

PREVALENCE AND MANAGEMENT OF IRON DEFICIENCY ANEMIA IN CHILDREN: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Even in affluent nations, IDA is still a significant public health issue, particularly for young children and women who are ready to have children.

Aims : This systematic review is to review the treatment and prevalence of iron deficiency anemia in children.

Methods: This study demonstrated compliance with all requirements by means of a comparison with the standards established by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. Thus, the specialists were able to guarantee that the research was as current as feasible. Publications released between 2014 and 2024 were considered for this search strategy. This was accomplished by utilizing a number of distinct online reference sites, including Pubmed, ScienceDirect, and SagePub. It was determined that reviews, previously published works, and partially completed works would not be included.

Result: In the PubMed database, the results of our search brought up 353 articles, whereas the results of our search on SCIENCE DIRECT brought up 8.865 articles, our search on SAGEPUB brought up 3.269 articles. The results of the search conducted for the last year of 2014 yielded a total 184 articles for PubMed, 4.071 articles for SCIENCE DIRECT and 1.144 articles for SAGEPUB. In the end, we compiled a total of 5 papers, 3 of which came from PubMed, 1 of which came from SCIENCE DIRECT and 1 of which came from SAGEPUB. We included five research that met the criteria.

Conclusion: In summary, with its haematological repercussions of anemia, IDA is a prevalent and significant children health concern. To assess the effects of IDA on immunity and neurocognition, additional research is necessary. The key to successfully treating children with IDA is early identification and diagnosis of the condition together with competent interpretation of laboratory tests.

Keyword: Iron deficiency anemia, children, prevalence

INTRODUCTION

A hemoglobin (Hb) value two standard deviations below the mean Hb concentration for a normal population of the same gender and age range is considered anemia, according to the World Health Organization. ID, which can be brought on by either excessive iron loss or inadequate intake, is a condition in which there is not enough iron to support normal physiological activities. While IDA marks the most severe end of the spectrum of ID, the first stage of ID begins with decreased iron reserves without anemia.^{1,2}

The most prevalent kind of anemia and the most common hematological illness in childhood and adolescence is iron deficiency anemia (IDA), which affects 20.1% of children and adolescents in industrialized nations between the ages of 0 and 4 and 5.9% between the ages of 5 and 14 (39 and 48.1% in underdeveloped nations). Reduced MCV and MCH, as well as Hb levels below the normal range for age and sex, are the hallmarks of this hypochromic and microcytic anemia.

A fetus, newborn, and child's growth all depend on iron as a nutrient. The amount of iron that is ingested and absorbed by the body depends on diet. The equilibrium between this nutrient's absorption and release from the cells where it is regenerated and stored determines its homeostasis.^{3,4}

Iron is liberated into the bloodstream and transported there by the plasma protein transferrin. It is also absorbed into the duodenum by enterocytes through nutrition, and it is recycled by macrophages from senescent erythrocytes and liver reserves. Insufficient iron is better absorbed by the intestines; excess iron is retained as hemosiderin in the liver, spleen, and bone marrow and as ferritin in enterocytes. Ferroportin, whose expression is dependent on hepcidin activity, mediates the release of free iron ions in the plasma, which is necessary for maintaining its homeostasis.⁴

Not related to anemia, mild to severe iron deficiency can cause weariness and/or a reduced ability to tolerate physical activity. The typical clinical appearance of moderate to severe iron deficiency involves tiredness and pallor, which are typical anemia symptoms. More specifically, there may be emotional and behavior difficulties accompanied by a reduction in academic performance, pica, mucous trophic lesions (stomatitis, glossitis), restless leg syndrome, and repeated infections. Early-life sideropenia has been linked to long-term neurocognitive deficits, lowered learning potential, and altered motor function.^{5,6}

Clinical trials evaluating different oral iron formulations, their dose, and duration are not reported.⁷ Consequently, despite the fact that textbooks often recommend taking 3 to 6 mg/kg/day of iron twice or three times a day, there is mounting evidence to support the use of smaller dosages in an effort to achieve comparable or even better efficacy and fewer side effects in both adults⁸⁻¹¹ and children.¹²⁻¹⁴

The most common kind of anemia in children is iron deficiency anemia. New horizons in diagnosis and therapy are being discovered daily, despite the fact that much has previously been learnt about this. In the presence of specific etiopathogenetic moments, such as concurrent infection, inflammation-related anemia, and genetic iron deficiency anemia refractory to oral treatment (IRIDA), the identification and characterization of the hepcidin molecule may aid in improving the definition of sideropenia and tracking the response to treatment. In terms of oral treatment, further research should be done on the usage of liposomal and glycinate preparations as early findings indicate they are effective and have less adverse effects than other formulations. New advancements in parenteral treatment for pediatric patients are anticipated.⁶

