



Systematic Literature Review: Effects of Different Forms of Iron Supplementation on Gut Microbiota Composition and Immune Function in Children with Iron Deficiency Anemia

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ABSTRACT

Background: Iron deficiency anemia (IDA) is a public health concern with this major global health concern seeming to be affecting the child population more, since it can prove detrimental to growth, cognitive functioning, and immune function. Though iron supplementation is the primary intervention for IDA treatment, its effects on gut microbiota and immune function are still not fully understood. Different forms of supplementation might have different effects on the gut microbiome and immunity. **Methods:** This systematic review examined studies published between 2014 and 2024 using electronic databases including PubMed, Scopus, and Cochrane Library. This review, abiding by the guidelines of PRISMA and following the PICOS construction, deals with children of ages comprising 0-12 years, diagnosed with IDA, investigating the various modes of delivering iron such as nano-iron, fortified foods, oral or parenteral iron, and their influence on gut microbiota composition and immune function. **Results:** Studies report variable responses of iron supplementation on gut microbiota and immunity based on formulation, dosage, and concurrent nutrient administration. Some studies show that there is no considerable change to the gut microbiota profiles resulting from synbiotic additions; however, they have also linked IDA with microbial dysbiosis. High-dose iron interventions tend to disrupt the gut microbiota and significantly increase the chances of infection, especially in settings with poor hygiene. On the other hand, even prebiotics have been tried to alleviate this side effect besides continuing iron therapies. **Conclusion:** Iron supplementation is necessary for treating IDA in children, and the effect on gut microbiota and immunity depend on various factors. The administration of prebiotics or adjusting doses could minimize side effects and benefit treatment. Future studies should be conducted with a focus on personalized intervention considering diet, environment, and microbiological factors to better manage IDA and alleviate adverse effects.

Keywords: iron; microbiome; gut microbiota; iron deficiency anemia; systematic review; meta-analysis; children.

INTRODUCTION

Iron deficiency anemia (IDA) remains the most common nutritional deficiency disorder worldwide, disproportionately affecting children in low- and middle-income countries. It is characterized by reduced hemoglobin levels due to inadequate iron availability, impairing oxygen transport and resulting in fatigue, cognitive impairments, and delayed growth. Among children, IDA poses significant challenges to developmental outcomes, including impaired immune responses, making them more susceptible to infections.

Iron supplementation has been a cornerstone in the management of IDA, employing various formulations such as ferrous salts, nano-iron particles, and iron-fortified foods. However, the administration of iron can alter the gut environment, as iron serves as a critical nutrient for both beneficial and pathogenic bacteria. While supplementation effectively addresses anemia, it may disrupt gut microbiota balance, potentially leading to dysbiosis and related gastrointestinal side effects.

The gut microbiota plays a crucial role in maintaining immune homeostasis and protecting against infections. Emerging evidence highlights that alterations in gut microbiota composition can have systemic effects, including modulating inflammatory responses and cytokine production. Despite this, the interplay between different forms of iron supplementation, gut microbial communities, and immune function in children remains underexplored.

Given the global burden of IDA and the increasing focus on personalized nutrition, it is imperative to evaluate how diverse iron supplementation strategies affect both gut and immune health in children. This systematic review aims to address this knowledge gap by synthesizing evidence on the impact of different iron formulations on gut microbiota composition and immune function. The findings will have critical implications for optimizing iron therapy, minimizing adverse effects, and informing public health strategies to combat pediatric IDA effectively.

In this review, we analyze the effects of various forms of iron supplementation on gut microbiota composition and immune function in children with iron deficiency anemia.

MATERIALS AND METHODS

We conducted this systematic review following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) reporting guidelines [26].

2.1. Search Strategy and Study Selection

Using an a priori research protocol, relevant articles in English were identified from Embase, Pubmed, Scopus, and CINAHL from inception to February 2019 in consultation with a senior research librarian. The bibliographies of identified articles were also examined in an ancestry search. To conduct a systematic review evaluating all studies exploring the effect of probiotics on iron status and iron absorption in human subjects, we did not limit the search by study type. The search terms were organized by database and include both MeSH and Keyword searches. A comprehensive search strategy will be developed using a combination of Medical Subject Headings (MeSH) terms and keywords. Example for PubMed: "((("Iron supplementation" OR "Iron supplements" OR "Nano-iron" OR "Fortified foods" OR "Parenteral iron") AND ("Gut microbiota" OR "Microbiome" OR "Gut flora" OR "Gut health") AND ("Immune function" OR "Cytokines" OR "Immune markers" OR "Immunity") AND ("Children" OR "Pediatrics") AND ("Iron deficiency anemia"))". Search engine filters included article, human, and 2010-2024. Screening of the reference lists of selected studies was carried out in order to find RCTs that were not retrieved using the methods mentioned above (snowball search method).

