

Oral manifestations in premature infants. A systematic review

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Abstract

Background Preterm delivery, defined as delivery occurring before 37 completed weeks of pregnancy, represents 6-10% of all births in developed countries. Preterm infants are characterized by a short prenatal development period and are at an increased risk of systemic disorders as a result of their immaturity. Few studies have analyzed oral alterations among preterm infants. This systematic review examines the orofacial characteristics most commonly found among preterm infants versus infants born at term, and evaluates their repercussions upon oral health and quality of life. **Methods** The search was limited to articles published in English or Spanish and that studied the prevalence of oral sequelae and alterations in preterm children. Their methodological quality was assessed based on the guidelines of the Joanna Briggs Institute (JBI). **Results** Most of the studies found the prevalence of structural enamel defects of the primary dentition to be greater among preterm infants. Other disorders such as structural enamel defects of the permanent dentition, caries, malocclusions or alterations in dental composition, size and development also appeared to be more frequent among preterm infants, though the supporting evidence was weak. **Conclusions** Further studies are needed, analyzing the association between preterm delivery and certain orofacial disorders such as caries, malocclusions and dental anomalies.

Background

The World Health Organization (WHO) defines preterm birth as delivery occurring before 37 completed weeks of pregnancy. Approximately one-quarter of all premature births are induced because of medical conditions that pose a health risk for the fetus, mother, or both. The rest of preterm births are spontaneous [1-6].

Preterm birth is associated with a number of genetic, socioeconomic and ethnic factors, as well as with stress, smoking and alcohol abuse during pregnancy, maternal age, weight and height, multiple pregnancies, a history of maternal periodontal disease, arterial hypertension or preeclampsia, and a history of premature deliveries [7-15]. Causes of preterm delivery related to the fetus include congenital malformations, restricted intrauterine growth, or intrauterine infections [16, 17].

Improvements in medical care have resulted in a decrease in mortality among preterm infants. This evidences the importance of conducting studies and implementing care programs targeted to this population [18-21]. Many preterm infants survive with physical and/or psychological sequelae, including respiratory distress syndrome, cardiac and renal disorders, increased susceptibility to infections, necrotizing enterocolitis, and metabolic, nutritional and neurological disorders, among other problems [22-32]. These complications often require invasive interventions and treatments such as orotracheal intubation or parenteral nutrition [33].

In addition to the systemic sequelae of prematurity, these patients can suffer a range of oral disorders. In this regard, pediatric dentists should be included in the multidisciplinary team in charge of caring for these children [18, 22, 34]. However, few recent studies can be found on this subject, and the existing

literature generally focuses on a single concrete oral manifestation, without addressing the global oral health of the preterm infant. The objectives of the present systematic review were to: (1) analyze the scientific evidence on the oral characteristics associated to preterm birth; (2) describe the prevalences of these oral characteristics in the preterm population and compare them with those found in infants born at term; and (3) identify areas referred to the integral oral health of premature infants requiring further research, and propose possible new fields for future studies.

The objectives of the present study were based on the CoCoPop format: “Condition” (oral sequelae) “Context” (worldwide) “Population” (preterm infants), with the purpose of framing the following CoCoPop question: “What is the prevalence of oral sequelae in preterm infants worldwide, as reported in scientific literature?”.

Material And Methods

Search strategy.

The present systematic review was carried out based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [35]. The literature search was carried out during January 2020, using the PubMed, Medline, Web of Knowledge, Scielo and Google Scholar databases with the keywords: “Preterm birth”, “Premature children”, “oral complications” and “dent*”. These keywords were inter-related using the boolean operator AND, yielding four search possibilities in each database: preterm birth” AND “oral complications; preterm birth” AND “dent*; premature children” AND “oral complications; premature children AND “dent*. After obtaining the search results, we eliminated duplicate publications and proceeded with article selection.

Selection of articles and data extraction

Based on the publications identified by the literature search, we established the following inclusion criteria:

- **Condition:** Publications evaluating the prevalence of oral sequelae and characteristics that might be associated to preterm birth.
- **Context:** No articles were excluded based on geographical factors.
- **Population:** Research on preterm children, considering as “preterm” every infant born before week 37 of pregnancy is completed.
- **Type of study:** Studies with a cross-sectional or longitudinal design.