Under the age of 14, molecules like ferrocaryxymaltose, which may be administered once and have mild to moderate side effects, may be a useful alternative, but they are not yet approved for use. The evidence suggests that vegetarian diets with a favorable safety profile may be observed when thinking about eating habits, as long as the doctor closely monitors them. Therefore, further research is required to advance our understanding of this common condition and the diagnostic and treatment approaches associated with it.⁶

METHODS

Protocol

The author of this study ensured that it complied with the standards by adhering to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. This is done to guarantee the accuracy of the results that are derived from the investigation. Thus, the specialists were able to guarantee that the research was as current as feasible. Publications released between 2014 and 2024 were considered for this search strategy. This was accomplished by utilizing a number of distinct online reference sites, including Pubmed, ScienceDirect, and SagePub. It was determined that reviews, previously published works, and partially completed works would not be included.

CRITERIA FOR ELIGIBILITY

In order to complete this literature evaluation, we looked at published research that discusses the prevalence and management of iron deficiency anemia in children. This is done to enhance the patient's therapy management and to offer an explanation. This paper's primary goal is to demonstrate the applicability of the issues that have been noted overall.

To be eligible to participate in the study, researchers had to meet the following requirements: 1) English must be used to write the paper. The manuscript must fulfill both of these conditions in order to be considered for publication. 2) A few of the examined studies were released after 2013 but prior to the time frame considered relevant by this systematic review. Editorials, submissions without a DOI, already published review articles, and entries that are nearly exact replicas of journal papers that have already been published are a few examples of research that are prohibited.

SEARCH STRATEGY

We used "iron deficiency anemia", "children" and "prevalence" out using the PubMed and SAGEPUB databases by inputting the words: ("iron deficiency anaemia"[All Fields] OR "anemia, iron deficiency"[MeSH Terms] OR ("anemia"[All Fields] AND "iron deficiency"[All Fields]) OR "iron-deficiency anemia"[All Fields] OR ("iron"[All Fields] AND "deficiency"[All Fields] AND "anemia"[All Fields]) OR "iron deficiency anemia"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) AND ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms] OR "prevalance"[All Fields] OR "prevalences"[All Fields] OR "prevalence s"[All Fields] OR "prevalent"[All Fields] OR "prevalently"[All Fields] OR "prevalents"[All Fields]) AND ("manage"[All Fields] OR "managed"[All Fields] OR "management s"[All Fields] OR "managements"[All Fields] OR "manager"[All Fields] OR "manager s"[All Fields] OR "managers"[All Fields] OR "manages"[All Fields] OR "managing"[All Fields] OR "managment"[All Fields] OR "organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields])) AND (2014:2024[pdat]) used in searching the literature.

