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SYSTEMATIC REVIEW

Are Premature Birth and Low Birth Weight Associated with Delay on the Eruption of Deciduous Teeth? A Systematic Review and Meta-analysis

Paula Dresch Portella[1], Gisele Marchetti[1], Leticia Wambier[2], Juliana Feltrin de Souza[1], Fabian Calixto Fraiz[1], José Vitor Nogara Borges de Menezes[1], Luciana Reichert da Silva Assunção[1]

[1]Pediatric Dentistry, Department of Stomatology, Federal University of Paraná, Curitiba, PR, Brazil.
[2]Pediatric Dentistry, Department of Stomatology, Positivo University, Curitiba, PR, Brazil.

Correspondence: Paula Dresch Portella, Avenida Prefeito Lothário Meissner, 632, Jardim Botânico, Curitiba, Paraná, Brazil. 80210-170. **E-mail:** pauladresch@hotmail.com

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ABSTRACT

Objective: To investigate whether children with premature birth (PB) and/or with low birth weight (LBW) have different tooth eruption patterns than those born at term or with normal weight. **Material and Methods:** Searches were performed in the PubMed, Cochrane Library, Sc1opus, Web of Science, LILACS, and BBO databases as well as the grey literature. Three independent reviewers were involved in study selection, data extraction, and bias assessment. The risk of bias was assessed using the Modified Newcastle-Ottawa Scale. Meta-analysis was conducted to compute the mean difference (MD) in mean chronological or adjusted age at the eruption of the first deciduous tooth between preterm children and those born at full term. The GRADE approach was used. **Results:** Among a total of 316 articles identified, 21 were eligible for inclusion and three were included in the meta-analysis. PB was associated with the delay in the first tooth deciduous eruption when chronological age was considered (MD: 1.36; 95%CI: 1.02–1.69) but not when considering adjusted age (MD: -0.30; 95%CI: -0.67–0.07). The evidence was graded as having very low quality. **Conclusion:** Based on a low certainty of evidence the PB is associated with the delayed eruption of the first deciduous tooth when considering chronological age but not when adjusted age is considered.

Keywords: Infant, Premature; Birth Weight; Study Characteristics; Meta-Analysis; Tooth Eruption.

Introduction

Premature birth increases neonatal morbidity and mortality rates in children under the age of five years around the world [1,2]. Moreover, preterm birth rates have been increasing in recent years in nearly all countries [3]. The global incidence was 9.6% in 2005 and increased to 11.08% in 2010 [4]. According to the World Health Organization, approximately 15 million children are born prematurely (before 37 gestational weeks) every year and more than 60% of preterm births occur in Africa and South Asia [2]. On average, 12% of children are born too early in lower income countries compared to 9% in higher income countries. Poorer families are also at higher risk within countries [4]. The cause of prematurity may be associated with socioeconomic, nutritional, biological, and environmental factors [5].

Preterm infants usually have low birth weight (LBW) [7], which is defined as less than 2500 g regardless of gestational age [7] and is an important public health indicator, especially in settings where an accurate assessment of gestational age is not possible [8]. The estimated global prevalence of LBW was 14.6% in 2000 and increased to 17.5% in 2015 [9]. Approximately 20.5 million livebirths in 2015 involved children with LBW, 91% of whom were from low- and middle-income countries, mainly in South Asia (48%) and sub-Saharan Africa (24%) [9].

Preterm and LBW children can suffer complications in nearly all organ systems during extrauterine life [10]. In early childhood, these children can have significant delays in different facets of physical and psychological growth and development. Numerous studies have shown that, like other tissues and organs of the body, the development of facial bones and the occlusion can be affected by premature birth and LBW [11-17]. Some authors report that premature birth [18-24] and low birth weight [21-31] lead to the delayed eruption of the deciduous teeth. However, when the age of the eruption of the first deciduous tooth is adjusted (considering the gestational age plus the infant's chronological age at the month of emergence of the first deciduous tooth), some studies found no delay in maturation or dental eruption in premature children and those born with LBW [18-20,22,23,32-34].

In 2004, a systematic review of the literature investigated the influence of prematurity and LBW on deciduous tooth eruption [13]. However, due to the small number of articles available at the time and the lack of longitudinal studies, the scientific evidence was too weak to determine whether premature birth and LBW alter the eruption pattern of the deciduous teeth. The study also did not perform meta-analysis, which has the advantage of evaluating quantitatively the association between prematurity/LBW and the occurrence of the delay in the eruption of the deciduous tooth.

Teething and the emergence sequence of deciduous teeth reflect a child's general physical health, especially with regards to the development of the endocrine/skeletal systems and nutrition status [19,27,29,35,36]. Moreover, deciduous tooth eruption may directly influence the progression of early childhood caries [12,36] and indicate the nutritional status of the mother during pregnancy [27,35]. Therefore, the eruption of the deciduous teeth, especially the first tooth, is of interest to parents/caregivers and health professionals.

The aim of the present systematic review and meta-analysis is to answer the following question: Do children born prematurely or with LBW have different tooth eruption patterns than those born at term or with normal weight? The null hypothesis is that there is no association between prematurity or birth weight and the eruption pattern of the deciduous teeth.

