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Dental Decay Phenotype in Nonsyndromic Orofacial Clefting

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Abstract

Although children with oral clefts have a higher risk for dental anomalies when compared with the general population, prior studies have shown conflicting results regarding their dental decay risk. Also, few studies have assessed dental decay risk in unaffected relatives of children with clefts. Thus, the question of increased risk of dental decay in individuals with oral clefts or their unaffected relatives is still open for empirical investigation. This study characterizes dental decay in the largest international cohort to date of children with nonsyndromic clefts and their relatives, as compared with controls, and it addresses whether families with oral clefts have a significantly increased risk for dental decay versus the general population. A total of 3,326 subjects were included: 639 case probands, 1,549 unaffected relatives, and 1,138 controls. Decay was identified from in-person dental examinations or intraoral photographs. Case-control differences were tested with regression analysis. No significant differences were shown in percentage decayed and filled teeth and decayed teeth in the primary dentition (dft, dt) and permanent dentition (DFT, DT) in cases versus controls. In the cleft region, no significant differences were seen in primary or permanent decay (dt, DT) when compared with controls. No difference was found with regard to cleft type and percentage dft, dt, DFT, and DT in case probands. Nonsignificant differences were found in unaffected siblings and parents versus controls (primary and permanent dentitions). Collectively, these findings indicate that individuals with nonsyndromic oral clefts and their families do not have a higher dental decay risk as compared with the general population. These results suggest that either genetic or environmental factors underlying a higher susceptibility for dental anomalies do not increase caries risk or that the seemingly higher risk for dental decay associated with increased dental anomalies in case probands may be superseded by possible greater access to dental care.

Keywords: dental caries susceptibility, craniofacial, oral health, genetic susceptibility, primary dentition, permanent dentition

Introduction

Untreated dental decay in the general population of the United States has been on the decline since 1971, largely due to fluoridation efforts, yet the disease still affects a considerable number of children and adults. According to the U.S. Department of Health and Human Services, the overall prevalence of untreated dental decay in the general population aged 2 to 74 y ranges from 15.6% to 23.7% (National Center for Health Services 2013). Children born with craniofacial conditions that affect the development and function of teeth and jaws are generally more susceptible to poor oral health (Cheng et al. 2007). This is often a result of genetic risk factors that cause structural deficiencies in the embryonic oral tissues, which lead to abnormalities in dental structure, shape, and number and then to crowding, ectopic eruptions, and malpositions, thereby complicating access to oral hygiene. These abnormalities also result in constant exposure of dental enamel and gingival tissues to the extraoral environment, which increases susceptibility to plaque accumulation and gingivitis. In addition, environmental risk factors, such as inadequate diet and poor oral hygiene habits, can cause or exacerbate damage in an already

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debilitated dentition (Dahllöf et al. 1989; Ahluwalia et al. 2004).

Children with orofacial clefting, the most common craniofacial birth defect, are at increased risk for dental anomalies (Howe et al. 2015). They also present with significantly increased plaque and gingival indices and increased bacterial loads when compared with controls (Bokhout et al. 1997; Lucas et al. 2000; Al-Wahadni et al. 2005; Parapanisiou et al. 2009; Hazza'a et al. 2011; Chopra et al. 2014; Sundell, Ullbro, et al. 2015); yet, their risk for dental decay is less well understood. The literature on dental decay is highly controversial, with multiple studies indicating a higher susceptibility for dental decay in both the primary and permanent dentitions (Dahllöf et al. 1989; Bian et al. 2001; Hewson et al. 2001; Besseling and Dubois 2004; Kirchberg et al. 2004; Parapanisiou et al. 2009; Zhu et al. 2010; Hazza'a et al. 2011; Kirchberg et al. 2012; King et al. 2013; Chopra et al. 2014; Sundell, Nilsson, et al. 2015) and with others showing no significant differences in decay risk as compared with the general population (Lages et al. 2004; Britton and Welbury 2010; Kirchberg et al. 2012; Freitas et al. 2013). These contradictory results may be due to the small sample sizes of prior studies (generally <200 subjects), geographically restricted study populations, and differences in access to oral health care. These sample limitations may inflate type I error and thus exaggerate statistical significance, reduce power for finding any real differences in dental decay between cases and controls, and make results highly specific to the study location and not generalizable to a broader population.