Then, all retrieved studies were merged into one list, duplicates were excluded, and each article was eligible for evaluation.

2.2. Eligibility Criteria

The criteria for article screening was determined a priori, with a focus on identification of journal articles that assessed the association between iron supplementation and iron deficiency anemia in human subjects especially in children. Following the database searches, two independent researchers (F.N.L. and A.F.) screened abstracts and titles to identify articles that fit the criteria for further review. Articles were included if they reported the effect of the exposure of interest (i.e., probiotics) on the outcomes of interest (iron status and iron absorption) in humans.

The exposure of interest includes, but was not limited to, studies involving children aged 0–12 years diagnosed with iron deficiency anemia and investigating any form of iron supplementation (e.g., nano-iron, fortified foods, oral iron tablets, parenteral iron). Two independent researchers (F.N.L. and A.F.) searched for additional articles by reviewing the references of articles selected from the abstract and title searches. Only articles available in English were included in the search. Once articles were identified for potential inclusion through an abstract and title search, two independent researchers (F.N.L. and A.F.) fully reviewed the selected articles and selected the final articles for the systematic review. Disagreements were resolved through discussion and consensus among all authors.

2.3. Data Extraction and Management

A data abstraction form was created to collect key information including study design, study population, on gut microbiota composition (e.g., alpha diversity, specific bacterial taxa) and/or immune function markers (e.g., inflammatory cytokines, infection rates, or antibody responses). Primary and secondary outcomes measured, and statistical analysis. Articles were organized by study design, randomized control trial or observational study, and outcome of interest with primary outcome: changes in gut microbiota composition (e.g., diversity, abundance of beneficial bacteria). and the secondary outcome: immune function markers (e.g., levels of inflammatory cytokines, infection rates). Two independent researchers (F.N.L. and A.F.) extracted information from each selected article independently and compared findings. All discrepancies were resolved by

discussion and consensus among all authors. Attempts were made to contact the authors of studies with unclear data.

2.4. Assessment Methodological Quality of Included Studies

The data extraction was performed by two independent researchers (F.N.L. and A.F.) The final data extracted were as follows: general characteristics of the study, study design, characteristics of the groups, The outcomes that were extracted include changes in gut microbiota composition from alterations in the relative abundance of the two groups of bacteria after they were classified as beneficial or potentially harmful. Randomized clinical trials (RCTs) were assessed based on several sources of bias: use of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, nonselective outcome reporting, and other measures of bias.

2.5. Statistical Analysis

All included studies were analyzed at the level of systematic review, and the studies that had quantitative data were analyzed at the level of a meta-analysis. For each evaluated variable, a Forest Plot diagram is presented along with the relative results, and a funnel plot for the evaluation of the publication bias is also produced. The desired results occur when studies fall within the area of the triangle (funnel). In situations where some studies report results that are very different from the rest, the meta-analysis considering the specific subject has been repeated without them in an effort to improve the heterogeneity index I^2 and τ . Meta-analysis was based on both the fixed and random effects models. As detailed information for each individual case was not available, the analysis was based on aggregated data reported in the studies. Data were extracted from the relevant studies after determining their significance. The meta-analysis software was the R statistical computing language (edition 4.3.0) [29], under the Microsoft Windows operating system, and with the specialized meta-analysis package meta [30,31]. In studies where mean value and standard deviation (SD) were not available, the median and 1st and 3rd quartiles were used in order to estimate the mean value and the relevant

SD using the method of Hozo et al. [32]. In the manuscript, maximum and minimum values were also reported, and an improved method for mean and SD proposed by Bland [33] was used. The Deep Meta Tool, Version 1, was used for these estimations [34]. In cases where only minimum and maximum values were reported, the range rule was used to estimate the SD, whereas the mean value was used as the median. For studies reporting case series with detailed information for each patient, the mean value and SD were calculated by the authors. Multiple groups treated with different agents reported in a single study were considered separate during the meta-analysis.

RESULTS

Initially, 290 results were identified, and 143 were excluded via title and abstract assessment. A total of 147 papers were retrieved, and 25 duplicates were excluded. The remaining 91 papers underwent full-text evaluation. Screening of the reference lists of these studies generated nine more studies for full-text evaluation. Following this step, five studies fulfilled the pre-determined inclusion and exclusion criteria. Four studies were excluded due to incomplete data per intervention group and two that were not accessible. The study selection process is presented in the following PRISMA flow chart (Figure 1).