Regarding the exclusion criteria, publications written in a language different from English or Spanish were excluded.

The selection of articles was made in duplicate by two independent reviewers. In the event of discrepancies, the decision to either include or exclude a publication was established by consensus

following debate. Finally, the data corresponding to each study were extracted by two independent operators and entered in a table. In the same way as in selecting the publications, discrepancies were debated until consensus was reached.

Evaluation of study quality

The methodological quality of each individual study included in the review was evaluated based on the checklist of the Joanna Briggs Institute (JBI) [36] for case-control studies. This checklist scored each article from 0 to 20 (positive response = 2 points; negative response = 0 points; “Unclear” or “Not applicable” = 1 point). Based on this score, the studies were classified as being of “Very poor quality” (0-5 points), “Poor quality” (6-10 points), “Sufficient quality” (11-15 points) or “High quality” (16-20 points).

Data availability

The data supporting the results of this systematic review are available as complementary files. The data may also be accessed upon request to the corresponding author.

Results

The literature search of the databases (Figure 1) yielded 2036 publications, and the complementary manual search yielded an additional 20 articles. After eliminating duplicate publications, evaluation of the titles and abstracts yielded a total of 214 studies for initial analysis. Of these, 111 were excluded mainly because the study subject was unrelated to the objectives of our review. A total of 49 publications were selected for full-text evaluation, based on the study design involved (cross-sectional and longitudinal trials).

Of the publications included in the present review (Figure 2), 29.6% corresponded to studies conducted in Brazil (the most numerous representation), while 18.5% were carried out in Sweden. Most of the studies had a cross-sectional design (64.8%), while 25.9% were retrospective longitudinal studies, and 9.3% were prospective longitudinal studies. The most widely investigated topic was structural defects in premature infants referred to both the primary and the permanent dentition (33% of all the included studies). Less frequent topics were dental development and composition (representing 9 and 6% of the studies, respectively).

Evaluation of the methodological quality of the studies

None of the 49 studies finally included in the systematic review were considered to be of “very poor quality”, while 8 were rated as “poor quality” (16.33%), 21 as “sufficient quality” (23.14%), and 20 as “high quality” (22.04%). The quality scores of these articles were between 6-20 points, and the mean score of all the selected articles was 14.16.

Discussion

Craniofacial alterations associated to intubation

Many premature infants require endotracheal intubation in the immediate postnatal period. This intervention is indicated when surfactant needs to be administered, aspirated foreign bodies must be removed, or mechanical ventilation is provided. An adverse effect of intubation is that it causes alterations in correct maxillofacial growth of the patient. Depending on the hospital center involved, intubation is via the oral or the nasal route, and this in turn determines the type of deformity produced [37].

The oral route is considered to be easier and less traumatic, though the tubes used in nasal intubation are easier to affix to the intubation site, thereby reducing the risk of accidental extubation [37]. While oral intubation has been associated with an increased incidence of dental malocclusions, according to some authors nasal intubation could give rise to nasal deformities, particularly in very low weight premature infants and in cases of prolonged intubation [38, 39]. Oral intubation can also give rise to a palatine sulcus or groove extending from the incisor foramen to the soft palate. This sulcus can be observed in approximately one-quarter of all premature infants and generally disappears with bone remodeling associated with the growth of the child [40, 41].

In sum, while not without adverse effects, nasal intubation appears to be safer than oral intubation, and moreover causes fewer sequelae.

Dental malocclusions

Premature infants have been found to be at an increased risk of suffering dental malocclusions. As has been commented above, this risk is related to oral intubation and to a greater susceptibility to develop mouth breathing and respiratory infections [1].

Premature infants have been shown to be 3.32-fold more likely to develop non-feeding sucking habits. This fundamentally may be due to difficulty in securing adequate breast-feeding and the use of a pacifier to stimulate sucking action and thus oral feeding [42-45]. No clear association can be postulated, however, since the studies on this subject are few and of low methodological quality.

The difficulty in achieving oral feeding may cause the patient to need parenteral nutrition for longer periods of time than infants born at term [46]. In some cases, this type of nutrition must be maintained for several months, reducing physiological attrition of the primary dentition and increasing the risk of malocclusions [47].

