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Research article

Association between developmental defects of enamel and early childhood caries in children under 6 years old: A systematic review and meta-analysis

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ABSTRACT

Early childhood caries (ECC) are an oral health problem worldwide in children under 6 years of age. This disease of rapid development has a multifactorial etiology, and one of the possible risk factors is developmental defects of enamel (DDE), such as hypoplasia and opacities. The aim of this systematic review was to evaluate the association between DDE and ECC in children under 6 years of age. An electronic search was conducted until March 2022 using Medline (PubMed), Scopus, Science-Direct, LILACS, Web of Science, Cochrane Library, EBSCO-Host, EMBASE, and Google Scholar and complemented with a manual search, with no restrictions on language or date of publication. Longitudinal studies of children under 6 years of age with primary dentition were included. A total of 1158 studies were found, of which 651 records were reviewed by title and abstract, and 24 articles were selected for full-text evaluation. Finally, nine studies that met the selection criteria were included in the qualitative synthesis. Study quality and certainty were assessed using the Newcastle-Ottawa scale and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool. Three cohort studies of good quality were included in the meta-analysis. A risk associated with DDE (RR = 1.94; 95% CI: 1.52–2.49) and a risk associated with enamel hypoplasia (RR = 5.45; 95% CI: 1.84–16.14) were found. The results for diffuse opacity (RR = 1.21; 95% CI: 0.18–8.15) and demarcated opacity (RR = 1.26; 95% CI: 0.43–3.65) were not significant. GRADE analysis presented low and very low certainty of evidence. It was concluded that there is an association between DDE and ECC. However, the results should be interpreted with caution because of the limitations of the study.

The protocol for this study has been registered in PROSPERO under identification number CRD42021238919.

1. Introduction

Early childhood caries (ECC) are defined as the presence of one or more cavitated or non-cavitated lesions or missing or filled teeth due to caries in the primary dentition of children younger than 6 years of age [1, 2]. The two key parameters for ECC are the age of the child and the involvement of the primary dentition; one characteristic is that its progression is often fast and can ultimately result in the complete destruction of teeth [1, 3, 4, 5, 6]. Recent studies have shown that the worldwide prevalence of ECC ranges from 23% to 90%; in the case of Latin America, it exceeds 50% [1, 7].

A variety of observational studies with good evidence have demonstrated the multifactorial etiology of dental caries in children, associating them with various factors such as biofilm, frequent sugar intake,

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malnutrition, high infection rates, and socioeconomic factors, among other factors [2, 3, 4, 5]. Some studies also suggest that developmental enamel defects predispose a child to ECC [2, 8, 9, 10].

During the process of enamel formation, alterations called developmental defects of enamel (DDE) can occur, presenting as enamel hypoplasia or opacities [11]. Hypoplasia is a quantitative defect characterized by the reduced thickness of the enamel, which can present as cavities, pits, or grooves and is characterized by the translucency of the enamel, which is classified as diffuse and demarcated opacities [11, 12]. DDE is the result of the damage produced during the amelogenesis stage, an event that causes a deficient formation in the quality and/or quantity of the enamel structure [13]. These alterations in the enamel are associated with carious lesions in the primary dentition [10].

Various studies in different parts of the world have reported variable percentages for the prevalence of DDE in deciduous dentition, which range from 25% to 79% [14, 15, 16, 17]. The most prevalent DDE is diffuse opacities and hypoplasia [13, 18, 19]. However, studies on DDE in primary dentition have provided unclear results, and there is a lack of evidence regarding this issue [20].

Currently, DDE is of great interest to researchers because this defective structure is highly susceptible to dental caries as it has been evidenced by ultrastructural analyses to involve the presence of less mineralized, more porous, and irregular enamel, which allows biofilm accumulation, favoring the development of carious lesions [18]. These alterations can cause tooth sensitivity, wear and/or enamel fractures, and high susceptibility to dental caries, which has a negative impact on children's quality of life [19, 20].

Previous systematic reviews have shown that DDE is associated with the likelihood of ECC [2, 10]. Because of a lack of consensus due to the differences in the teeth examined, study design, the methods used for the detection of defects, DDE classification, and the high degree of heterogeneity of the studies, research findings remain unclear [10, 21]. Moreover, there is no systematic review that addresses the association with ECC based on the different types of DDE, that is hypoplasia and opacities, using only longitudinal studies. The present systematic review considered only longitudinal studies as they are more accurate to study the development of dental caries over time. Dental caries can take 24 months to develop [22, 23], therefore, longitudinal studies would be more appropriate to evaluate this pathology. In addition, case-control and cohort studies represent a higher and stronger level of scientific evidence, compared to cross-sectional studies, according to the latest pyramid of scientific evidence proposed by Murad *et al.* [24].

Due to the need for solid, accessible, and up-to-date evidence for clinical decision-making, this systematic review and meta-analysis aimed to evaluate the association between DDE and ECC in children under 6 years of age.

2. Methods

The present article followed the guidelines of writing according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [25] (Table 1). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42021238919 after a preliminary search was performed.

The question addressed for the systematic review was "What is the association between DDE and ECC in children under 6 years of age?"

The PECO strategy was utilized:

P: children under 6 years old
E: the presence of DDE
C: absence of DDE
O: development of ECC

2.1. Eligibility criteria

Studies investigating the association between DDE and the prevalence of ECC in a representative sample of children were included.

For the article search, the included studies were systematic reviews and meta-analyses as well as cohort and case-control studies that included a control group. Both systematic reviews and meta-analyses were considered only for conducting a manual search of the reference lists.

The study designs that were excluded were cross-sectional studies, experimental studies, letters to the editor, literature reviews, and animal studies.

Cross-sectional studies were excluded because ECC is a disease that develops over time, and its progression is best evaluated via longitudinal studies [22, 23].

The conditions of the participants were as follows:

Inclusion criteria included children in preschool under 6 years of age, presenting with primary dentition and the absence of any systemic condition.

Exclusion criteria included children with any fixed or removable appliances, the presence of molar-incisor hypomineralization, and dental fluorosis.

2.2. Search strategy

An electronic search was conducted and updated through March 16, 2022, using the following databases: Medline (PubMed), Scopus, Science Direct, LILACS, Web of Science, Cochrane Library, EBSCO-Host, and EMBASE complemented with a search of Google Scholar as well as a manual search. Keywords were selected from the DeCs-health science descriptors, the Medical Subject Headings (MeSH) of the U.S. National Library of Medicine, and uncontrolled vocabulary. In addition, a manual search of the reference lists of the selected systematic reviews was performed. Articles were selected based on predefined eligibility criteria, with no restrictions on language or publication date and no definite time of follow-up, using the web application Rayyan QCRI; studies that were either published or approved for publication were considered. The references were organized using a reference manager software (Mendeley desktop, Elsevier). Systematic reviews and meta-analysis were not considered for inclusion among the final selection of studies for the qualitative and quantitative analyses, as only references of the primary studies included in those articles were considered.

The terms were combined to refine the search results, and the following keywords were used: "Developmental Defects of Enamel," "Enamel Defects," "Dental Enamel Hypoplasia" [Mesh], "Dental Hypoplasia," "Enamel Hypoplasia," "Opacities," "Dental Caries" [Mesh], Caries, "Caries Experience," "Tooth Cavity," "Tooth Decay," "Primary Tooth," "Primary Teeth," "Primary Dentition," "Tooth, Deciduous" [Mesh], "Deciduous Tooth," "Deciduous Teeth," and "Pre-school."

