REVIEWS

Association between Dental Anomalies and Orofacial Clefts: A Meta-analysis

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Abstract: ***Objectives:*** *To conduct a systematic review and meta-analysis to assess whether individuals with nonsyndromic orofacial clefts (OCs) display a higher frequency of dental anomalies (DAs) when compared with individuals without OCs.*

Methods: *A literature search of indexed databases (PubMed, Cochrane, Web of Science, Embase, Scopus, and LILACS) was conducted without language restriction up to and including February 1, 2020. Cross-referencing was used to further identify articles. Several cleft teams across the United States and Europe were contacted to obtain unpublished data. The eligibility criteria were observational studies with original data that statistically compared individuals with OC without syndromes and those without OC on any type of DA in primary and/or permanent dentition. Random effects meta-analysis through the Mantel-Haenszel estimator was used to evaluate the association between OC and DA based on odds ratios (ORs) with 95% confidence intervals (CIs).*

Results: *The literature search generated 933 records, and 75 full-text articles were reviewed. Twenty-six studies encompassing 15,213 individuals met the inclusion criteria. The meta-analysis revealed statistically significant associations between OC and agenesis (OR, 14.2; 95% CI, 9.4 to 21.3), supernumerary teeth (OR, 5.7; 95% CI, 3.3 to 9.7), developmental enamel defects (OR, 5.6; 95% CI, 3.5 to 9.0), microdontia (OR, 14.8; 95% CI, 4.0 to 54.6), peg-shaped anterior teeth (OR, 12.2; 95% CI, 3.6 to 41.2), taurodontism (OR, 1.7; 95% CI, 1.0 to 2.7), tooth malposition and/or transposition (OR, 5.6; 95% CI, 2.8 to 11.5), tooth rotation (OR, 3.2; 95% CI, 1.3 to 8.2), and tooth impaction (OR, 3.6; 95% CI, 1.1 to 12.2). The OR estimates of the reviewed studies exhibited significant heterogeneity ($P < 0.0001$). No association was observed between OC and fusion and/or gemination.*

Conclusion: *Within the limitations of this study, the available evidence suggests that individuals with OCs are more likely to present with a range of DAs than their unaffected peers.*

Knowledge Transfer Statement: *The findings of the current review suggest that individuals with orofacial clefts (OCs) are more likely to present with a range of dental anomalies than their unaffected peers. Understanding the association between OCs and dental anomalies is essential in guiding clinicians during treatment-planning procedures and is important*

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A supplemental appendix to this article is available online.

in raising our awareness of the possible need for future dental treatment for patients with OCs.

Keywords: cleft lip, cleft palate, anodontia, supernumerary tooth, microdontia, developmental enamel defects

Introduction

Nonsyndromic orofacial cleft (OC) refers to a heterogeneous group of disorders that involve the lips (cleft lip) and/or palate (cleft palate) of approximately 1 per 700 liveborn babies. Midface development entails a complex process of initiation, growth, morphogenesis, and fusion of the primary and secondary palatal shelves. This process is controlled by reciprocal epithelial-mesenchymal interactions regulated by multiple signaling pathways and transcription factors. At 6 wk of embryogenesis, the maxillary processes fuse with the medial nasal process to form the upper lip and primary palate. The palatal shelves grow bilaterally along the sides of the tongue and then elevate and fuse to form the secondary palate. Failure during any stage of this process results in orofacial clefting (Dixon et al. 2011). OCs are considered the consequence of a cascade of events, including environmental factors, such as maternal tobacco smoking and alcohol consumption (Lorente et al. 2000), and/or genetic factors, such as mutations in interferon regulatory factor 6 (*IRF-6*) and Msh homeobox 1 (*MSX1*) genes, which play a critical rule in embryonic development (Dixon et al. 2011). Although OCs occur in infants with syndromes such as Pierre Robin, DiGeorge, and Treacher Collins, the majority of cases of OC are nonsyndromic, where OC occurs without syndromes or craniofacial anomalies (Dixon et al. 2011).

Teeth originate from the dental lamina through molecular and cellular interactions between the epithelium and underlying mesenchyme, involving a series of reiterative actions among specific signaling molecules, receptors, and transcription factors (Brook et al. 2014). Dental anomalies (DAs) may be induced through disturbances to the intraoral environment due to deficiencies in mesenchymal tissue or perturbations in signaling pathways between the ectodermal and mesenchymal cell layers (Ranta 1986). Various DAs, including agenesis, hypoplasia, and tooth malposition, were observed among individuals with OCs regardless of their cleft phenotype (Schroeder and Green 1975; Germec-Cakan et al. 2018; Korolenkova et al. 2019). The largest study to date combined DAs data from different cleft types into 1 group after analysis, since in general no difference was observed among cleft phenotypes (Howe et al. 2015). Previous investigators stated that most studies investigating DAs among individuals with OCs included different cleft phenotypes in their samples but did not differentiate their results according to cleft phenotypes (Akcam et al. 2010). Korolenkova et al. (2019) observed a statistically significant difference in the prevalence of DAs among individuals who received different primary lip surgical procedures, which suggests that factors other than the cleft phenotype may play a role in the development of DAs.

Although a previous systematic review attempted to explore the prevalence of DAs in individuals with isolated OCs (Tannure et al. 2012), the authors reported several limitations due to the limited evidence available: they had to input some of the missing data, and only 6 studies qualified for meta-analysis. Since then, a growing body of research has examined the association between OCs and DAs, which has never been synthesized or systematically reviewed. Our objective is to conduct a comprehensive and up-to-date systematic review and meta-analysis to summarize and collate the evidence regarding DAs and nonsyndromic OCs.

Methods

Research Question

This systematic review was conducted according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses; Moher et al. 2010) and the PECO format (patients = children, adolescents, and adults; exposure = presence of nonsyndromic OCs; control = absence of OCs; outcome = DAs). The addressed question was "Is there an association between DAs and nonsyndromic OCs?"

