Iran J Pediatr. 2022 August; 32(4):e124071.
doi: 10.5812/ijp-124071.
Published online 2022 July 23.
Systematic Review

Iron Deficiency Anemia in Children with and Without Dental Caries: A Systematic Review and Meta-Analysis

Narjes Amrollahi [1,*] and Mohammad Javad Tarrahi [2]

[1] Department of Pediatric Dentistry, Dental Research Center, Dental Research Institute, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran
[2] Department of Epidemiology and Biostatistics, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran

[*] *Corresponding author*: Department of Pediatric Dentistry, Dental Research Center, Dental Research Institute, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: +98-3137925539, Email: narges1amr@yahoo.com

Received 2022 April 03; **Revised** 2022 May 09; **Accepted** 2022 May 25.

Abstract

Context: Dental caries is a complication affecting the health of society, so it is vital to manage. Most children with early childhood caries (ECC) are believed to undergo anemia, altered physical growth patterns, and low weight.
Objectives: This study aimed to evaluate the relationship between dental caries and iron deficiency anemia (IDA) in children.
Evidence Acquisition: The medical subject headings (MeSH) and non-MeSH were applied to choose the search terms. English language case-control studies assessing blood factors associated with IDA in children with and without dental caries were potentially eligible. Two independent researchers carried out an electronic search to retrieve studies published in the English language on Scopus, ProQuest, PubMed, and Web of Science databases in October 2020. Initially, 494 articles were obtained. Of them, 17 were eligible for inclusion, of which eight studies were eliminated. The meta-analysis was done using the comprehensive meta-analysis software (version 2, Biostat). The forest plots estimated the mean difference and depicted the results of the meta-analysis. The Egger's and Begg's tests assessed the publication bias.
Results: A significant difference was observed in serum ferritin levels between the case and control groups, with a mean difference of -0.230 (95% confidence interval (CI): -0.446 to -0.015; P value = 0.008). Blood hemoglobin and mean corpuscular volume (MCV) levels indicated significant mean differences of -0.991 (95% CI: -1.813 to -0.169) and -0.807 (95% CI: -1.336 to -0.279), respectively (P value < 0001). In the case group, all three blood parameters were significantly lower.
Conclusions: Hemoglobin, serum ferritin, and MCV levels are lower in children with dental caries than in caries-free children.

Keywords: Child, Dental Caries, Anemia, Iron Deficiency

1. Context

Early childhood caries (ECC) is a form of dental caries that influences the primary teeth in children under 6 years (1, 2). Severe dental caries affect children's growth, development, and health (3) and can negatively influence the parents and community socially and economically (4). Dental caries can cause oral pain, interfering with eating and sleeping and making a child underweight (5, 6) and stunted (7-9). It is believed that infants with severe dental caries are anemic, scrawny, and ill-fed and undergo changes in physical growth patterns, thereby suffering from nutritional deficiency anemia, especially iron deficiency, and poor oral health-related quality of life (OHRQOL) (10).

Anemia in children can have several etiologies. The common causes of anemia are (1) iron deficiency anemia; (2) anemia of acute blood loss; (3) anemia of chronic inflammation; (4) anemia of malnutrition; and (5) inherited hemoglobinopathy. Iron deficiency anemia is the most common cause of anemia (11). Numerous factors such as genetic and dietary factors, inflammatory processes, and environmental factors like dental caries and low socioeconomic status are involved in iron deficiency anemia (IDA) (12-14).

The association between ECC and IDA as two multifactorial parameters is bidirectional. Diet is highly associated with ECC and IDA separately, and a relationship may exist between these two parameters. Prolonged breastfeeding may be associated with both ECC and IDA. Toothache in ECC can affect a child's overall health. Impaired chewing due to caries in children can decrease the consumption of iron-rich foods such as meat and nuts. Besides, IDA may cause damage to developing central nerves, leading to disabilities and negatively impacting the children's quality of life (15-17).

Some studies reported that children with severe early childhood caries (S-ECC) were significantly more likely to undergo IDA (18, 19). In contrast, others reported that anemia was not significantly linked to the number of decayed and filled teeth or surfaces (20) and found no causal association between S-ECC and anemia (21, 22). Gurunathan et al. (23) also revealed in their review that children with S-ECC seemed to have significantly higher odds of IDA. In addition, Folayan et al. (24) indicated that anemia had an inverse relationship with ECC in older preschool children.

Inconsistent results in the review of evidence show an inconclusive association between anemia and ECC. To the researchers' knowledge, there is no macro-level information about the association between these two public health issues. Understanding this association might help design low-cost and effective interventions using the common risk factor approach and address at-risk children in regions with the most widespread problems. On the other hand, identifying this potential relationship between dental caries and IDA will help pediatricians, pediatric dentists, health care policymakers, and family physicians promote child health and implement preventive policies.

2. Objectives

The purpose of this systematic review was to provide a meticulous summary of all primary research in this field and analyze their data to find a possible relationship between iron deficiency anemia and dental caries.

3. Evidence Acquisition

This systematic review was performed according to the guidelines of preferred reporting items for systematic reviews and meta-analysis (PRISMA statement) (25).

3.1. Search Strategy

Relevant studies were searched after defining a well-focused PECO question and the inclusion and exclusion criteria (Table 1) based on the study subject. Due to the discrepancies in the results of the studies, the present study only used the case-control studies conducted in this field to obtain more reliable results. The included articles examined blood factors (O, outcome) in children (P, population) with dental caries (E, exposure) versus caries-free children (C, comparison).