An example of the searching strategy used in PubMed is as follows (("Dental Enamel Hypoplasia" [Mesh] OR "Enamel Defects" OR "Developmental Defects of Enamel" OR "Dental Hypoplasia" OR "Opacities" OR "Enamel Hypoplasia") AND ("Dental Caries" [Mesh] OR "Tooth Decay" OR "Tooth Cavity") AND ("Tooth, Deciduous" [Mesh] OR "Primary Tooth" OR "Primary Dentition" OR "Deciduous Tooth" OR "Deciduous Teeth" OR "Primary Teeth")). No limits were set, similar to the approach of Costa *et al.* [10]. The complete search strategy for all of the included databases is shown in Table 2.

The definitions considered for the development of this systematic review were the following:

- ECC: caries development in children under 6 years old [26, 27, 28].
- DDE: quantitative or qualitative alterations in the enamel [12], considering:

Table 1. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7–8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8–9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8–9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9–10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9–10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11–15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15–16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. https://doi.org/10.1371/journal.pmed1000097.

Table 2. Complete list of search strategies.

Database/Search engine	Filter	Search strategy
PubMed	None	((“Dental Enamel Hypoplasia” [Mesh] OR “Enamel Defects” OR “Developmental Defects of Enamel” OR “Dental Hypoplasia” OR “Opacities” OR “Enamel Hypoplasia”) AND (“Dental Caries” [Mesh] OR “Tooth Decay” OR “Tooth Cavity”) AND (“Tooth, Deciduous” [Mesh] OR “Primary Tooth” OR “Primary Dentition” OR “Deciduous Tooth” OR “Deciduous Teeth” OR “Primary Teeth”))
Scopus	Article title, Abstract, Keywords	(“Dental Enamel Hypoplasia” OR “Enamel Defects” OR “Developmental Defects of Enamel” OR “Dental Hypoplasia” OR “Opacities” OR “Enamel Hypoplasia”) AND (“Tooth, Deciduous” OR “Primary Tooth” OR “Primary Dentition” OR “Deciduous Tooth” OR “Deciduous Teeth” OR “Primary Teeth”) AND (“Dental Caries” OR “Tooth Decay” OR “Tooth Cavity”)
Web of Science	None	(“Dental Enamel Hypoplasia” OR “Enamel Defects” OR “Developmental Defects of Enamel” OR “Developmental enamel defects” OR “Dental Hypoplasia” OR Opacities OR “Enamel Hypoplasia”) AND (“Dental Caries” OR “Early Childhood caries” OR “Tooth Decay” OR “Tooth Cavity” OR Caries OR “Caries experience”) AND (“Tooth, Deciduous” OR “Primary Tooth” OR “Primary Dentition” OR “Deciduous Tooth” OR “Deciduous Teeth” OR “Primary Teeth” OR Pre-school*)
Science Direct	Review and Research articles	(“developmental defects of enamel” OR “enamel defects” OR hypomineralization OR “enamel hypoplasia”) AND (“dental caries” OR “tooth decay”) AND (“deciduous teeth” OR “primary dentition”)
LILACS	None	(“Dental Enamel Hypoplasia” OR “Enamel Defects” OR “Dental Hypoplasia” OR “Enamel Hypoplasia”) AND (“Dental Caries”) AND (“Primary Teeth” OR “Deciduous Teeth” OR “Deciduous Tooth” OR “Children”)
Cochrane Library	Trials	“Enamel defect” AND Caries
EBSCO	None	(“Dental Enamel Hypoplasia” OR “Enamel Defects” OR “Developmental Defects of Enamel” OR “Dental Hypoplasia” OR “Opacities” OR “Enamel Hypoplasia”) AND (“Dental Caries” OR “Tooth Decay” OR “Tooth Cavity”) AND (“Tooth, Deciduous” OR “Primary Tooth” OR “Primary Dentition” OR “Deciduous Tooth” OR “Deciduous Teeth” OR “Primary Teeth”)
Google scholar	None	Early Childhood Caries AND enamel defects
EMBASE	None	(“Dental Enamel Hypoplasia” OR “Enamel Defects” OR “Developmental Defects of Enamel” OR “Developmental enamel defects” OR “Dental Hypoplasia” OR Opacities OR “Enamel Hypoplasia”) AND (“Dental Caries” OR “Early Childhood caries” OR “Tooth Decay” OR “Tooth Cavity” OR Caries OR “Caries experience”) AND (“Tooth, Deciduous” OR “Primary Tooth” OR “Primary Dentition” OR “Deciduous Tooth” OR “Deciduous Teeth” OR “Primary Teeth” OR Pre-school*)

- Enamel hypoplasia: quantitative deficiency of enamel, either localized or general lack of enamel surface [11, 29, 30].
- Diffuse opacity: diffuse opacity of enamel of white color presented as a translucent alteration of the enamel to a variable degree [11, 29, 30].
- Demarcated opacity: delimited opacities of the enamel of white, yellow, or brown color, involving an alteration in the translucency of the enamel to a variable degree [11, 29, 30].

The first stage of the study selection was performed by two reviewers (SCS and KHUK) to remove articles that were irrelevant based on the title and abstract, and in case of discrepancy, a third reviewer (MBBH) was involved to resolve the issue. The same reviewers then performed the second stage of study selection independently and in duplicate after reading the articles' full text, and any discrepancy was resolved by the same third reviewer. The final data extraction was performed by four reviewers (KHUK, JCBL, CRY, and ZRA) and verified by a final reviewer (GTR), and any disagreement was resolved by consensus.

2.3. Assessment of risk of bias and quality of evidence

Quality assessment was performed for each included study in duplicate and independently by two reviewers (GPS and JAM) using the Newcastle-Ottawa scale (NOS) [31]. Discrepancies were resolved by consensus with the participation of a third evaluator when necessary (KHUK). The NOS tool is a classification system that assigns a maximum of nine stars in three categories: selection of participants (four stars), comparability (two stars), and measurement of exposure in case-control studies and outcomes in cohort studies (three stars).

The following factors were considered in the comparability assessment: number of dental caries, type of DDE, sex, and age.

To determine the level of quality of each included study, results were converted to good, fair, and poor quality based on previous studies [32, 33] as follows:

- Good quality: 7–9 stars
- Fair quality: 5–6 stars
- Poor quality: 0–4 stars

The certainty of the evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool [34]. The assessment was evaluated in duplicate by two reviewers (GPS and JCBL), and discrepancies were resolved with the participation of a third evaluator (KHUK).

2.4. Risk of caries assessment

Subgroup analysis was performed according to the type of DDE: enamel hypoplasia, diffuse opacity, and demarcated opacity. Based on the articles found, primary second molar hypomineralization was not considered.

The risk for ECC was assessed considering DDE in general, as well as enamel hypoplasia and diffuse and demarcated opacities independently. The adjusted odds ratio (aOR) and adjusted relative risk (aRR), P-values, and 95% confidence intervals (CIs) were obtained for all studies and, if not directly provided, were calculated manually and individually.

Data extraction was processed using the Review Manager software (RevMan 5.4) [35] of the Cochrane Collaboration. Relative risk (RR) was obtained for DDE, enamel hypoplasia, diffuse opacity, and demarcated opacity.

Heterogeneity was assessed using the analysis of x^2 and the I^2 index. A random-effects model was used for the meta-analysis when heterogeneity as determined by the I^2 index was above 50%, considering a confidence interval of 95%. For I^2 values $<50\%$, a fixed-effects model was used. Measurements of relative risk (RR) and frequencies for the studies were used for the statistical analysis, with a significance level of 0.05.