DATA RETRIEVAL

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

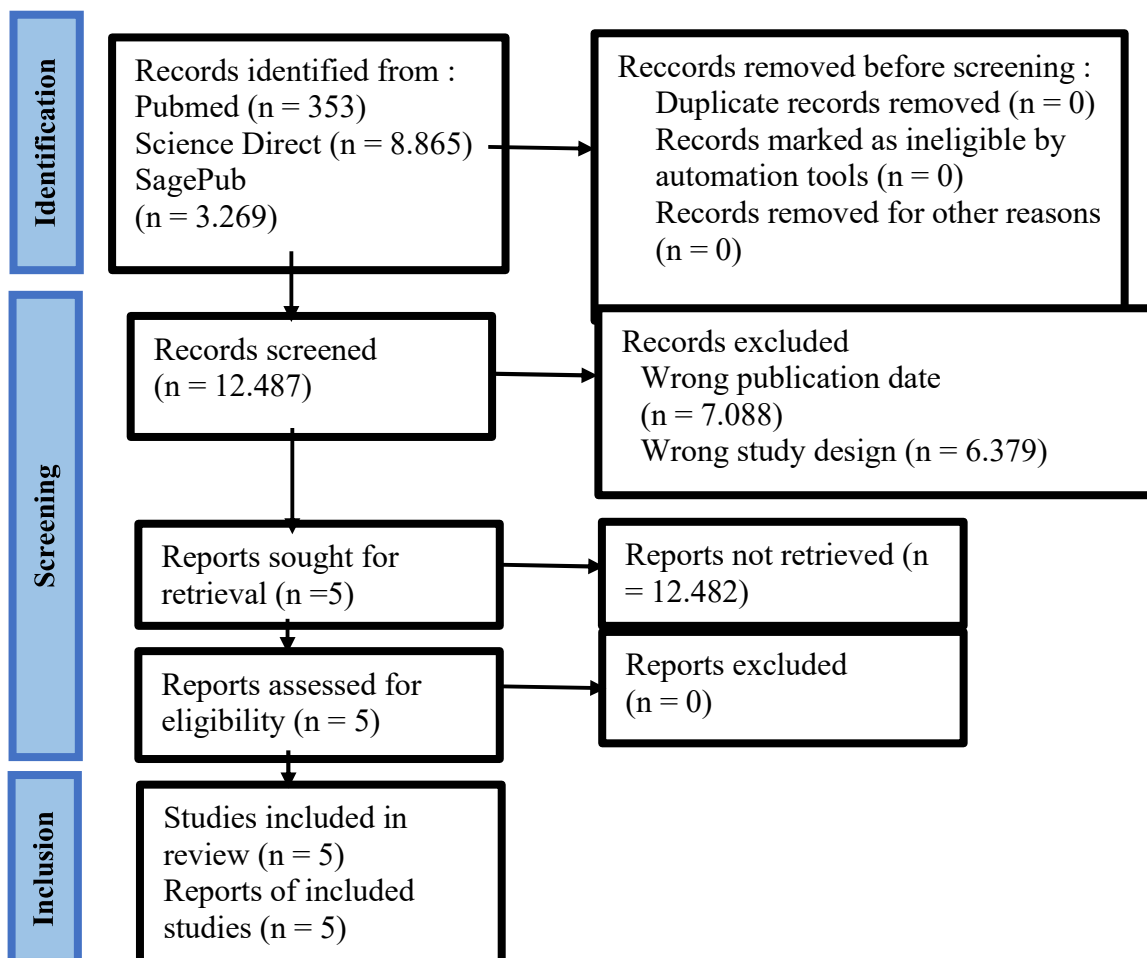


Figure 1. Prisma Flow Diagram

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

QUALITY ASSESSMENT AND DATA SYNTHESIS

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 353 articles, whereas the results of our search on SCIENCE DIRECT brought up 8.865 articles, our search on SAGEPUB brought up 3.269 articles. The results of the search conducted for the last year of 2014 yielded a total 184 articles for PubMed, 4.071 articles for SCIENCE DIRECT and 1.144 articles for SAGEPUB. In the end, we compiled a total of 5 papers, 3 of which came from PubMed, 1 of which came from SCIENCE DIRECT and 1 of which came from SAGEPUB. We included five research that met the criteria.

Carboo, et al¹⁵ (2023) showed that reduced levels of vitamin D have been linked to higher risks of iron deficiency anemia (IDA) and anemia. Strategies for preventing anemia should take into account a person's vitamin D status, particularly in areas where iron and vitamin D deficiency coexist.

Sunardi, et al¹⁶ (2021) showed that among children aged 6-36 months, the prevalence of anemia was 29.4%. Two dietary variables were shown to be strongly connected with anemia as risk factors: consumption of cow's milk formula and intake of zinc.

Wegmuller, et al¹⁷ (2023) showed that the hepcidin-guided screen-and-treat approach to iron administration was successful in lowering the total amount of iron administered; however, it was not as effective as the WHO's standard of care in terms of morbidity or safety outcomes, and it was much less effective at raising hemoglobin and treating iron deficiency and anemia.

Table 1. The literature include in this study

| Author | Origin | Method | Sample | Result |
|---|--------------|-----------------------|--------------|---|
| Carboo et al, 2023¹⁵ | South Africa | Randomized study | 172 patients | Across the board, those with 25(OH)D < 30 ng/mL had a substantially greater frequency of IDA (64.7 % vs 43.0 %, p = 0.023) and were linked to a higher risk of IDA in the crude analysis (OR: 2.434 1.114, 5.318, p = 0.026). In the undernourished children, serum 25(OH)D < 30 ng/mL was linked to greater than five times (OR: 5.386, 95%CI: 1.528, 18.985, p = 0.009) and four times (OR: 4.046, 95%CI: 1.022, 16.009, p = 0.046) higher risks of anemia and IDA, respectively. TNF-α levels in the whole group was significantly reduced by 55.7 percent (p = 0.008) after taking vitamin D supplements. |
| Sunardi et al, 2021¹⁶ | Indonesia | Cross sectional study | 180 patients | The average hemoglobin level was 11.4 ± 1.7 mg/dL, and 29.4% of the population had anemia. There was a strong correlation found between the following factors and an |