On a related question, few studies have examined dental decay among unaffected relatives of children with clefts as compared with controls or the general population and have found no increased risk among first-degree relatives (de Castilho et al. 2006; Al-Dajani 2009). Since unaffected relatives likely carry more cleft risk genes than the general population (Weinberg et al. 2006), it is possible that they are more susceptible to dental decay. The 2 previous studies mentioned do not seem to support this; however, they utilized small samples (<300). Therefore, employing a larger cohort is needed for a more comprehensive and conclusive assessment of dental decay risk in the unaffected relatives of children with clefts.

This study characterizes dental decay in the largest international consortium to date with dental data for children with nonsyndromic clefting, their unaffected siblings, parents, and controls. The large sample size allows us to more conclusively test the hypothesis that children with clefting have a significantly increased risk of dental decay as compared with the general population. Also, this sample allows us to more definitively evaluate the risk of dental decay among unaffected family members versus controls. Furthermore, it allows us to test for decay risk differences by cleft types; by primary, mixed, and permanent dentitions, and, finally, by decay risk inside versus outside the cleft region.

Methods

Sample

A total of 3,326 subjects were recruited from multiple cleft centers in the United States, including Colorado, Iowa, Pennsylvania, and Texas, and internationally, from Colombia, Guatemala, Hungary, Patagonia, and Puerto Rico. These subjects were separated into Caucasian and Latin American groups via self-reported race/ethnicity (Table 1). Internal review board (IRB) approval was attained at each site by the appropriate IRB process and committee, with a coordinating IRB at the University of Pittsburgh (IRB 0405013). The same protocol was used for every site. This study conforms to STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology).

The total sample included 639 case probands (mean age of dentitions, years: primary, 3.27; mixed, 8.32; permanent, 18.61) with nonsyndromic cleft lip and palate, cleft palate, and cleft lip; 1,549 unaffected relatives, including parents (37.25) and siblings (primary, 3.74; mixed, 8.73; permanent, 17.63 dentitions); and 1,138 controls, including control probands, parents, and siblings (primary, 3.64; mixed, 8.47; permanent, 30.87; Table 1 and Appendix Table 2). Cases and controls were grouped into primary, mixed, and permanent dentition groups instead of family units, thereby making observations unrelated and independent. The primary, mixed, and permanent dentitions of case probands (children with clefts) and unaffected siblings were compared with control-matching dentitions. Unaffected parents' permanent dentitions were compared with control-matching dentitions. Exclusion criteria can be found in the online Appendix.

Questionnaires recording dental history, including dental extractions, were collected on all subjects. Two additional types of data were collected: in-person dental examinations (n = 1,206) and intraoral photos (n = 2,120; Appendix Figs. 1, 2). A minimum of 5 photographs were taken per subject (maxillary and mandibular occlusal, right and left lateral, anterior biting) to appropriately display the entire oral cavity (Appendix Figs. 3, 5). The photo rater (B.J.H.) was blinded to study site, sex, age, cleft status (in absence of obvious clefting), and family relation. For details on dental examination and intraoral photos, see the online Appendix.

Dental Decay

Following the oral health status examination guidelines of the World Health Organization (2013), dental decay was defined as cavitated gross decay, as identified with intraoral photos and in-person dental examinations. No radiographs were used to identify decay. Filled teeth were defined as any restorations consisting of composite, amalgam, or full or partial coverage inlay, onlay, or crown, as identified with intraoral photos and in-person dental examinations. Percentage decayed and filled teeth and decayed teeth for permanent (DFT, DT) and primary (dft, dt) dentitions were used instead of number of DFT/dft for a more clinically meaningful assessment. DT/dt and DFT/dft were used instead of DMFT/dmft due to a lack of information regarding the reason for missing teeth for the majority of subjects in primary and permanent dentitions. Decayed and filled teeth for permanent (DFT, DT, FT) and primary (dft, dt, ft) dentitions were examined separately to further define decayed status with descriptive statistics (Appendix Tables 3–5). Percentage DFT, dft, DT, and dt in the whole mouth (maxilla and mandible—first molar to first molar), maxillary anterior

Table 1. Study Population and Cleft Type.

Sites	All (Control)	PB: CLO, CLP, CPO	Caucasian (Control)	Latin American (Control)
Colorado	59 (0)	4, 10, 1	59 (0)	0
Iowa	576 (217)	29, 59, 22	568 (214)	8 (3)
Pittsburgh	212 (20)	3, 16, 16	210 (20)	2 (0)
Texas	331 (0)	15, 70, 0	304 (0)	27 (0)
Hungary	683 (311)	25, 56, 22	683 (311)	0
Colombia	493 (123)	14, 86, 0	0	493 (123)
Guatemala	405 (251)	5, 37, 3	0	405 (251)
Patagonia	356 (46)	15, 85, 15	148 (21)	208 (26)
Puerto Rico	211 (99)	3, 17, 9	0	211 (99)
Total	3326 (1138)	115, 436, 88	1,972 (636)	1,354 (502)

		Dentition Group		
PB	Region	Primary Only	Mixed	Permanent Only
CLO (115)	Caucasian (79)	22	38	19
	Latin American (36)	8	10	18
CLP (436)	Caucasian (237)	64	103	70
	Latin American (199)	44	59	96
CPO (88)	Caucasian (67)	23	35	9
	Latin American (21)	8	10	3

All values are presented as *n*.
CLO, cleft lip only; CLP, cleft lip and palate; CPO, cleft palate only; PB, proband.

