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Early Childhood Caries and Iron Deficiency Anaemia: A Systematic Review and Meta-Analysis

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Keywords
Early childhood caries · Iron deficiency anaemia · Systematic review · Quality of life

Abstract
Identification of the association between Early Childhood Caries (ECC) and Iron Deficiency Anaemia (IDA) will aid paediatricians and paediatric dentists to enhance health promotion measures to reduce the related morbidity in children. This systematic review aims to determine an evidence-based association between ECC and IDA. A systematic search was carried out from MEDLINE via PubMed, EMBASE, LILACS, Cochrane Oral Health Group's Specialized Register, CINAHL via EBSCO, Web of Science, and Scopus up to May 2020. Hand searching and grey literature screening were also conducted. Cross-sectional, case-control, and cohort studies in English language which assessed the association was included. Two reviewers independently assessed the study quality and extracted the outcome data. A total of 1,434 studies were identified. Fourteen studies qualified for qualitative review and 7 of them for a meta-analysis. In comparison with children not affected by ECC, those affected had an increased likelihood of IDA (OR = 6.07 [3.61, 10.21]). The meta-analysis showed no statistical difference when comparing blood parameters (Hb, MCV, and serum ferritin) in children with and without ECC. This systematic review demonstrates an association between ECC and increased odds of IDA rather than it being the cause for IDA. Further longitudinal studies with robust methodology are required to determine an evidence-based association.
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Introduction

Early Childhood Caries (ECC) is defined as the presence of one or more decayed (noncavitated or cavitated lesions), missing or filled (due to caries) surfaces, in any primary tooth of a child less than 6 years of age [Pitts et al., 2019]. With more than 600 million children having been affected by ECC worldwide, it remains the most

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prevalent disease in children, with a significant impact on society [Pitts et al., 2019]. Similar to ECC, Iron Deficiency Anaemia (IDA) in children is influenced by several factors. Iron deficiency is defined as "a condition in which there are no mobilizable iron stores with signs of a compromised supply of iron to tissues, and severe stages of iron deficiency being associated with anaemia" [WHO, 2001]. World Health Organization (WHO) recognizes iron deficiency as the most common and widespread nutritional deficiency affecting 1.62 billion people with the highest prevalence of 47.4% in preschool children [WHO, 2001]. IDA causes irreversible short- and long-term damages in the developing central nervous system of children, resulting in cognitive and motor disabilities leaving a negative impact on their quality of life [Grantham-McGregor and Ani, 2001].

In addition to the immediate distress caused by a toothache, ECC can have long-term adverse health outcomes on children, affecting their overall growth and development [Abanto et al., 2011]. The resulting discomfort caused by ECC on mastication can interfere with a child's nutritional intake, leading to decreased consumption of iron-rich foods such as meat and nuts [Sheiham, 2006]. With diet being strongly associated with ECC and IDA separately [Miller, 2013; Sheiham et al., 2015], we propose a relationship may exist between these 2 entities. Additionally, excessive consumption of cow's milk or prolonged breastfeeding may contribute to both ECC and IDA during early childhood [Skalicky et al., 2006]. Few authors hypothesize that the inflammatory process associated with ECC could impact erythropoiesis which further influences the iron levels [Tang et al., 2013]. However, the exact pathophysiological mechanism is still equivocal.

Regardless of the pervasive nature of both iron deficiency and dental caries globally, limited research exists to corroborate an association between these 2 entities. A few supports a potentially positive association between IDA and caries experience in children, while a few others report ECC as a significant risk factor for IDA [Schroth et al., 2013; Tang et al., 2013; Abed et al., 2014]. However, some authors have proposed ECC and IDA as separate, unrelated entities, providing mixed and conflicting evidence [Sadeghi et al., 2012; Nur et al., 2016]. With existing literature, it has been challenging to arrive at a definitive understanding of this cycle, and thus the association between ECC and IDA remains ambiguous. Identification of this oral-systemic relationship will aid paediatricians, paediatric dentists, health care policymakers, and family physicians in enhancing the current preventive and health promotion measures to reduce the burden of ECC and IDA in children. Thus, the present systematic review was aimed to evaluate the available literature in this domain and determine an evidence-based association between ECC and IDA.

Methods

This review was registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42020184059) in May 2020 and reporting was done in accordance with the PRISMA guidelines [Liberati et al., 2009].

Selection Criteria

The research question was: Is ECC associated with IDA in children aged 0–6 years? The focused PECO question was defined as follows:

1. Population: Children (0–6 years of age).
2. Exposure: Presence of ECC.
3. Comparison: Absence of ECC.
4. Outcome: IDA as assessed by haemoglobin (Hb), serum ferritin, and Mean Corpuscular Volume (MCV).

This study included cross-sectional, case-control, and cohort studies. The search was limited to studies in English language. Letters to the editor, case reports, in vitro studies, animal studies, experimental studies, randomized controlled trials, reviews, conference abstracts, guidelines, studies on dental caries and IDA and, studies on children with special health care needs were excluded.