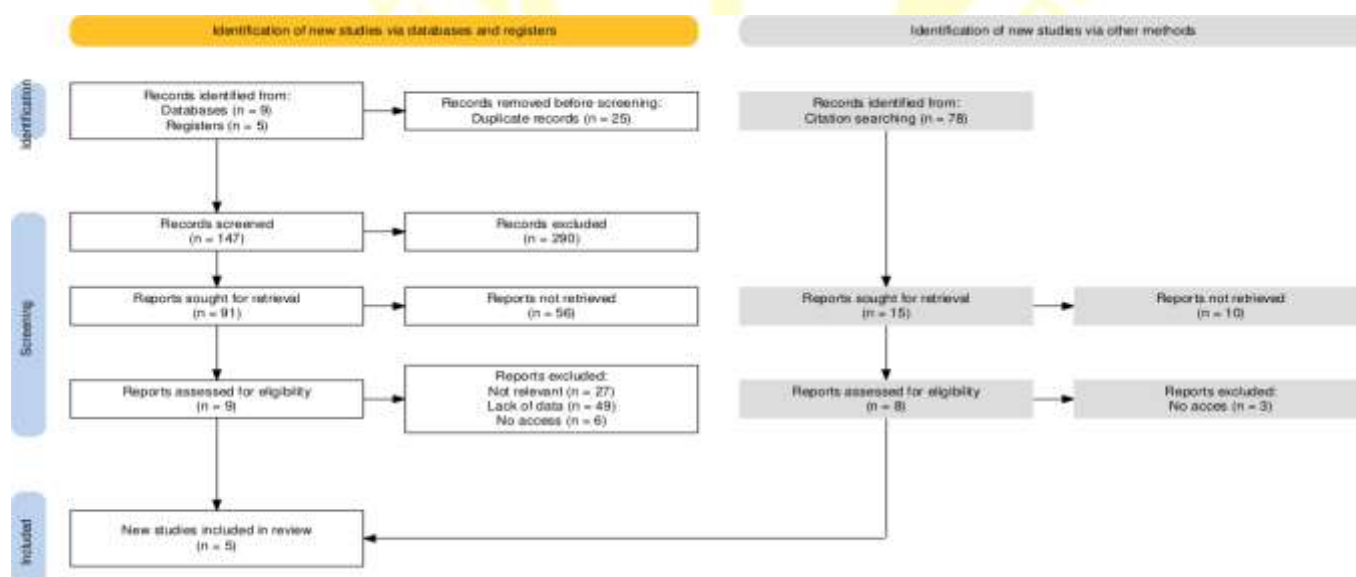


Figure 1. PRISMA flow chart for the study selection process and outcomes.

3.1 Study Characteristics and Participant

This systematic literature review evaluated studies investigating the effects of different forms of iron supplementation on gut microbiota composition and immune function in children with iron deficiency anemia (IDA). The included studies varied in design, geographic location, supplementation protocols, and measured outcomes. Most were randomized controlled trials (RCTs), complemented by observational studies and cross-sectional analyses. Geographic settings spanned high-prevalence regions such as Sub-Saharan Africa, South Asia, and Latin America, alongside developed nations for comparative insights. The forms of iron supplementation analyzed included oral iron salts (e.g., ferrous sulfate, ferrous fumarate), iron-fortified foods, heme-based iron, and novel formulations like lactoferrin or encapsulated iron. Intervention durations ranged from 4 weeks to 6 months, focusing on changes in gut microbiota composition (e.g., abundance of beneficial vs. pathogenic bacteria) and immune outcomes, such as cytokine profiles, inflammation markers, and infection rates.

3.2 Ages

The participants, aged 0 months to 12 years, were primarily children within the critical developmental window of 6 months to 5 years. All were diagnosed with IDA based on standard criteria, such as hemoglobin levels, serum ferritin, and transferrin saturation. Baseline nutritional assessments often included dietary iron intake, malnutrition prevalence, and coexisting micronutrient deficiencies like vitamin A or zinc. Exclusion criteria frequently applied to chronic illnesses or conditions affecting gut health, such as celiac disease. Socioeconomic background and environmental hygiene, noted as potential confounding factors, were highlighted in some studies due to their influence on gut microbiota and infection susceptibility. These characteristics provided a comprehensive understanding of the interplay between iron supplementation, gut health, and immune function in this vulnerable population.

Table 1. Details of studies included in the analysis.