The key terms were selected based on the medical subject headings (MeSH) and non-MeSH terms in simple terms or combinations. The major search terms consisted of "dental caries," "child," and "iron deficiency anemia." The searched databases included Scopus, ProQuest, PubMed, and ISI Web of Science. No filters were applied except for age group (< 18 years) and language (English). The search strategy retrieved the articles involving (anemia OR anemia iron deficiency OR low serum iron level OR iron-deficient* anemia OR iron-deficient* anemia OR low iron status) AND (optimal iron level OR control OR no anemic OR optimal iron status) AND (caries OR carious OR tooth decay OR teeth decay OR dental caries OR cavitated caries lesion OR cavitated carious lesion OR dental caries and child* OR early childhood caries OR tooth decay and child* OR severe early childhood caries OR baby bottle caries) AND (primary teeth OR primary tooth OR deciduous teeth OR deciduous tooth OR deciduous OR primary dentition OR teeth, deciduous OR tooth, deciduous OR pediatric dentistry OR dentistry for children OR pedodontics OR child dentistry). Two authors found other studies independently through hand-searching of key journals, checking the references of the articles included in the study, and personal communication with experts in the field. In this review, articles were included published between 1990 and 2020 (publication period).

3.2. Selection of Studies

A reference management system (EndNote) was used to upload all the potentially eligible studies and eliminate the duplicate ones. Using the search strategy developed, two trained reviewers independently searched the above-mentioned databases. Two reviewers were encouraged to work with the third one, who was experienced in the process of systematic reviews, to attend relevant training. The reviewer's article selection should be based on the inclusion and exclusion criteria. Specified consensus and third reviewer methods were used to resolve discrepancies and design a data extraction form based on PECO. The reviewers then reviewed the abstracts of the articles and chose those that met the inclusion criteria. They screened the full texts of the chosen abstracts and excluded some of them. The correlation coefficients between the two researchers' search results were 0.94 and 1 in the abstract and full-text, respectively. The third researcher who made the final decision resolved disagreements between the two researchers.

3.3. Data Extraction

Two researchers independently extracted data from different studies as a table (Table 2). The variables included the author's name, publication year, children's age, the sample size of children in the case and control groups, type of study, the mean and standard deviation of blood parameters in the case and control groups, and a brief conclusion of each study.

3.4. Assessment of Risk of Bias

Based on the Newcastle-Ottawa scale (NOS), each study was evaluated for inner-methodological risk of bias. The

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
English language case-control studies investigating iron deficiency anemia in children with and without dental caries	Case reports
	Editorial letters
	Pilot studies
	Historical reviews
	Studies in languages other than English
	Cohorts
	Cross-sectional studies

risk of bias in the included studies was assessed by the NOS modified for observational studies (25). The scale domains consisted of comparability of the groups, measurement of exposure and outcomes, and selection of cases and controls. Studies were classified as having low, moderate, and high methodological quality according to the NOS scores < 5, 5 - 7, and > 7, respectively. This quality assessment was utilized merely for the descriptive section, not the inferential part.

3.5. Statistical Analysis

Using the comprehensive meta-analysis software (version 2, Biostat), a meta-analysis was conducted to determine the relationship between anemia and the prevalence of dental caries in children. The random-effects model determined the standard mean difference in continuous data at a 95% confidence interval (CI). The P value and I^2 statistics analyzed heterogeneity in studies. Thus, a P value < 0.05 or an $I^2 > 50\%$ showed heterogeneity. Forest plots estimated the mean difference and depicted the results of the meta-analysis. The Egger's and Begg's tests assessed publication bias.

4. Results

4.1. Study Selection

Figure 1 illustrates the flow diagram of the search strategy. A total of 494 articles [139 on ProQuest, eight on Web of Science, 211 on Scopus, and 136 on MEDLINE (PubMed)] were obtained. Excluding the duplicate and irrelevant articles, the abstracts of 29 articles were analyzed. Finally, 17 articles were subjected to full-text analysis, but eight were excluded because they were cross-sectional and did not have a control group to compare.

4.2. Quantitative Analysis

The study of Deane et al. (33) could not be included in the meta-analysis because blood factors were not reported precisely. Finally, eight studies were included in the meta-analysis. Table 3 presents the descriptive results and parameters of each study.

4.3. Risk of Bias

Table 3 indicates a detailed assessment of the risk of bias. The NOS is a star rating system with eight items that assigns a maximum of nine stars to three domains, including selection (four stars), comparability (two stars), and exposure measurement (risk factor) in case-control studies (three stars). The quality was highly different among studies; one study indicated low quality, six studies showed moderate quality, and two studies demonstrated high quality.

4.4. Study Characteristics

All the reviewed articles were case-control studies that assessed the blood factors associated with IDA among 1,116 participants in the case (children with dental caries) and control (caries-free children) groups. Of the eight articles included in the systematic review, seven (18, 26-28, 30-32) evaluated blood ferritin levels, and seven assessed hemoglobin levels (18, 26-30, 32). Moreover, six studies (18, 26-30) evaluated mean corpuscular volume (MCV).

Abed et al. (26) assessed other blood factors like HCT, red blood cells (RBCs), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW), total iron-binding capacity (TIBC), and serum iron. Shaoul et al. (27) measured RDW, iron, and transferrin in addition to the major blood factors evaluated in this systematic review. Packed cell volume (PCV) and MCHC were also evaluated in the study by Bansal et al. (29).

Among the studies included, three (26, 30, 31) compared children with ECC with caries-free children. While in four (18, 26, 29, 30) studies, children with severe early childhood caries were compared with caries-free children. In Nayak et al. (32) study, children with DMFT more than zero were compared with caries-free children.

Table 2. The Main Characteristics of Studies Included in Systematic Review [a]