Search Strategy

An extensive search of the literature was performed using the following databases: MEDLINE via PubMed, EMBASE, LILACS, Cochrane Oral Health Group's Specialized Register, CINAHL via EBSCO, Web of Science, and SCOPUS. We deviated from the protocol by searching 2 additional databases, Web of Science Core Collection, and SCOPUS. Also, grey literature databases Open Grey, Google Scholar, PsycExtra, and NTIS were searched for relevant studies. Additional databases were included to expand the search and identify pertinent literature in this domain.

The MeSH terms used were: "child," "pre-schooler," "infant," "dental caries," "iron, deficiency," and "anaemia." A search strategy was initially developed for MEDLINE and later adapted for other databases. The search strategy was ((((((("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) OR ("child"[MeSHTerms]OR"child"[AllFields]))OR("infant"[MeSH Terms] OR "infant"[All Fields])) OR toddler[All Fields]) OR ("child, preschool"[MeSH Terms] OR ("child"[All Fields] AND "preschool"[All Fields]) OR "preschool child"[All Fields] OR "preschooler"[All Fields])) AND (("dental caries"[MeSH Terms] OR ("dental"[All Fields] AND "caries"[All Fields]) OR "dental caries"[All Fields]) OR (Early[All Fields] AND "childhood"[All Fields] AND ("dental caries"[MeSH Terms] OR ("dental"[All Fields] AND "caries"[All Fields]) OR "dental caries"[All Fields] OR "caries"[All Fields])))) AND (("iron"[MeSH Terms] OR "iron"[All Fields]) OR (("iron"[MeSH Terms] OR "iron"[All Fields]) AND ("deficiency"[Subheading] OR "deficiency"[All Fields])))) AND ("anaemia"[All Fields] OR "anaemia"[MeSH Terms] OR "anaemia"[All Fields]). Search was restricted to articles

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published from 1998 to May 2020, as the term ECC has been used from the year 1998. Hand searching of some key journals which included *Community Dental Health*, *International Journal of Paediatric Dentistry*, *Pediatrics*, *Paediatric Dentistry*, *European Archives of Paediatric Dentistry*, *European Journal of Paediatric Dentistry*, *Paediatric Dental Journal*, *Community Dentistry, and Oral Epidemiology* and *International Journal of Clinical Paediatric Dentistry* were carried out. Attempts to obtain grey literature were made by screening SHODHGANGA (national dissertation abstracts database), PsycExtra, NTIS, Open Grey and, the first 100 links on Google Scholar. Cross-referencing of relevant articles was done.

Selection of Studies

All the titles and abstracts of the identified studies were independently assessed by 2 reviewers (H.N.E. and A.A.) against the inclusion criteria. Full texts of the articles grouped as "uncertain" and "included" were obtained and assessed. Agreement concerning study inclusion was achieved by discussion. Finally, the total number of included studies was arrived at after exclusion at various levels. The reasons for the exclusion of studies were recorded at each stage. Any ambiguity between the review authors was resolved by consensus with the third reviewer (M.S.M.).

Data Extraction and Quality Assessment

A standardized, pre-pilot-tested form was used by the 2 reviewers (H.N.E. and A.A.) for the recording of data from the included studies. The following parameters were excerpted from the studies: year of publication, journal, title, author(s), author's institutional affiliation, age, gender, sample size, diagnostic methods used, index used for ECC, blood parameters, OR/RR, CI, p value, outcomes, and assessment of any confounders. The authors of the study were contacted in cases of insufficient information. Quality assessment was also carried out independently (H.N.E. and U.N.). Third reviewer (M.S.M.) was consulted to resolve disagreements between the reviewers. For the case-control and cohort studies, the quality assessment was performed according to the Newcastle-Ottawa Assessment scale (NOS) [Wells et al., 2013], while the modified Newcastle-Ottawa assessment scale [Modesti et al., 2016] was used for the cross-sectional studies. The methodological quality of a study was measured by the number of stars the study received. The NOS uses a star rating system by which the stars are allocated across 3 categories: selection of the study group, the comparability of groups, and outcomes. Each criterion could be awarded a maximum of 1 star for each numbered item, except for the "Comparability" criterion, in which a maximum of 2 stars can be scored. The maximum numbers of stars implying low risk-of-bias were 7 for cross-sectional and 9 for case-control and cohort studies. A moderate risk-of-bias was inferred for scoring between 6 and 8 stars, and 5 or fewer stars meant a high risk-of-bias in case-control and cohort studies. Cross-sectional studies with a rating between 4 and 6 stars were evaluated as having moderate risk-of-bias, and those with 3 or fewer stars were recorded as having high risk-of-bias.