(canine to canine), maxilla (first molar to first molar), and mandible (first molar to first molar) were evaluated for the primary, mixed, and permanent dentitions. Dental decay in relation to cleft type (cleft lip and palate, cleft palate, and cleft lip) was examined in the primary and permanent dentitions.

Image/Oral Cavity Analysis

Within the forms (Appendix Figs. 1, 2), appropriate teeth were marked as either primary or permanent, and each tooth was marked as "present or missing." Decay and filled status was marked as appropriate for each tooth (see example in Appendix Figs. 4, 6). Analyses were completed on all primary teeth (A to T) and permanent teeth from first molar to first molar in each arch. The second and third permanent molars were excluded due to their inconsistent visualization in intraoral photographs.

Calibration

Calibration was completed with the photorater (B.J.H.) against 2 experienced dentists and coauthors (L.M.M.U. and A.R.V.). Intrarater reliability (kappa) for B.J.H. was 0.95. Interrater reliability among all 3 raters was 0.91 to 0.93. Testing was completed to determine the reliability between the in-person dental examination form and the intraoral photo form on 158 subjects who had both forms, with tests showing almost perfect agreement between forms (kappa >90%). For a detailed description of calibration procedures, see the online Appendix.

Statistical Methods

Descriptive analyses were completed for all variables in the sample. DFT and dft scores were calculated for the permanent and primary dentitions, respectively. Separate scores were registered for filled (ft/FT) and decayed (dt/DT) teeth. These scores were estimated for the whole mouth, maxilla, mandible, and anterior maxilla. Percentages of decayed, filled, and decayed and filled teeth in the extant teeth were calculated. These percentages were used as the outcome measure.

Age and sex variables were initially evaluated for confounding effects on case-control comparisons of the outcome measures (details in online Appendix). For the primary and mixed dentitions, analyses were completed via nonparametric *t* tests (Wilcoxon rank sum test) with no adjustment for dental age and sex. For the permanent dentition, regression analyses (general linear modeling) of case-control status, allowing for adjustment of age and sex (Appendix Table 1), were completed by considering the DFT and dft percentages in each area of the mouth. See the online Appendix for further details on regression analyses.

After Bonferroni correction for multiple testing, a P value $<1.4 \times 10^{-4}$ was selected as the threshold for significance. All analyses were completed with SAS 9.4 (SAS Institute, Inc.).

Results

Analyses by Cleft Type

Results did not show any significant differences among the cleft types (cleft palate, cleft lip and palate, cleft lip) in terms of primary percentage dft, dt, ft (P values ranged from 0.06 to 0.48) or permanent percentage DFT, DT, FT (P values ranged from 0.03 to 0.24; Tables 1 and 2). Due to there being no difference among the cleft types in case probands, all cleft types were combined as 1 group for subsequent analyses.

Table 2. Cleft Type and Mean Proportion of Decayed and/or Filled Teeth: Primary and Permanent Dentitions.

					P Value[a]		
	All	*P* Value	CAUC	LAM	CAUC vs. LAM	CAUC Cleft Diff	LAM Cleft Diff
			Primary dentitions				
dft	0.46		0.39	0.61	0.06		
CPO	0.58	0.20	0.50	0.83	0.40	0.09	0.54
CLP	0.48		0.45	0.54	0.50		
CLO	0.28		0.14	0.76	0.01		
dt	0.35		0.24	0.56	0.002		
CPO	0.43	0.64	0.31	0.78	0.17	0.45	0.49
CLP	0.35		0.26	0.48	0.06		
CLO	0.28		0.14	0.76	0.01		
ft	0.11		0.14	0.05	0.13		
CPO	0.06	0.17	0.19	0.06	0.54	0.19	0.62
CLP	0.13		0.19	0.05	0.10		
CLO[b]	—		—	—	—		
Probands, *n*							
CPO	70		52	18			
CLP	231		140	91			
CLO	75		58	17			
Total	376		250	126			
			Permanent dentitions[c]				
DFT	0.21		0.16	0.27	0.61		
CPO	0.12	0.16	0.06	0.21	0.57	0.49	0.35
CLP	0.24		0.19	0.31	0.77		
CLO	0.11		0.13	0.07	0.96		
DT	0.11		0.09	0.13	0.76		
CPO	0.09	0.14	0.05	0.14	0.57	0.41	0.33
CLP	0.13		0.11	0.16	0.93		
CLO	0.02		0.03	<0	0.38		
FT	0.10		0.07	0.13	0.67		
CPO[d]	—	0.51	—	—	—	0.67	0.72
CLP	0.11		0.08	0.15	0.74		
CLO	0.09		0.09	0.10	0.10		
Probands, *n*							
CPO	40		28	112			
CLP	298		154	144			
CLO	74		50	24			
Total	412		232	180			