Eligibility Criteria

The eligibility criteria were original observational studies that statistically compared individuals with OCs without syndromes and those without OCs on any type of DA in the primary and/or permanent dentitions. All types of nonsyndromic OCs were included: cleft lip, cleft palate, cleft lip and palate with or without cleft alveolus, and other cleft types. Studies without a control group and studies of syndromic individuals were excluded. For studies containing syndromic and nonsyndromic individuals, syndromic individuals were excluded, and only individuals with nonsyndromic OCs were included. Studies without original data (e.g., letters to editors, opinions) were excluded. Case reports, case series, and reviews were also excluded, but the reference lists of these articles were reviewed to identify potentially eligible studies.

Information Sources, Search Strategy, and Study Selection

Indexed databases (PubMed, Cochrane Central Register of Controlled Trials, Web of Science, Embase, Scopus, and LILACS) were searched without language restriction up to and including February 1, 2020. The electronic search included the following Medical Subject Headings terms and keywords: Cleft Lip; Cleft Palate; Cleft Lip and Palate; Dental Anomalies; Tooth Abnormalities; Teeth Agenesis; Anodontia; Hypodontia, Oligodontia; Supernumerary Tooth; Supplemental Tooth; Mesiodens; Paramolar; Distomolar; Developmental Enamel Defects; Hypoplasia; Hypocalcification; Microdontia; Peg-shaped Teeth; Taurodontism; Root Dilaceration; Dens Invaginatus; Dens

in Dente; Dens Evaginatus; Dentin Dysplasia; Teeth Fusion; Tooth Gemination; Curved Maxillary Central Incisors; Tooth Transposition; Tooth Malposition; Tooth Rotation; Tooth Impaction. The specific search strategy for each database is available in the Appendix.

Two reviewers (T.M. and I.L.A.) performed the electronic search and evaluated studies for eligibility. The same 2 authors independently screened the titles and abstracts of the retrieved articles, and the full text of potentially eligible articles was reviewed. Reference lists of pertinent articles and gray literature were searched to identify articles that might have been missed during the previous steps. Any disagreement was resolved via discussion between reviewers. The interexaminer Cohen kappa coefficient score was 0.95. Two reviewers (T.M. and I.L.A.) used a data extraction form to abstract data independently. The following study characteristics were extracted: country, study design, patient population (sample size, age, sex, and dentition type), matching factors, type of OC, observed DAs, outcome assessment methods, and quality assessment.

Types of DAs

Any method of DA assessment was considered, including clinical examination, photographs, study models, dental radiographs (panoramic, occlusal, periapical, and computed tomography scans), and medical and dental records. The following types of DAs were evaluated: numerical (teeth agenesis [anodontia, hypodontia, or oligodontia] and supernumerary tooth [supplemental tooth, mesiodens, paramolar, or distomolar]), morphologic (developmental enamel defects [hypoplasia and/or hypocalcification], microdontia, peg-shaped teeth, taurodontism, root dilaceration, dens invaginatus [dens in dente], dens evaginatus, dentine dysplasia, teeth fusion, tooth gemination, and curved maxillary central incisors), and positional (tooth transposition, malposition, rotation, and impaction). Our comparison was based on the number of individuals with DAs in the cleft versus noncleft groups rather than the cleft versus noncleft sides in the cleft group because surgical interventions, even in unilateral cases, could affect the cleft and noncleft sides (Howe et al. 2015).

Quality Assessment

The quality assessment was performed independently by 2 reviewers (T.M. and I.L.A.) using a modified Newcastle-Ottawa Scale to rate the quality of each article, control for bias, and gain a better understanding of the findings (Wells et al. n.d.). Disagreements between reviewers were resolved through a discussion. For every article, 9 criteria were analyzed, such as a clear description of the study objectives, inclusion criteria, and examiner's calibration. For each criterion, a score of – and + were allotted for "not reported" and "reported," respectively, and the combined frequency of reporting for each criterion was assessed.

Meta-analysis

Random effects meta-analysis through the Mantel-Haenszel estimator was used to evaluate the association between OCs and DAs with odds ratios (ORs) and 95% confidence intervals (CIs). Random effect models were chosen because the studies came from various populations and one might expect variation in the genetic and environmental background. The heterogeneity of the studies was evaluated with the I^2 statistic. Publication bias was assessed with funnel plots when >10 studies were available. All analyses were performed with Review Manager 5.4 software (Cochrane Community).

Results

Study Selection

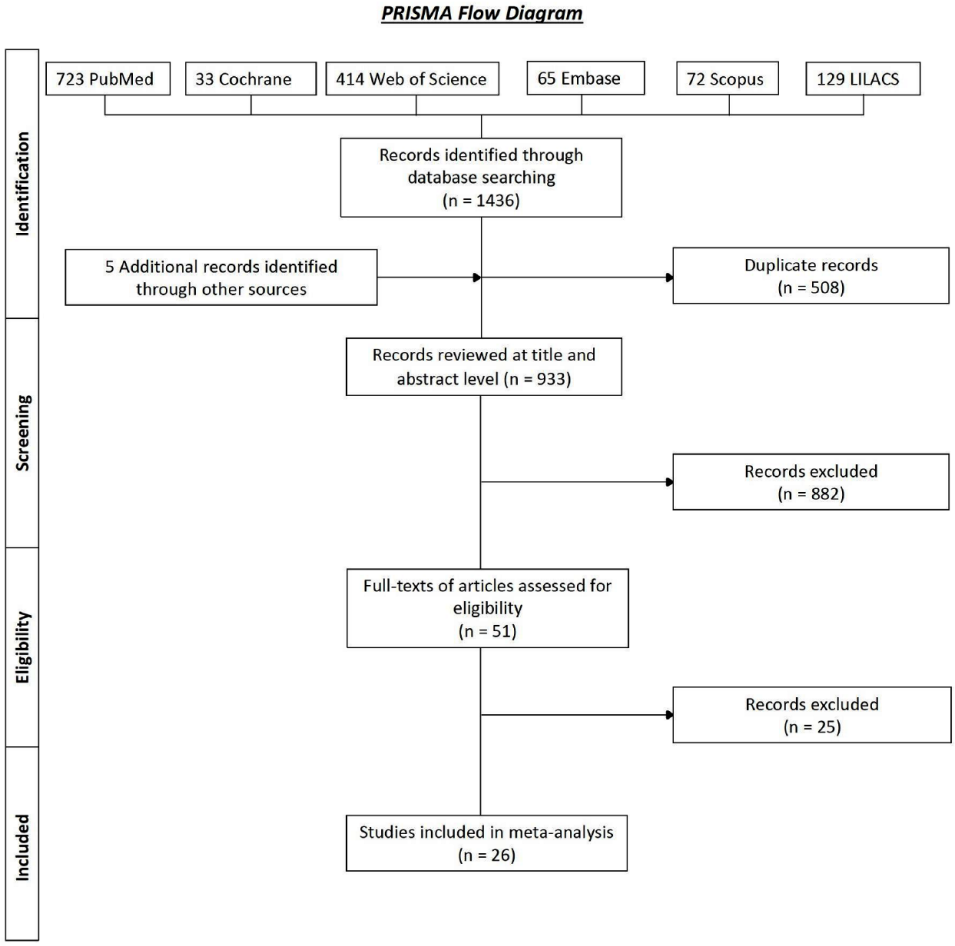
The literature search generated 1,441 records, and 1,390 articles were excluded after title/abstract screening and duplicate removal. Fifty-one studies were initially identified as being potentially eligible, of which 25 were excluded after full-text review. In total, 26 studies were included and processed for data extraction (Fig. 1) updating the previous systematic review that included only 6 studies (Tannure et al. 2012).