Certainty of Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to determine the evidence, quality, and grade its strength from included studies in the meta-analysis [Balshem et al., 2011]. The GRADE approach to rating the quality of evidence considers the risk-of-bias, results inconsistency, the indirectness of evidence, the imprecision, and other factors as reasons for evaluating the quality. The quality of assessment was rated as high, moderate, low, and very low levels of evidence.

Data Analysis

Review Manager software version 5.4 was used to carry out the meta-analysis. A meta-analysis for the included articles was performed after extracting summary quantitative estimates (mean and SD) for Hb, MCV, and serum ferritin outcomes and pooled qualitative data (percentage) for IDA outcome. Pooled effect sizes of mean difference and odds ratio were estimated for quantitative and qualitative data, respectively, in the forest plots. Heterogeneity was evaluated by means of the χ^2 test (χ^2) and the I-square index (I^2). An I^2 value >50% was considered indicative of substantial heterogeneity, and random-effects model for meta-analysis was used.

Results

Study Selection

The search yielded a total of 1,434 articles – 1,254 studies through an electronic database search, and 180 studies through other sources (hand searching, grey literature, and cross-referencing). After removal of duplicates, 1,252 reports were reviewed for titles and abstracts. Of these, 1,101 studies were excluded, resulting in 151 studies for full-text screening. Following full-text screening for eligibility, 137 articles were excluded for various reasons (e.g., outcomes other than IDA and ECC, narrative reviews, animal studies, unmatched age groups, and other reasons). The characteristics of excluded studies are presented as online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000520442). Finally, 14 studies were included in the qualitative analysis and 7 studies in the meta-analysis. The PRISMA flowchart summarizes the selection process in Figure 1.

Study Characteristics

The review included data of 1,770 participants inclusive of 1,364 cases with ECC and 406 controls without ECC. The articles originated from 7 different locations: Canada, Israel, India, Taiwan, Turkey, Egypt, and Iran. About 63 authors contributed to the study of the association of ECC with IDA.

Regarding caries data, 6 studies [Szeto et al., 2012; Tang et al., 2013; Bansal et al., 2016; Nur et al., 2016; Singh et al., 2016; Nagarajan et al., 2017] used validated WHO criteria (dmft/deft) whereas other 8 studies did not mention the criteria used to record caries. Several parameters were reported for the assessment of IDA – serum ferritin, Hb, MCV, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, haematocrit,

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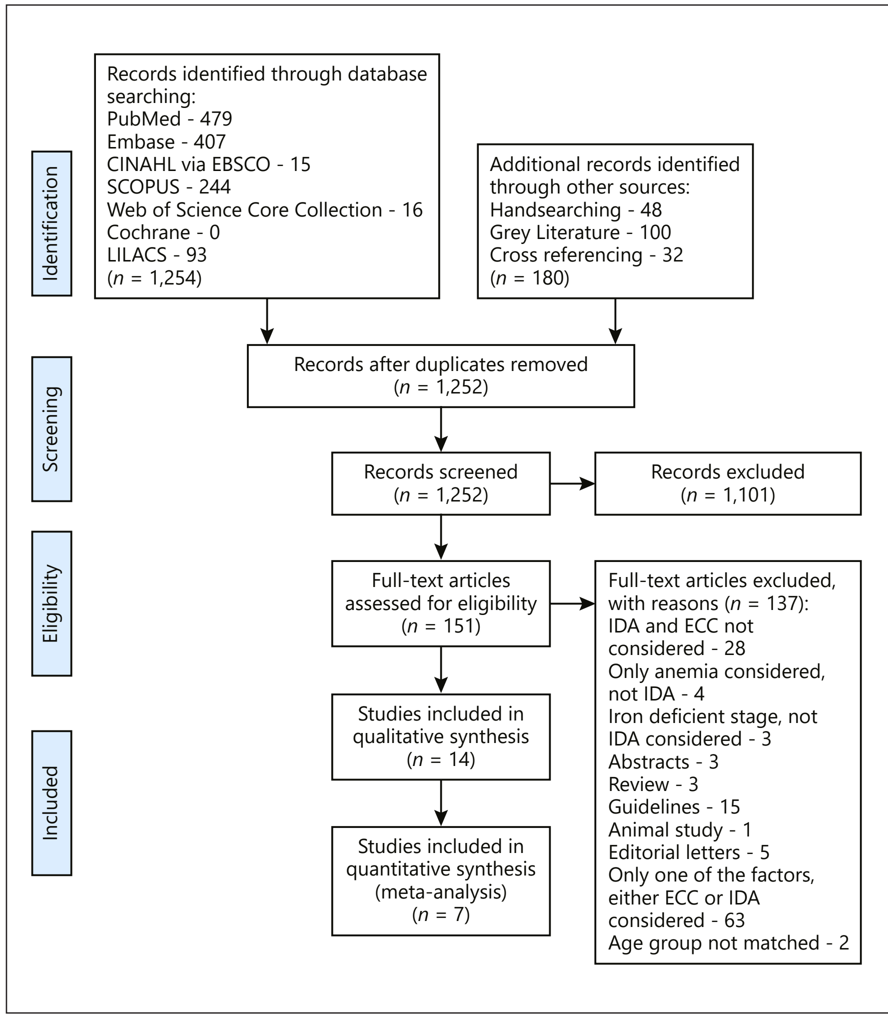

Fig. 1. PRISMA flowchart. ECC, early childhood caries; IDA, iron deficiency anaemia.