No	Title Year/Country	Methods	Results	Conclusion
1	No Difference Between Iron Supplementation Only and Iron Supplementation with Synbiotic Fermented Milk on Iron Status, Growth, and Gut Microbiota Profile in Elementary School Children with Iron Deficiency (Helmyati et al., 2018) Indonesia	This research was an experimental study with pre and post test conducted on 59 iron deficient children. Subjects were given iron supplementation in syrups (IS group) or given iron supplementation in syrup with fermented milk (containing synbiotic Lactobacillus plantarum Dad 13 and fructo-oligosaccharide) (ISFM group) for 3 months.	The ¹ results showed no significant difference of gut microbiota profile between the IS and ISFM groups ($p>0.05$). There is no difference on the iron status, height, weight, and gut microbiota profile of iron-deficient primary school children received iron supplementation only or iron supplementation with synbiotic fermented milk. ²	Iron supplementation with or without synbiotic fermented milk had similar effects on iron status, growth, and gut microbiota in iron-deficient elementary school children.
2	Iron deficiency anemia-related gut microbiota dysbiosis in infants and young children: A pilot study	Ten infants and young children were recruited at a tertiary university hospital (Vilnius, Lithuania) with diagnosis of nutritional IDA	The study found distinct microbial signatures in infants and young children with iron deficiency anemia (IDA) compared to healthy	The study found distinct microbial signatures in infants and young children with iron deficiency anemia (IDA) compared

No	Title Year/Country	Methods	Results	Conclusion
	(Muleviciene et al., 2018) Italy	(serum hemoglobin <110 g/L, ferritin <12 µg/L, and/or reticulocyte-hemoglobin equivalent <28 pg) meeting the following criteria: (1) anemia diagnosed for the first time in life (2) otherwise healthy and not taking medicines for at least 4 weeks (3) singleton pregnancy, and (4) vaginally delivered. Ten healthy children (HC) meeting the same (2-4) criteria served as controls. The study was approved by the Vilnius Regional Committee for Biomedical Research Ethics. Informed consent was obtained	controls, including increased relative abundance of Enterobacteriaceae and Veillonellaceae, and reduced abundance of Coriobacteriaceae, which could be related to the impact of iron deficiency on the gut microbiome.	to healthy controls, including increased relative abundance of Enterobacteriaceae and Veillonellaceae, and reduced abundance of Coriobacteriaceae, which could be related to the impact of iron deficiency on the gut microbiome.

No	Title Year/Country	Methods	Results	Conclusion
		from the parents of all individual participants included in the study.		
3	The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: a review (Paganin et al., 2017) Switzerland	The study design was a randomized, controlled trial with two 4-month trials in Kenyan infants, with a primary outcome of gut microbiome composition and secondary outcomes of iron status, hemoglobin, and incidence of diarrhea. The two trials were analyzed both separately and combined.	- Iron-containing micronutrient powders (MNPs) and iron supplements can modestly increase the risk of diarrhea in infants and young children, especially in areas with poor hygiene and high prevalence of enteropathogens. - Reducing the iron dose in MNPs while maximizing absorption, and adding prebiotics like galacto-oligosaccharides, may help mitigate the adverse effects of iron on the gut microbiome and reduce the risk of diarrhea.	The paper reviews the effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children, particularly in Sub-Saharan Africa, where iron-deficiency anemia is common, and finds that high-dose iron interventions can adversely affect the gut microbiome and increase the risk of diarrhea.

No	Title Year/Country	Methods	Results	Conclusion
4	Effects of iron supplementation on dominant bacterial groups in the gut, faecal SCFA and gut inflammation: a randomised, placebo-controlled intervention trial in South African children (Dostal et al., 2014) South Africa	- Randomized, placebo-controlled intervention trial - 38-week duration - - Participants: - Iron-deficient children (n=22 received iron supplements, n=27 received placebo) - - Iron-sufficient children (n=24 as reference group) - - Measurements: - Fecal samples collected at baseline, 2 weeks, 12 weeks, and 38 weeks - - Analyzed for: - - Abundance of 10 gut bacterial groups (qPCR) - Fecal short-chain fatty acid concentration (HPLC) - Gut inflammation (fecal calprotectin)	- Iron supplementation improved iron status in iron-deficient children without significantly increasing gut inflammation. - Iron supplementation did not significantly affect the dominant bacterial groups in the gut or the concentration of short-chain fatty acids. - - There were no significant differences in gut bacterial composition or short-chain fatty acid levels between iron-deficient, iron-sufficient, and iron-supplemented children.	Iron supplementation did not significantly affect the gut microbiome, short-chain fatty acids, or gut inflammation in African children with low enteropathogen burden.
5	A Review of the Effect of Iron Supplementation	Not mentioned (the study design is not explicitly stated in the	- Iron supplementation can have negative effects on the gut	This paper reviews the evidence on the