CAUC, Caucasian; CLO, cleft lip only; CLP, cleft lip and palate; CPO, cleft palate only; dft/DFT, decayed and filled teeth (primary/permanent dentition); diff, difference; dt/DT, decayed teeth (primary/permanent dentition); ft/FT, filled teeth (primary/permanent dentition); LAM, Latin American; PB, proband.

[a]$P < 1.4$ E-04 (or $P < 0.00014$) indicates significance.

[b]No ft in primary dentition of case probands with CLO; therefore, no meaningful comparison.

[c]All mean proportions for permanent dentitions are based on adjustment for age and sex.

[d]No FT in permanent dentition of case probands with CPO; therefore, no meaningful comparison.

Primary Dentition

Results for the whole mouth, maxilla, mandible, and the anterior maxilla did not show any significant increase in percentage dft or dt when the primary teeth of case probands or unaffected siblings were compared with controls. As displayed in Table 3, similar percentage dft/dt was found in case probands and controls for the whole mouth (7.4%/5.1% vs. 7.1%/6.8%), maxilla (11.4%/8.1% vs. 10.6%/9.9%), mandible (4.1%/2.5% vs. 2.9%/2.9%), and the anterior maxilla (9.9%/8.15% vs. 8.2%/7.8%). We also compared case probands with unaffected siblings, and no significant differences in dft or dt were found.

Mixed Dentition

Results for all subjects in the mixed dentition (primary and permanent teeth were analyzed separately) for the whole mouth, maxilla, mandible, and anterior maxilla did not show any significant increase in percentage dft, dt, DFT, or DT when case proband or unaffected siblings were compared with controls (Table 4). Case probands and controls showed similar percentage dft/dt for the whole mouth in the primary dentition (21.7%/10.6% vs. 21.7%/14.0%) and percentage DFT/DT for the whole mouth in the permanent dentition (1.6%/1.0% vs. 1.7%/0.4%). Even in the area of the cleft (anterior maxilla), case probands had similar percentage dft/dt (13.9%/9.8% vs.

Table 3. Percentage Decayed and/or Filled Teeth in the Primary Dentition.

	PB (*n* = 169)		SIB (*n* = 88)		CTRL (*n* = 81)		*P* Value[a]		
Area of Mouth	dft	dt	dft	dt	dft	dt	PB-CTRL	SIB-CTRL	PB-SIB
All									
Whole	7.4	5.1	5.9	3.2	7.1	6.8	0.89, 0.95	0.68, 0.08	0.68, 0.78
Maxilla	11.4	8.1	7.6	4.9	10.6	9.9	0.49, 0.78	0.32, 0.05	0.50, 0.59
Mandible	4.1	2.5	3.7	1.0	2.9	2.9	0.06, 0.36	0.22, 0.40	0.99, 0.61
Anterior maxilla[b]	9.9	8.15	7.5	6.1	8.2	7.8	0.59, 0.93	0.91, 0.79	0.60, 0.83
	PB (n = 109)		SIB (n = 66)		CTRL (n = 42)				
Caucasian									
Whole	6.4	4.1	3.5	1.5	4.3	4.2	0.39, 0.58	0.87, 0.14	0.23, 0.25
Maxilla	10.5	7.1	4.1	2.2	6.1	5.9	0.70, 0.67	0.58, 0.14	0.24, 0.20
Mandible	3.7	1.9	2.6	0.5	2.8	2.8	0.62, 0.25	0.75, 0.14	0.85, 0.59
Anterior maxilla[b]	8.0	5.8	3.3	2.1	5.7	5.3	0.71, 0.97	0.69, 0.41	0.35, 0.34
	PB (n = 60)		SIB (n = 22)		CTRL (n = 39)				
Latin American									
Whole	9.2	7.0	13.1	8.55	10.1	9.6	0.65, 0.20	0.28, 0.74	0.14, 0.12
Maxilla	13.1	9.9	18.6	13.3	15.3	14.1	0.59, 0.18	0.50, 0.93	0.21, 0.19
Mandible	4.7	3.5	6.8	2.7	3.1	3.1	0.14, 0.55	0.12, 0.59	0.70, 0.97
Anterior maxilla[b]	13.3	12.1	20.8	19.2	11.0	10.5	0.37, 0.75	0.10, 0.11	0.24, 0.14