Material and Methods

Protocol and Registration

The present systematic review was registered in the PROSPERO database (protocol number: CRD42020182188) and was conducted in accordance with the recommendations of the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) [37] and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statements [38]. This study was developed at the Federal University of Paraná, Brazil, from September 2020 to November 2021.

Search Strategy

The PECOS strategy (Participants, Exposure, Comparison, Outcome, and Study design) was used for the present review: Participants – children; Exposure – prematurity and low birth weight; Comparison – non-preterm or non-low birth weight children; Outcome – deciduous tooth eruption; Study design – observational studies (cross-sectional, case-control, and cohort studies).

The search terms were defined based on the controlled vocabulary (MeSH terms) of the PubMed database and free keywords. Within each search strategy, terms were combined using the Boolean operator "OR" and concepts were combined using the Boolean operator "AND". The PubMed search strategy was adapted to each of the electronic databases searched (the Cochrane Library, Scopus, Web of Science, the Latin American and Caribbean Health Sciences Literature [LILACS], and the Brazilian Library in Dentistry [BBO]) (Table 1). No restrictions were imposed regarding language or year of publication. To expand the search, the terms related to the participants were new-born; infant, children; childhood; and other synonyms. For exposure, terms related to preterm child and low birth weight were included, such as infant, premature; premature birth; birth weight; and low birth weight infant. For outcome, terms related to tooth eruption were included, such as teething; eruption chronology; tooth eruption; and others (Table 1).

Grey literature was accessed through abstracts from Google Scholar, the System for Information on Grey Literature in Europe (SIGLE), as well as the International Association for Dental Research (IADR) and its regional divisions (1990–2021). The Theses Full Text, ProQuest Dissertations, and Capes Theses databases were used to search for dissertations and theses.

Table 1. Electronic databases and search strategy.

Pubmed = 147 (16/09/2021)		
#1 ((((((((((((((((((((((((child[MeSH Major Topic]) OR infant[MeSH Terms]) OR adolescent[MeSH Terms]) OR child[Title/Abstract]) OR infant[Title/Abstract]) OR adolescent[Title/Abstract]) OR "pediatric patients"[Title/Abstract]) OR children[Title/Abstract]) OR "preschool children"[Title/Abstract]) OR childhood[Title/Abstract]) OR "early childhood"[Title/Abstract]) OR schoolchildren[Title/Abstract]) OR newborn[Title/Abstract]))))	**#2** ((((((((((((((((((premature birth[MeSH Terms]) OR infant, premature[MeSH Terms]) OR birth weight[MeSH Terms]) OR term birth[MeSH Terms]) OR infant, low birth weight[MeSH Terms]) OR premature[Title/Abstract]) OR fullterm[Title/Abstract]) OR "full term"[Title/Abstract]) OR "premature birth"[Title/Abstract]) OR "infant premature"[Title/Abstract]) OR "premature infant"[Title/Abstract]) OR "birth weight"[Title/Abstract]) OR "term birth"[Title/Abstract]) OR "Fullterm Birth"[Title/Abstract]) OR "Non premature"[Title/Abstract]) OR "preterm birth"[Title/Abstract]) OR "premature delivery"[Title/Abstract]) OR prematurity[Title/Abstract]) OR "low birth weight infant"[Title/Abstract]))))	**#3** ((((((tooth eruption[MeSH Terms]) OR "tooth eruption"[Title/Abstract]) OR teething[Title/Abstract]) OR "oral growth"[Title/Abstract]) OR "eruption chronology"[Title/Abstract] OR "teeth eruption" [Title/Abstract]))
#1 AND #2 AND #3		
Cochrane Library = 1 (18/09/2021)		