These values of cumulative frequency of consistency and inconsistency were due to the low number of good quality studies found;

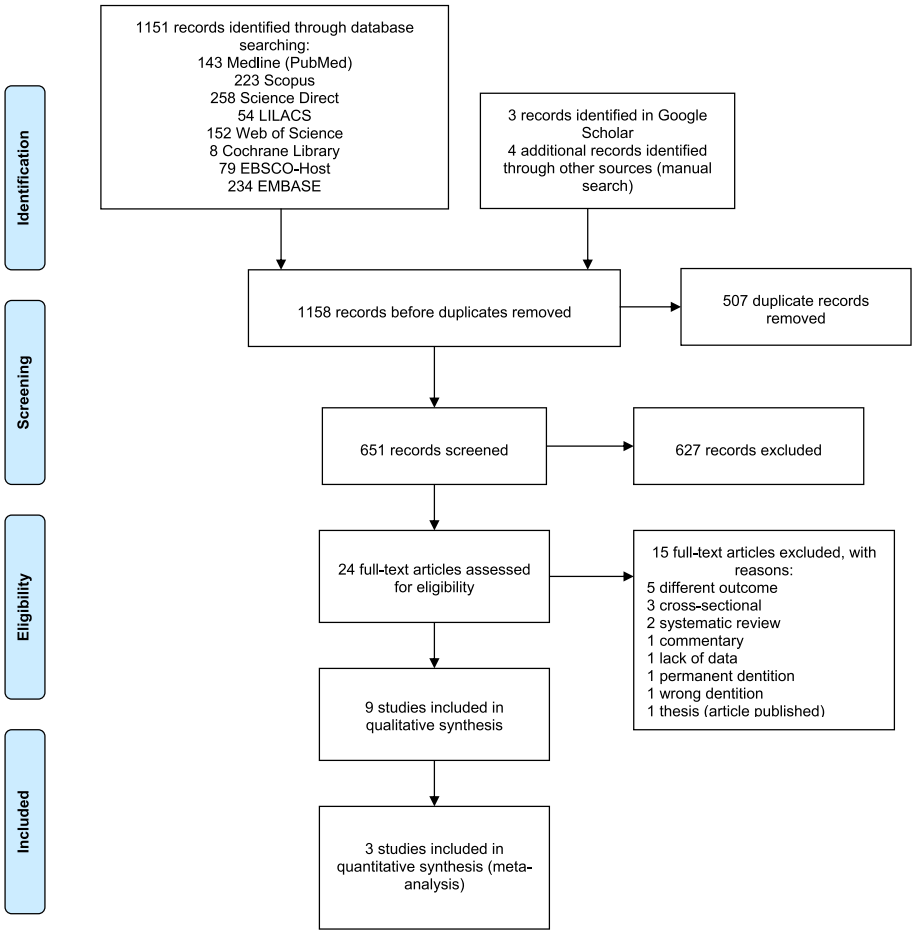


Figure 1. PRISMA flow chart.

however, no risk of bias was identified. A subgroup analysis was performed, and a meta-regression analysis was not necessary.

3. Results

After the search, a total of 1158 articles were found, including four systematic reviews. After the elimination of 507 duplicated articles, a total of 651 articles were analyzed by title and abstract. A total of 627 articles were excluded based on their title and abstract because they were not related to the topic, reported different outcomes, or were from different populations, resulting in 24 studies that were ultimately selected for full-text assessment. After reading the full text, nine articles were included for the qualitative synthesis, and three were included for the quantitative synthesis (meta-analysis), as presented in the flow chart (Figure 1).

For the study selection, reviewer calibration was performed previously to obtain a suitable inter-rater reliability value (K = 0.7). This calibration process consisted of unifying the criteria among reviewers by selecting studies from a predetermined set of 20 articles and then comparing the results with the selection of an expert (GTR).

The list of articles selected for full-text evaluation is included in Table 3, while articles excluded at the full-text stage and the exclusion reason as well as the studies included for the qualitative analysis are presented in Table 4. For all studies with missing data, the authors were contacted, and the article was dismissed if they failed to reply.

The language of the final articles included was predominantly English, and the studies were from various countries (Brazil, Australia, the United States, and China). All of the studies were published between 2006 and 2020. Of the nine items, 50% received funding. Among the included studies, the participants were male and female children under 6 years of age. A summary of the extracted data, including country, study design, sample size, age, the index used, results, and remarks, is presented in Table 5.

3.1. Level of evidence and risk of bias (quality)

Quality assessment was performed for each of the nine longitudinal studies (cohort and case-control). Previously, a calibration of the two evaluators was performed with an expert (KHUK) by unifying criteria and evaluating different articles using the NOS scale, thus achieving an appropriate value of kappa for both the case-control (K = 0.9) and cohort (K = 0.8) studies, with a final kappa value (K = 0.729), which showed high concordance.

Of the nine articles included, six were cohort studies [8, 9, 14, 36, 37, 38], and three were case-control studies [39, 40, 41]. Based on all records included, two studies determined the risk of DDE in general [38, 40], four studies included hypoplasia and diffuse and demarcated opacity [8, 14, 36, 41], two exclusively included hypoplasia [9, 39], and one study included hypoplasia and opacities [37].

All studies included in the qualitative analysis were evaluated according to their quality using the NOS tool [31] for both case-control and cohort studies; four articles of good quality, three of fair quality, and two of poor quality were found (Table 6). The decisions by item are listed in Table 7.

The certainty level was evaluating using the GRADE tool [34]. Analysis was performed for each outcome included in the meta-analysis, and the grade of recommendations was obtained (Table 8). A low certainty of evidence was determined for the association between DDE and ECC, and very low level of certainty was determined for the association of

Table 3. Complete list of studies evaluated in full-text.