Author	Age	Type of Study	Study Group (S)	Control Group (C)	Parameters	Conclusion
1- Abed et al. (26)	2 - 5 years	Case-control	100 children with early dental caries	50 caries-free children	1- Hb (g/dL): S: 10.01 ± 0.83; C: 11.80 ± 0.91 2- Red blood cells (RBCs): S: 4.17 ± 0.35; C: 4.52 ± 0.44 3- HTC (%): S: 30.27 ± 3.45; C: 36.29 ± 3.78 4- Mean corpuscular volume (MCV): S: 72.56 ± 4.96; C: 80.3± 6.35 5- Mean corpuscular hemoglobin (MCH) (pg): S: 24.05 ± 1.91; C: 26.18 ± 2.02 6- MCHC (g/dL): S: 33.16 ± 1.66; C: 32.62 ± 1.32 7- Serum iron (mg/mL): S: 0.40 ± 0.10; C: 0.73 ± 0.23 8- Serum ferritin (ng/mL): S: 31.86 ± 18.2; C: 40.96 ± 21.1	All parameters, except for red cell distribution width (RDW) and total iron-binding capacity (TIBC), were significantly lower in the case group (P < 0.05)
2- Shaoul et al. (27)	3 - 18 years	Case-control	30 children with severe dental caries	30 caries-free children	1- Hb (g/dL): S: 11.22 ± 0.46; C: 12.45 ± 0.71 2- MCV (fL): S: 75.8 ± 4.7; C: 82.9 ± 7.7 3- RDW (%): S: 15.0 ± 1.2; C: 12.8 ± 1.4 4- Ferritin (ng/mL): S: 14.2 ± 6.2; C: 30.6 ± 13.9 5- Iron (mcg/dL): S: 47.5 ± 11.4; C: 75.2 ± 19.0 6- Transferrin (mg/dL): S: 285.1 ± 34.9; C: 262.1 ± 31.5	All parameters, except for RDW and transferrin, were significantly lower in the case group (P < 0.0001); RDW and transferrin were significantly higher in the case group (P < 0.0001 and P = 0.01, respectively)
3- Schroth et al. (18)	Under 72 months	Case-control	144 children with S-ECC	122 caries-free children	1- Ferritin (μg/L): S: 29.1 ± 18.4; C: 30.2 ± 17.4 2- Hemoglobin (g/L); S: 109.8 ± 8.7; C: 121.7 ± 7.6 3- MCV: S: 78.3 ± 5.3; C:78.5 ± 3.8	Ferritin and MCV levels did not differ significantly between the groups (P = 0.62 and P = 0.74 respectively), and children with S-ECC had significantly lower mean hemoglobin levels than controls (P < 0.001)
4- Iranna Koppal et al. (28)	2 to 6 years	Case-control	30 children with SECC	30 caries-free children	1- Ferritin (μg/L): S: 29.33 ± 24.29; C: 76.05 ± 84.74 2- Hemoglobin (gm/dL); S: 9.49; C: 10.73 3- MCV: S: 75.70; C: 83.10	The serum ferritin, hemoglobin, and MCV levels were significantly lower in the case group than in the control group (P < 0.05)
5- Bansal et al. (29)	2 - 6 years	Case-control	30 children with S-ECC	30 controls	1- Hemoglobin (Hb) (g/dL): S: 11.3 ± 1.5; C: 12.8 ± 2.0 2- MCV (μm^3): S: 74.0 ± 7.5; C: 87.5 ± 11.0 3- MCHC (g/dL): S: 32.8 ± 2.6; C: 33.2 ± 1.7 4- Packed cell volume (PCV) (%): S: 34.7 ± 2.5; C: 38.5 ± 6.0	All parameters (Hb, MCV, and PCV), except for MCHC, were significantly lower in the case group (P = 0.002, P < 0.001, and P = 0.002, respectively)
6- Shamsaddin et al. (30)	2 - 6 years	Case-control	157 children with ECC	83 caries-free children	1- Hb (g/dL): S: 12.31 ± 1.10; C: 12.38 ± 1.02 2- Ferritin (ng/mL): S: 34.58 ± 25.01; C: 34.63 ± 19.16 3- MCV: S: 76.81 ± 5.66; C: 77.61 ± 4.59	No significant differences were detected in the three parameters (P > 0.05)
7- Jayakumar and Gurunathan (31)	< 72 months	Case-control	79 children with ECC	35 ECC-free children	Ferritin: S: 28.22 ± 20.65; C: 37.40 ± 24.20	Children with ECC had lower ferritin levels than children without ECC (P > 0.05)
8- Nayak et al. (32)	5 - 12 years	Case-control	119 children with DMFT > 0	47 caries-free controls	1- Hb (g/dL): S: 11.82 ± 1.29; C: 12.57 ± 0.92 2- Ferritin (ng/mL): S: 30.71 ± 21.54; C: 31.06 ± 19.32	Only was Hb significantly lower in the case group

[a] Values are expressed as mean ± SD.