#1 MeSH descriptor: [Child] explode all trees #2 MeSH descriptor: [Adolescent] explode all trees #3 MeSH descriptor: [Infant] explode all trees #4 ("pediatric patient"):ti,ab,kw (Word variations have been searched) #5 ("preschool children"):ti,ab,kw #6 (childhood):ti,ab,kw #7 ("early childhood"):ti,ab,kw #8 (schoolchildren):ti,ab,kw #9 (newborn):ti,ab,kw #10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	#11 MeSH descriptor: [Premature Birth] explode all trees #12 MeSH descriptor: [Infant, Premature] explode all trees #13 MeSH descriptor: [Birth Weight] explode all trees #14 MeSH descriptor: [Term Birth] explode all trees #15 MeSH descriptor: [Infant, Low Birth Weight] explode all trees #16 (prematu*):ti,ab,kw #17 (fullterm):ti,ab,kw #18 ("full term"):ti,ab,kw #19 ("fullterm birth"):ti,ab,kw #20 ("non premature"):ti,ab,kw #21 ("preterm birth"):ti,ab,kw #22 ("premature delivery"):ti,ab,kw #23 (infant near premature):ti,ab,kw #24 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23	#25 MeSH descriptor: [Tooth Eruption] explode all trees #26 (Teething):ti,ab,kw #27 ("oral growth"):ti,ab,kw #28 ("eruption chronology"):ti,ab,kw #29 #25 or #26 or #27 or #28
#10 AND #24 AND #29		
Scopus = 106 (18/09/2021) – (LIMIT-TO (SUBJAREA, "DENT"))		
#1 ((TITLE-ABS-KEY (child*) OR TITLE-ABS-KEY (adolescent?) OR TITLE-ABS-KEY (infant) OR TITLE-ABS-KEY ("pediatric patient") OR TITLE-ABS-KEY ("preschool children") OR TITLE-ABS-KEY (childhood) OR TITLE-ABS-KEY ("early childhood") OR TITLE-ABS-KEY (schoolchildren) OR TITLE-ABS-KEY (newborn)))	**#2** ((TITLE-ABS-KEY ("premature birth") OR TITLE-ABS-KEY ("infant premature") OR TITLE-ABS-KEY ("birth weight") OR TITLE-ABS-KEY ("term birth") OR TITLE-ABS-KEY ("infant low bith weight") OR TITLE-ABS-KEY (prematu*) OR TITLE-ABS-KEY (fullterm) OR TITLE-ABS-KEY ("full term birth") OR TITLE-ABS-KEY ("non premature") OR TITLE-ABS-KEY ("preterm birth") OR TITLE-ABS-KEY ("premature delivery") OR TITLE-ABS-KEY ("premature near infant")))	**#3** (TITLE-ABS-KEY ("t??th eruption") OR TITLE-ABS-KEY (teething) OR TITLE-ABS-KEY ("oral growth") OR TITLE-ABS-KEY ("eruption chronology"))) AND (LIMIT-TO (SUBJAREA , "DENT"))
#1 AND #2 AND #3		
Web of Science = 34 (17/09/2021) - filter: DENTISTRY ORAL SURGERY MEDICINE OR PEDIATRICS		
#1 (TOPIC: (child*) OR TOPIC: (adolescent$) OR TOPIC: (infant) OR TOPIC: ("pediatric patient") OR TOPIC: ("preschool children") OR TOPIC: (childhood) OR TOPIC: ("early childhood") OR TOPIC: (schoolchildren) OR TOPIC: (newborn)	**#2** TOPIC: ("premature birth") OR TOPIC: ("infant premature") OR TOPIC: ("birth weight") OR TOPIC: ("term birth") OR TOPIC: ("infant low birth weight") OR TOPIC: (prematu*) OR TOPIC: (fullterm) OR TOPIC: ("full term") OR TOPIC: ("non premature") OR TOPIC: ("preterm birth") OR TOPIC: ("premature delivery") OR TOPIC: ("infant near premature")	**#3** TOPIC: ("t??th eruption") OR TOPIC: (teething) OR TOPIC: ("oral growth") OR TOPIC: ("eruption chronology")
#1 AND #2 AND #3		
Lilacs and BBO = 25 (18/09/2021) – filter: (db:("LILACS" OR "BBO"))		
(mh:child or mh:infant or mh:adolescent or "pediatric patients" or "pacientes pediátricos" or children or crianças or niños or "preschool children" or "pré-escolares" or preescolares or childhood or infancia or "early childhood" or "primeira infância" or "niñez temprana" or schoolchildren or "crianças em idade escolar" or "ninõs de escuela" or newborn or "recém-nascido" or "recién nacido")	(mh:"premature birth" or mh:"infant, premature" or mh:"birth weight" or mh:"term birth" or mh:"infant, low birth weight" or premature or prematuro or fullterm or "à termo" or "a término" or "full term" or "fullterm birth" or "nascimento a termo" or "nacimiento a término complete or "non premature" or "não-prematura" or "no prematura" or "preterm birth" or prematurity or prematuridade or precocidad)	(mh:"tooth eruption" or teething or "oral growth" or "crescimento oral" or "crecimiento oral" or "eruption chronology" or "cronologia de erupção" or "cronología de la ruptura" or "teeth eruption" or "erupção dos dentes" or "erupción de dientes")
#1 AND #2 AND #3		

Eligibility Criteria

Cohort, cross-sectional, and case-control studies investigating the association between deciduous tooth eruption and premature birth and/or low birth weight were included. Studies without non-preterm children,

those that did not evaluate tooth eruption patterns, those not involving preterm or low birth-weight children, and those that investigated the association between tooth eruption and other systemic factors were excluded.

Screening and Selection

The article selection process involved the analysis of the titles and abstracts of the studies retrieved during the initial searches of the databases based on the criteria described above. Articles found in more than one database were considered only once. When there was insufficient information in the title and abstract to determine the inclusion of an article, the full text was analyzed.

The full-text analyses and selection of articles that met the eligibility criteria were performed by three independent reviewers (P.D.P., G.M., and L.R.S.A.). The same reviewers extracted information on the study design, characteristics of the participants, number of participants, how the data were obtained, and outcomes (Table 2). To ensure that the data were collected in line with the research question, a pilot test was conducted using a sample of eight primary studies. In this stage, the data extraction form was standardized and the reviewers were trained to use it.

Risk of Bias

Two independent reviewers (G.M. and P.D.P.) employed the criteria of the Modified Newcastle-Ottawa Scale (NOS) [39] to appraise the risk of bias of the studies selected for the present systematic review. The reviewers were previously trained for the NOS criteria, using theoretical and practical steps, and divergences of opinion between the reviewers during the risk of bias assessment were resolved by a third reviewer (L.R.S.A.). Each article could have a maximum score of 9 points divided among the different sections of the scale: patient selection (generalization and applicability - 4 points), comparability of groups (2 points), and exposure measurements (3 points). The studies were subsequently classified as having a high (0-3 points), moderate (4-6 points), or low (≥ 7 points) risk of bias [40].