Nº	Database	Title	Authors	Journal	Volume	Issue	Pages	Year
1	PubMed	Dental Caries and Developmental Defects of Enamel in the Primary Dentition of Preterm Infants: Case-Control Observational Study.	Schüler IM, Haberstroh S, Dawczynski K, Lehmann T, Heinrich-Weltzien R.	Caries research	52	1	22–31	2018
2	PubMed	Developmental defects of enamel and caries in primary teeth.	Foulds H.	Evidence-based dentistry	18	3	72–73	2017
3	PubMed	Risk of Dental Caries in Primary Teeth with Developmental Defects of Enamel: A Longitudinal Study with a Multilevel Approach.	Paixão-Gonçalves S, Corrêa-Faria P, Ferreira FM, Ramos-Jorge ML, Paiva SM, Pordeus IA.	Caries research	53	6	667–674	2019
4	PubMed	Developmental defects of enamel in primary teeth - findings of a regional German birth cohort study.	Wagner Y.	BMC oral health	17	1	10	2016
5	PubMed	Association between enamel hypoplasia and dental caries in primary second molars: a cohort study.	Hong L, Levy SM, Warren JJ, Broffitt B.	Caries research	43	5	345–53	2009
6	PubMed	A longitudinal controlled study of factors associated with mutans streptococci infection and caries lesion initiation in children 21–72 months old.	Law V, Seow WK.	Pediatric dentistry	28	1	58–65	2006
7	Scopus	A longitudinal observational study of developmental defects of enamel from birth to 6 years of age	Seow WK, Leishman SJ, Palmer JE, Walsh LJ, Pukallus M, Barnett AG.	JDR Clinical and Translational Research	1	3	285–291	2016
8	Scopus	Case-control study of early childhood caries in Australia	Seow WK, Clifford H, Battistutta D, Morawska A, Holcombe T.	Caries Research	43	1	25–35	2009
9	Scopus	Developmental defects of enamel and dental caries in the primary dentition: A systematic review and meta-analysis	Costa FS, Silveira ER, Pinto GS, Nascimento GG, Thomson WM, Demarco FF.	Journal of Dentistry	60		7-Ene	2017
10	Science Direct	Association between developmental defects of enamel and dental caries: A systematic review and meta-analysis	Vargas-Ferreira F, Salas MMS, Nascimento GG, Tarquinio SBC, Faggion CM, Peres MA, Thomson WM, Demarco FF.	Journal of Dentistry	43	6	619–628	2015
11	EBSCO	Developmental defects of enamel in the deciduous incisors of infants born preterm: Prospective cohort.	Cortines AADO, Corrêa-Faria P, Paulsson L, Costa PS, Costa LR.	Oral Diseases	25	2	543–549	2019
12	EBSCO	The Influence of Enamel Defects on the Development of Early Childhood Caries in a Population with Low Socioeconomic Status: A Longitudinal Study.	Oliveira AFB, Chaves AMB, Rosenblatt A.	Caries Research	40	4	296–302	2006
13	EBSCO	The relationship of enamel defects and caries: a cohort study.	Targino AGR, Rosenblatt A, Oliveira AF, Chaves AMB, Santos VE.	Oral Diseases	17	4	420–426	2011
14	Lilacs	Situação de saúde bucal de crianças na primeira infância em creches de Salvador, Bahia	Cabral MBB de S, Mota ELA, Cangussu MCT, Vianna MIP.	Revista Baiana de Saúde Pública	41	3	595–613	2017
15	Lilacs	Defeitos de desenvolvimento de esmalte e cárie dentária em dentes decíduos: uma abordagem multinível	Paixão-Gonçalves S.	Repositório UFMG			91–91	2017
16	Web of Science	The Association Between Developmental Defects of Enamel and Early Childhood Caries in American Indian Children: A Retrospective Chart Review	Pierce A, Zimmer J, Levans A, Schroth RJ.	Pediatric dentistry	42	2	127–132	2020
17	Web of Science	Bacterial colonization, enamel defects and dental caries in 4-6-year-old mono- and dizygotic twins	Ooi G, Townsend G, Seow WK.	International Journal of Paediatric Dentistry	24	2	152–160	2014
18	Google Scholar	Risk Factors for Early Childhood Caries: A Systematic Review and Meta-Analysis of Case Control and Cohort Studies	Kirthiga M, Murugan M, Saikia A, Kirubakaran R.	Pediatric Dentistry	41	2	95–112	2019
19	Google Scholar			International Journal of Paediatric Dentistry	30	1	17-Nov	2020

(*continued on next page*)

Table 3 (*continued*)

Nº	Database	Title	Authors	Journal	Volume	Issue	Pages	Year
		Developmental enamel defects are associated with early childhood caries: Case-control study	Corrêa-Faria P, Paixão-Gonçalves S, Ramos-Jorge ML, Paiva SM, Pordeus IA.					
20	Google Scholar	Impact of hypomineralized teeth and sociobehavioral aspects on caries development: a prospective cohort study.	Silva CMDC, Ambrosano GMB, Mialhe FL.	Brazilian Journal of Oral Sciences	14	4	299–305	2015
21	Manual search	Factors associated with the development of dental caries in children and adolescents in studies employing the life course approach: a systematic review	Abreu LG, Elyasi M, Badri P, Paiva SM, Flores-Mir C, Amin M.	European Journal of Oral Sciences	123	5	305–311	2015
22	Manual search	Impact of enamel defects on early caries development in preschool children	Carvalho JC, Silva EF, Gomes RR, Fonseca JA, Mestrinho HD.	Caries Research	45		353–360	2011
23	Manual search	The contribution of life course determinants to early childhood caries: a 2-year cohort study	Zhou Y, Yang JY, Lo ECM, Lin HC.	Caries Research	46		87–94	2012
24	Manual search	Caries experience in deciduous dentition of rural Chinese children 3–5 years old in relation to the presence or absence of enamel hypoplasia	Li Y, Navia J M, Bian, JY.	Caries research	30	1	15-Ago	1996

enamel hypoplasia and ECC, diffuse opacities and ECC, and demarcated opacities and ECC.

3.2. Measurement of exposures and outcomes

All of the articles included in the narrative synthesis and meta-analysis were analyzed using the NOS for both the three case-control studies and the six cohort studies. After the evaluation of risk of bias, four studies of good quality, including one case-control and three cohort studies, were found. For the meta-analysis, only good-quality cohort studies were included.

The majority of studies reported that the examiners had undergone training and calibration to perform the clinical examination and reported results for the coefficient of kappa of 0.83–0.93.

Various indices for the evaluation of DDE and ECC were utilized in the nine articles included. For the evaluation of DDE, the DDE index of the

Table 4. Final studies excluded after full-text assessment, AND studies included in the qualitative analysis.

Nº	Study	Study design	Decision	Exclusion reason
EXCLUDED STUDIES				
1	Li *et al.*, 1996	Cross-sectional	Excluded	Cross-sectional design
2	Law and Seow, 2006	Cohort (prospective)	Excluded	Different outcome
3	Carvalho *et al.*, 2011	Cross-sectional	Excluded	Cross-sectional design
4	Ooi *et al.*, 2014	Cohort (prospective)	Excluded	Different outcome
5	Abreu *et al.*, 2015	Systematic review	Excluded	Wrong population
6	Silva *et al.*, 2015	Cohort (prospective)	Excluded	Different outcome
7	Vargas-Ferreira *et al.*, 2015	Systematic review	Excluded	Permanent dentition
8	Wagner, 2016	Cohort (prospective)	Excluded	Different outcome
9	Costa *et al.*, 2017	Systematic review	Excluded	Systematic review
10	De Sousa Cabral *et al.*, 2017	Cross-sectional	Excluded	Cross-sectional design
11	Foulds, 2017	Commentary	Excluded	Commentary
12	Paixão-Gonçalves, 2017	Cohort (prospective)	Excluded	Thesis (published article included [8])
13	Schüler *et al.*, 2018	Case-control	Excluded	Lack of data
14	Cortines *et al.*, 2019	Cohort (prospective)	Excluded	Different outcome
15	Kirthiga *et al.*, 2019	Systematic review	Excluded	Systematic review
INCLUDED STUDIES				
Nº	Study	Study design	Decision	
1	Seow *et al.*, 2009	Case-control	Included	
2	Pierce *et al.*, 2020	Case-control	Included	
3	Corrêa-Faria *et al.*, 2020	Case-control	Included	
4	Oliveira *et al.*, 2006	Cohort (prospective)	Included	
5	Hong *et al.*, 2009	Cohort (prospective)	Included	
6	Targino *et al.*, 2011	Cohort (prospective)	Included	
7	Zhou *et al.*, 2012	Cohort (prospective)	Included	
8	Seow *et al.*, 2016	Cohort (prospective)	Included	
9	Paixão-Gonçalves *et al.*, 2019	Cohort (prospective)	Included	

Table 5. Summary data from the included studies in the systematic review.