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packed cell volume, red cell distribution width, serum iron, and total iron binding capacity. IDA is diagnosed by abnormal values in 2 of 3 blood tests [Clarke et al., 2006]. Serum ferritin was used as a diagnostic parameter in 9 studies [Clarke et al., 2006; Shaoul et al., 2012; Iranna Koppal et al., 2013; Schroth et al., 2013; Abed et al., 2014; Ahmed et al., 2014; Nagarajan et al., 2017; Shamsaddin et al., 2017; Deane et al., 2018] Hb in 13 studies [Clarke et al., 2006; Shaoul et al., 2012; Szeto et al., 2012; Iranna Koppal et al., 2013; Schroth et al., 2013; Tang et al., 2013; Abed et al., 2014; Bansal et al., 2016; Nur et al., 2016; Singh et al., 2016; Nagarajan et al., 2017; Shamsaddin et al., 2017; Deane et al., 2018] and, MCV as a diagnostic estimate in 12 studies [Clarke et al., 2006; Shaoul et al., 2012; Iranna Koppal et al., 2013; Schroth et al., 2013; Tang et al., 2013; Abed et al., 2014; Bansal et al., 2016; Nur et al., 2016; Singh et al., 2016; Nagarajan et al., 2017; Shamsaddin et al., 2017; Deane et al., 2018]. Besides IDA assessment in ECC affected population, 8 studies tested the association between ECC and other domains such as body weight, body mass index [Clarke et al., 2006; Shaoul et al., 2012; Szeto et al., 2012; Tang et al., 2013; Abed et al., 2014; Nagarajan et al., 2017; Shamsaddin et al., 2017] and 25-hydroxyvitamin D [Deane et al., 2018]. A summary of descriptive characteristics of the included studies is described in Table 1.

Risk of Bias and Certainty of Evidence

The Newcastle-Ottawa Scales for cohort and case-control studies and the modified Newcastle-Ottawa Scale for cross-sectional studies were used for qualitative assessment of the included studies, which is listed in online supplementary Table 2. A high risk-of-bias elucidating low quality was demonstrated in 2 cross-sectional studies. Moderate risk-of-bias implying moderate quality was demonstrated in 1 cohort, 3 case-control, and 8 cross-

Table 1. Characteristics of included studies

No	Author and year	Sample size	Age	Gender	ECC index	IDA parameters	Outcomes
Cohort study							
1	Nagarajan et al. 2017	30	2–6 years	–	Deft	Hb MCV Serum ferritin MCHC PCV	Resolution of S-ECC can lead to improvement in growth and nutritional status of the child
Case-control							
2	Schroth et al. 2013	266 (cases-144, controls-122)	4.8±14.1 months	Case: 144 Male-70, Female-74 Control: 122 Male-66, Female-56	–	Hb MCV Serum ferritin	Children with S-ECC appear to be at significantly greater odds for iron deficiency and IDA than cavity-free children
3	Abed et al. 2014	150 (cases-100; controls-50)	2–6 years	Cases: 100 Male-51, Female-49 Controls: 50 Male-16, Female-34	–	Hb MCV Serum ferritin MCHC RBC RDW TIBC MCH Haematocrit Serum iron	Children with early dental caries have greater odds of developing IDA
4	Deane et al. 2018	266 (cases-144, controls-122)	4.8±14.1 months	Case: 144 Male-70, Female-74 Control: 122 Male-66, Female-56	–	Hb MCV Serum ferritin	ECC sample, more likely to have IDA
Cross-sectional							
5	Clarke et al. 2006	46	2–5.4 years	Male-28 Female-18	–	Hb MCV Serum ferritin	ECC may be a risk marker for IDA
6	Shaoul et al. 2012	60 (cases-30, controls-30)	Case: 5.65±2.6 years Control: 5.8±2.4 years	Case-30 Male-17, female-13; Control-30 Male-16 female-14	–	Hb MCV Serum ferritin RDW Iron Transferrin	ECC may be a contributing factor for IDA
7	Szeto et al. 2012	99	18–72 months	Male-62 Female-37	Dmfs	Hb Serum ferritin Zinc protoporphyrin	Children with S-ECC appear to be at significantly greater odds for iron deficiency and IDA than cavity-free children
8	Iranna Koppal et al. 2013	60 (Cases-30, controls-30)	2–6 years	–	–	Hb MCV Serum ferritin	Children with early dental caries have greater odds of developing IDA
9	Tang et al. 2013	101	2–5 years	Male-63 Female-38	Defs	Hb MCV Haematocrit RBC MCH Serum iron TIBC Transferrin saturation	ECC may be a contributing factor for IDA
10	Ahmed et al. 2014	80	2–5 years	–	–	Serum ferritin	No statistically significant association between ECC stages and IDA