Our assessment was based on the number of participants with at least 1 DA. Studies reporting the total number of teeth with DAs (Rawashdeh and Abu Sirdaneh 2009), instead of the number of individuals, were excluded. Studies grouping DAs (e.g., combining peg-shaped incisors and hypoplasia; Walker et al. 2009) were excluded if the number of participants with each anomaly was not identified after checking the supplemental data files and contacting the corresponding authors. Articles that were unclear about excluding individuals with syndromic OCs were excluded if the syndromic status of the participants was not obtained after contacting the corresponding authors (Chopra et al. 2014; Kulas et al. 2016; Kamble et al. 2017). When studies reported outcome per >1 age group or dentition (Howe et al. 2015; Sundell et al. 2016), each age group/dentition was included separately in the analysis. Multiple attempts were made to contact authors to get the overall results per individual when outcomes were reported per maxilla or mandible separately (Howe et al. 2015). Two separate meta-analyses for microdontia/peg-shaped anterior teeth were performed because several studies referred to microdontia as teeth with smaller-than-normal size (Howe et al. 2015; Germec-Cakan et al. 2018) while others focused only on peg-shaped anterior teeth (Küchler et al. 2011; Răducanu et al. 2015).

General Characteristics of the Included Studies

In total, the 26 studies that assessed the prevalence of DAs involved 15,213 participants with sample sizes ranging from 60 to 1,848. Of the 26 included

Figure 1. PRISMA flow diagram. The search strategies, the list of excluded studies, and the reasons for exclusion are shown in the Appendix.



studies 5 were conducted in the United States, 8 in Europe, 7 in South America, and 6 in Asia. Eighteen studies reported the male/female percentage across the study and control groups, which ranged from 49% to 71% male and 29% to 51% female to 34% to 63% male and 37% to 66% female, respectively. Such findings support the previously indicated predominance of males in the OC population (Mossey et al. 2009). Concerning the age of the participants, 14 studies noted the mean and age range across study groups, while the remaining studies included either mean age or age range or did not report either. Among the 19 studies that cited the age range, all but 3 included an age range between 3 and 36 y. Of the 26 studies, 18 indicated matching of participants by age, sex, ethnicity, socioeconomic status, and/or other criteria. All studies documented the types of OCs (Table 1).

Main Study Outcomes

Among the types of DAs studied, 17 studies evaluated numeric DAs (agenesis and/or supernumerary teeth); 24 studies observed crown/root morphologic DAs (developmental enamel defects, taurodontism, microdontia, peg-shaped teeth, fusion, and/or gemination); and 7 studies assessed positional DAs (transposition, malposition, rotation, and/or impaction; Table 2). The following crown/root morphologic irregularities were reported in the studies but not included in the meta-analysis: curved maxillary centrals, excess or exaggerated or irregular mamelons, T-shaped laterals, root dilaceration, malformed premolars or first molars, missing or reduced hypocone, fused protocone and metacone, labial tubercles, supplementary cusp, chisel-shaped teeth, dens evaginatus, dens invaginatus, amelogenesis imperfecta, dentinogenesis imperfecta, and dentin dysplasia.

Results of the Meta-analysis

The meta-analysis revealed strong statistically significant associations between OCs and tooth agenesis, microdontia, and peg-shaped

Table 1.
General Characteristics of Included Studies.