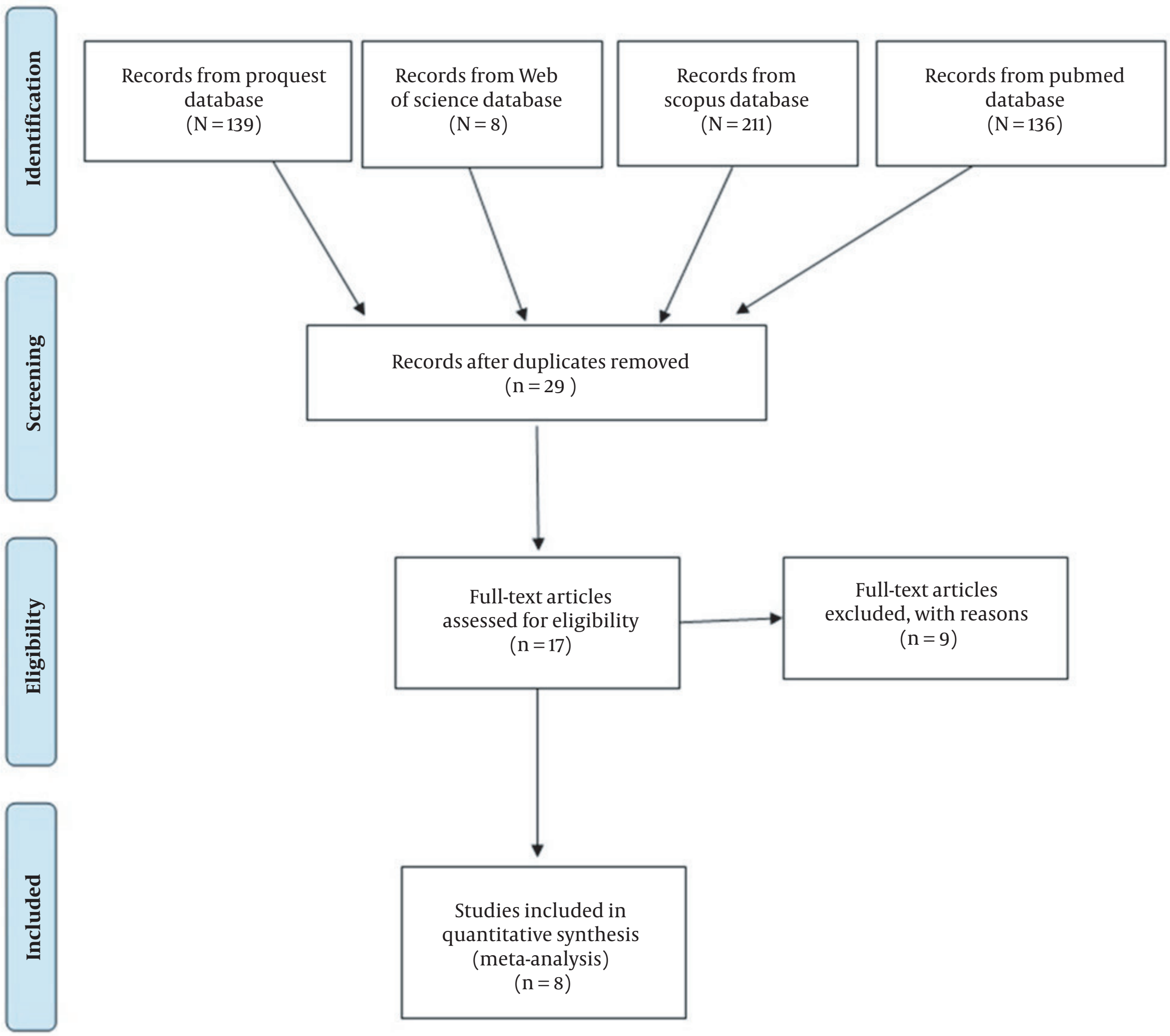

Figure 1. Flow diagram of the search strategy

Table 3. Quality of Evidence of Included Studies Based on the Newcastle-Ottawa Scale (NOS) [a]

Variables	Abed et al. (26)	Shaoul et al. (27)	Schroth, et al. (18)	Iranna Koppal et al. (28)	Bansal et al. (29)	Shamsaddin et al. (30)	Jayakumar and Gurunathan (31)	Nayak et al. (32)	Deane et al. (33)
Adequate case definition	*	*	*	-	*	*	*	*	-
Representativeness of the cases	-	-	-	-	-	*	-	-	-
Selection of controls	-	-	*	-	-	-	-	-	*
Definition of controls	-	-	-	-	*	*	*	*	-
Comparability of cases and controls	*	*	**	*	*	*	-	*	**
Ascertainment of exposure	*	*	*	*	*	*	*	*	*
The same method of ascertainment for cases and controls	*	*	*	*	*	*	*	*	*
Non-response rate	*	*	*	-	*	*	*	*	*
Methodological quality	Mod	Mod	High	Low	Mod	High	Mod	Mod	Mod

[a] NOS methodological quality: Low: Under five; Moderate: Five to seven; High: Above seven.

In all studies included in the systematic review, except for two (27, 32), the studied children were under six years. A statistician (MT) assessed the studies included in the meta-analysis were assessed by a statistician (MT). The funnel plot and Begg's test determined the heterogeneity among these studies.

4.5. Serum Ferritin Outcome

Six articles with a similar methodology evaluated blood ferritin levels as a mean and SD. The heterogeneity showed P = 0.029 and I^2 = 59.942 %, and a random-effects model was used for the meta-analysis. The meta-analysis results indicated a statistically significant difference in serum ferritin levels between the case and control groups, with a mean difference of -0.230 (95% CI: -0.446 to -0.015; P value = 0.008). Serum ferritin level was significantly lower in the case group. Figure 2 shows the forest plots of serum ferritin levels (18, 26, 30-32).

4.6. Hb Outcome

Four articles with a similar methodology evaluated hemoglobin levels as a mean and SD. The heterogeneity showed P > 0.000 and I^2 = 95.766 %, and a random-effects model was used for the meta-analysis. The results also showed a statistically significant difference in blood hemoglobin levels between the case and control groups, with a mean difference of -0.991 (95% CI: -1.813 to -0.169) (P value < 0001). Blood hemoglobin levels were significantly lower in the case group. Figure 3 shows the forest plots of Blood hemoglobin levels (18, 26, 29, 30).

4.7. MCV Outcome

Five articles with a similar methodology reported MCV as a mean and SD. The heterogeneity showed P> 0.000 and I^2 = 90.867%, and a random-effects model was used for the meta-analysis. The meta-analysis results indicated a significant difference in MCV between the case and control groups, with a mean difference of 0.807 (95% CI: -1.336 to -0.279) (P value < 0001). Thus, MCV was significantly lower in the case group. Figure 4 shows the forest plots of MCV (18, 26, 27, 29, 30).

5. Discussion

Early childhood caries is a severe tooth decay that influences infants and young children. These children undergo iron deficiency, growth retardation, and weight loss due to malnutrition, poor chewing ability, and pain (3, 8). Disturbed sleep quality causes inadequate growth in these children due to decreased production of glucosteroids (34).

On the other hand, anemia can occur as a result of factors such as genetic (congenital) factors, inflammatory processes, nutritional factors, and environmental factors like dental caries and low socioeconomic status (13, 35). According to the World Health Organization (WHO), IDA is confirmed if at least two out of three parameters (MCV, serum ferritin, and Hb) are lower than normal (36). The present systematic review provided a meticulous summary of the relationship between iron deficiency anemia and dental caries in children by considering all available case-control studies.

Different factors like socioeconomic condition, diet, race, and sleep patterns can affect anemia. These factors vary in various communities (12, 24, 37). One of the differences between this study and similar studies is that this study only included case-control studies to reduce the possible socioeconomic effects in different societies. Studies were done in communities with different socioeconomic conditions that may affect multifactorial variables such as dental caries and IDA. Having a case group and control group in each community and considering them in the meta-analysis can reduce the effect of community differences. On the other hand, the age group considered in this study differs from other studies; our study included children up to the age of 18, but other studies usually included children with early childhood caries.

