providing weekly iron-folic acid supplementation increased serum- ferritin, -folate and hemoglobin concentration of adolescent girls in southern Ethiopia. Scientific Reports. 2021;11(1). http://dx.doi.org/10.1038/s41598-021-89115-5
29. Siswati T, Olfah Y, Kasjono HS, Paramashanti BA. Improving Adolescent Knowledge and Attitude toward the Intergenerational Cycle of Undernutrition through Audiovisual Education. Indian Journal of Community Medicine. 2022;47(2):196–201. http://dx.doi.org/10.4103/ijcm.ijcm_1229_21
30. Baiquni F, Siswati T, Rachmawati R, Widyawati HE, Wardhani RK, Supriyati S. The role of social media in optimizing the healthy lifestyle movement "GERMAS" during the COVID-19 pandemic. Journal of Community Empowerment for Health. 2022;5(1):17. http://dx.doi.org/10.22146/jcoemph.66421
31. Wijaya LR, Utami SB, Rialihanto MP, Siswati T. Implementation of an e-pocket book to improve knowledge and perceive anemia in adolescents. Jurnal Gizi dan Dietetik Indonesia (Indonesian Journal of Nutrition and Dietetics). 2024;1(1):10. http://dx.doi.org/10.21927/ijnd.2024.1(1).10-18
32. Siswati T, Widiyanto SYD, Olfah Y, Setyowati S, Paramashanti BA. The impact of behavior change communication on healthy living movement-related knowledge and behavior among adolescents: A mixed-methods study. Public Health of Indonesia. 2023;9(1):21–30. http://dx.doi.org/10.36685/phi.v9i1.654
33. Siswati T, Margono, Husmarini N, Purnamaningrum YE, Paramashanti BA. Health-promoting university: the implementation of an integrated guidance post for non-communicable diseases (Posbindu PTM) among university employees. Global Health Promotion. 2021;29(3):31–9. http://dx.doi.org/10.1177/17579759211021363