Summary Measures and Summary of Results

The studies eligible for systematic review had different outcome evaluation methods: presence/absence of deciduous tooth, number of deciduous teeth at the time of the clinical examination, and mean chronological age or mean adjusted age (considering the gestational age plus the infant's chronological age) at the eruption of the first deciduous tooth. Meta-analysis was performed for each exposure reported in at least two studies.

The meta-analyses were conducted using a random effects model to compute the mean difference in mean chronological or adjusted age at the eruption of the first deciduous tooth between premature and non-premature (control) children. The random effect model was used when a high level of heterogeneity between the studies it was expected, due the standard errors estimated using those models are generally more conservative than those estimated with fixed effects. The entire analysis was performed using the RevMan software (version 5.4.1, Cochrane, USA). We restricted the meta-analysis to studies that were classified as having a moderate or low risk of bias.

Certainty of Evidence Using GRADE Approach

The quality of each meta-analysis (body of evidence) was determined using the Grading of Recommendations: Assessment, Development, and Evaluation (GRADE) (http://www.gradeworkinggroup.org/) [41]. The body of evidence for observational studies is initially

classified as low using the GRADE framework. This classification can be upgraded if the study exhibits certain strengths, such as a large effect size (one- or two-level upgrade) and the demonstration that plausible confounders or other biases increase the confidence in the estimated effect (one-level upgrade). However, the certainty of evidence should only be upgraded if no serious limitations are found regarding the five aspects that reduce the quality of the evidence: risk of bias, imprecision, inconsistency, indirectness, and effects of residual confounding [42].

Results

Study Selection

The primary search of the electronic databases and other searches resulted in the retrieval of 316 studies. After the removal of duplicates, 223 studies were considered. Seventy-three studies were pre-selected based on the title, 38 of which were excluded after reading the abstract, resulting in 35 studies to be submitted to full-text analysis for the determination of eligibility (Figure 1). After this phase, 14 studies were excluded: 1) studies without non-preterm children (n = 7), 2) studies that did not evaluate the tooth eruption pattern (n = 6), and 3) studies without preterm and low birth-weight children (n = 1). Thus, 21 studies were considered eligible and were included in the present systematic review.

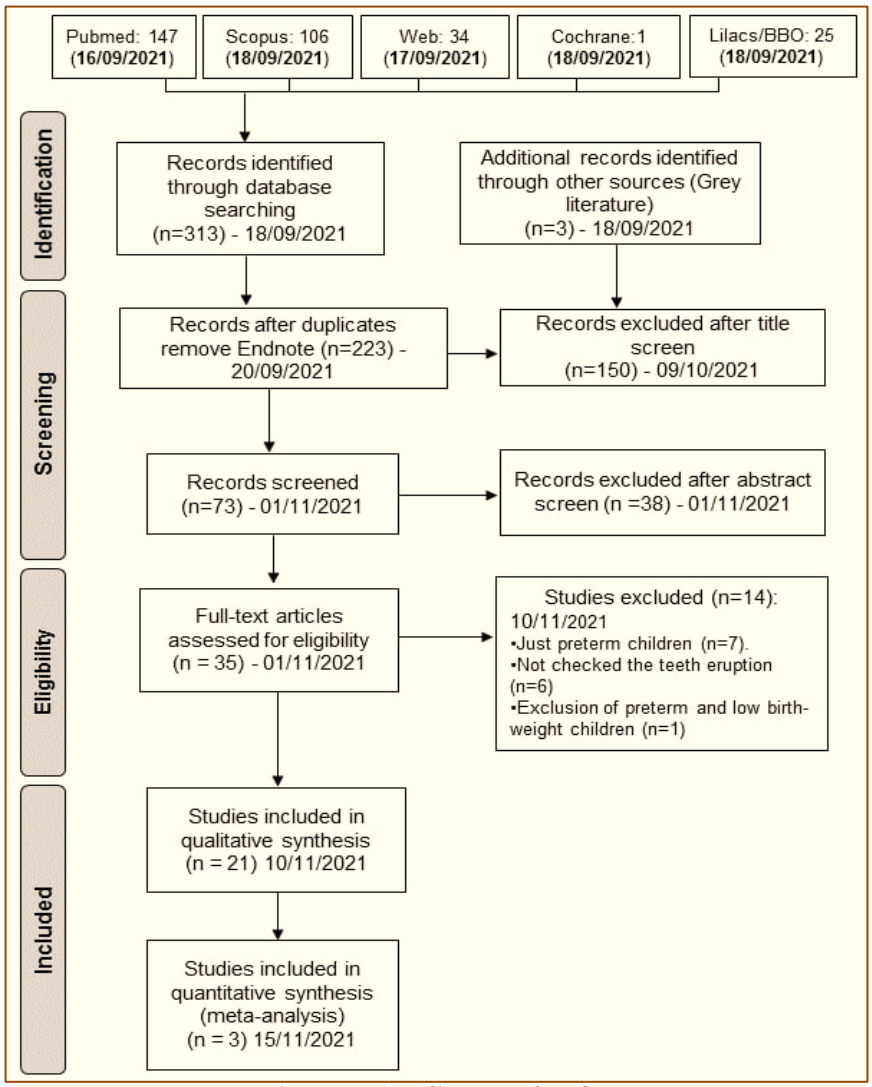

Figure 1. Flow diagram of study.