Of the studies included in the meta-analysis, six (18, 26, 28, 30-32) with a similar methodology evaluated blood ferritin, four (18, 26-30, 32) assessed hemoglobin levels, and five (18, 26, 27, 29, 30) evaluated MCV. The results indicated that MCV, hemoglobin, and blood ferritin levels were significantly lower in children with dental caries than in those without dental caries.

Several theories have indicated a relationship between ECC and IDA in children with dental caries. Inflammation in ECC can induce cytokine production, which can hinder erythropoiesis and decrease hemoglobin and iron levels. A probable effect of severe caries on children is that chronic dental abscesses and pulpitis influence their growth by causing chronic inflammation, which influences metabolic pathways where cytokines affect erythropoiesis. For example, interleukin-1 (IL-1), which has a wide range of activities against inflammation, can inhibit erythropoiesis. This hemoglobin inhibition can induce anemia due to decreased erythrocyte production in the bone marrow (38).

On the other hand, iron deficiency can destroy the functions of the salivary gland in children and decrease the buffering capacity and dental caries (39). Moreover, ECC-induced malnutrition and chewing inability cause iron deficiency and anemia. A nutritional and health survey showed a prevalence rate of 0.2% - 6.2% for iron deficiency in children aged 4 - 6 years. Various studies have shown

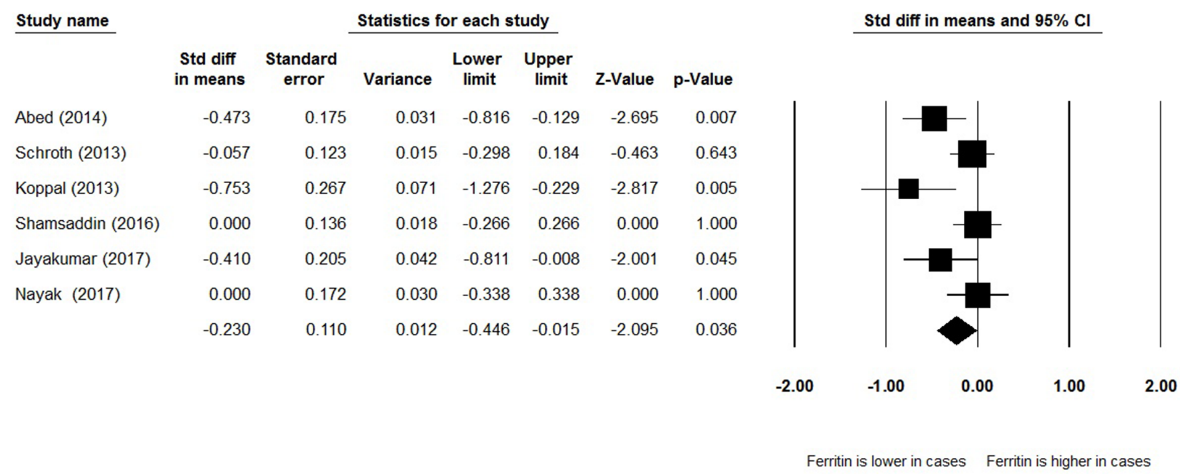

Figure 2. Forest plot of serum ferritin level

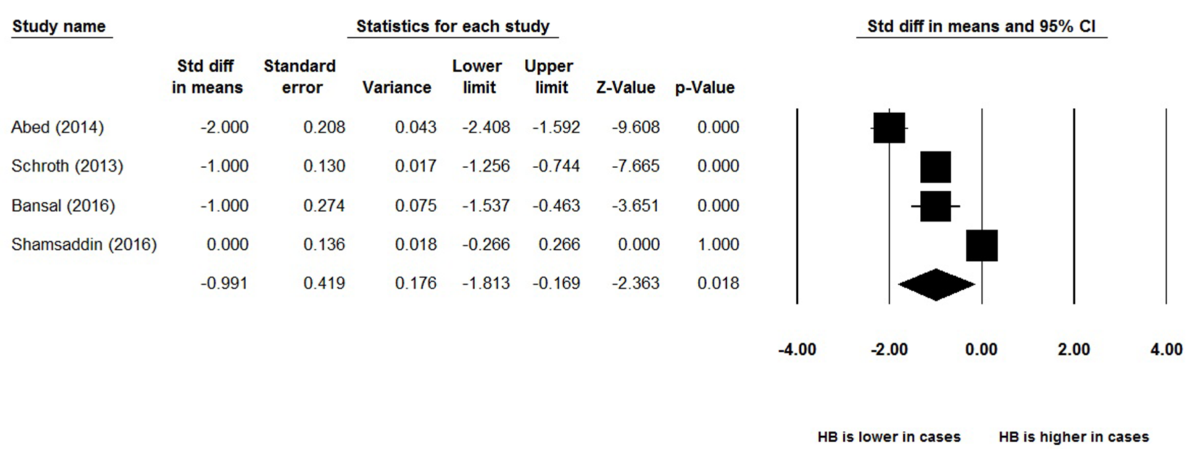

Figure 3. Forest plot of blood hemoglobin level

a higher prevalence of iron deficiency and anemia in children with ECC, which results in discomfort and pain. Thus, they have difficulty chewing iron-rich foods, which may cause nutritional deficiencies, including low iron levels. The dietary factors such as a high intake of beverages and carbohydrates and low meat consumption decrease iron levels and cause dental caries (24).

Tang et al. (40) and Shaoul et al. (27) reported a high prevalence of IDA, due to bad eating habits, in children with severe childhood caries. They found that altered food habits could relieve pain and reduce IDA. Further, chronic infections decrease Hb levels, which may contribute to anemia (41).