As a consequence of the mentioned risk factors, some authors consider that preterm children may have a higher prevalence of maxillary compression, associated to a high-arched palate, posterior crossbite and an elongated facial shape [48, 49]. Other authors have reported no differences in terms of the prevalence of malocclusion, but they have found differences in the prevalence of alterations in head diameter [50].

Paulsson et al. [51] suggested that there is not enough scientific evidence to affirm a relationship between prematurity and malocclusion problems. In their opinion, this is because of the multifactorial etiology of malocclusion.

Germa et al. [49] analyzed the differences in the prevalence of posterior crossbite and anterior open bite between a group of 399 patients born at term and a group of 23 premature patients. The prevalence of posterior crossbite was significantly greater in the study group (35%) than in the control group ($p=0.03$). Anterior open bite was likewise more prevalent in the premature infants (30%) than among the infants born at term (28%), though in this case statistical significance was not reached ($p=0.54$).

In 2008, Paulsson et al [18] conducted a comparative study on the need for orthodontic treatment in a sample of premature children versus a control group. The prevalence of overbite and of diastemas was significantly greater in the 73 preterm patients than in the 41 patients born at term.

Primožic et al. [52], on comparing the prevalence of malocclusions in a group of 80 premature infants with a birth weight of less than 2500 g versus a control group of 113 patients born at term and with normal birth weight, recorded no statistically significant differences between the two groups. However, this study was of poor methodological quality, with limited orthodontic exploration and perinatal information compiled from parent surveys.

In another study carried out by Maaniitty et al. [53], very preterm children showed a greater risk of crowding and increased overbite in primary dentition when compared to a control group of full-term children. In contrast, when these groups were examined in the early mixed dentition phase, no differences were found between the two groups in relation to occlusal traits.

Although research in this field is still limited, an association could be suggested between premature birth and an increased need for orthodontic treatment. Such patients require periodic pediatric dental and orthodontic monitoring from an early age.

Structural defects of the primary dentition

The circumstances of premature birth can result in structural anomalies of the enamel of the primary dentition, as evidenced by a number of publications [22, 44, 54-62]. The results of these studies are summarized in Table 1.

In the event of damage during odontogenesis, the tooth does not experience a subsequent remodeling process. Structural alterations are therefore permanent [63, 64]. Structural defects of both the primary and the permanent dentition imply an increased risk of caries and aesthetic problems. Furthermore, the associated increase in dental sensitivity has a negative impact upon the quality of life of the patient, which in turn can result in worsened oral hygiene [54, 65].

Table 1. Prevalence of primary dentition enamel defects in the reviewed studies.

Author	Country	Control group (at term)	Study group (preterm)	Prevalence of enamel defects (at term)	Prevalence of enamel defects (preterm)	
Cruvinel, 2011 [66]	Brazil	n=40 5-10 years	n=40 5-10 years	62.5% 7.5%	65% 37.5%	p=0.8161 Delimited opacities p=0.0013 Hypoplasias
Pinho, 2011 [55]	Brazil	n=171 1-5 years	n=34 1-5 years	16%	36%	p=0.001
Gravina, 2013 [54]	Brazil	n=96	n=96	28.1% 8.3%	18.8% 37.5%	p=0.173 Opacities p<0.001 Hypoplasias
Correa-Faria, 2013 [62]	Brazil	n=338 3-5 years	n=33 3-5 years	28.70%	33.30%	p=0.576
Pimlott, 1985 [59]	Canada		n=106 1-8 years		38%	No statistical analysis
Aine, 2000 [67]	Finland	n=64 1-2 years	n=32 1-2 years	20% 2% 19%	78% 66% 13%	p<0.001 p<0.001 Hypoplasias p=0.438 Diffuse opacities
Franco, 2007 [64]	Brazil	n=61 1-3 years	n=61 1-3 years	24.60% 3.3% 24.6%	57.40% 21.3% 52.5%	p<0.001 Enamel defects p=0.002 Hypoplasias p=0.002 Opacities
D'Oliveira-Ferrini, 2008 [44]	Brazil	n=52 2-4 years	n=52 2-4 years	8% 4%	50% 23%	p<0.001 Delimited opacities p=0.004 Hypoplasias
Schüler, 2017 [68]	Germany	n=64 3-4 years	n=64 3-4 years	20.3%	65.6%	p<0.01