Characteristics of Included Articles

The information extracted from the 21 eligible studies is displayed in Table 2. Only observational studies were selected. Thirteen were cross-sectional studies with comparison groups [18,20,21,23,25,28-31,34,43-46] and seven were cohort (longitudinal) studies [19,22,24,26,27,47,48]. The mean age of the participants included in the studies ranged from 1.18 to 12 years. The number of children ranged from 54 to 3,066. Verma et al. [29] and Bailit et al. [47] had the highest numbers of participants among the studies included.

Table 2. Summary of studies selected for present systematic review.

Study ID	Study Design	Sample size (% male)	Mean patient age mean (SD) in years	Cut-off for preterm (PT)	Cut-off for low birth weight (LBW)	Outcome	Conclusion	Country
Aktoren et al. [21]	Cross-sectional	176 (52.2)	1.18 (0.50)	≤37 weeks	<2500g	Age at eruption of first deciduous tooth	PT and LBW: delay in eruption of first tooth	Turkey
Backstrom et al. [19]	Longitudinal	90 (46.7)	n.r.	n.r.	-	Chronological age at eruption of first deciduous tooth and number of teeth at 1 and 2 years of age.	PT girls: delay in eruption of first tooth	Finland
Bailit et al. [47]	Longitudinal	3066 (49.3)	8.49 (n.r.)	-	n.r.	Number of teeth	Association between lowest weight and longest eruption delay	Japan
Bastos et al. [43]	Cross-sectional	359 (52.6)	6 (n.r.)	<37 weeks	<2500g	Eruption of first maxillary left molar at 6 years of age and number of pairs erupted at 6 months of age	Association between LBW and number of pairs erupted at 6 months of age	Brazil
Castro et al. [46]	Cross-sectional	520 (53.6)	1.82 (0.57)	-	<2500g	Delay in eruption of first deciduous tooth	No statistically significant association between LBW and delayed eruption	Brazil
Delgado et al. [27]	Longitudinal	273 (n.r.)	n.r.	-	≤3000g	Number of teeth	LBW: delay in tooth eruption	Guatemala
Golden et al. [18]	Cross-sectional	167 (n.r.)	n.r.	≤37 weeks	-	Chronological and adjusted age at eruption of first deciduous tooth	PT: Delay in eruption of first tooth considering chronological ate; no delay considering adjusted age.	United States of America
Grivu et al. [25]	Cross-sectional	571 (52.7)	n.r.	-	≤3000g	Age at eruption of first deciduous tooth	LBW: delay in eruption of first tooth.	n.r.
Haddad et al. [44]	Cross-sectional	870 (52.5)	n.r.	-	<2500g	Number of teeth	LBW: same number of teeth as controls (normal birth weight)	Brazil

Khalifa et al. [22]	Longitudinal	250 (48.8)	n.r.	<37 weeks	≤2500g	Chronological and adjusted age at eruption of first deciduous tooth	PT and LBW: Delay in eruption of first tooth considering chronological ate; no delay considering adjusted age	Egypt
Merglova et al. [34]	Cross-sectional	189 (n.r.)	1 (n.r.)	<37 weeks	<1500g	Number of teeth	No statistically significant association between PT and delay in eruption	Czech Republic
Mielnik et al. [30]	Cross-sectional	123 (n.r.)	n.r.	n.r.	<3000g	Age at eruption of first deciduous tooth	Association between lowest weight and longest eruption delay	Turkey
Pavicin et al. [23]	Cross-sectional	592 (52.9)	n.r.	<37 weeks	≤2500g	Chronological and adjusted age at eruption of first deciduous tooth	PT and LBW: delay in eruption of first tooth. PT: No delay considering adjusted age.	Croatia
Ramos et al. [20]	Cross-sectional	146 (n.r.)	n.r.	n.r.	<2500g	Chronological and adjusted age at eruption of first deciduous tooth	PT and LBW: Delay in eruption of first tooth considering chronological ate; no delay considering adjusted age.	Brazil
Rezende et al. [45]	Cross-sectional	250 (58.8)	n.r.	≤37 weeks	≤2400g	Presence of deciduous teeth	No statistically significant association between PT and LBW and delay in eruption	Brazil
Sajjadian et al. [28]	Cross-sectional	143 (42.6)	n.r.	-	<2500g	Age at eruption of first deciduous tooth	LBW: delay in eruption of first tooth	Iran
Silveira et al. [48]	Longitudinal	333 (49.5)	n.r.	-	≤2500g	Time of eruption of each deciduous teeth	No statistically significant association between LBW and delay in eruption	Brazil
Trupkin et al. [26]	Longitudinal	82 (n.r.)	n.r.	-	<2500g	Presence of deciduous teeth	LBW: delay in eruption of first tooth	United States of America
Verma et al. [29]	Cross-sectional	1601 (56.4)	n.r.	-	<2500g	Presence of deciduous teeth	LBW: delay in eruption of first tooth	India
Wang et al. [24]	Longitudinal	223 (53.6)	n.r.	≤37 weeks	<2500g	Chronological age at eruption of first deciduous tooth	LBW: delay in eruption of first tooth	China
Wong et al. [31]	Cross-sectional	54 (n.r.)	12 (n.r.)	-	<2500g	Partial or complete eruption of permanent teeth	LBW: delay in eruption of first tooth	China

n.r.: not reported.