Schroth et al. (18) reported that MCV and ferritin levels were not significantly different between the groups (P = 0.62 and P = 0.74, respectively), and children with S-ECC had significantly lower mean hemoglobin levels than controls. Shamsaddin et al. (30) also found no significant differences between the case and control groups in ferritin, MCV, and hemoglobin levels. Likewise, Nayak et al. (32) showed that serum ferritin level was not significantly different between the case (children with dental caries) and control (caries-free children) groups, whereas the hemoglobin level was significantly lower in the case group. However, Abed et al. (26) Shaoul et al. (27), and Iranna Koppal et al. (28) indicated that hemoglobin, MCV, and serum ferritin were significantly lower in the case group than in the control group.

Most studies (8, 26, 28-31) in this systematic review included children below six years; in contrast, Nayak et al.

Study name	Statistics for each study						
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Abed (2014)	-1.308	0.189	0.036	-1.678	-0.938	-6.922	0.000
Shaoul (2011)	-1.049	0.275	0.076	-1.589	-0.510	-3.810	0.000
Schroth (2013)	-0.219	0.123	0.015	-0.461	0.023	-1.773	0.076
Bansal (2016)	-1.456	0.290	0.084	-2.025	-0.887	-5.013	0.000
Shamsaddin (2016)	-0.176	0.136	0.018	-0.443	0.090	-1.296	0.195
	-0.807	0.270	0.073	-1.336	-0.279	-2.996	0.003

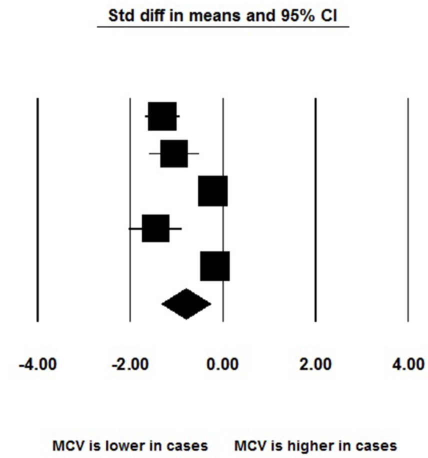

Figure 4. Forest plot of mean corpuscular volume (MCV)

(32) evaluated 5 to 12-year-old children, and Shaoul et al. (27) included children aged 3 - 18 years. However, all studies compared two groups with and without dental caries in terms of blood parameters. Some studies in the systematic review recruited children with ECC (26, 32, 33), and others included children with severe ECC (18, 27, 30, 31). Nayak et al. (32) recruited children with DMFT $>$ 0 in the case group. However, all studies recruited caries-free children in their control groups.

Gurunathan et al. (23) and Folayan et al. (24), in their review articles, examined the association between iron deficiency anemia and dental caries in children. However, they did not statistically analyze the results of the studies but examined the results qualitatively. Gurunathan et al. (23) showed that children with S-ECC had significantly higher odds of IDA, while Folayan et al. (24) indicated that anemia had an inverse relationship with ECC.

Anemia may not be directly caused by ECC but may be induced by elevated milk consumption in early childhood. Due to the discrepancies in the results of the studies, the present study meta-analyzed the case-control studies to obtain more reliable results. This systematic review showed that children with dental caries had significantly higher odds of hemoglobin, ferritin, and MCV levels and IDA than caries-free controls. Dentists and primary care providers should know about this oral-systemic relationship. Therefore, dentists and doctors should consider dental caries a risk factor for anemia while treating young children. Doctors should know that nutritional deficiencies are probably followed by dental caries, which may be present in their patients. Dentists should also know that children with dental caries are at risk of developing nutritional deficiencies that may influence their long-term health.

On the one hand, the long-term consumption of milk and milk bottles for more than two years can expose children to ECC and malnutrition because they do not take enough iron and other nutrients. Hence, ECC, iron deficiency, and other nutritional complications are more likely to occur in this group of children (42, 43). Multiple dental caries make it difficult for children to chew foods, especially meat, which reduces the absorption of nutrients in the intestine. As a result, children tend to consume sugary drinks to create a feeling of satiety to avoid meat and substances containing iron (34, 44). Dietary factors inducing iron deficiency (high beverage and low meat intake) can also anticipate dental caries (19). In the end, whether caries causes IDA or IDA results in caries in children remains unclear, indicating the need for further cohort studies with larger sample sizes among various communities.

5.1. Conclusions

Iron deficiency anemia was more prevalent in children with dental caries. Hemoglobin, MCV, and serum ferritin levels are lower in children with dental caries than in caries-free ones. Further high-quality research is recommended to gain a better insight into the association between dental caries and IDA in children.

Footnotes

Authors' Contribution: Study concept and design, Narjes Amrollahi; Acquisition of data, Narjes Amrollahi; Analysis and interpretation of data, Narjes Amrollahi and Mohammad Javad Tarrahi; Drafting of the manuscript, Narjes

Amrollahi; Critical revision of the manuscript for important intellectual content, Narjes Amrollahi; Statistical analysis, Mohammad Javad Tarrahi; Study supervision, Narjes Amrollahi.

Conflict of Interests: The authors declare no conflict of interests.

Data Reproducibility: The data in this study are briefly presented in Table 2 or available in references 27 - 33 and 18.

Funding/Support: The authors declare no funding or grant for this manuscript.