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Table 1 (continued)

No	Author and year	Sample size	Age	Gender	ECC index	IDA parameters	Outcomes
11	Bansal et al. 2016	60 (cases-30; controls-30)	2–6 years	Cases: 30 Male-17, Female-13 Controls: 30 Male-16, Female-14	Deft	Hb MCV MCHC PCV	S-ECC as a risk marker for anaemia due to iron deficiency
12	Nur et al. 2016	160	2–6 years	80 males 80 females	Deft	Hb MCV MCHC MCH RBC RDW Haematocrit	Causal relationship between S-ECC and anaemia could not be confirmed
13	Singh et al. 2016	60 (cases-30; controls-30)	2–6 years	Cases: 30 Male-17, Female-13 Controls: 30 Male-16, Female-14	Deft	Hb MCV MCHC PCV	S-ECC and anaemia are definitely interrelated
14	Shamsaddin et al. 2017	240 (cases-157; controls-83)	2–6 years	Male-116 Female-124	–	Hb MCV Serum ferritin	No significant associations between ECC and blood parameters

ECC, early childhood caries, IDA, iron deficiency anaemia; MCV, mean corpuscular volume; Hb, haemoglobin; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration.

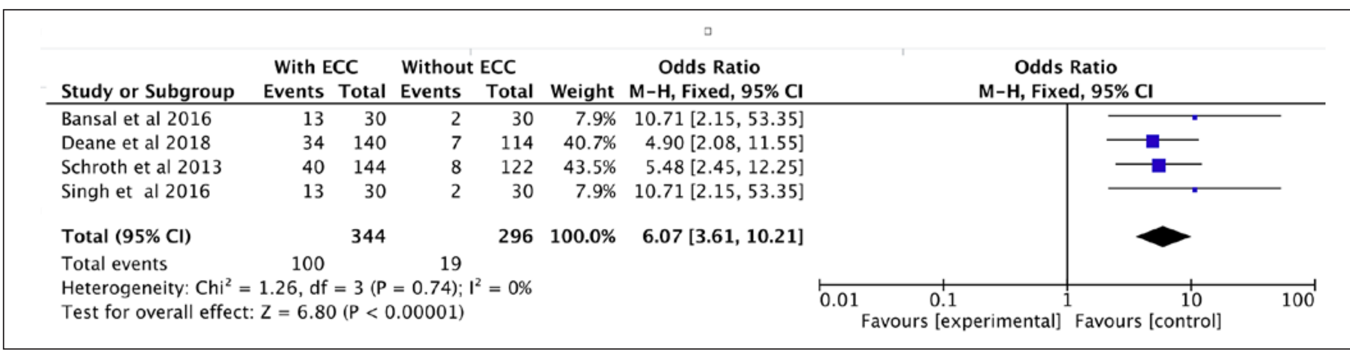

Fig. 2. Forest plot comparing IDA between children with and without ECC. ECC, early childhood caries.

sectional studies. Low risk-of-bias was not reported in any of the included studies.

The level of evidence inferred from this systematic review by the GRADE approach indicates a high certainty for an association between ECC and IDA. The certainty of the evidence was very low on the association between Hb, serum ferritin, MCV, and ECC. The GRADE is presented in online supplementary Table 3.

Quantitative Analysis: Synthesis of the Results

Seven studies from the 14 included studies provided data for the conduct of a meta-analysis. A study by Shaoul et al. [2012], was not included in the quantitative analysis as the data have been presented for the age-group 3–18 years.

Iron Deficiency Anaemia Outcome

The analysis indicated significantly higher odds (OR = 6.07 [3.61, 10.21], $p < 0.00001$) of IDA in the ECC group than the non-ECC group as seen in Figure 2. Heterogeneity ($\chi^2 = 1.26$, $I^2 = 0\%$, $p = 0.74$) was not detected among the 4 included articles. Hence, a fixed-effects model of the meta-analysis was used.