Study (Year; Country)	Sample Size (Male:Female:Unknown)		Age, y, Mean ± SD (Range)		Groups Matched for . . .	Pattern of Orofacial Clefts
	Cleft Group	Control Group	Cleft Group	Control Group		
De Stefani (2019; Italy)	233 (151:82)	1,000 (471:529)	10.7 ± 2.8 (7 to 15)	10.3 ± 2.3 (7 to 15)	Age	u/bCLP
Korolenkova (2019; Russia)	369 (214:115)	500 (NR)	11.0 ± 4.5 (6 to 17)	11.1 ± 3.8 (6 to 17)	Age	u/bCL, u/bCLP, CP
Shen (2019; China)	239 (143:96)	469 (246:223)	16 (9 to 34)	20 (10 to 36)	Ethnicity, socioeconomic status	u/bCLP
Yezioro-Rubinsky (2020; Colombia)	210 (128:82)	210 (128:82)	NR (5 to 12)	NR (5 to 12)	Age, sex	u/bCLP
Allam (2018; USA)	41 (29:12)	60 (30:30)	9.7 ± 1.9 (6 to 16)	12.4 ± 1.8 (NR)	NR	u/bCLP
Cakan (2018; Turkey)	88 (48:40)	250 (113:137)	14.1 ± 6.4 (7 to 45)	15.2 ± 7 (11 to 45)	Age, ethnicity, socioeconomic status	CP, u/bCLP
Sundell (2016; Sweden)[a]	139 (80:59)	313 (148:165)	1: 5.4 ± 0.5 (4 to 6). 2: 10.4 ± 0.6 (9 to 11)	1: 5.2 ± 0.3 (4 to 6). 2: 10.1 ± 0.3 (9 to 11)	Age	CL, CP, CLP
Howe (2015; USA, Guatemala, Hungary, Nigeria, Argentina, and the Philippines)[b]	915 (541:374)	933 (415:518)	9.8 (<1 to 74)	25.9 (<1 to 74)	NR	u/bCL, CP, u/bCLP
Răducanu (2015; Romania)	48 (33:15)	1,447 (903:545)	15.1 ± 0.2 (12.5 to 17.3)	14.2 ± 0.1 (11.5 to 17.7)	NR	uCL, CP, u/bCLP
Shashni (2015; India)	23 (NR)	50 (NR)	6.55 ± 1.8 (4 to 9)	6.55 ± 1.3 (4 to 9)	Age, sex, socioeconomic status	CLP
Melo Filho (2015; Brazil)	88 (47:41)	300 (160:140)	14.3 (NR)	14.3 (NR)	Age, ethnicity, socioeconomic status	u/bCL, CP, u/bCLP
Weckwerth (2016; Brazil)	724 (357:367)	250 (91:159)	NR (>16)	NR (>16)	NR	uCL, CP, uCLP
Campbell (2014; USA)[c]	342 (220:122)	364 (231:133)	9.9 (4.5 to 22)	9.9 (4.7 to 22.5)	Age, sex, and ethnicity	CL, CP, u/bCLP
Saldias-Vargas (2014; Brazil)	100 (59:41)	50 (17:33)	NR (6 to 12)	NR (6 to 12)	NR	CP, u/bCLP
Carpentier (2014; Belgium and the Netherlands)	1: 123 (77:46). 2: 81 (NR)	100 (NR)	1: 13.6 ± 2.6 (9.2 to 26.9). 2: NR (13 to 18)	NR (11 to 14)	NR	CL ± A, CA, CP, u/bCLP
Maheshwari (2013; India)	30 (NR)	30 (NR)	8.4 ± 4.0 (4 to 15)	8.9 ± 3.3 (4 to 15)	Age, sex, socioeconomic status	CL ± A, CP, CLP
de Lima Pedro (2012; Brazil)	321 (177:144)	321 (168:153)	9.5 ± 2.1 (6 to 14)	9.3 ± 3.2 (6 to 14)	Age, sex, ethnicity, socioeconomic status	u/bCL, CP, u/bCLP
Wong (2012; China)	231 (123:108)	231 (NR)	13.8 (12 to 16)	NR (12 to 16)	Age, sex, date of panoramic radiographs ± 30 d	CL, CP, u/bCLP
Küchler (2011; Brazil)	128 (NR)	30 (NR)	NR (NR)	NR (NR)	NR	CL, CLP
Camporesi (2010; Italy)	156 (92:64)	1,000 (482:518)	10.3 (4.2 to 16.3)	NR (NR)	NR	u/bCLP
Parapanisiou (2009; Greece)	41(23:18)	41 (23:18)	10.5 ± 3.4 (4 to 18)	10.7 ± 3.0 (4 to 18)	Age, sex, orthodontic treatment	u/bCLP, CP

(continued)

Table 1. (continued)

Study (Year; Country)	Sample Size (Male:Female:Unknown)		Age, y, Mean ± SD (Range)		Groups Matched for . . .	Pattern of Orofacial Clefts
	Cleft Group	Control Group	Cleft Group	Control Group		
Letra (2007; Brazil)	500 (NR)	500 (NR)	17.3 (4 to 59)	36.8 (4 to 94)	Ethnicity	uCL, CP, u/bCLP, unknown cleft types
Eerens (2001; Belgium)	54 (34:20)	250 (123:127)	8.9 (4.2 to 13.1)	9.8 (4 to 14.9)	Age, ethnicity	CLA, CP, CLP
Quezada (1988; Netherlands)	100 (70:30)	38 (17:21)	1: 6.5 ± 2 (NR). 2: 8.8 ± 3 (NR)	1: 6.5 ± 2 (NR). 2: 8.8 ± 3 (NR)	Age, ethnicity	u/bCLP
Schroeder (1975; USA)	56 (35:21)	94 (50:44)	11.9 (NR)	13.1 (NR)	Ethnicity	u/bCL, uCLA, CP, CPA, uCLPA, bCLP
Jordan (1966; USA)	105 (65:37:3). 10 fetuses (5:2:3)	87 (NR). 800 fetuses (NR)	NR (3 to 12). Fetuses: NR (10 to 40 wk)	NR (3 to 12). Fetuses: NR (NR)	Ethnicity	CL, CLA, CP, CLP, other

A, cleft alveolus; b, bilateral; CL, cleft lip; CLP, cleft lip and palate; CP, cleft palate; NR, not reported; u, unilateral.
[a]One individual with syndromic cleft was excluded from our analysis.
[b]We were able to include unpublished data through collaboration with the corresponding authors.
[c]Twenty-two individuals with syndromic cleft were excluded from our analysis.

anterior teeth (ORs >12.0; Fig. 2). Statistically significant associations were also observed between OCs and supernumerary teeth, developmental enamel defects, malposition and/or transposition, rotation, and impaction (ORs >3.2). Furthermore, a borderline statistically significant association was found between OCs and taurodontism (OR, 1.7; 95% CI, 1.0 to 2.7). No association was observed between OCs and teeth fusion and/or gemination. Generally, the odds ratio estimates of the reviewed studies exhibited significant heterogeneity ($P < 0.0001$), with an I^2 statistic ranging from 0% to 95%. The funnel plot was asymmetrical.