References

1. No Authors Listed. Policy on Early Childhood Caries (ECC): Classifications, Consequences, and Preventive Strategies. *Pediatr Dent*. 2017;**39**(6):59–61. [PubMed: 29179321].
2. Manton DJ. Child Dental Caries - A Global Problem of Inequality. *EClinicalMedicine*. 2018;**1**:3–4. doi: 10.1016/j.eclinm.2018.06.006. [PubMed: 31193614]. [PubMed Central: PMC6537533].
3. Schroth RJ, Harrison RL, Moffatt ME. Oral health of indigenous children and the influence of early childhood caries on childhood health and well-being. *Pediatr Clin North Am*. 2009;**56**(6):1481–99. doi: 10.1016/j.pcl.2009.09.010. [PubMed: 19962032].
4. Jabbarifar SE, Ahmady N, Sahafian SA, Samei F, Soheillipour S. Association of parental stress and early childhood caries. *Dent Res J (Isfahan)*. 2009;**6**(2):65–70. [PubMed: 21528033]. [PubMed Central: PMC3075457].
5. Singh A, Purohit BM. Malnutrition and Its Association with Dental Caries in the Primary and Permanent Dentition: A Systematic Review and Meta-Analysis. *Pediatr Dent*. 2020;**42**(6):418–26. [PubMed: 33369551].
6. So M, Ellenikiotis YA, Husby HM, Paz CL, Seymour B, Sokal-Gutierrez K. Early Childhood Dental Caries, Mouth Pain, and Malnutrition in the Ecuadorian Amazon Region. *Int J Environ Res Public Health*. 2017;**14**(5). doi: 10.3390/ijerph14050550. [PubMed: 28531148]. [PubMed Central: PMC5452000].
7. Penafiel D, Termote C, Lachat C, Espinel R, Kolsteren P, Van Damme P. Barriers to Eating Traditional Foods Vary by Age Group in Ecuador With Biodiversity Loss as a Key Issue. *J Nutr Educ Behav*. 2016;**48**(4):258–68 e1. doi: 10.1016/j.jneb.2015.12.003. [PubMed: 26865357].
8. Schroth RJ, Jeal NS, Kliewer E, Sellers EA. The relationship between vitamin D and severe early childhood caries: a pilot study. *Int J Vitam Nutr Res*. 2012;**82**(1):53–62. doi: 10.1024/0300-9831/a000094. [PubMed: 22811377].
9. Schroth RJ, Levi JA, Sellers EA, Friel J, Kliewer E, Moffatt ME. Vitamin D status of children with severe early childhood caries: a case-control study. *BMC Pediatr*. 2013;**13**:174. doi: 10.1186/1471-2431-13-174. [PubMed: 24160554]. [PubMed Central: PMC4231606].
10. Mansoori S, Mehta A, Ansari MI. Factors associated with Oral Health Related Quality of Life of children with severe -Early Childhood Caries. *J Oral Biol Craniofac Res*. 2019;**9**(3):222–5. doi: 10.1016/j.jobcr.2019.05.005. [PubMed: 31193595]. [PubMed Central: PMC6536671].
11. Albaroudi IN, Khodder M, Al Saadi T, Turk T, Youssef LA. Prevalence, diagnosis, and management of iron deficiency and iron deficiency anemia among Syrian children in a major outpatient center in Damascus, Syria. *Avicenna J Med*. 2018;**8**(3):92–103. doi: 10.4103/ajm.AJM_169_17. [PubMed: 30090748]. [PubMed Central: PMC6057158].
12. Mohamed WE, Abou El Fadl RK, Thabet RA, Helmi M, Kamal SH. Iron deficiency anaemia and early childhood caries: a cross-sectional study. *Aust Dent J*. 2021;**66 Suppl 1**:S27–36. doi: 10.1111/adj.12842. [PubMed: 33840096].
13. Szeto AC, Harrison RL, Innis SM. Caries, iron deficiency and food security in low income, minority children. *Can J Dent Hyg*. 2012;**46**(4).
14. Mantadakis E, Chatzimichael E, Zikidou P. Iron Deficiency Anemia in Children Residing in High and Low-Income Countries: Risk Factors, Prevention, Diagnosis and Therapy. *Mediterr J Hematol Infect Dis*. 2020;**12**(1). e2020041. doi: 10.4084/MJHID.2020.041. [PubMed: 32670519]. [PubMed Central: PMC7340216].
15. Plessow R, Arora NK, Brunner B, Tzogiou C, Eichler K, Brugger U, et al. Social Costs of Iron Deficiency Anemia in 6-59-Month-Old Children in India. *PLoS One*. 2015;**10**(8). e0136581. doi: 10.1371/journal.pone.0136581. [PubMed: 26313356]. [PubMed Central: PMC4552473].
16. Strauss WE, Auerbach M. Health-related quality of life in patients with iron deficiency anemia: impact of treatment with intravenous iron. *Patient Relat Outcome Meas*. 2018;**9**:285–98. doi: 10.2147/PROM.S169653. [PubMed: 30214332]. [PubMed Central: PMC6118263].
17. Dimaisip-Nabuab J, Duijster D, Benzian H, Heinrich-Weltzien R, Homsavath A, Monse B, et al. Nutritional status, dental caries and tooth eruption in children: a longitudinal study in Cambodia, Indonesia and Lao PDR. *BMC Pediatr*. 2018;**18**(1):300. doi: 10.1186/s12887-018-1277-6. [PubMed: 30217185]. [PubMed Central: PMC6137874].
18. Schroth RJ, Levi J, Kliewer E, Friel J, Moffatt ME. Association between iron status, iron deficiency anaemia, and severe early childhood caries: a case-control study. *BMC Pediatr*. 2013;**13**:22. doi: 10.1186/1471-2431-13-22. [PubMed: 23388209]. [PubMed Central: PMC3575235].
19. Clarke M, Locker D, Berall G, Pencharz P, Kenny DJ, Judd P. Malnourishment in a population of young children with severe early childhood caries. *Pediatr Dent*. 2006;**28**(3):254–9. [PubMed: 16805358].
20. Ramos-Gomez FJ, Weintraub JA, Gansky SA, Hoover CI, Featherstone JD. Bacterial, behavioral and environmental factors associated with early childhood caries. *J Clin Pediatr Dent*. 2002;**26**(2):165–73. doi: 10.17796/jcpd.26.2.t6601j3618675326. [PubMed: 11878278].
21. Sadeghi M, Darakhshan R, Bagherian A. Is there an association between early childhood caries and serum iron and serum ferritin levels? *Dent Res J (Isfahan)*. 2012;**9**(3):294–8. [PubMed: 23087734]. [PubMed Central: PMC3469895].
22. Nur BG, Tanrıver M, Altunsoy M, Atabay T, Intepe N. The prevalence of iron deficiency anemia in children with severe early childhood caries undergoing dental surgery under general anesthesia. *Pediatr Dent J*. 2016;**26**(2):83–7. doi: 10.1016/j.pdj.2016.04.002.
23. Gurunathan D, Swathi A, Kumar M. Prevalence of Iron Deficiency Anemia in Children with Severe Early Childhood Caries. *Biomed Pharmacol J*. 2019;**12**(1):219–25. doi: 10.13005/bpj/1630.
24. Folayan MO, El Tantawi M, Schroth RJ, Vukovic A, Kemoli A, Gaffar B, et al. Associations between early childhood caries, malnutrition and anemia: a global perspective. *BMC Nutr*. 2020;**6**:16. doi: 10.1186/s40795-020-00340-z. [PubMed: 32467766]. [PubMed Central: PMC7197144].
25. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;**62**(10):e1–34. doi: 10.1016/j.jclinepi.2009.06.006. [PubMed: 19631507].
26. Abed NT, Aly IA, Deyab SM, Ramoon FM. The relation between early dental caries and iron-deficiency anaemia in children. *Med Res J*. 2014;**13**(2):108–14.
27. Shaoul R, Gaitini L, Kharouba J, Darawshi G, Maor I, Somri M. The association of childhood iron deficiency anaemia with severe dental caries. *Acta Paediatr*. 2012;**101**(2):e76–9. doi: 10.1111/j.1651-2227.2011.02448.x. [PubMed: 21883449].
28. Iranna Koppal P, Sakri MR, Akkareddy B, Hinduja DM, Gangolli RA, Patil BC. Iron deficiency in young children: a risk marker for early childhood caries. *Int J Clin Pediatr Dent*. 2013;**6**(1):1–6. doi: 10.5005/jp-journals-10005-1176. [PubMed: 25206178]. [PubMed Central: PMC4034631].
29. Bansal K, Goyal M, Dhingra R. Association of severe early childhood caries with iron deficiency anemia. *J Indian Soc Pedod Prev Dent*. 2016;**34**(1):36–42. doi: 10.4103/0970-4388.175508. [PubMed: 26838146].