CTRL, control; dft, decayed and filled teeth (primary dentition); dt, decayed teeth (primary dentition); PB, proband; SIB, sibling.
[a]*P* values recorded as dft, dt. $P < 1.4$ E-04 (or $P < 0.00014$) indicates significance.
[b]Canine-canine.

9.1%/9.0%) and percentage DFT/DT (1.6%/1.0% vs. 1.7%/0.4%). Furthermore, controls displayed a higher percentage decay when compared with unaffected siblings (14.0% vs. 6.3%, respectively), yet this difference did not reach statistical significance. When case probands were compared with unaffected siblings, no significant differences were found in percentage dft, dt and DFT, DT, respectively. Within the anterior maxilla of the primary dentition of this group, there were not enough unaffected siblings with decay to formulate a meaningful statistical comparison with case probands.

Permanent Dentition

Results for the whole mouth, maxilla, mandible, and anterior maxilla did not show any significant increase in percentage DFT or DT when case probands, unaffected siblings, or parents were compared with controls (Table 5). The overall percentage DFT in the whole mouth was elevated but not significant when unaffected parents were compared with controls (22.3% vs. 15.2%, $P = 0.008$). Interestingly, case probands displayed a lower percentage DFT in the whole mouth ($P = 0.001$), maxilla ($P = 0.004$), and mandible ($P = 0.0005$) when compared with controls. However, these results did not reach statistical significance. Percentage DT was similar between case probands and controls in all areas of the mouth, including the area of the cleft (4.7% vs. 4.0%, respectively). Lastly, no significant difference was seen in percentage DFT or DT when case probands were compared with unaffected siblings in all areas of the mouth.

Sex Differences in Dental Decay

Sex differences in percentage DFT/dft for primary, mixed, and permanent dentitions in all areas of the mouth were tested, and no significant differences were found.

Discussion

Children with oral clefts may have greater risk factors for poor oral health than the general population. Risk factors include those related to the cleft itself and/or secondary to surgical repair, such as deficiencies in embryonic tissue to form adequate dental structures, abnormal formation of specific muscles of facial expression, and excess soft tissue scarring leading to impaired circumoral soft tissue movements, oral continence, oral access and hygiene, speech production, and eating difficulties (Trotman et al. 2000; Trotman et al. 2005; Trotman et al. 2007; Barlow et al. 2012). The timing of the primary and secondary surgical repairs (3 to 6 and 9 to 12 mo, respectively; Ziak et al. 2010; Jeyaraj et al. 2014) also coincides with the crown completion of the primary anterior teeth and calcification of the maxillary permanent incisors, which may result in insults to the developing tooth, causing dental anomalies such as hypoplasia and leading to weakened tooth structure (Ash 1993; Howe et al. 2015).

Furthermore, children with clefting may have poor oral hygiene habits due to poor self-motivation, lack of family support, difficulty in cleansing malpositioned teeth, and prolonged use of orthodontic appliances. In addition, they may have increased oral bacterial loads due to oronasal communication

Table 4. Percentage Decayed and/or Filled Teeth in the Mixed Dentition: Primary and Permanent.