No	Title Year/Country	Methods	Results	Conclusion
	on the Gut Microbiota of Children in Developing Countries and the Impact of Prebiotics (Iddrisu et al., 2024) United Kingdom	abstract, but it appears to be a systematic review or meta- analysis examining the existing evidence on the effects of iron supplementation and prebiotics on the gut microbiota in children with iron deficiency)	microbiota of children in developing countries. - Providing prebiotics alongside iron supplements has the potential to be a more effective strategy for combating iron deficiency and anemia in children in the developing world.	effects of iron supplementation on the gut microbiota in children in developing countries, and whether prebiotics can mitigate the adverse gut- related effects of iron supplementation.

DISCUSSION

The findings from the reviewed studies indicate a wide range of impacts that iron supplementation has on gut microbiota and immune function in children with iron deficiency anemia (IDA). These effects are influenced by factors such as the type of iron formulation, dosage, and the inclusion of co-administered nutrients like prebiotics or synbiotics. For instance, Helmyati et al. (2018) observed no significant differences in gut microbiota composition, iron status, or growth parameters between children receiving iron supplementation alone and those supplemented with iron alongside synbiotic fermented milk containing *Lactobacillus plantarum* Dad 13 and fructo-oligosaccharides. This finding suggests that synbiotics may not always provide additional benefits, particularly in populations where dietary and environmental factors are relatively controlled.

On the other hand, the study by Muleviciene et al. (2018) highlighted significant microbial dysbiosis in children with IDA compared to healthy controls. The IDA group exhibited increased relative abundances of *Enterobacteriaceae* and *Veillonellaceae* and decreased levels of *Coriobacteriaceae*. These changes underscore the disruptive effect of iron deficiency itself on gut microbiota, which could impair nutrient absorption and immune function. Such microbial imbalances are critical to address during supplementation, as they could exacerbate gut health issues if left unmanaged.

Dostal et al. (2014) further explored the effects of iron supplementation in a randomized, placebo-controlled trial conducted in South Africa. This study demonstrated that while iron supplementation effectively improved iron status in iron-deficient children, it did not significantly alter dominant bacterial groups in the gut or short-chain fatty acid (SCFA) concentrations. Moreover, the study found no evidence of increased gut inflammation, as measured by fecal calprotectin levels, in children receiving iron supplementation. These findings suggest that iron supplementation may not always provoke adverse changes in gut microbiota composition, particularly in populations with a lower burden of enteropathogens. In contrast, Paganin et al. (2017) reviewed data from trials conducted in Sub-Saharan Africa, highlighting the risks associated with high-dose iron interventions. These interventions were linked to an increased incidence of diarrhea and adverse alterations in gut microbiota, especially in areas with poor hygiene and a high prevalence of enteric pathogens. To mitigate such risks, the study recommended reducing iron dosages in micronutrient powders (MNPs) and incorporating prebiotics like galacto-oligosaccharides. Such strategies could enhance iron absorption while minimizing its adverse effects on the gut microbiome. Iddrisu et al. (2024) provided a broader perspective through a systematic review that emphasized the potential of prebiotics in alleviating the negative gut-related effects of iron supplementation. Prebiotics can support the growth of beneficial gut bacteria, thereby counteracting the dysbiosis often associated with iron supplementation. This dual approach of combining iron with prebiotics not only addresses IDA but also promotes a healthier gut environment, which is particularly

beneficial for children in developing countries where gut health challenges are more pronounced.

CONCLUSION

The studies reviewed underscore the importance of tailoring iron supplementation strategies to the specific needs and contexts of children with IDA. While iron supplementation is vital for correcting anemia and supporting growth and development, its effects on gut microbiota and immune function can vary widely. High-dose iron regimens, particularly in regions with poor sanitation, may disrupt gut microbiota and increase the risk of infections. Therefore, optimizing iron supplementation strategies through reduced dosages, the inclusion of prebiotics, or the use of synbiotic formulations could enhance outcomes by balancing efficacy with safety.

Future research should prioritize personalized approaches that consider regional dietary patterns, environmental conditions, and baseline microbiota compositions. Such targeted strategies are essential for improving the management of IDA in children, minimizing potential side effects, and promoting long-term health and well-being.

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