A systematic review conducted by Jacobsen et al. [69] concluded that there is a relationship between premature delivery and structural enamel defects of the primary dentition - with hypoplasia being the most common alteration. This relationship has been confirmed by the great majority of the studies included in our review, with the observation of a significantly higher prevalence of primary dentition

enamel defects in premature infants. These anomalies may be attributed to both local and systemic factors. Among the latter, mention can be made of hypoxia, respiratory distress syndrome, infections and nutritional disorders, among others. With regard to the local factors, both intubation and laryngoscopic maneuvering to place the tube have been associated to primary dentition enamel defects [48].

Seow et al. [70, 71] reported a higher prevalence of structural defects of the primary dentition in premature infants that have been intubated, and these defects were moreover seen to show a predilection for the teeth of the left hemiarch. This supports the role of local etiological factors in the structural anomalies [70-72]. In concordance with this possible etiology, Takaoka et al. [22] found the prevalence of enamel defects in premature patients to be significantly greater ($p < 0.05$) in the upper central incisors and upper left lateral incisor. Thus, the defects were located on the midline and in the upper left hemiarch, as a result of positioning of the neonatologist in maneuvering the laryngoscope with the right hand.

Similar results were obtained by Cortines et al. [73]. In their sample, enamel defects were more prevalent in very preterm and extremely preterm children who needed intubation during the neonatal period, and they were more frequently found in the maxillary left incisors of these children.

The abovementioned dental structural sequelae are associated to an increased risk of caries; as a result, preventive measures should be adopted in these patients, and their parents and caregivers should be instructed on correct buccodental health.

Structural defects of the permanent dentition

In the same way that premature delivery has been associated with an increased prevalence of primary dentition enamel defects, it has also been postulated to have a similar impact upon the permanent dentition.

As can be seen in Table 2, most of the authors describe the prevalence of enamel defects of the permanent dentition to be significantly higher in premature infants than in infants born at term. Jacobsen et al. [69] suggested that there is no association between preterm delivery and structural enamel defects of the permanent dentition. However, research in this field is limited, and further high quality studies are needed to confirm these observations.

On the other hand, some authors suggest a possible relationship between premature delivery and Molar-Incisor Hypomineralization (MIH) - though the results of the reviewed studies have been contradictory [57, 65, 74-78]. Here again, further high quality studies are needed to clarify the association between MIH and premature delivery. The results of the studies on this subject are summarized in Table 2.

Table 2. Prevalence of permanent dentition enamel defects in the reviewed studies.

Author	Country	Control group (at term)	Study group (preterm)	Prevalence of enamel defects (at term)	Prevalence of enamel defects (preterm)	
Aine, 2000 [67]	Finland	n=64 9-10 years	n=32 9-10 years	36% 11% 25%	84% 38% 47%	p<0.001 Enamel defects p=0.002 Hypoplasias p=0.031 Isolated opacities
Arrow, 2009 [74]	Australia	n=506 6-9 years	n=30 6-9 years	47% 22%	63% 20%	p=0.023 Diffuse opacities p=0.023 Delimited opacities
Brogårdh-Roth, 2011 [65]	Sweden	n=82 10-12 years	n=82 10-12 years	16%	38%	p=0.002 MIH
Cruvinel, 2011 [66]	Brazil	n=40 5-10 years	n=40 5-10 years	62.5% 7.5%	65% 37.5%	p=0.8161 Delimited opacities p=0.0013 Hypoplasias
De Lima, 2015 [75]	Brazil	n=511 11-14 years	n=83 11-14 years	18%	18.4%	No statistical analysis
Lai, 1997 [61]	Australia	n=25 8-11 years	n=25 8-11 years	4% 40%	68% 88%	p<0.001 Hypoplasias p<0.001 Enamel defects

Dental composition and structure

In a study carried out by Rythen et al. [79], the enamel of the primary dentition of premature patients was seen to contain lesser concentrations of calcium and a larger carbon content than among the children of the control group. On the other hand, previously published studies recorded increased enamel porosity of the primary dentition in preterm infants, as well as an increase in the number of Retzius striae (incremental growth lines) of the enamel [80, 81]. Zanolli et al. [82] in turn observed thicker neonatal lines in the primary dentition of premature infants, evidencing a greater extent of hypomineralized enamel in these patients. It has been suggested that this lesser mineralization of the teeth in preterm infants may be due to a diminished incorporation of minerals from the mother after delivery, which in these patients occurs in an earlier stage of dental formation [70].