Data were collected through questionnaires/interviews administered to mothers in five studies [23,27,30,46,47], questionnaires/interviews administered to mothers and clinical examinations in nine studies [18,20,24,28,29,31,43,44,45], medical records in two studies,19,21 and medical records and clinical examinations in five studies [22,25,26,34,48].

From the 21 included studies, two had premature birth as the exposition [18,19], ten reported the low birth weight [25-29,31,45-47] and nine studies, the two expositions [20-24,30,34,43,45]. Six studies [20,27,29,34,43,42] reported that the use of the criteria developed by the World Health Organization (WHO) [2] for the classification of exposure and 15 studies did not specify references for the criteria used [18,19,21-26,28,30,31,45-48]. For the diagnosis of tooth eruption, 14 studies considered a tooth erupted when any part of the dental crown pierced the gum and was visible in the oral cavity [18,20-24,26-29,34,43,44].

Appraisal of Risk of Bias

Table 3 shows the results of the risk of bias appraisal using the Modified Newcastle-Ottawa Scale. Thirteen studies had a high risk [18,20,21,25-28,30,34,43-45,47], three had a moderate risk [19,23,46], and five had a low risk of bias [22,24,29,31,48].

Table 3. Risk of bias analysis of selected studies according to the Newcastle-Ottawa Scale.

Study Identification	Selection	Comparability	Outcome	Risk of Bias
Aktoren et al. [21]	★★★	-	★★	High
Backstrom et al. [19]	★★	★★	★★★	Moderate
Bailit et al. [47]	★★★	-	★	High
Bastos et al. [43]	★★★★	-	★★	High
Castro et al. [46]	★★	★★	★★	Moderate
Delgado et al. [27]	★★★	-	★★★	High
Golden et al. [18]	★★	-	★★	High
Grivu et al. [25]	★	-	★	High
Haddad et al. [44]	★★	-	★★	High
Khalifa et al. [22]	★★★	★	★★★	Low
Merglova et al. [34]	★	-	★★★	High
Mielnik et al. [30]	-	-	★	High
Pavicin et al. [23]	★★	★★	★★	Moderate
Ramos et al. [20]	★	-	★★★	High
Rezende et al. [45]	★	-	★★	High
Sajjadian et al. [28]	★	★	★★★	High
Silveira et al. [48]	★★★	★	★★	Low
Trupkin et al. [26]	★★	-	★★★	High
Verma et al. [29]	★★★	★	★★★	Low
Wang et al. [24]	★★★★	★	★★★	Low
Wong et al. [31]	★★★★	★★	★★	Low

High risk of bias: 0 to 4 stars; Moderate risk of bias: 5 to 6 stars; Low risk of bias: 7 to 9 stars.

Meta-Analysis

Eighteen studies were not included in the meta-analysis [18-21,25-31,34,42-48]. Thirteen studies had a high risk of bias (3 points on the Modified Newcastle-Ottawa Scale) [18,20,21,25-28,30,34,43-45,47], three had outcome or exposure assessments not compatible with other studies [29,31,46], and two did not measure the outcome using mean and standard deviation values [19,48].

For the meta-analysis, data were combined from the three studies that had the same exposure (premature birth) and outcome (mean chronological or adjusted age at the eruption of the first deciduous tooth) [22-24]. Meta-analysis of low birth weight and mean age at the eruption of the first deciduous tooth was not performed due to a lack of data.

Heterogeneity was assessed using Cochran's Q and quantified using the I^2 statistic. The I^2 statistic is used to analyze variability among studies that is not due to chance. According to the Cochrane Handbook [49], an I^2 less than 30% in a meta-analysis is indicative of low heterogeneity.

Two meta-analyses were performed (Figure 2) to determine differences between preterm and non-preterm children: 1) Mean chronological age at the eruption of the first deciduous tooth (Figure 2A); and 2) mean adjusted age at the eruption of the first deciduous tooth (Figure 2B). Premature birth was associated with the delay in the eruption of the first deciduous tooth when mean chronological age was considered (mean difference: 1.36; 95% CI: 1.02 to 1.69; $p < 0.0001$). In contrast, premature birth was not associated with the delay in the eruption of the first deciduous tooth when mean adjusted age was considered (mean difference: -0.30; 95% CI: -0.67 to 0.07; $p = 0.11$).

Low heterogeneity in the data was observed in the meta-analysis of premature birth and mean chronological age (chi-square test, $p = 0.93$; $I^2 = 0$) and mean adjusted age (chi-square test, $p = 0.25$; $I^2 = 23$) at the eruption of the first deciduous tooth.