A separate quantitative analysis has been carried with 2 studies [Schroth et al., 2013; Deane et al., 2018] where

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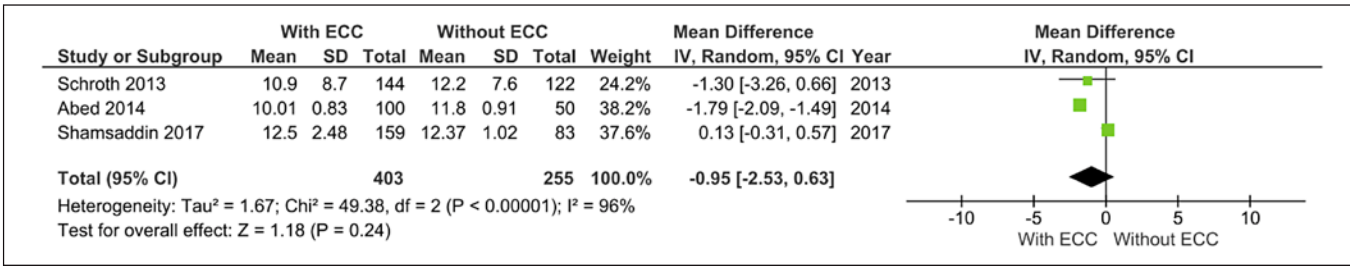

Fig. 3. Forest plot comparing Hb between children with and without ECC. Hb, haemoglobin; ECC, early childhood caries.

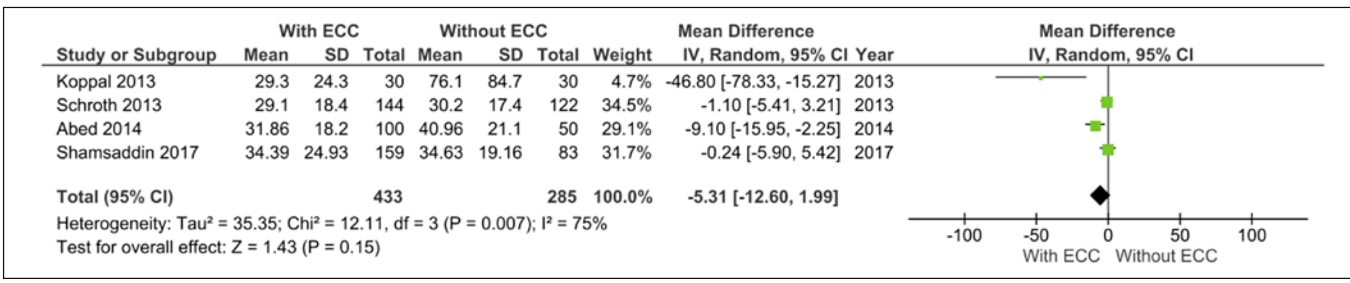

Fig. 4. Forest plot comparing serum ferritin between children with and without ECC. ECC, early childhood caries.

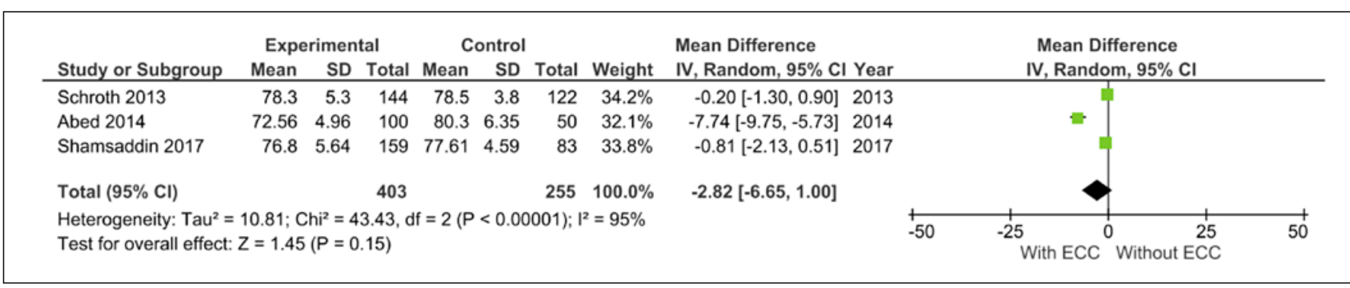

Fig. 5. Forest plot comparing MCV between children with and without ECC. ECC, early childhood caries; MCV, mean corpuscular volume.

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the results were adjusted for socio-economic status (SES). The odds of having IDA among the ECC affected population was 5.2.

Hb Outcome

No statistically significant difference in the ECC group and the non-ECC group (difference in means [DM] = 0.95 [−2.53, 0.63], $p > 0.05$) was seen in the 3 included studies depicted in Figure 3. Lower Hb levels were seen in the ECC group than in the control group (non-ECC). Because of the high heterogeneity ($\chi^2 = 49.38$, $I^2 = 96\%$, $p < 0.00001$), a random-effects meta-analysis was performed.

Serum Ferritin Outcome

Four studies included in the analysis revealed no statistically significant difference between the ECC group and the non-ECC group (difference in means [DM] = 5.31 [−12.60, −1.99], $p < 0.15$). Analysis revealed lower ferritin levels in the ECC group than the control group (non-ECC) as shown in Figure 4. Due to high heterogeneity ($\chi^2 = 12.11$, $I^2 = 75\%$, $p < 0.007$), a random-effects meta-analysis was performed.