	PB (*n* = 255)		SIB (*n* = 167)		CTRL (*n* = 189)		*P* Value[a]		
Area of Mouth	dft/DFT	dt/DT	dft/DFT	dt/DT	dft/DFT	dt/DT	PB-CTRL	SIB-CTRL	PB-SIB
All primary									
Whole	21.7	10.6	15.9	6.3	21.7	14.0	0.66, 0.22	0.11, 0.004	0.03, 0.05
Maxilla	23.4	12.1	15.8	6.8	23.4	16.0	0.71, 0.42	0.06, 0.004	0.01, 0.02
Mandible	16.1	6.2	17.1	5.7	17.1	11.6	0.99, 0.02	0.87, 0.02	0.87, 0.66
Anterior maxilla[b]	13.9	9.8	3.1	2.1	9.1	9.0	0.09, 0.82	—[c]	—[c]
All permanent									
Whole	1.6	1.0	1.4	0.6	1.7	0.4	0.64, 0.56	0.89, 0.95	0.76, 0.62
Maxilla	2.2	0.8	1.5	0.8	2.4	0.5	0.87, 0.61	0.49, 0.78	0.37, 0.45
Mandible	1.2	1.0	1.3	0.4	0.5	0.2	0.57, 0.44	0.06, 0.36	0.12, 0.84
Anterior maxilla[b]	1.1	0.5	0.6	0.2	0.8	0.1	0.54, 0.28	0.59, 0.93	0.26, 0.35
	PB (*n* = 176)		SIB (n = 127)		CTRL (*n* = 95)				
CAUC primary									
Whole	21.1	9.2	16.2	5.0	18.3	13.5	0.33, 0.10	0.68, 0.002	0.09, 0.07
Maxilla	22.5	10.3	16.1	5.6	18.7	14.6	0.34, 0.21	0.54, 0.004	0.07, 0.03
Mandible	17.4	6.0	18.1	5.2	19.0	14.9	0.75, 0.004	0.56, 0.0005	0.74, 0.32
Anterior maxilla[b]	14.0	8.3	2.4	1.1	6.0	6.0	0.11, 1.00	—[c]	—[c]
CAUC permanent									
Whole	1.1	0.7	1.3	0.3	0.2	0.2	0.60, 0.43	0.68, 0.002	0.78, 0.62
Maxilla	1.6	0.7	1.0	0.2	1.4	0.4	0.91, 0.61	0.54, 0.004	0.51, 0.20
Mandible	1.0	0.7	1.5	0.5	0.3	0	0.51, 0.20	0.56, 0.0005	0.11, 0.47
Anterior maxilla[b]	1.2	0.8	0.2	0	0.4	0	0.20, 0.12	0.02, 0.004	0.11, 0.07
	PB (*n* = 79)		SIB (*n* = 40)		CTRL (*n* = 94)				
LAM primary									
Whole	23.0	13.8	14.9	10.2	25.2	14.5	0.98, 0.71	0.18, 0.91	0.15, 0.62
Maxilla	25.3	16.0	15.2	10.6	27.9	17.4	0.93, 0.62	0.12, 0.69	0.11, 0.37
Mandible	13.0	6.6	13.6	7.4	15.0	8.1	0.78, 0.62	0.64, 0.68	0.46, 0.43
Anterior maxilla[b]	13.8	12.8	5.2	5.2	12.2	12.0	0.30, 0.41	0.23, 0.29	0.06, 0.10
LAM permanent									
Whole	2.8	1.672	1.576	1.3	2.6	0.5	0.49, 0.70	0.88, 0.77	0.15, 0.62
Maxilla	3.4	1.114	2.971	2.4	3.5	0.6	0.61, 0.76	0.97, 0.43	0.11, 0.37
Mandible	1.7	1.576	0.83	0	0.7	0.5	0.83, 0.86	0.69, 0.35	0.46, 0.43
Anterior maxilla[b]	1.0	0	1.720	1.1	1.3	0.2	0.83, 0.35	0.84, 0.53	0.06, 0.10

CAUC, Caucasian; CTRL, control; dft/DFT, decayed and filled teeth (primary/permanent dentition); dt/DT, decayed teeth (primary/permanent dentition); LAM, Latin American; PB, proband; SIB, sibling.

[a]*P* values recorded as dft, dt or DFT, DT (as applicable). $P < 1.4$ E-04 (or $P < 0.00014$) indicates significance.

[b]Canine-canine.

[c]Cell size too small for meaningful comparison; only 4 of 167 unaffected siblings with dft, anterior maxilla.

acting as a reservoir for bacteria (Ahluwalia et al. 2004; Weiss et al. 2005; Parapanisiou et al. 2009). This is supported in previous studies using gingival index, plaque scores, bacterial loads of mutans streptococci and lactobacilli, and oral clearance of sugars, which found that children with orofacial clefting have statistically significant increases in these indices as well as dmft/DMFT when compared with controls (Dahllöf et al. 1989; Bokhout et al. 1997; Ahluwalia et al. 2004; Al-Wahadni et al. 2005; Hazza'a et al. 2011; Freitas et al. 2013; Chopra et al. 2014; Sundell, Nilsson, et al. 2015). Therefore, since dental decay is a multifactorial disease related to many of these risk factors, one may hypothesize that children with oral clefts have increased dental decay risk.