Study	Country	Design	Age	Sample (groups)	Follow-up	DDE index	Caries index	DDE evaluated	Results	Remarks	Quality
Seow *et al.*, 2009 [39]	Australia	Case-control	0–4 years old	617 children (156 cases, 461 controls)	No description	Modified DDE index – Pascoe and Seow (1994)	deft – WHO (1987)	Enamel hypoplasia	ECC risk for Enamel hypoplasia (all children)[a]: OR = 4.04 (2.44–6.71) ECC risk for Enamel hypoplasia (childcare children): OR = 4.24 (0.98–18.28); p < 0.05 ECC risk for Enamel hypoplasia (public clinic children): OR = 0.99 (0.14–7.25); p < 0.05	One of the risk indicators for ECC in childcare children was the enamel hypoplasia.	Fair
Pierce *et al.*, 2020 [40]	United States	Case-control	12–84 months old	557 children (181 cases, 376 controls)	No description	Not specified	deft – WHO CIPD score	DDE (in general)	Caries risk for DDE: OR = 3.8 (2.31–6.19); p < 0.001 ECC risk for DDE: OR = 4.24 (2.48–7.26); p < 0.001 Severe-ECC risk for DDE: OR = 3.4 (2.19–5.28); p < 0.001	The prevalence of DDE was relatively high (67.7%). Children with DDE were significantly more likely to present dental caries, ECC, or severe ECC.	Poor
Corrêa-Faria *et al.*, 2020 [41]	Brazil	Case-control	2–5 years old	196 children (98 cases, 98 controls)	No description	DDE index – FDI (1992)	deft – WHO (1997)	DDE (in general) Enamel hypoplasia Diffuse opacity Demarcated opacity	ECC risk for DDE: aOR = 1.94 (1.03–3.65); p < 0.05 ECC risk for Enamel hypoplasia[a]: OR = 1.53 (0.42–5.61) ECC risk for Diffuse opacity[a]: OR = 1.64 (0.78–3.44) ECC risk for Demarcated opacity[a]: OR: 3.39 (1.49–7.71)	The presence of DDE is a predisposing factor for the appearance of ECC.	Good

(*continued on next page*)

Table 5 (*continued*)

Study	Country	Design	Age	Sample (groups)	Follow-up	DDE index	Caries index	DDE evaluated	Results	Remarks	Quality
Oliveira *et al.*, 2006 [14]	Brazil	Cohort (prospective)	12–36 months old	228 children (180 exposed, 48 non-exposed)	24 months	DDE index – FDI (1992)	deft – WHO (1997)	DDE (in general) Enamel hypoplasia (missing enamel, reduced thickness)	ECC risk for DDE: RR = 14.9 (2.1–105.1); p < 0.0001 ECC risk for Hypoplasia (missing enamel)[a]: RR = 42.61 (28.95–62.73) ECC risk for Diffuse opacity[a]: RR = 7.15 (4.37–11.70) Reduced thickness hypoplasia: 0 cases of dental caries Demarcated opacity: 0 cases of dental caries	The presence of DDE is strongly associated with the development of ECC.	Fair
Hong *et al.*, 2009 [9]	United States	Cohort (prospective)	0–9 years old	491 children (19 exposed, 472 non-exposed)	9 years	Russel criteria (1961)	Warren *et al.*, criteria (2002)	Enamel hypoplasia (primary second molars)	Caries risk for enamel hypoplasia: At 5 years old: RR = 2.17 (1.17–4.05); p = 0.03 At 9 years old: RR = 1.52 (0.98–2.38), p = 0.07	Enamel hypoplasia is a significant predictor of childhood dental caries.	Good
Targino *et al.*, 2011 [36]	Brazil	Cohort (prospective)	12–54 months old	275 children (at 54 month-old: 182 exposed, 42 non-exposed)	42 months	DDE index – FDI (1992)	deft – WHO (1997)	DDE (in general) Enamel hypoplasia (missing enamel, reduced thickness) Diffuse opacity Demarcated opacity	ECC risk for DDE: RR = 1.85 (1.09–3.13); p < 0.05 ECC risk for Hypoplasia (missing enamel)[a]: RR = 14.93 (12.47–17.89) ECC risk for hypoplasia (reduced thickness)[a]: RR = 0.88 (0.37–2.11) ECC risk for Diffuse opacity[a]: RR = 2.89 (2.17–3.85) ECC risk for Demarcated opacity[a]: RR = 0.68 (0.26–1.81)	DDEs are a predisposing factor for ECC. There was a strong relationship between ECC and DDE in children aged 18–54 months.	Good

(*continued on next page*)

Table 5 (*continued*)

Study	Country	Design	Age	Sample (groups)	Follow-up	DDE index	Caries index	DDE evaluated	Results	Remarks	Quality
Zhou *et al.*, 2012 [37]	China	Cohort (prospective)	8–32 months old	225 children (no description)	2 years	DDE index – FDI (1992)	deft – WHO (1997)	Enamel hypoplasia Enamel opacities	ECC incidence density ratio (IDR) for Hypoplasia: Adjusted IDR = 4.85 (1.92–12.28); $p < 0.001$ ECC incidence density ratio (IDR) for opacities: Adjusted IDR = 1.69 (0.76–3.76); $p = 0.201$	Enamel hypoplasia increases the risk of dental caries in affected teeth.	Fair
Seow *et al.*, 2016 [38]	Australia	Cohort (prospective)	2–6 years old	725 children (74 exposed, 651 non-exposed)	4 years	Modified DDE index – Clarkson and O'Mullane (1989)	deft – WHO	DDE (in general) Pits Missing enamel Hypoplasia with yellow-brown opacities	Caries risk for DDE[a]: RR = 2.06 (1.63–2.61) Hazard Ratio (HR) by DDE type: Pits: HR = 6.0 (2.4–14.6), $p < 0.001$ Missing enamel: HR = 5.5 (3.8–7.8), $p < 0.001$ Hypoplasia with yellow-brown opacities: HR = 4.5 (1.8–11.3), $p < 0.002$	Enamel hypoplasia is associated with an increased risk of caries. DDEs are a strong determinant of dental caries in the primary dentition.	Poor
Paixão-Gonçalves *et al.*, 2019 [8]	Brazil	Cohort (prospective)	2–5 years old	339 children (113 exposed, 226 non-exposed)	2 years	DDE index – FDI (1992)	deft – WHO (1997)	DDE (in general) Enamel hypoplasia Diffuse opacity Demarcated opacity	Caries risk for DDE[a]: RR = 1.98 (1.50–2.61) Caries risk for Enamel hypoplasia[a]: RR = 4.56 (3.31–6.29) Caries risk for Diffuse opacity[a]: RR = 0.46 (0.17–1.20) Caries risk for Demarcated opacity[a]: RR = 1.96 (1.27–3.00)	The study confirms the association between DDE and dental caries in the primary dentition. Enamel hypoplasia and previous dental caries are risk factors for carious lesions in the primary dentition.	Good

ECC: early childhood caries, DDE: developmental defects of enamel, OR: odds ratio, RR: relative risk.

[a] Risk values calculated manually (95% CI, $p < 0.05$).

Table 6. Evaluation of the quality of the studies included according to the Newcastle-Ottawa Scale (NOS).

Study	Country	NOS			Final score	Quality[a]
		Selection	Comparability	Exposure		
CASE-CONTROL STUDIES						
Seow *et al.* 2009 [39]	Australia	★★	★★	★★	6	Fair
Pierce *et al.* 2020 [40]	United States	★★		★★	4	Poor
Corrêa-Faria *et al.* 2020 [41]	Brazil	★★★	★★	★★	7	Good
COHORT STUDIES						
Oliveira *et al.* 2006 [14]	Brazil	★★★	★	★★	6	Fair
Hong *et al.* 2009 [9]	United States	★★★	★★	★★	7	Good
Targino *et al.* 2011 [36]	Brazil	★★★	★★	★★★	8	Good
Zhou *et al.* 2012 [37]	China	★★	★★	★★	6	Fair
Seow *et al.* 2016 [38]	Australia	★★		★★	4	Poor
Paixão-Gonçalves *et al.* 2019 [8]	Brazil	★★★	★★	★★★	8	Good

[a] Quality assessment: Good quality (7–9 stars), fair quality (5–6 stars) and poor quality (0–4 stars) as classified on previous studies [32, 33].

Table 7. Decision by item of evaluation of the studies included according to the Newcastle-Ottawa Scale (NOS).