Although the dental composition of preterm infants has not been widely investigated to date, it is an interesting field for future research, since it could be related to other variables that are more difficult to study, such as the mineral status of other tissues – including bone – and the nutritional status of the child.

Caries risk

Some authors point to an increased risk of caries in preterm infants, due mainly to the aforementioned structural anomalies of the dental enamel [33, 83]. The results of the studies on this subject are summarized in Table 3.

Table 3. Prevalence of caries in the reviewed studies.

Although most of the published findings support the association between preterm birth and an increase in caries risk, some studies have failed to record statistically significant differences [57, 89, 90]. Furthermore, a recent systematic review and meta-analysis did not find differences in the prevalence of caries between preschool children born preterm versus full term (91).

With regard to other risk factors for dental caries, Merglova et al. (92) investigated the oral microbiota of a group of 24 premature 12-month-old infants versus a control group of 45 patients of the same age born at term. The presence of *Streptococcus mutans* was identified in all the samples of the control group, but in only 4.2% of the samples of the preterm group – the difference being statistically significant ($p < 0.05$). Nevertheless, further studies are needed to confirm this possible association.

Another study recorded greater bacterial plaque and gingivitis scores, a lesser unstimulated salivary flow, and an increased bacterial burden in preterm adolescents, resulting in an increased risk of caries in this population (93).

All the above underscores the importance of parent and caregiver education, as well as the need to incorporate a pediatric dentist to the multidisciplinary team in charge of preterm infant care.

Chronology of tooth emergence

Author, year	Country	Control group (at term)	Study group (preterm)	Prevalence of caries (at term)	Prevalence of caries (preterm)	
Saraiva, 2007 [83]	Brazil	n=2914 2-5 years	n=275 2-5 years	14.70%	26.3%	p=0.01
Tanaka, 2014 [57]	Japan	n=1962 3 years	n=93 3 years	21.10%	12.90%	P>0.05
Rajshekar, 2011 [84]	India	n=250 6 years	n=250 6 years	38.80%	48%	p<0.05
Campus, 2009 [85]	Italy	n=5005 4 years	n= 533 4 years	20.80%	25.50%	p<0.05
Dos Santos Junior, 2014 [86]	Brazil	n=291 3-4 years	n=29 3-4 years	13.70%	82.80%	p<0.01
Schüler, 2017 [68]	Germany	n=64 3-4 years	n=64 3-4 years	10.9%	17.2%	p<0.05
Soares, 2020 [87]	Suecia	n= 3920 3 years	n=234 3 years	6%	6%	p=0.557
Alshehhi, 2019 [88]	United Arab Emirates	n=62 5-10 years	n=62 5-10 years	17.7%	38.7%	P<0.05

The alterations in general development observed in preterm infants suggest that there also may be a delay in dental development in these patients. Backström et al. (94) studied a group of 30 preterm infants initially at 1-2 years of age and again at 9-11 years of age, using the method of Demirjian to quantify dental development versus a control group. In the primary dentition, the age at eruption of the first tooth was greater in the study group (9 months of chronological age and 7 months of corrected age) than in the control group (6 months). In contrast, in the permanent dentition, no statistically significant differences in dental development were observed between the two groups (p=0.14).

In contrast, Paulsson et al. (95) used the same method to assess dental development in extremely preterm children. The latter showed delayed permanent teeth development when compared to the controls (children born full-term).

Another similar study likewise found age at eruption of the first primary tooth to be significantly greater in premature patients (8.44 months) than in patients born at term (7.05 months) (p<0.001). However, in the same sample, these differences were no longer significant on considering corrected infant age instead of chronological age (96). Wang et al. obtained similar results in their sample [97].