Quality Assessment of the Included Studies

Nine quality assessment criteria were established. "A clear description of objectives, outcomes, methods of outcome assessment, and the methods of statistical analysis" was found in all the selected studies. "Appropriate selection of a representative sample" was found in only 1 study. Eighteen studies matched the study and control groups, and 14 studies reported examiners' calibration. All studies except 1 cited the inclusion criteria, and all studies but 6 mentioned the exclusion criteria. In summary, 1, 19, and 6 studies had high-, moderate-, and low-quality assessment scores, respectively (Table 3).

Discussion

The current work represents the most comprehensive worldwide meta-analysis of the association between OCs and DAs. Previously unpublished original data from the United States, Guatemala, Hungary, Nigeria, Argentina, and the Philippines were included through collaboration with several cleft teams. DAs were more prevalent among case probands than controls. Agenesis was regarded as the most frequently observed DA, followed by supernumerary teeth, developmental enamel defects, and microdontia/peg-shaped anterior teeth. DAs were seen in most cleft types and in the cleft side and the noncleft side, lending support to the hypothesis of complex multifactorial etiology behind dental abnormalities in individuals with OCs.

Previous studies hypothesized that the cleft environment may be responsible for the increased prevalence of DAs in individuals with OCs (Howe et al. 2015). Germec-Cakan et al. (2018) and Konstantonis et al. (2017) observed a significant association between unilateral cleft lip and palate and ipsilateral-lateral incisor agenesis and between bilateral cleft lip and palate and bilateral-lateral incisor agenesis. In contrast, Letra et al. (2007) and Matern et al. (2012) observed a unilateral cleft subphenotype involving agenesis of the lateral incisor on the contralateral side. In other words, left lateral incisor agenesis correlates with right unilateral cleft. Moreover, Küchler et al. (2011) and Korolenkova et al. (2019) reported a higher prevalence of agenesis outside the cleft area, which arguably suggests that DAs and OCs may have some common genetic links in their pathogenesis (Howe et al. 2015). These links, which were addressed by several genetic studies (van den Boogaard et al. 2000; Slayton et al. 2003), refer to the

Table 2.
Summary of Examined Dentition, Observed Anomalies, and Methods of Outcome Assessment.

Study (Year; Design)	Examined Dentition (Specific Tooth)	Observed Dental Anomalies	Methods of Outcome Assessment
De Stefani (2019; case-control)	Permanent (excluding third molars)	Agenesis	Panoramic radiographs
Korolenkova (2019; cross-sectional)	Permanent	Agenesis, supernumerary teeth, synodontia, dens invaginatus, amelogenesis imperfecta, dentinogenesis imperfecta, dentine dysplasia, taurodontism, developmental enamel defects, odontodysplasia	Clinical and radiographic examination (panoramic radiographs and computed tomography scans)
Shen (2019; cross-sectional)	Permanent (excluding third molars, supernumerary teeth, and unerupted teeth)	Developmental enamel defects (modified developmental defects of enamel index)	Clinical examination, medical and dental records, panoramic radiographs
Yezioro-Rubinsky (2020; case-control)	Permanent (excluding third molars)	Agenesis, supernumerary teeth, dilaceration, taurodontism, impaction, transposition, rotation, microdontia	Panoramic radiographs
Allam (2018; cross-sectional)	Permanent (incisors and first molars)	Enamel defects (hypomineralization)	Intraoral photographs and medical records
Cakan (2018; cross-sectional)	Late mixed or permanent (max anteriors and premolars)	Agenesis, supernumerary, microdontia, macrodontia	Study casts, medical and dental records, panoramic radiographs, and intra- and extraoral photographs
Sundell (2016; case-control)	Primary and permanent	Enamel defects (hypomineralization/hypoplasia)	Clinical examination
Howe (2015; case-control)	Primary and permanent (anteriors, premolars, and first molars)	Hypoplasia, microdontia, impaction, rotation, displacement, supernumerary, agenesis	Dental history, clinical examination, and/or intraoral photographs
Răducanu (2015; cross-sectional)	Permanent	Supplementary cusp, hypoplasia, double tooth, peg-shaped incisors, dilaceration, chisel shaped, dens invaginatus	Study models, clinical records, and radiographs
Shashni (2015; cross-sectional)	NR	Developmental enamel defects, hypoplasia (developmental defects of enamel index)	Clinical examination
Melo Filho (2015; case control)	Permanent (mand first and second molars)	Taurodontism	Clinical records and panoramic radiograph
Weckwerth (2016; cross-sectional)	Permanent	Taurodontism, root dilaceration, transposition	Panoramic radiographs and medical records
Campbell (2014; cross-sectional)	Permanent	Transposition, agenesis, peg-shaped	Panoramic radiographs
Saldias-Vargas (2014; cross-sectional)	Permanent (central incisors and first molars)	Developmental enamel defects (modified developmental defects of enamel index)	Clinical examination
Carpentier (2014; case-control)	Permanent (max premolars)	Hypoplasia	Intraoral photographs
Maheshwari (2013; cross-sectional)	Permanent	Agenesis, supernumerary, microdontia and macrodontia, hypoplasia, malposition	Clinical and radiographic examination (panoramic, occlusal, and periapical views)

(continued)

Table 2. (continued)