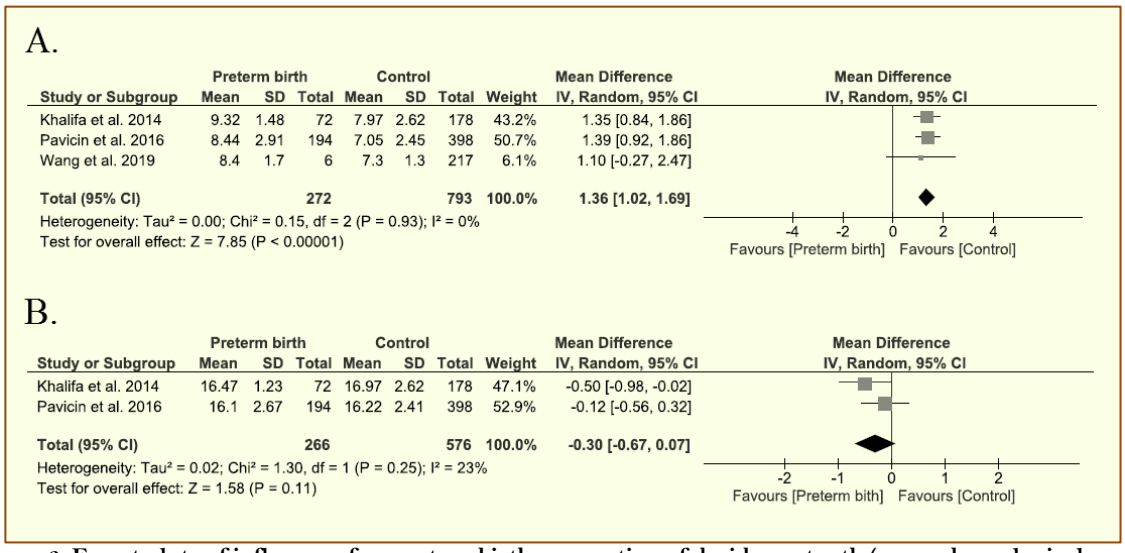

Figure 2. Forest plots of influence of premature birth on eruption of deciduous tooth (mean chronological age at eruption of deciduous tooth - A, mean adjusted age at eruption of deciduous tooth - B).

Appraisal of Certainty of Evidence

The observational studies were considered to have a low level of evidence according to the GRADE approach. The certainty of evidence was classified as not serious with regards to the risk of bias in the studies included in the meta-analysis. Both meta-analyses were performed using studies with a moderate or low risk of bias. Studies with some important bias in their results were considered to have moderate quality. If a study did not control for the risk of bias, the certainty of evidence was downgraded one level. Thus, the certainty of evidence of both meta-analyses was considered very low. Inconsistency (heterogeneity) was also classified as not serious. However, imprecision was found in the two meta-analyses (chronological and adjusted age at deciduous tooth eruption considering premature birth) because the confidence interval included "0" (Table 4).

Table 4. Assessment of quality of body of evidence (GRADE).

Participants (studies)	Certainty Assessment: Risk of Bias	Inconsistency	Indirect Evidence	Imprecision	Bias of Publication	Overall Certainty of Evidence	Number of Events of Study (%): Control	Premature Birth	Summary of Results: Potential Absolute Effects: Risk with Control	Difference of Risk with Premature Birth
Chronological age at the eruption of deciduous tooth										
1065 (3 observational studies)	Not serious	Not serious	Not serious	Serious[a]	None	⨁◯◯◯ very low	793	272	Mean chronological age at eruption of deciduous tooth (rated: months) was 0	MD 1.36 higher (1.02 higher to 1.69 higher)
Adjusted age at the eruption of deciduous tooth										
839 (2 observational studies)	Not serious	Not serious	Not serious	Serious[a]	None	⨁◯◯◯ very low	573	266	Mean adjusted age at eruption of deciduous tooth (rated: months) was 0	MD 0.3 lower (0.62 lower to 0.03 higher)

CI: Confidence Interval; MD: Mean Difference; [a]The confidence interval was high.

Discussion

Systematic reviews and meta-analyses have the highest level of scientific evidence, as such investigations can assess consistency across studies regarding a research question and summarize the findings for the development of recommendations for future studies [50]. To the best of our knowledge, this is the first systematic review with meta-analysis to assess the consistency of evidence regarding the influence of premature birth on the eruption pattern of deciduous teeth. Considering the high prevalence of premature birth and the consequences to oral health [11-17], understanding its influence on the tooth eruption pattern is essential to identifying groups of children at greater risk of delayed tooth eruption. This identification is important for several dentistry areas and also others health professionals to base their clinical decisions on monitoring the eruption of children's deciduous teeth and counselling parents, since abnormalities in tooth eruption in children may be indicative of nutritional problems as well as problems in the skeletal and endocrine systems [19,27,29,35,36].

The determination of the influence of premature birth and low birth weight on tooth eruption is complex, as several genetic and local factors can affect the eruption pattern [11-14,32,33]. Although associations between premature birth and oral health conditions have been studied in recent years, the association with tooth eruption has not yet been fully clarified. Only one previous systematic review was conducted to investigate this association. The authors concluded that if the age of preterm children is adjusted, there is no delay in the tooth eruption process in comparison to children born at term [14]. The present study is the first to conduct meta-analysis to assess the influence of premature birth on mean (chronological and adjusted) age at the eruption of the first deciduous tooth. Furthermore, a broad search strategy was performed in multiple databases with no restrictions regarding language or year of publication. In contrast, the authors of the previous systematic review restricted their search to PubMed [14].