CASE-CONTROL STUDIES

Study	Selection[a]				Comparability[b]		Exposure[c]			Subtotal	Total
	1	2	3	4	1A	1B	1	2	3		
Seow *et al.* 2009 [39]	★	-	-	★	★	★	★	★	-	2,2,2	6
Pierce *et al.* 2020 [40]	★	★	-	-	-	-	★	★	-	2,0,2	4
Corrêa-Faria *et al.* 2020 [41]	★	★	★	-	★	★	★	★	-	3,2,2	7

COHORT STUDIES

Study	Selection[d]				Comparability[e]		Outcome[f]			Subtotal	Total
	1	2	3	4	1A	1B	1	2	3		
Oliveira *et al.* 2006 [14]	★	-	★	★	★	-	★	★	-	3,1,2	6
Hong *et al.* 2009 [9]	★	★	★	-	★	★	-	★	★	3,2,2	7
Targino *et al.* 2011 [36]	★	-	★	★	★	★	★	★	★	3,2,3	8
Zhou *et al.* 2012 [37]	★	-	★	-	★	★	-	★	★	2,2,2	6
Seow *et al.* 2016 [38]	★	-	★	-	-	-	-	★	★	2,0,2	4
Paixão-Gonçalves *et al.* 2019 [8]	★	★	★	-	★	★	★	★	★	3,2,3	8

[a] Selection: (1) Adequate case definition; (2) Representativeness of the cases; (3) Selection of controls; (4) Definition of controls.
[b] Comparability: (1A) Comparability of cases and controls by study controls for most important factor; (1B) Comparability of cases and controls by study controls for any additional factor.
[c] Exposure: (1) Ascertainment of exposure; (2) Same method of ascertainment for cases and controls; (3) Non-response rate.
[d] Selection: (1) Representativeness of the exposed cohort; (2) Selection of the non-exposed cohort; (3) Ascertainment of exposure; (4) Outcome of interest not present at start of study.
[e] Comparability: (1A) Comparability of cohorts by study controls for most important factor; (1B) Comparability of cohorts by study controls for any additional factor.
[f] Outcome: (1) Assessment of outcome; (2) Adequate follow-up for outcome to occur; (3) Adequacy of follow-up of cohorts.

Fédération Dentaire Internationale (FDI) [42] was the most widely used; it includes codes for hypomineralization (diffuse opacity and demarcated opacity) and hypoplasia (missing enamel and reduction in thickness).

For ECC, as they affected primary dentition, most of the studies evaluated the lesions of dental caries by decayed, extracted, and filled (deft) for primary teeth, according to the World Health Organization's (WHO) parameters [43].

3.3. Risk of caries according to DDE classification

For the meta-analysis, only the high-quality cohort studies were considered, which included only three studies in total [8, 9, 36]. Meta-analysis of case-control studies was not performed because only one case-control study presented good quality [41], and a meta-analysis with a combination of data between case-control and cohort studies was considered inappropriate. Figure 2 shows the risk of ECC found for each category of DDE evaluated, including all DDE in general, enamel hypoplasia, diffuse opacities, and demarcated opacities. The forest plot in Figures 2a and 2b represent only those with significant RR greater than one associated with DDE (RR = 1.94; 95% CI: 1.52–2.49) and enamel hypoplasia (RR = 5.45; 95% CI: 1.84–16.14). Figures 2c and 2d show a RR of greater than one, which is not significant, associated with diffuse opacity (RR = 1.21; 95% CI: 0.18–8.15) and demarcated opacity (RR = 1.26; 95% CI: 0.43–3.65).

Heterogeneity of the study (I^2) and p-value ($p < 0.01$) were also calculated. The results showed a measure of consistency of heterogeneity of 0% ($Z = 5.26$, $p < 0.00001$) for the presence of DDE, 97% ($Z = 3.06$, $p < 0.002$) for enamel hypoplasia, 93% ($Z = 0.20$, $p = 0.84$) for diffuse opacity, and 76% for demarcated opacity ($Z = 0.43$, $p = 0.67$). This determined the use of a fixed-effect model for the presence of DDE in general and the use of a random-effect model for enamel hypoplasia, diffuse opacity, and demarcated opacity.

4. Discussion

The results of the present study showed that children under 6 years old affected by DDE had twice the risk of developing caries, compared to those with no DDE. The children with enamel hypoplasia presented as

Table 8. Certainty assessment of outcomes according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.

Outcome	Certainty assessment							№ of patients		Effect		Certainty	Importance
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	With DDE	Without DDE	Relative (95% CI)	Absolute (95% CI)		
Presence of DDE associated with ECC	2	observational studies	not serious	not serious	not serious	not serious	none	134/447 (30.0%)	535/6021 (8.9%)	RR 1.94 (1.52–2.49)	84 more per 1,000 (from 46 more to 132 more)	⊕⊕◯◯ Low	IMPORTANT
Presence of Enamel Hypoplasia associated with ECC	3	observational studies	not serious	very serious[a]	not serious	very serious[b, c]	very strong association	212/356 (59.6%)	750/9788 (7.7%)	RR 5.45 (1.84–16.14)	341 more per 1,000 (from 64 more to 1,000 more)	⊕◯◯◯ Very low	IMPORTANT
Presence of Diffuse Opacities associated with ECC	2	observational studies	not serious	very serious[a]	not serious	serious[b]	none	62/559 (11.1%)	670/9316 (7.2%)	RR 1.21 (0.18–8.15)	15 more per 1,000 (from 59 fewer to 514 more)	⊕◯◯◯ Very low	IMPORTANT
Presence of Demarcated Opacities associated with ECC	2	observational studies	not serious	serious[d]	not serious	serious[b]	none	22/239 (9.2%)	670/9316 (7.2%)	RR 1.26 (0.43–3.65)	19 more per 1,000 (from 41 fewer to 191 more)	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; RR: risk ratio.

Explanations.

[a] Very high level of heterogeneity between studies.

[b] Few events in some studies.

[c] Wide confidence interval.

[d] High level of heterogeneity between studies.

much as five times higher risk of developing ECC, while children with diffuse or demarcated opacities, do not present a risk of developing ECC.

The prevalence of DDE ranges from 25% to 79% [14, 15, 16, 17], and is highly variable depending on the sample size of the various studies. Moreover, according to Oliveira *et al.* [14], 78.9% of infants at 36 months of age already have at least one tooth affected. Within these defects, enamel hypoplasia is observed, presented as the absence of enamel or as a reduction of the thickness of enamel, as is hypomineralization, also known as opacities, which may appear as diffuse or demarcated [3, 4, 44]. These defects may be found in both permanent and primary dentition, and diverse studies have associated the presence of DDE in primary dentition with risk factors such as low birth weight [5, 44], malnutrition [3], problems during pregnancy [4], premature delivery [5, 18], infections during childhood [5], lack of breastfeeding [4], social factors [4, 5], sex, and age [45].

DDE are alterations in the normal development of tooth enamel, which can affect its quantity or quality [11, 12] and may make affected teeth more susceptible to the development of carious lesions. Several studies have associated the development of dental caries with DDE, considering them to be risk factors for caries [8, 14, 36]. Although there have been previous systematic reviews of this topic, they have included cross-sectional studies or studies in children with mixed or permanent dentition, with no quality evaluation of the evidence used [10, 46]. Moreover, the role of the different types of DDE and their association with ECC remain unclear.