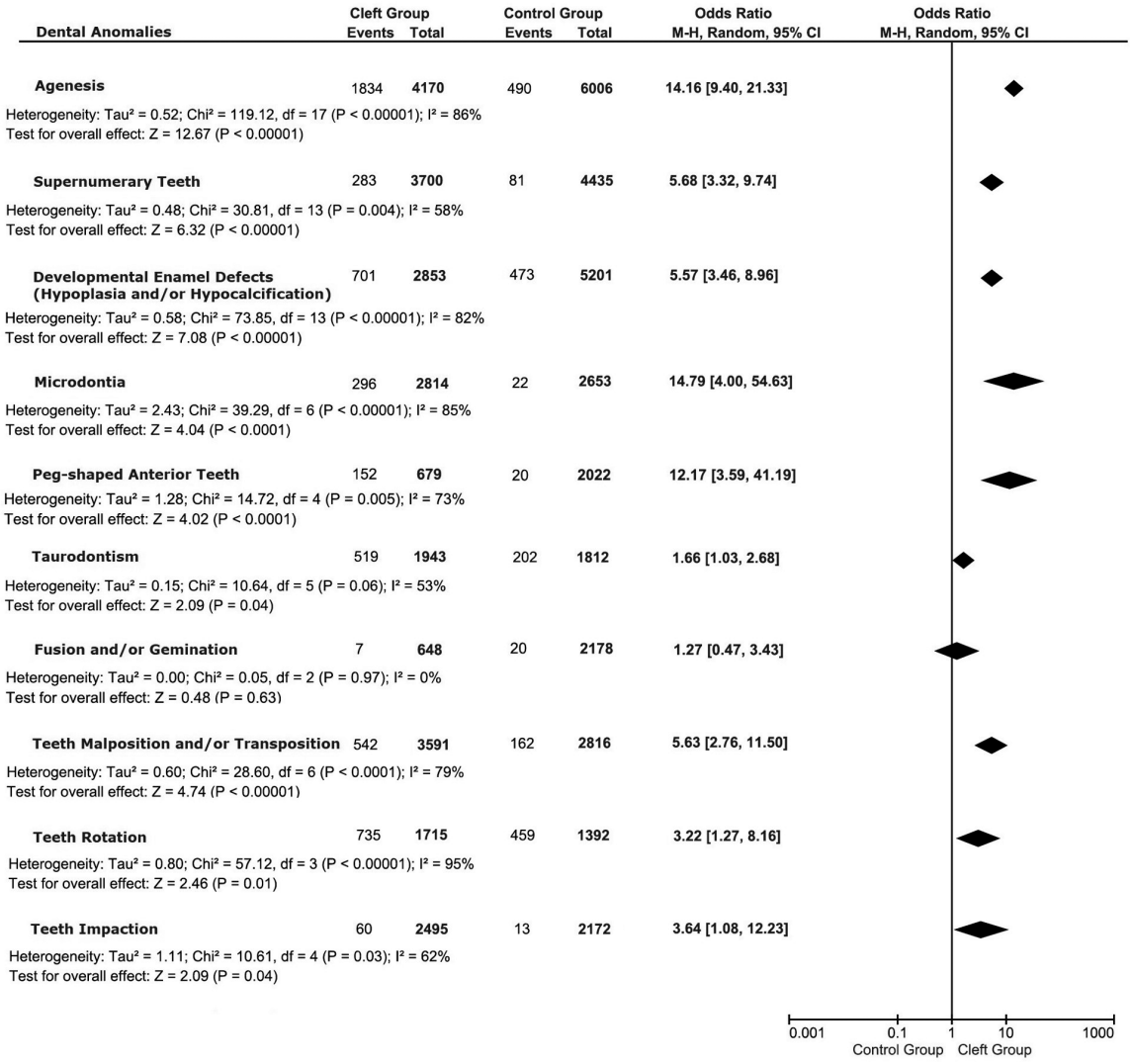
Study (Year; Design)	Examined Dentition (Specific Tooth)	Observed Dental Anomalies	Methods of Outcome Assessment
de Lima Pedro (2012; case-control)	Permanent (excluding the anteriors on cleft side and third molars)	Agenesis, microdontia, supernumerary, malposition, impaction, taurodontism	Dental and medical records, panoramic and periapical radiographs, dental casts, and intraoral photographs
Wong (2012; cross-sectional)	Permanent	Agenesis, supernumerary, taurodontism, double tooth, dens evaginatus, microdontia	Study models, medical and dental records, and radiographs (panoramic, occlusal, and periapical views)
Küchler (2011; cross-sectional)	Permanent	Agenesis, peg-shaped lateral, supernumerary teeth	Study models, clinical records, and radiographs
Camporesi (2010; cross-sectional)	Primary and permanent (max)	Supernumerary, agenesis, hypoplasia, anomaly in size/shape	Clinical examination, study casts, and intraoral photographs, as well as medical, dental, and radiographic records (panoramic, occlusal, and/or periapical)
Parapanisiou (2009; cross-sectional)	Primary and permanent	Hypoplasia, supernumerary, agenesis, rotated teeth	Clinical and radiographic examination (panoramic views)
Letra (2007; cross-sectional)	Permanent	Agenesis, microdontia, supernumerary teeth, malposition, impaction, malformation, transposition	Clinical examination, radiographs, and medical records
Eerens (2001; cross-sectional)	Primary and permanent (excluding the max laterals on cleft side)	Agenesis, asymmetry of dental development	Orthopantomogram and patient records
Quezada (1988; cross-sectional)	Primary (central incisors and max first and second molars) and permanent (incisors, first molars, and mand first premolars)	Agenesis, supernumerary, morphologic irregularities of the crown[a]	Study models, panoramic radiographs, and family history
Schroeder (1975; cross-sectional)	Permanent (incisors, canines, and mand first molars)	Agenesis, supernumerary, morphologic irregularities of the crown[a]	Study models, radiographs, and medical and dental histories
Jordan (1966; cross-sectional)	Primary, mixed, and permanent	Agenesis, supernumerary, morphologic irregularities of the crown[a]	Fetuses and study models

mand, mandibular; max, maxillary; NR, not reported.
[a]Morphologic irregularities of the crown include the following: curved max centrals, excess mamelons, exaggerated mamelons, peg-shaped anterior teeth, T-shaped laterals, malformed mand and/or max first molars, malformed premolars, missing hypocone, reduced hypocone, fused protocone and metacone, irregular mamelons, and labial tubercles.

regulation of ectodermal-mesenchymal correlation signal pathways (Wong et al. 2014; Qin and Cai 2015). Seo et al. (2013) observed an association between genetic disturbances of *PAX9* and *MSX1* genes and tooth agenesis within and outside the cleft area. Maxillary lateral incisors calcification starts around 1 y after birth (Ash 1993). Therefore, the anatomic defect of the cleft may explain the DAs associated with lateral incisors, given their early initiation and calcification. During the formation of the primary palate, a lack of fusion between the maxillary and medial nasal prominences may result in insufficient mesenchyme to support the formation of tooth buds. If the remaining tissue of the tooth bud is incapable of developing into a viable tooth or is defective, agenesis or microdontia could occur (Ranta 1986). However, dental lamina hyperactivity or tooth bud division as a result of its close proximity to OC may result in supernumerary teeth (Schulze 1953; Liu 1995; Vichi and Franchi 1995; Howe et al. 2015).