Prior dental decay studies provide conflicting results in this population, which may be due to small and unrepresentative samples and variation in decay detection methods, such as the use of radiographs, in-person dental examinations, dental records, and questionnaires, with use of different decay documentation methods (DMFT vs. DFT). Also, little is known about whether relatives of children with clefts carry greater risks for decay than the general population. We provide the largest study to date of dental decay in children with clefts, their relatives, and controls. Our findings indicated no significant differences in dental decay risk for the primary, mixed, and permanent dentitions in case probands or unaffected family members as compared with controls. Furthermore, all differences were small and not always in the direction of greater risk among children with clefts or their relatives versus controls.

In the primary dentition, percentage dft and dt were similar between case probands (7.4% and 5.1%) and controls (7.1% and 6.8%). These rates among cases are much lower than those

Table 5. Percentage of Decayed and/or Filled Teeth in the Permanent Dentition.

	PB (*n* = 215)		SIB (*n* = 209)		PAR (*n* = 1,085)		CTRL (*n* = 868)		*P* Value[a]			
Area of Mouth	DFT	DT	DFT	DT	DFT	DT	DFT	DT	PB-CTRL	SIB-CTRL	PAR-CTRL	PB-SIB
All												
Whole	10.2	3.4	7.2	2.2	22.3	4.9	15.2	3.4	0.007, 0.02	0.10, 0.09	0.001, 0.17	0.007, 0.40
Maxilla	12.5	4.0	8.2	2.7	29.8	6.3	20.5	4.6	0.02, 0.09	0.26, 0.18	0.008, 0.25	0.002, 0.20
Mandible	6.9	2.1	5.7	1.3	12.8	2.6	7.7	1.5	0.003, 0.01	0.009, 0.07	0.003, 0.14	0.18, 0.64
Anterior maxilla[b]	8.3	4.7	3.8	1.6	19.8	5.2	13.3	4.0	0.05, 0.02	0.74, 0.63	0.15, 0.78	0.005, 0.01
	PB (*n* = 98)		SIB (*n* = 124)		PAR (*n* = 636)		CTRL (*n* = 499)					
CAUC												
Whole	10.1	2.4	6.9	2.7	20.9	3.7	16.9	3.07	0.03, 0.26	0.06, 0.007	0.70, 0.26	0.05, 0.67
Maxilla	12.2	3.6	7.7	2.8	27.9	4.5	22.5	4.0	0.04, 0.15	0.10, 0.05	0.41, 0.15	0.03, 0.85
Mandible	7.6	1.0	5.6	2.1	13.4	2.5	10.3	10.3	0.10, 0.90	0.13, 0.01	0.67, 0.90	0.19, 0.41
Anterior maxilla[b]	7.2	3.8	3.4	1.2	18.8	3.8	14.7	3.3	0.26, 0.08	0.42, 0.32	0.75, 0.08	0.12, 0.14
	PB (*n* = 117)		SIB (*n* = 85)		PAR (*n* = 449)		CTRL (*n* = 369)					
LAM												
Whole	10.3	4.3	7.6	1.6	24.4	6.6	12.8	3.9	0.06, 0.04	0.63, 0.78	0.10, 0.44	0.02, 0.13
Maxilla	12.7	4.3	8.9	2.5	33.0	9.0	17.9	5.4	0.15, 0.42	0.94, 0.95	0.25, 0.46	0.002, 0.20
Mandible	6.4	3.0	5.8	0.2	12.0	2.8	4.1	0.9	0.0009, 0.001	0.004, 0.73	0.002, 0.004	0.40, 0.08
Anterior maxilla[b]	9.3	5.4	4.4	2.2	21.4	7.2	11.4	5.0	0.09, 0.18	0.86, 0.92	0.15, 0.24	0.02, 0.11

CAUC, Caucasian; CTRL, control; DFT, decayed and filled teeth (permanent dentition); DT, decayed teeth (permanent dentition); LAM, Latin American; PAR, parent; PB, proband; SIB, sibling.
[a]*P* values recorded as DFT, DT. $P < 1.4$ E-04 (or $P < 0.00014$) indicates significance.
[b]Canine-canine.

in prior studies, which ranged from 26.3% to 91.4%; however, the rates of controls are closer to prior studies, especially for dt (Bokhout et al. 1996, 1997; Bian et al. 2001; Besseling and Dubois 2004; Sundell, Nilsson, et al. 2015). In the permanent dentition of case probands, the percentage DFT and DT in our study (ranging from 6.9% to 12.5%) were also lower than those in previous studies, which ranged from 20% to 96% (Williams et al. 2001; Besseling and Dubois 2004; Kirchberg et al. 2004; Al-Dajani 2009). The high percentage DFT, DT, dft, and dt among probands in prior studies may be due to differences in decay detection and identification. We identified dental decay as visible gross decay predominately via intraoral photographs, similar to visual inspection under World Health Organization guidelines with the added advantage that photographs can be examined multiple times for confirmation. However, some areas of decay that are more accurately detected by tactile examination, such as pit and fissure decay and cavitated hypomineralized areas, may not have been adequately captured in our study (Bokhout et al. 1997; Sundell, Nilsson, et al. 2015; Sundell, Ullbro, et al. 2015). Further discussion regarding decay detection is in the online Appendix.