The last of the analyzed studies, published by Ramos et al. [98], recorded no statistically significant differences in age at eruption of the first primary tooth between the control group (30.1 weeks) and the group of premature patients (34.6 weeks). This study was considered to be of poor methodological quality, however, and the information referred to both gestational age and age at eruption of the first primary tooth was obtained from the parents, not through exploration.

The scientific literature suggests that the difference between chronological age and corrected age exerts some influence in determining a possible delay in eruption of the primary dentition. However, other authors speak of delayed eruption in premature infants as being attributable to systemic factors [63].

There are few studies of good methodological quality in this field. Further research is therefore needed on dental development and eruption among premature infants.

Tooth size

In the same way as has been observed in relation to dental growth and development, some authors have described lesser overall growth among premature infants, evidenced by lower percentiles referred to both body weight and height. Such findings again may suggest an impact upon the final size of both the primary and the permanent teeth in premature infants.

Some studies [99] have reported comparatively smaller permanent teeth in premature infants. However, it is not yet clear whether this smaller size reflects a decrease in global size of the tooth or a decrease in the thickness of the enamel layer. In support of the latter hypothesis, Seow et al. [100] reported lesser enamel thickness in the primary dentition of preterm infants compared with infants born at term. In contrast, other authors have reported no statistically significant differences between premature patients and the controls in terms of the size of the primary teeth [101, 102].

The crown size of the permanent dentition is reportedly smaller in preterm infants, though further studies are needed to confirm this. Moreover, one of the reviewed studies only measured the permanent incisors and first molars [101, 103]. Therefore, with regard to tooth size, the available data are limited, and the studies are generally of insufficient quality. The evaluation of differences in primary and permanent tooth size between premature infants and patients born at term could be an interesting field for future research.

Other oral manifestations

Other oral problems inherent to premature infants include lacerations caused during intubation [33, 48], as well as the accumulation of bilirubin in the developing dental tissues, associated to the neonatal cholestasis seen in some premature children – giving rise to a greenish color of the primary dentition [104]. There have also been reports of an increased prevalence of anomalies in dental shape, affecting particularly the permanent upper lateral incisors [16].

Lastly, it has been postulated that premature infants may be at an increased risk of dental and maxillofacial traumatism due to their delayed motor coordination. A cross-sectional study has found no

evidence of such an increased risk [105], though another publication reported statistically significant differences in the frequency of dental trauma between premature infants (21%) and patients born at term (6%) ($p=0.02$) [44]. In any case, further studies on dental and maxillofacial trauma in preterm children are required before it can be concluded that premature delivery is a risk factor for traumatizations of this kind.

Limitations of the study

One of the main limitations of our study has been the need to resort to articles with a cross-sectional or longitudinal design, which are associated with the lowest levels of scientific evidence. This proved necessary because of the study subject involved, and we attempted to limit the problem by evaluating the methodological quality of each selected publication individually.

In the same context, the protocols guiding most systematic reviews focus on clinical trials, and in this regard we had to adapt our own approach to observational studies or resort to less solid protocols.

Conclusions

Cross-sectional studies were the most frequent publications in the present systematic review, followed by retrospective observational studies. The most widely investigated oral manifestations in premature infants were structural enamel defects, followed by caries and malocclusions.

Structural enamel defects of the primary dentition were the most common alterations according to the consulted literature. Both caries and malocclusions were more frequent in premature patients, though the results of the different studies were heterogeneous in this regard.

Other less widely studied orofacial disorders were enamel defects of the permanent dentition, as well as alterations in dental composition and size, and in tooth development and eruption. Such anomalies should be addressed by future studies.

The existence of oral sequelae in children born at term stresses the need for the pediatric dentist to form part of the multidisciplinary team in charge of preterm infant health care, with the purpose of defining prevention and care strategies for premature patients, and thus ensuring improved future quality of life.

List Of Abbreviations

World Health Organization (WHO).

Condition, Context, Population (CoCoPop).

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Joanna Briggs Institute (JBI).

Molar-Incisor Hypomineralization (MIH).