Our analysis showed that individuals with OCs are likely to have more DAs than their unaffected peers. Unlike their unaffected peers, individuals with OCs undergo surgical interventions that may affect the developmental stages of

Figure 2. Forest plot shows the associations between orofacial clefts and dental anomalies.



anterior teeth (Howe et al. 2015). The reason is that the timing of the primary lip and secondary palate surgery, which generally takes place around 3 to 6 mo and 9 to 12 mo, respectively (Ziak et al. 2010), coincides with the completion of anterior deciduous teeth crowns and the calcification of maxillary permanent incisors. These surgical procedures can also influence the development of posterior permanent tooth buds or induce teeth displacement and rotation, possibly explaining the incidence of agenesis of premolars, impactions, and dental malpositions (Ranta 1986; Spauwen et al. 1993; Lekkas et al. 2000). Agenesis of lateral incisors and enamel defects of anterior teeth and premolars seem to correlate with the treatment protocol in terms of the utilized surgical technique, the reduction of the blood supply due to tissue tension and scarring associated with palatal defects, and the absence of early orthodontic treatment to optimize the position of maxillary fragments (Carpentier et al. 2014; Korolenkova et al. 2019). In conclusion, the extent to which DAs are a secondary consequence of cleft anomalies, surgical procedures, or mutations in genes that are involved in signaling pathways remains enigmatic.

In our analysis, the OR of having DAs in individuals with OCs varied considerably among studies. Such differences may be attributed to the high heterogeneity of included studies (I^2 = 0% to 95%) or the ethnic variability, as well as the variation in type, severity, and/or laterality of OCs (Sundell et al. 2016; Germec-Cakan et al. 2018). In the case of numeric DAs, it can also be attributed to the lack of radiographs in 2 studies (Jordan et al. 1966; Howe et al. 2015). Howe et al. (2015) suggested that the lack of radiographic access might not have influenced their diagnosis of agenesis, since their estimates were close to studies based on radiographic images; however, this might not apply to supernumerary teeth, given that the authors observed lower rates of supernumerary teeth as compared with studies that relied on radiographs,

Table 3.
Quality Assessment Criteria for Eligibility Studies.

Study (Year)	1	2	3	4	5	6	7	8	9
De Stefani (2019)	+	+	+	−	−	+	−	+	+
Korolenkova (2019)	+	+	+	−	−	+	−	+	+
Shen (2019)	+	+	+	+	+	+	−	+	+
Yezioro-Rubinsky (2020)	+	+	+	+	+	+	+	+	+
Allam (2018)	+	+	+	+	+	−	−	+	+
Cakan (2018)	+	+	+	+	−	+	−	+	+
Sundell (2016)	+	+	+	+	+	+	−	+	+
Howe (2015)	+	+	+	+	+	−	−	+	+
Răducanu (2015)	+	+	+	+	−	−	−	+	+
Shashni (2015)	+	+	+	+	−	+	−	+	+
Melo Filho (2015)	+	+	+	+	+	+	−	+	+
Weckwerth (2016)	+	+	+	+	+	−	−	+	+
Campbell (2014)	+	+	+	−	+	+	−	+	+
Saldias-Vargas (2014)	+	+	+	−	+	−	−	+	+
Carpentier (2014)	+	+	+	+	+	−	−	+	+
Maheshwari (2013)	+	+	+	+	−	+	−	+	+
de Lima Pedro (2012)	+	+	+	+	−	+	−	+	+
Wong (2012)	+	+	+	+	+	+	−	+	+
Küchler (2011)	+	+	+	+	−	−	−	+	+
Camporesi (2010)	+	+	+	+	+	−	−	+	+
Parapanisiou (2009)	+	+	+	+	+	+	−	+	+
Letra (2007)	+	+	+	+	−	+	−	+	+
Eerens (2001)	+	+	+	−	+	+	−	+	+
Quezada (1988)	+	+	+	+	−	+	−	+	+
Schroeder (1975)	+	+	+	+	−	+	−	+	+
Jordan (1966)	+	+	−	−	−	+	−	+	+

Clear description of the 1) study objectives, 2) study outcomes, 3) inclusion criteria, 4) exclusion criteria, 8) outcome assessment methods, and 9) statistical analysis methods. Study 5) describes examiners' calibration and reports the calibration coefficient, 6) details matching of the study and control groups, and 7) describes an appropriate sampling method of all study participants through randomization. Quality assessment scores: 0 to 6 (low), 7 or 8 (moderate), and 9 (high).

arguably because it is difficult to detect impacted supernumerary teeth without a radiograph. Performing a subanalysis of agenesis by excluding studies that did not rely on radiographs did not result in a material change: there was a small decrease of the OR, by 3.8%, from 14.16 to 13.62. Determination of agenesis should be based on the participant's age when the tooth bud is visible on the radiograph; according to this criterion, Küchler et al. (2011), Camporesi et al. (2010), and Letra et al. (2007) considered second premolar agenesis only in individuals older than 8 y. Previous orthodontic and/or surgical interventions should be considered when assessing agenesis to avoid overestimation of the

outcome if teeth were extracted during such treatment protocols (Proffit 1994). De Lima Pedro et al. (2012) excluded individuals who required teeth extraction during cleft surgery and/or orthodontic treatment, while it was unclear if others excluded such participants (Eerens et al. 2001; Camporesi et al. 2010; Kamble et al. 2017). In summary, the considerable variation in the observed OR among various studies may be attributed to the high heterogeneity and methodological differences across such studies.