In examining cleft type, no significant differences were seen in the primary or permanent dentitions in regard to cleft type and decay. This is different from previous studies, which found more decay with cleft lip and palate (Bian et al. 2001; Besseling and Dubois 2004; Mutarai et al. 2008; Britton and Welbury 2010; Moura et al. 2013). Notably, no significant differences in dental decay were found between the cleft area (canine to canine) and the rest of the maxillary dentition. See the online Appendix for further discussion on cleft type.

One possible reason for the lack of significant findings in cleft probands and unaffected relatives in the current study may be explained by plausible opposite biological genetic mechanisms. Some cleft etiologic genes may also have biological roles in tooth formation and enamel mineralization, yet their function is antagonistic. Thus, a genetic variant may be deleterious for cleft risk yet confer protection against caries. Therefore, carriers of such variants may appear to have increased cleft risk yet decreased caries risk. The understanding of the functional overlap among genes acting in different areas of craniofacial development, which may be synergistic or antagonistic, constitutes a challenge for future genotype-phenotype correlation studies. We hope that such studies will shed some light into the complex relations between cleft and decay genetic risk factors. Another explanation may be somewhat related to recruitment of our study population from cleft centers. In these comprehensive care settings, children affected with orofacial clefts and their unaffected family members are educated about oral health and the need for dental care, and they may also receive or be referred for dental treatment. Thus, their seemingly increased caries risk may have been superseded by increased access to dental care, thereby emphasizing the importance and impact of dentists as part of the cleft team. We also adjusted for age differences between cases and controls in the regression analyses of permanent dentition decay, since we found age to be a confounder in the total samples and in the 2 groups defined by self-reported race/ethnicity. However, case-control differences in permanent dentition decay may become more prominent with age with differentially increasing decay risk. Identifying such potential effect heterogeneity requires large samples with longitudinal

data that allow for case-control comparisons at different ages (see discussion in online Appendix).

To consider race/ethnicity as a potential confounder, individuals were classified, ex post, per their self-reported ethnicity into 2 very broad groups: Caucasian versus non-Caucasian Latin American. There are potential errors in such self-reported data and in the aggregation of admixed ancestral backgrounds into very broad groups that could mask finer differences among subgroups within each of these broader groups that reflect different ancestral admixtures (e.g., Hispanic vs. non-Hispanic Whites; different levels of admixture among European, African, and Native ancestries within those who report themselves as non-Caucasian in the Latin American subsample). Therefore, it is possible that our case and control groups differ in their ancestral backgrounds in ways that are not adequately accounted for by these broad categories (see discussion on ethnicity in online Appendix). Although our study provides the largest sample to date (at least twice as large as samples of prior studies), it is not sufficient for a more thorough examination of potential heterogeneity in case-control differences in these dental phenotypes across key factors, such as race/ethnicity, type of clefting, and genetic risks.

From a clinical perspective, characterization of the dental decay phenotype in case probands and their unaffected family members is important to the clinician and to family members to understand possible outcomes related to orofacial clefting and the reparative surgical procedures. Our findings of no increased caries risk in children with clefts and their relatives suggest that oral health prevention approaches implemented by cleft teams can lower the caries risk to that of the general population; as such, this is an encouraging finding from this study. This does not mean that children with clefts do not have unique risk factors affecting oral health. Thus, continuing to identify specific dental decay risk factors in this population via tailored caries risk assessment tools and future genetic studies will be important for developing targeted prevention strategies and overcoming decay risk in susceptible populations.

Author Contributions

B.J. Howe, M.E. Cooper, S.M. Weinberg, M.L. Marazita, L.M. Moreno Uribe, contributed to conception, design, data acquisition, analysis, and data interpretation, drafted and critically revised the manuscript; J.M. Resick, N.L. Nidey, L.C. Valencia-Ramirez, A.M. Lopez-Palacio, D. Rivera, A.R. Vieira, contributed to conception, design, and data acquisition, drafted and critically revised the manuscript; G.L. Wehby, contributed to conception, design, and data interpretation, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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