In children under 6 years of age, the development of ECC is a problem of oral health concern, and it is one of the most prevalent chronic diseases in children [47]. The presence of cavities in primary dentition is also considered a predictor of the development of caries in permanent dentition [48, 49], it is highly important to address this health problem from a very early age. As an oral disease with a high number of cases in children—it has been reported in approximately 50% of preschoolers worldwide [47]—it is of utmost importance to recognize the various risk factors for its development. As DDE are considered to constitute a risk factor for the development of ECC in several studies, the following systematic review aimed to evaluate the association between DDE and ECC prevalence in children under 6 years of age.

The results of the meta-analysis showed that children who had teeth affected by DDE had nearly twice the risk of developing caries, compared to those with no DDE (RR = 1.94; 95% CI: 1.52–2.49). Based on this, the present study identified DDE as a risk factor for dental caries in primary dentition, as reported in the systematic reviews conducted by Costa *et al.* [10] and Kirthiga *et al.* [2]. In Costa *et al.*'s [10] the risk values obtained were slightly higher (OR = 3.32, CI: 2.41–4.57). This may have been because both cross-sectional and longitudinal studies were included, and there was no categorization according to the quality of studies, unlike in this meta-analysis. In addition, Kirthiga *et al.*'s [2] review considered only two studies for their meta-analysis, which obtained a much higher value (OR = 14.62, CI: 6.10–35.03) than that of the present study. Kirthiga *et al.* [2] considered the study of Oliveira *et al.* [14] as part of their meta-analysis, which presented very wide confidence intervals (OR = 14.9, CI: 5.48–38.63) that may have affected their final results. In this meta-analysis, de Oliveira *et al.*'s [14] study, although included in the qualitative synthesis, was not considered for the quantitative analysis because it did not present good quality. In the Vargas-Ferreira *et al.*'s [46] systematic review, which evaluated the association between DDE and the development of dental caries in children and adolescents among 6–14 years old, they found an RR = 2.22 (CI: 1.39–3.54), very similar to this study. Thus, regardless of age, DDE can be considered a risk factor for the development of dental caries.

Although the present results are consistent with previous systematic reviews regarding DDE as a risk factor for dental caries, the role of each DDE type in the prevalence of ECC remains unclear. Within the classification of DDE, there is a higher prevalence of diffuse opacities and hypoplasia [36, 50, 51], although the results differ slightly from what was

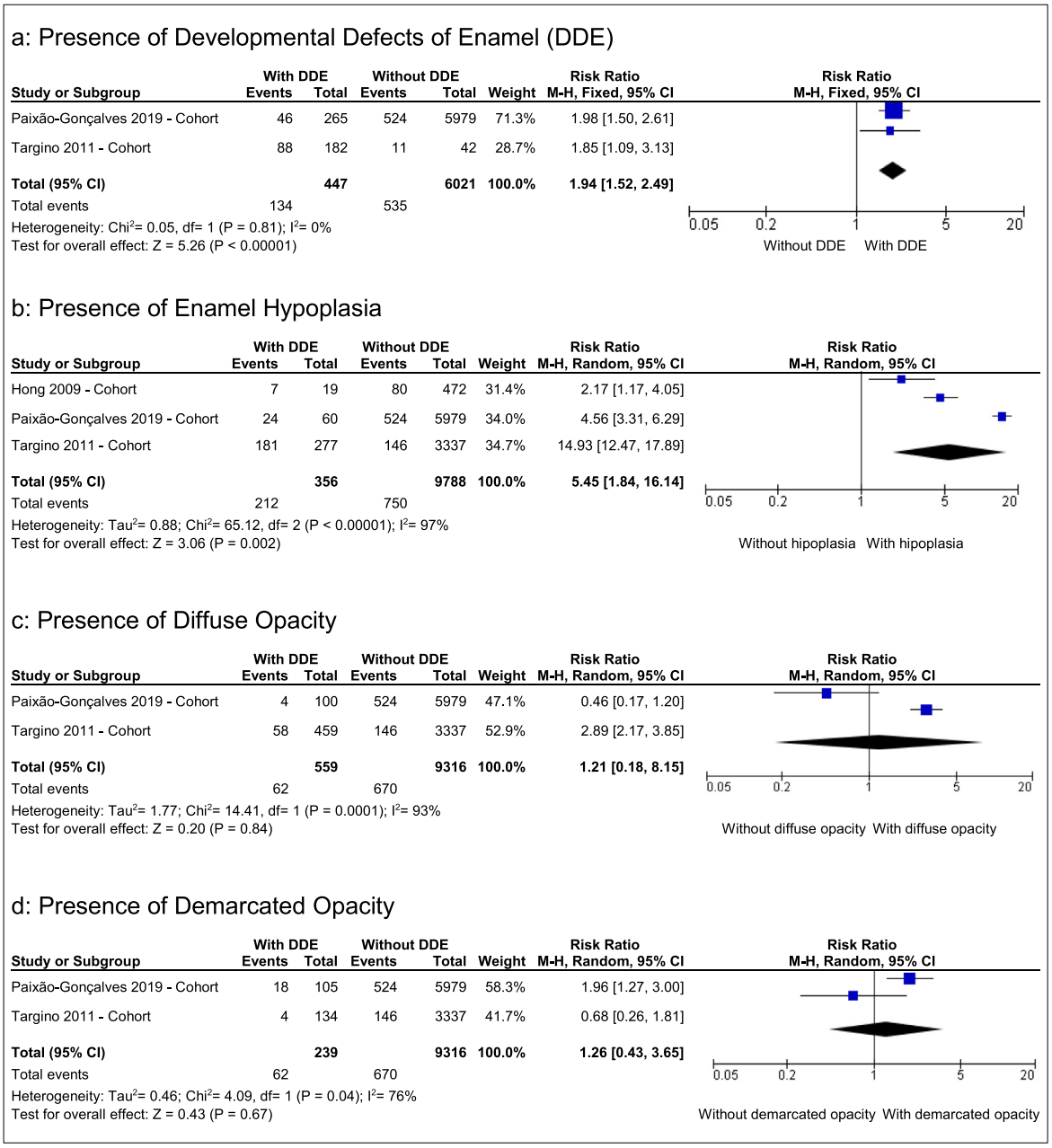


Figure 2. Risk Factors found by DDE classification. (a) Forest-plot showing the presence of DDE as a significant risk factor for ECC. (b) Forest-plot showing the presence of Enamel hypoplasia as a significant risk factor for ECC. (c) Forest-plot showing the presence of Diffuse Opacity as a non-significant risk factor for ECC. (d) Forest-plot showing the presence of Demarcated Opacity as a non-significant risk factor for ECC. Study heterogeneity (I^2) and related p value ($p < 0.01$) were also calculated.

found in a preliminary study conducted by the authors of the present study showing that in a population of children from 2 to 5 years old in the region of Pichanaki, Peru, there was a higher prevalence of demarcated opacities when analyzing the second primary molars.

In this meta-analysis, regarding the data of enamel hypoplasia, the risk of caries increased, as children with enamel hypoplasia presented as much as five times higher risk of developing ECC (RR = 5.45; 95% CI: 1.84–16.14). It should be noted that only for Targino *et al.*'s [36] study was missing enamel considered as hypoplasia. However, when assessing the diffuse and demarcated opacities, the risk was not only less than that for hypoplasia, but neither opacity type presented significant results. Diffuse opacities were not considered a risk factor for ECC (RR = 1.21; 95% CI: 0.18–8.15), and in the same way, demarcated opacities were not considered a risk (RR = 1.26; 95% CI: 0.43–3.65).

Costa *et al.*'s [10] systematic review showed that children with enamel hypoplasia presented a risk of developing dental caries (OR = 4.28, CI: 2.4–8.15), as did children with diffuse opacities (OR = 1.42, CI: 1.15–1.76). In addition, regarding demarcated opacities, Costa *et al.* did not find any associated risk (OR = 2.62, CI: 0.85–8.12). Based on the different results regarding diffuse opacities in Costa *et al.*'s analysis, the role of opacities in the development of dental caries remains unclear.