A subanalysis according to sex could not be performed, because most included studies did not report the raw data regarding the prevalence of DAs across sexes. It is important to note, however, that this study was not designed to estimate the effect of sex on the occurrence of DAs; thus, attempting to explore such association in studies that fit our eligibility criteria only (i.e., studies with a control group) might be the reason why limited data were available. Nevertheless, the majority of studies that evaluated the effect of sex found no statistically significant association (Ranta 1972; Ribeiro et al. 2002; Akcam et al. 2010; Carpentier et al. 2014; Howe et al. 2015; Germec-Cakan et al. 2018). Other studies that did not investigate the effect of sex cited literature stating that sex is not a confounding factor (De Stefani et al. 2019). Baek et al. (2007) contradicted previous reports suggesting a sex-dominant pattern for maxillary lateral incisor and second premolar agenesis; however, the authors did not include the *P* value. As such, the difference might not have been statistically significant, or it may be a representation of a type I error.

In the current review, 2 studies revealed no association between cleft phenotype and microdontia (Letra et al. 2007; Germec-Cakan et al. 2018). According to Germec-Cakan et al. (2018) and Walker et al. (2009), the predominantly affected teeth by microdontia were on the cleft side. In contrast, de Lima Pedro et al. (2012) and Letra et al. (2007) noted that the affected teeth were mostly on the noncleft side. Investigators proposed an association between maxillary lateral incisor microdontia in patients with unilateral cleft lip and palate and lateral incisor agenesis of the contralateral side, which led the authors to hypothesize the existence of "unsuccessful" bilateral clefts (Letra et al. 2007; de Lima Pedro et al. 2012; Germec-Cakan et al. 2018). However, previous studies in the general population also reported this finding (Lyngstadaas et al. 1996; Garib et al. 2010), which suggests that microdontia may represent a variable expression of the same developmental defect that results in agenesis (Lyngstadaas et al. 1996; Pinho et al. 2005). Performing a subanalysis according to cleft type was infeasible given that the available studies offered limited data on the prevalence of DAs across various cleft phenotypes, likely because our research question was not designed to answer this hypothesis; thus, such analysis would also be biased because a considerable part of the literature was excluded due to the lack of a control group. The included studies were highly heterogeneous, comprising >35 DAs and >7 cleft types. This is compounded by a lack of reporting on side of laterality. That is, most studies that report on unilateral cleft do not note the position of the cleft (whether it is on the right or left side), and studies do not indicate the location of the missing tooth, for example, in relation to the cleft (is the missing tooth on the same side or contralateral one?). In summary, our findings suggest a positive association between OCs and DAs; however, the exact association with cleft type remains obscure.

Limitations

The quality assessment suggests that our included studies had methodologic limitations that could have influenced the results. The convenience sampling method and modest sample sizes of most studies made it difficult to evaluate associations. Confidence in the findings of any systematic review stem from the methodology used. An expanded search strategy involving electronic, manual, and gray literature ensured that all relevant literature was potentially explored. Although the quality assessment and data extraction processes followed a strict reproducible protocol, the ability of any secondary review to offer clear and unambiguous conclusions is always limited by the quality and heterogeneity of the included literature. The quality of studies that were relevant to our review was variable, with most studies presenting with low- to moderate-quality assessment scores and considerably high heterogeneity. Regarding the epidemiologic studies, selection, diagnosis, and publication are the predominant types of bias in question. Selection bias was of particular concern because most studies were based on a convenience sampling method. Although the diagnosis of DAs can be relatively simple, there are many types of DAs to consider, and researchers need to take all types of DAs into account. In our review, diagnostic bias was relatively low because all studies were clear about their diagnostic criteria. However, 2 studies lacked radiographs, which might have influenced their diagnosis of DAs (Jordan et al. 1966; Howe et al. 2015). While publication bias may explain an asymmetrical funnel plot, heterogeneity among the included studies could have also contributed. For example, 2 studies among the 18 reporting agenesis had zero events in the control group, which makes the estimated odds ratio ∞. Three studies had only 1 event in the control group. These extremely small event numbers make the estimates of ORs and their standard deviations very unstable. The event rate in the cleft group changes from 2% to 80%. Another limitation is that the present review was not designed to explore the effect of sex, cleft types, and/or laterality on the occurrence of DAs. In summary, conclusions from the current work must be drawn with some caution. There is intrinsic bias in the reported results of the meta-analysis given the methodology of comparing observational studies rather than

randomized controlled trials. Although statistically significant associations between OCs and DAs were observed, biases and heterogeneity precluded confidence in the actual strength of associations.

Conclusion

In conclusion, the present meta-analysis shows that individuals with OCs are more likely to present with various DAs than their unaffected counterparts. DAs were common in both sexes, in most cleft types, and in the cleft and noncleft sides. Future studies are needed with sound designs in terms of a systematically sampled study population with explicitly stated eligibility criteria. Researchers should carefully consider participants' age, previous orthodontic and/or surgical treatments, cleft phenotype, and a clear description of the validity and reliability of the measurements. Understanding the association between OCs and DAs is essential in guiding treatment-planning procedures and raising our awareness of the possible need for future dental treatment for patients with OCs.

Author Contributions

T. Marzouk, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; I.L. Alves, C. Pendleton, T.K. Peter, contributed to data acquisition, critically revised the manuscript; C.L. Wong, D.T. Kopycka-Kedzierawski, C.S. Morrison, H. Malmstrom, contributed to data interpretation, critically revised the manuscript; L. DeLucia, contributed to data interpretation, drafted and critically revised the manuscript; C.M. McKinney, E.T. Shope, contributed to conception, design, and data interpretation, drafted and critically revised the manuscript; B.J. Howe, contributed to conception, design, data acquisition, and interpretation, drafted and critically revised the manuscript; M.L. Marazita, contributed to data acquisition and interpretation, critically revised the manuscript; H. Wang, contributed to data analysis and interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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