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| | | | | increased risk of anemia: not consuming cow's milk formula; insufficient consumption of lipids, protein, calcium, vitamin D, iron, zinc, vitamin A, vitamin C, vitamin B6, and vitamin B12. The only variables that were shown to be associated with anemia were the use of cow's milk formula and zinc intake. |
| Wegmuller et al, 2023¹⁷ | Switzerland | Controlled study | 783 patients | Neither of the two screen-and-treat regimens met the predetermined non-inferiority margin of -5 g/L and were significantly less effective at improving hemoglobin (-5.6 g/L [98.3% CI -9.9 to -1.3] in the 12 mg screen-and-treat group and -7.8 g/L [98.3% CI -12.2 to -3.5] in the 6 mg screen-and-treat group). The iron dosage was decreased to 6.1 mg per day with the 12 mg screen-and-treat regimen and to 3.0 mg per day with the 6 mg screen-and-treat regimen. 316 individuals had 580 adverse events recorded, eight of which were severe enough to need hospitalization, mostly as a result of diarrheal illness (one [1%] in the control group, three [2%] in the 12 mg screen-and-treat group, and four [3%] in the 6 mg screen-and-treat group). Diarrhea (145 occurrences [25%]), upper respiratory tract infections (194 [34%]), lower respiratory tract infections (62 [11%]), and skin infections (122 [21%]) were the most frequent causes of non-serious adverse events (n=572). The research treatments were not found to be associated with any adverse effects. |
| Clark et al, 2017¹⁸ | China | Cohort study | 955 patients | Iron level and breastfeeding were related (P <.001). In Zhejiang, formula-fed newborns had 0% IDA, but breastfed infants had 27.5%. When compared to formula-fed babies, the chances of iron deficiency/IDA were higher in breastfed and mixed-fed infants: the odds ratio for breastfed vs formula-fed infants was 28.8 (95% CI, 3.7-226.4) and for mixed-fed versus formula-fed infants was 11.0 (95% CI, 1.2-103.2). In Hebei, 2.8% of formula-fed |

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| | | | | newborns and 44.0% of breastfed infants had IDA. The chances of IDA were higher in the mixed-fed vs. formula-fed group (21.0 95% CI, 7.3-60.9) and breastfed compared. formula-fed (78.8 95% CI, 27.2-228.1) after covariable correction. |
| Powers et al, 2015¹⁹ | USA | Randomized study | 1,217 patients | The majority of responders would recommend ferrous sulfate as a therapy (N = 335, 84%), split twice daily (N = 272, 68%), and dosed at 6 mg/kg/day (N = 248, 62%). After anemia has resolved and serum ferritin has returned to normal, the suggested length of iron therapy varied greatly, ranging from 0 to 3 months. The majority of responders (N = 327, 83%) suggested ferrous sulfate for a teenager with IDA and excessive menstrual bleeding, with dosage determined by the number of pills taken each day. The most common recommendation for IDA patients who did not respond to oral treatment was intravenous iron therapy, which included 15% (N = 60) using low molecular weight iron dextran, 48% (N = 188) using iron sucrose, and 17% (N = 68) using ferric gluconate. |

Clark, et al¹⁸ (2017) showed that iron deficiency/IDA was frequent and breastfed infants had higher odds of having it at nine months of age compared to mixed-fed infants. While there is no denying the advantages of nursing, our results support the notion that in many situations, breastfeeding later in infancy identifies infants who are at risk for iron deficiency/IDA.

Powers, et al¹⁹ (2015) showed that responding ASPHO members' approaches to diagnosing and treating pediatric IDA varied greatly. More study on IDA management is required, as there is currently insufficient data to support therapeutic decision-making.

DISCUSSION

The most common hematological condition affecting children is iron deficiency anemia (IDA), which affects 20.1% of children in developed nations between the ages of 0 and 4 and 5.9% of children between the ages of 5 and 14 (between 39 and 48.1% in underdeveloped nations). Even though IDA has been known about for a while, there are still unanswered questions and opportunities to enhance how this illness is managed.