The results of this meta-analysis demonstrate that within the different types of DDE, enamel hypoplasia represents a true risk for the development of dental caries, as reported by Costa *et al.* [10]. This may occur

because hypoplasia, most notably the missing enamel, can form undermined surfaces, such as cavities, pits, or grooves [11, 12], which may allow for greater retention of dental plaque, as well as areas with reduced tooth enamel, which can lead to lower protection against cariogenic bacteria-generated acids, with the subsequent progression of carious lesions. Moreover, in the meta-analysis of the different types of DDE, the heterogeneity was considerable for enamel hypoplasia, diffuse opacity, and demarcated opacity. It is possible that, due to the nature of the studies, the different sample amounts, ages, and follow-up of participants may have been reflected in the heterogeneity. In addition, unlike Targino *et al.* [36] and Paixão-Gonçalves *et al.* [8], who used the FDI index for DDE, Hong *et al.* [9] used a different index and also examined hypoplasia in the second primary molars, which may have been reflected in the high heterogeneity of the hypoplasia analysis.

Enamel hypoplasia is a type of defect that involves the enamel surface and is associated with reduced and localized thickness [30, 52]; it is typically the most prevalent of all DDE and generates risk of developing carious lesions [9, 39, 53]. The prevalence of hypoplasia has been reported to be 28% [54] and is considered a significant predictor of dental caries in children under 6 years old [9, 55]. Opacities involve an alteration in the translucency of the enamel to a varying degree; they can appear in white, cream, yellow, or brown colors and vary greatly in their extension, location, and distribution [30, 52]. The prevalence of demarcated opacities is variable, having been reported as low as 5.0% [50], while diffuse opacities are commonly more prevalent (23.1%) [50]; similarly, these opacities have been associated with caries development [37]. Although the results of the present study only obtained significant values for hypoplasia, that opacities could also play an important role in the development of ECC should not be ruled out. Therefore, more studies are needed to address the association of the different types of DDE in relation to the development of dental caries.

DDE constitute a risk factor for the development of ECC, and enamel hypoplasia presents an even higher risk for the development of dental caries, as evidenced in this study. Thus, early management of these issues is of utmost importance to prevent the progression of carious lesions. The present study considered only cohort studies with the best quality for this meta-analysis in addition to stratifying the results into subgroups according to the type of DDE. The results may be valuable for decision-making regarding the prevention of dental caries in primary dentition, however, they should be interpreted with caution. Based on the certainty level, only low and very low levels of certainty were determined for all the outcomes studied, including the association of DDE and ECC, enamel hypoplasia and ECC, diffuse opacities and ECC, and demarcated opacities and ECC. The quality of evidence was low due to serious inconsistency and imprecision, due to the high heterogeneity of the studies included in each meta-analysis, few events reported, and wide confidence intervals. Moreover, the meta-analyses only included 2 to 3 studies, possibly affecting the certainty level.

Ismail *et al.* [22], who studied the progression of caries on the primary tooth surface level over a period of two years, showed that the rate of progression of moderate caries is 9.6 times higher than that of healthy surfaces. The initial and moderate carious surfaces progressed to extensive caries 6.1 and 20.6 times, respectively, relative to the healthy surfaces. This indicates that the progression of caries over time is necessary for evaluation, especially on non-healthy surfaces. Based on the progression of dental caries over time, cross-sectional studies were not considered in our analysis, as it is known that ECC is a multifactorial disease that takes time to develop. According to previous studies [22, 23], this development can take 24 months, as can diagnosis; therefore, longitudinal studies would be more accurate for studying the development of dental caries. In addition, cross-sectional studies represent lower and weaker scientific health evidence, compared to case-control and cohort studies, according to the latest pyramid of scientific evidence proposed by Murad *et al.* [24]. Moreover, they are not considered appropriate for use in providing clinical recommendations, as stated by the SIGN guidelines, in comparison to longitudinal studies [56]. The previous systematic reviews that have been published [2, 10] included cross-sectional studies, which may have reduced the level of evidence and the degree of clinical recommendation of the studies; therefore, the focus of the present systematic review and meta-analysis was to search for only case-control and cohort studies.

Regarding the application of the results found in the present study, children under 6 years of age need to be evaluated for the presence of any kind of DDE, as this condition could represent a risk of developing ECC. Populations with a high prevalence of these enamel defects should be monitored to avoid the progression of carious lesions from an early age. Although the results of this study showed a significant risk of ECC for both DDE in general and hypoplasia, the meta-analyses were performed with only three studies; therefore, the results should be interpreted carefully. It is possible that teeth with hypoplasia may be more vulnerable to the development of dental caries than those with opacities. However, it should not be ruled out that both hypoplasia and opacities could manifest a high risk for ECC. Considering that DDE may be a risk factor for ECC, it is important to consider that all children under 6 years of age with primary dentition who present any kind of DDE may require more extensive dental care to prevent the development and progression of ECC.

As few good-quality studies on the subject address the association between each type of DDE and ECC, it is necessary to perform good-quality longitudinal studies to elucidate the true role according to the type of DDE, differentiating between hypomineralization (diffuse and demarcated opacities) and hypoplasia (missing enamel and reduced thickness) in children under 6 years of age.

5. Limitations

This review had several limitations, including the limited number of studies on the subject, with the majority being cross-sectional studies and few being longitudinal studies. Likewise, regarding the small number of studies on DDE related to ECC, we received limited responses from the authors when we contacted them. In addition, among the nine articles included, the quality varied greatly, with only four studies showing good quality, three showing fair quality, and two showing low quality. These limitations have implications for future research.

There was no standardization among studies to measure the results of both dental caries and DDE. Some studies evaluated these variables in a general way, while others did so according to the different types, including enamel hypoplasia and opacities, which meant that not all of the included studies were comparable.

Regarding the certainty of evidence, the GRADE analysis showed a low and very low level of evidence. An additional limitation was that the meta-analysis was conducted using only three studies; thus, the findings should be considered with extreme caution because this limitation results in evidence of very low strength.

6. Conclusion

The association between DDE and ECC has been demonstrated based on the results of this systematic review and meta-analysis. In addition, within the types of DDE, enamel hypoplasia represented a risk for the development of dental caries in children under 6 years old. A low level of certainty was determined for the association between DDE and ECC, and very low levels of certainty were determined for enamel hypoplasia, diffuse opacities, and demarcated opacities in relation to ECC.

Children with DDE may, therefore, require more dental care to prevent the development and progression of ECC. However, the results of this systematic review and meta-analysis should be interpreted with caution because of the limitations of the study.

Declarations

Author contribution statement

Sara Castañeda-Sarmiento; Karin Harumi Uchima Koecklin; Mayra Belen Barahona Hernandez; Gary Pereda Santos; Julio César Bruno Luyo; Catherine Ruiz-Yasuda; Zenaida Rojas Apaza: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Julio César Sánchez Sotomayor: Analyzed and interpreted the data.

David Paredes Adasme; Dayhanne Alexsandra Torres Ricse; Marycielo Evelin Mendoza Ballena; Abad Salcedo; Laura Ricardina Ramirez-Sotelo; Laura Ricardina Ramirez-Sotelo; Daniel José Blanco-Victorio: Contributed to analysis tools or data.

Jessica Arieta-Miranda: Performed the experiments; Analyzed and interpreted the data.

Gilmer Torres-Ramos: Conceived and designed the research; Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data associated with this study has been deposited at “The protocol of the systematic review was registered online in PROSPERO” under the accession number CRD42021238919.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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