MCV Outcome

Three studies comparing MCV values between the ECC and the non-ECC groups were included. No statistically significant difference was exhibited between the groups (difference in means [DM] = −2.82 [−6.65, 1.00], $p = 0.15$) in Figure 5. Random-effects meta-analysis was used due to high heterogeneity ($\chi^2 = 43.43$, $I^2 = 95\%$, $p = 0.15$).

Discussion

The present systematic review was undertaken in a structured approach to identify pertinent literature examining the correlation between ECC and IDA. Meta-analysis revealed higher odds (OR-6) of IDA among children affected by ECC. In 11 studies [Clarke et al., 2006; Shaoul et al., 2012; Szeto et al., 2012; Iranna Koppal et al., 2013; Schroth et al., 2013; Tang et al., 2013; Bansal et al., 2016; Nur et al., 2016; Singh et al., 2016; Nagarajan et al., 2017; Deane et al., 2018], children with ECC were reported to be at high risk for IDA, whereas 3 studies found no association between caries experience and IDA [Ahmed et al., 2014; Nur et al., 2016; Shamsaddin et al., 2017].

Serum ferritin, an acute-phase protein, is indicative of body-iron reserves. Low ferritin is indicative of the depleted iron stores in the body that is needed to maintain Hb level for good health [Clarke et al., 2006]. Four cross-sectional studies [Shaoul et al., 2012; Iranna Koppal et al., 2013; Schroth et al., 2013; Bansal et al., 2016] included in the review revealed significantly lower serum ferritin levels in children with ECC than caries-free children. No association between serum ferritin levels and the deft index was reported in Venkatesh Babu and Bhanushali [2017], which is in concordance with results from Sadeghi et al. [2012] and Clarke et al. [2006].

Quantitative analysis comparing Hb levels in children with and without ECC revealed no statistically significant association. This could be attributed to the varied confounding factors such as no standardized cut-off values and varied sample population. Also, based on the GRADE assessment, the evidence of this synthesis was found to be of very low quality, and thus cannot be trusted to derive any conclusions. Shaoul et al. [2012] hypothesized the association between Hb levels and ECC to the inflammatory response of the body to rampant caries (specifically in cases of pulpitis or abscess). Associated inflammation with ECC triggers a cascade of reactions which lead to cytokine release that inhibit erythropoiesis, causing reduced Hb levels. Occult blood loss due to the inflammatory process and local infection also influence blood parameters. Sadeghi et al. [2012] found an inverse, statistically significant association between serum iron levels and caries experience in children.

Low levels of MCV are suggestive of microcytic anaemia, which is a characteristic of IDA. This association can be ascribed to an altered sleeping pattern in the child due to nocturnal pain, which leads to decreased glucosteroid production, which further influences iron levels [Acs et al., 1999]. Shaoul et al. [2012] and Bansal et al. [2016] reported statistically significant lower MCV values in children with ECC, but Schroth et al. [2013] reported no significant differences in MCV levels between the ECC and non-ECC groups.

A significant difference in the values of Hb, serum ferritin, and MCV has been seen 4–6 months following dental rehabilitation in children with ECC in a study by Shaoul et al. [2012] which reported that the resolution of ECC leads to a parallel resolution of IDA without treatment for iron deficiency. A similar study by Nagarajan et al. [2017] also confirmed improvement in IDA following the management of ECC without iron supplements. Elevated haematological parameters could be due to the cessation of pain and the improvement of the children's nutritional status following dental rehabilitation. In both studies, the baseline blood parameters revealed Hb values indicative of a mild form of anaemia as predefined by the WHO. However, these results are to be interpreted with caution, since both studies reported moderate risk-of-bias. Moreover, because of the observational design of the study, we cannot conclude that modification ECC will influence IDA. The authors of this review are of the opinion that further evidence-based longitudinal research with a robust methodology is imperative to confirm whether total rehabilitation of ECC alone would be adequate for management of children with ECC and IDA.

Schroth et al. [2009] concluded that ECC has an impact on the child's oral health-related quality of life, growth, development, and well-being. Untreated caries and associated infection can cause pain, discomfort, and reduced food intake, leading to decreased consumption of iron-rich foods such as meat and nuts, while the child tends to satisfy hunger with excessive consumption of bovine milk or sugar-rich beverages [Sheiham, 2006]. Ziegler [2011] and Ferri et al. [2014] reported that casein and calcium present in cow's milk has a negative impact on the iron absorption. Therefore, excessive consumption of bovine milk can impair iron absorption in children. In addition, there are reports of infants having developed IDA, owing to the occult intestinal blood loss on excessive consumption of cow's milk [Ziegler, 2011]. Pertaining to increased consumption of bovine milk only one of the included studies, Szeto et al. [2012] have assessed their effects and reported that iron deficient chil-

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dren consumed 3 or more cups of milk per day in comparison to other children. Thus, excessive consumption of cow's milk and decreased intake of iron-rich foods due to masticatory pain might have an impact on the iron stores in the body. Bonuck and Kahn [2002] reported that prolonged bottle use, which is a risk factor for ECC, is associated with increased risk of IDA, since children become habituated to drinking milk or sugary drinks rather than consuming a well-balanced diet. Prolonged breastfeeding, a common factor which increases the odds of both ECC and IDA [Tsai et al., 2014; Peres et al., 2017] has not been considered in any of the included studies. Thus, prolonged bottle use could be another common explanatory variable for ECC and IDA.