Declarations

Ethics approval and consent to participate.

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The authors declare that the data supporting the findings of this study are available within the article and its supplementary information files.

Competing interests

The authors declare that they have no conflicts of interest in relation to the present study.

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Authors' contributions

Literature search, article selection, extraction of data and evaluation of study quality were carried out by two authors (LVC and EPP). LVC also drafted the manuscript. EPP, JISE, JML, ARE and PPP supervised the process and corrected and approved the final manuscript.

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Additional File Legends

Additional File 1. .docx Annex I: Characteristics of the included studies.

Additional File 2. .docx Annex II: Quality assessment of the included studies.

Additional File 3. .doc PRISMA 2009 Checklist.

Figures



PRISMA 2009 Flow Diagram

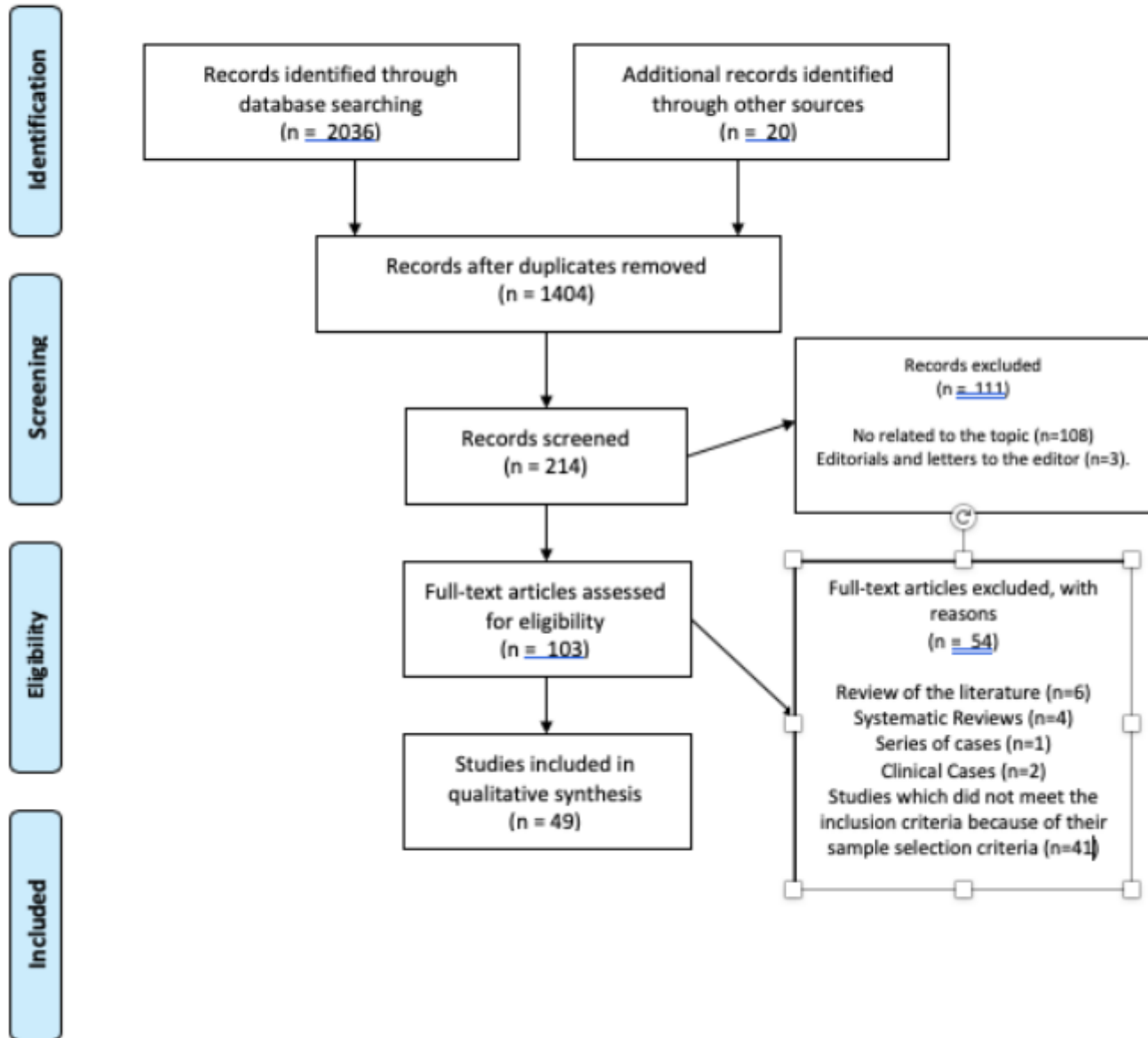


Figure 1

PRISMA flowchart of the literature search.