Prior to analysis, the BRINDA technique was used to correct the amounts of ferritin and sTfR for inflammation. Serum ferritin concentrations less than 12 µg/L were considered iron deficient. The definition of iron deficiency erythropoiesis (IDE) was sTfR > 8.3 mg/L. Tissue iron deficiency was defined as BIS < 0 mg/kg, and body iron storage (BIS) was computed as $-\log_{10}((sTfR \text{ in mg/L} \times 1000)/\text{ferritin in } \mu\text{g/L}) - 2.8229$ [28, 29]. sTfR/log ferritin was used to generate the transferrin-ferritin index (TR-F index), with a cut-off of > 5.6 designating a shortage of bone marrow iron reserves. For altitudes more than 1000 meters above sea level, hemoglobin values were corrected by deducting 0.2 g/dL. Hb < 11.0 g/dL was the definition of anemia, while IDA was defined as the co-occurrence of anemia, sTfR > 8.3 mg/L, and/or ferritin concentration < 12 µg/L.^{20,21}

Numerous observational studies have linked vitamin D (vitD) status to anemia. Experimental research indicates that vitD and iron metabolism may interact.²² By binding to the vitamin D receptor (VDR) on the hepcidin gene, which results in the suppression of its transcription and a decrease in hepcidin mRNA levels, vitamin D may, on the one hand, improve

iron status and erythropoiesis by inhibiting the production of hepcidin, the primary regulator of systemic iron homeostasis.²³⁻²⁵

Carboo, et al measured serum 25(OH)D, haemoglobin (Hb), ferritin and soluble transferrin receptor in 121 undernourished and 51 non-undernourished children in clinics in the North-West Province of South Africa. Serum 25(OH)D levels below 30 ng/mL were linked to four times higher odds of undernutrition and five times higher odds of anemia in the undernourished children, but lower odds of anemia were seen in the non-undernourished children. Though not statistically significant, supplementation with three doses of 50,000 IU of vitamin D produced encouraging increases in ferritin, BIS, and hemoglobin.¹⁵

In Indonesia, Sunardi et al did study with 180 subjects. The average hemoglobin level was 11.4 ± 1.7 mg/dL, and 29.4% of the population had anemia. There was a strong correlation found between the following factors and an increased risk of anemia: not consuming cow's milk formula; insufficient consumption of lipids, protein, calcium, vitamin D, iron, zinc, vitamin A, vitamin C, vitamin B6, and vitamin B12. The only variables that were shown to be associated with anemia were the use of cow's milk formula and zinc intake. In conclusion, 29.4% of children between the ages of 6 and 36 months had anemia.¹⁶

Globally, the most common nutritional condition is iron deficiency. Iron supplementation has been linked to substantial negative consequences in children throughout low-income countries, has a poor effectiveness, and produces gastrointestinal side-effects that restrict compliance. The iron dosage was decreased to 6.1 mg per day with the 12 mg screen-and-treat regimen and to 3.0 mg per day with the 6 mg screen-and-treat regimen. 316 individuals had 580 adverse events recorded, eight of which were severe enough to need hospitalization, mostly as a result of diarrheal illness. Diarrhea (145 occurrences [25%]), upper respiratory tract infections (194 [34%]), lower respiratory tract infections (62 [11%]), and skin infections were the most frequent causes of non-serious adverse events (n=572).¹⁷

Multiple logistic regression assessed associations between feeding pattern and iron status by Clark, et al. Iron deficiency/IDA was frequent and breastfed infants had higher odds of having it at nine months of age compared to mixed-fed infants. While there is no denying the advantages of nursing, our results support the notion that in many situations, breastfeeding later in infancy identifies infants who are at risk for iron deficiency/IDA. It is necessary to establish protocols for identifying and preventing iron deficiency/IDA in breastfed newborns.¹⁸

Powers, et al did survey of pediatric hematology/oncology specialist with 1.217 patients. The majority of responders suggested ferrous sulfate as a therapy, split twice daily at a level of 6 mg/kg/day. After anemia has resolved and serum ferritin has returned to normal, the suggested length of iron therapy varied greatly, ranging from 0 to 3 months. The majority of responders suggested ferrous sulfate for a teenager with IDA and excessive menstrual bleeding, with dosage determined by the number of pills taken each day. Intravenous iron therapy was most commonly advised for IDA patients who did not respond to oral treatment; 48% of these patients used iron sucrose, 17% ferric gluconate, and 15% low molecular weight iron dextran.¹⁹

CONCLUSION

In summary, with its haematological repercussions of anemia, IDA is a prevalent and significant children health concern. To assess the effects of IDA on immunity and neurocognition, additional research is necessary. The key to successfully treating children with IDA is early identification and diagnosis of the condition together with competent interpretation of laboratory tests.

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