WHO [2001] considers iron deficiency to be the most common form of micronutrient malnutrition globally. Psoter et al. [2008] have cited malnutrition to have an adverse impact on the quality of saliva in early childhood. Reduced salivary flow affects the buffering capacity of saliva thereby inhibiting its caries preventive action. Bahdila et al. [2019] have reported increased caries susceptibility among the children with IDA. Iron has a cariostatic effect, due to the protective acid resistant coatings containing hydrous iron covering the enamel surface which prevents dissolution of enamel. To nucleate the formation of apatite, these ions adsorb salivary calcium and phosphate ions, replacing the minerals dissolved during the caries process. Iron could have a significant inhibitory effect on the growth of *Streptococcus mutans*, the early establishment of which directly relates to the severity of dental caries [Iranna Koppal et al., 2013].

ECC and IDA both are multifactorial diseases which are influenced by underlying social determinants of health such as SES [Kirthiga et al., 2019; Martín-Masot et al., 2019]. A cause and effect relation can be determined only if all the confounding factors are taken into consideration, as these factors mask the true association between ECC and IDA [da Silva et al., 2016]. Previous studies have established the impact of low SES in ECC and IDA [Yang et al., 2018; Knoblauch et al., 2019]. Thus, SES not being considered in majority of the included studies may compromise the validity of these studies. SES was assessed in 5 of the included studies but was adjusted in only 2 [Schroth et al., 2013; Deane et al., 2018]. Confounding factors can exert a distorting influence and therefore should be minimized with an adjustment procedure in the multivariate analysis. Meta-analysis adjusted for SES revealed an OR of 5.29.

In addition to SES, potential confounding factor pertaining to IDA and ECC include the reference values of blood parameters used for determination of IDA in the included studies which show high heterogeneity, and diet. However, diet has been considered in 3 of the included studies, but neither adjustments nor correlations have been attempted to explain its association to ECC and IDA.

WHO [2001] defines cut-off values for Hb in children between 6 to 59 months of age as 110 g/L and serum ferritin as <12 μg/L and haematocrit value as 6.83 mmol/L for children below 5 years of age. However, these reference values were considered only by Schroth et al. [2013]. Comparing the WHO reference values with the children affected by ECC in the included studies, the sample population in Schroth et al. [2013] and Deane et al. [2018] were anaemic, while a lower ferritin levels were reported by Clarke et al. [2006] and Schroth et al. [2013].

The first limitation of the study is the inclusion of cross-sectional studies, which present with a lower quality of evidence. Hence, a cause and effect relation was difficult to ascertain, and its interpretation limited by potential confounding effects of other established risk factors such as diet and low SES which could not be controlled for in the studies included. The direction of association thus could not be inferred from the available studies. Second limitation is that studies varied with regard to the sample's age, culture, the index used for reporting ECC, and parameters for assessing IDA. Third limitation is that the included studies could not and did not make an attempt to identify the plausible mechanism between ECC and IDA.

Despite these impediments, the clinical importance of this systematic review is that ECC and IDA could be potentially interrelated. The results presented herein establish the importance of awareness of this oral-systemic relationship among physicians and dentists treating young children. Nutritional deficiencies should alert the health care provider of the possibility of ECC, which could be a potential explanation for nutritional impairment in these patients. For dental professionals, ECC affected children should be considered for nutritional deficiencies that may impact their long-term health and well-being. Identification of predictive factors of low iron levels (such as ECC) could facilitate effective interventions before the long-term consequences of iron deficiency can ensue. Based on the conventional risk factor approach for infants and children, recognizing this relationship could help design feasible and optimal preventive strategies worldwide.

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Conclusion

This systematic review demonstrates an association between ECC and increased odds of IDA rather than it being the cause for IDA. However, the cause and effect relation or direction of association could not be inferred between these entities. Prospective studies with robust methodology are required to determine whether children with ECC may be more vulnerable to IDA and to further evaluate the temporal association implying causality.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Harshini Nivetha Easwaran, Anitha Annadurai, M.S. Muthu, Aruna Sharma, Sneha S. Patil, Priya Jayakumar, Aarthi J, and Uma Nagarajan contributed to the conception, design, data acquisition, analysis and interpretation, and drafted and critically revised the manuscript.Umapthy Pasupathy contributed to the study design, and data analysis and critically revised the manuscript. Umesh Wadgave contributed to data acquisition, analysis, and interpretation and critically revised the manuscript. All authors gave their final approval and agree to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary materials. Further enquiries can be directed to the corresponding author.

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