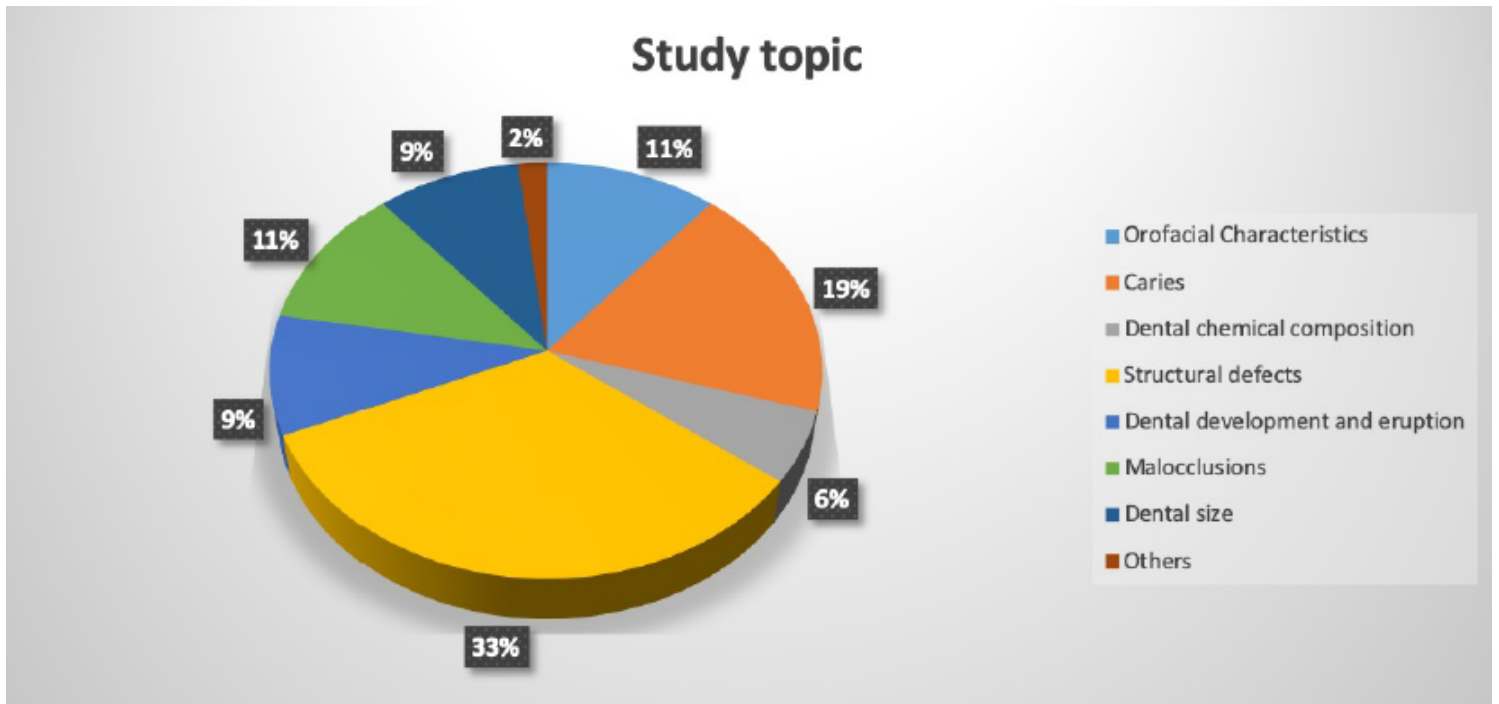


Figure 2

Principal study topics of the publications included in the review.

Supplementary Files

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