30. Shamsaddin H, Jahanimoghadam F, Poureslami H, Haghdoost AA. The association between growth factors and blood factors with early childhood caries. *Journal of Oral Health and Oral Epidemiology*. 2017;**6**(4):196–202.
31. Jayakumar A, Gurunathan D. Estimation of ferritin levels in children with and without early childhood caries - A case-control study. *Journal of Advanced Pharmacy Education and Research*. 2017;**7**:15–7. doi: 10.5958/0976-5506.2018.01424.9.
32. Nayak P, Pratinidhi SA, More G, Zope R, Banerjee S. Association between DMFT Score and Iron Studies in Children up to 12 Years. *MMJ-A Journal by MIMER Medical College, Pune, India*. 2017;**1**(2):18–22. doi: 10.15713/ins.mmj.17.
33. Deane S, Schroth RJ, Sharma A, Rodd C. Combined deficiencies of 25-hydroxyvitamin D and anemia in preschool children with severe early childhood caries: A case-control study. *Paediatr Child Health*. 2018;**23**(3):e40–5. doi: 10.1093/pch/pxx150. [PubMed: 29769814]. [PubMed Central: PMC5951085].
34. Sheiham A. Dental caries affects body weight, growth and quality of life in pre-school children. *Br Dent J*. 2006;**201**(10):625–6. doi: 10.1038/sj.bdj.4814259. [PubMed: 17128231].
35. Abdallah MA, Abed HH, Hamza G, Alsahafi EN. The association between dmft index and haemoglobin levels in 3–6 year-old Saudi children with anaemia: A cross sectional study. *J Taibah Univ Medical Sci*. 2016;**11**(1):72–6. doi: 10.1016/j.jtumed.2015.11.008.
36. Sundararajan S, Rabe H. Prevention of iron deficiency anemia in infants and toddlers. *Pediatr Res*. 2021;**89**(1):63–73. doi: 10.1038/s41390-020-0907-5. [PubMed: 32330927].
37. Peirano PD, Algarin CR, Chamorro RA, Reyes SC, Duran SA, Garrido MI, et al. Sleep alterations and iron deficiency anemia in infancy. *Sleep Med*. 2010;**11**(7):637–42. doi: 10.1016/j.sleep.2010.03.014. [PubMed: 20620103]. [PubMed Central: PMC3632071].
38. Fraenkel PG. Anemia of Inflammation: A Review. *Med Clin North Am*. 2017;**101**(2):285–96. doi: 10.1016/j.mcna.2016.09.005. [PubMed: 28189171]. [PubMed Central: PMC5308549].
39. Mahantesha T, Reddy KM, Ellore V, Ramagoni N, Iitagi V, Ks A. Evaluation and association of iron deficiency anemia with salivary pH and buffering capacity in children aged 6-12 years. *Natl J Physiol Pharm Pharmacol*. 2014;**4**(3):229. doi: 10.5455/njppp.2014.4.230420142.
40. Tang RS, Huang MC, Huang ST. Relationship between dental caries status and anemia in children with severe early childhood caries. *Kaohsiung J Med Sci*. 2013;**29**(6):330–6. doi: 10.1016/j.kjms.2012.10.003. [PubMed: 23684139].
41. Fraenkel PG. Understanding anemia of chronic disease. *Hematology Am Soc Hematol Educ Program*. 2015;**2015**:14–8. doi: 10.1182/asheducation-2015.1.14. [PubMed: 26637695].
42. Parkin PC, DeGroot J, Maguire JL, Birken CS, Zlotkin S. Severe iron-deficiency anaemia and feeding practices in young children. *Public Health Nutr*. 2016;**19**(4):716–22. doi: 10.1017/S1368980015001639. [PubMed: 26027426].
43. Oliveira MA, Osorio MM. [Cow's milk consumption and iron deficiency anemia in children]. *J Pediatr (Rio J)*. 2005;**81**(5):361–7. doi: 10.2223/JPED.1386. [PubMed: 16247536].
44. Grant CC, Wall CR, Brewster D, Nicholson R, Whitehall J, Super L, et al. Policy statement on iron deficiency in pre-school-aged children. *J Paediatr Child Health*. 2007;**43**(7-8):513–21. doi: 10.1111/j.1440-1754.2007.01128.x. [PubMed: 17635678].