Considering the influence of premature birth on age at the eruption of the first deciduous tooth, all studies included in the meta-analysis had similar findings and methodology [22-24], which contributed to a lower heterogeneity of the meta-analyses. The authors used the same criteria to assess the outcome and the classification of prematurity. When chronological age was considered, all the studies found a delay in the eruption of the first deciduous tooth when compared to non-preterm children. In the other hand, when age at the eruption of the first deciduous tooth was adjusted (i.e., postnatal chronological age in weeks' minus adjustment for prematurity [40 weeks minus gestational age in weeks]), the studies of Khalifa et al. [22] and Pavacin et al. [23] found no association between prematurity and delayed eruption of primary teeth. This finding was also reported in other observational studies included in the present systematic review [18,19] and likely occurred because the shorter intrauterine time is taken into consideration when an age correction is performed [11,12]. Although the mean difference of the timing of the deciduous teeth eruption between preterm and non-preterm was low, it is important to consider that the studies did not consider the different stages of prematurity. It is suggested that extremely preterm infants may have a longer delay in the tooth eruption compared to other preterm children [18,45]. This aspect should be included in future research.

The association between low birth weight and age at which the first deciduous tooth erupted was not tested in a meta-analysis due to the lack of data. Low birth weight was associated with the delay in deciduous tooth eruption considering chronological age in eleven studies in the present systematic review [21-31]. However, Castro et al. [46], Haddad et al. [44], Rezende et al. [45], and Silveira et al. [48] found no association. Ramos et al. [20] found no delay among children with low birth weight only when age at the eruption of the first deciduous tooth was adjusted. This divergence in the results among studies may be explained by the scarcity of observational studies with multivariate analysis, which enables considering the influence of low birth weight alone. As preterm children usually have LBW [6], there may be an association between this exposure and the delay in deciduous tooth eruption, but the relation may not be causal. Further studies are needed to broaden knowledge on this issue.

The present review showed that although numerous studies have addressed the influence of premature birth and low birth weight on the tooth eruption pattern, improvements in the data collection method and multiple statistical approaches are needed to test multiple exposures related to the delayed deciduous tooth eruption. The primary studies employed different study designs (cross-sectional with a control group [18,20,21,23,25,28-31,34,43-46] and cohort [19,22,24,26,27,47,48]). In the classic pyramid of evidence, these designs produce different levels of evidence, with the cohort design at the top of observational studies. Among the twenty studies evaluated in the present systematic review, only four [23,31,43,46] presented adjusted measures considering the covariates of the association; two studies presented multivariate analysis [23,43]; and two studies reported adjusted data through a stratified analysis [31,46].

A limitation of the present study is related to the difficulty in determining the exact moment of tooth eruption. Some studies used the reports of caregivers of the children to assess the outcome, which may be a source of considerable bias. Even in the cohort studies [19,22,24,26,27,47,48], clinical examinations were performed at different intervals of time, which makes it difficult to estimate the average eruption of the first deciduous tooth in months. Inconsistent methods for obtaining the outcome may increase the risk of bias in these studies. Moreover, several studies did not perform a sample size calculation and used convenience samples from hospitals and medical institutes [18-20,24-28,30,34,45-48], which reduces the external validity of the articles. In this sense, future reviews may perform meta-analyses with subgroups or sensitivity tests to mitigate risks of bias and allow new quantitative analyses. Regarding the association between LBW and the eruption of the first

deciduous tooth, further studies are needed with well-designed methods that enable meta-analysis. Moreover, different cut-off points for LBW, including extremely low birth weight, should be considered. According to the GRADE approach [42], the quality of the evidence gathered by the meta-analyses was very low, which means that there is very little evidence of the estimated effect and it may be substantially different from what was measured.

Conclusion

The results of the present systematic review suggest that premature birth is significantly associated with the delay in deciduous tooth eruption when taking chronological age into account. When adjusted age was considered, however, no significant difference was found in mean age at the eruption of the first deciduous tooth between preterm and non-preterm children. Understanding the factors that can interfere with the timing of deciduous teeth emergence is important for clinical practice in dental areas such as orthodontics, forensic expertise, anthropology and pediatric dentistry and other areas of health. These results can serve as a basis for guidance for caregivers who can often experience anxiety and several questions in the first few months after their child's premature birth. However, as the findings were taken from only three observational studies with limitations regarding the certainty of evidence, caution should be taken when interpreting these results.

Authors' Contributions

PDP	https://orcid.org/0000-0001-6429-2936	Conceptualization, Methodology, Software, Formal Analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review and Editing and Visualization.
GM	https://orcid.org/0000-0002-1651-0692	Conceptualization, Methodology, Investigation and Writing - Original Draft.
LW	https://orcid.org/0000-0002-9696-0406	Software, Validation, Writing - Review and Editing and Supervision.
JFS	https://orcid.org/0000-0001-9969-3721	Conceptualization, Methodology, Software, Formal Analysis, Writing - Original Draft, Writing - Review and Editing, Visualization and Supervision.
FCF	https://orcid.org/0000-0001-5290-7905	Writing - Review and Editing.
JVNBM	https://orcid.org/0000-0001-9178-0898	Writing - Review and Editing.
LRSA	https://orcid.org/0000-0002-7380-8583	Conceptualization, Formal Analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review and Editing, Visualization, Supervision, Project Administration.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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