

Deciduous-dentition malocclusion predicts orthodontic treatment needs later: Findings from a population-based birth cohort study

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Introduction: Estimating orthodontic treatment need in the permanent dentition using information from the deciduous-dentition malocclusion may assist in defining the time for appropriate orthodontic intervention. Our objective was to investigate whether malocclusion in the deciduous teeth predicts orthodontic treatment need in the permanent dentition. **Methods:** Two oral health studies nested in a birth cohort were carried out at ages 6 ($n = 359$) and 12 ($n = 339$) years. Open bite, crossbite, and canine malocclusion were assessed in the deciduous teeth. Orthodontic treatment need was determined in the permanent dentition using the dental esthetic index. Prevalence ratios were estimated using 2 dental esthetic index cutoff points: highly desirable/mandatory orthodontic treatment and only mandatory orthodontic treatment. We tested all combinations of the deciduous malocclusion and the outcomes, controlling for confounders. **Results:** Children with only open bite and those with concurrent open bite and canine malocclusion were more likely to have either highly desirable/mandatory orthodontic treatment or only mandatory orthodontic treatment needs by age 12. The combination of crossbite and open bite in the deciduous teeth was associated with the highest risk of need for mandatory orthodontic treatment. **Conclusions:** Malocclusion in the deciduous teeth is a risk factor for orthodontic treatment need in the permanent dentition. Children with malocclusion at a young age should be monitored regularly, and caregivers may be able to better prepare for possible orthodontic treatment. (Am J Orthod Dentofacial Orthop 2015;147:492-8)

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Severe malocclusion in the permanent dentition has been associated with bullying,¹ poorer oral health-related quality of life,² and self-dissatisfaction with appearance characteristics.³ Malocclusion in the permanent dentition can be measured indirectly through the estimation of treatment need. For example, the dental aesthetic index (DAI) was developed as an indicator of the social acceptability of occlusal conditions and as a screening tool to assist in prioritizing the need for orthodontic treatment, thereby assisting in the allocation of scarce public resources.⁴

Our understanding of the complex and multifactorial etiology of malocclusion remains limited. Skeletal pattern, genetically determined, is considered its most important determinant.⁵ On the other hand, anthropologic studies on secular trends suggest that environmental factors—for instance, changes in feeding habits toward a more refined diet, premature deciduous tooth loss caused by caries,⁶ nonnutritive sucking habits,⁷ bottle feeding,^{7,8} and early weaning⁷—also contribute to variations in occlusal traits.^{6,9} Moreover, a few cohort studies have suggested that malocclusion in the deciduous dentition is a determinant of a permanent-dentition malocclusion.¹⁰⁻¹² For example, an Angle Class I molar relationship was found

to be more common among Nigerian children who had had an initially flush terminal plane and mesial step relationships in the deciduous dentition.¹⁰

Identification and classification of the risk for orthodontic treatment need in the permanent dentition using information on deciduous-dentition malocclusions may assist in defining the most appropriate intervention stage and providing the appropriate orthodontic therapy, thereby minimizing costs. The few studies that have investigated whether a deciduous-dentition malocclusion is a risk factor for malocclusion or need for orthodontic treatment in the permanent dentition have not controlled for confounding using multivariable analysis or taken life-course characteristics into account.¹⁰⁻¹² Moreover, they have not investigated the role of the number and type of different deciduous-dentition malocclusions. The most favorable research design for investigating such issues is a prospective cohort study.

The aim of this study was to investigate whether malocclusion in the deciduous dentition is a risk factor for orthodontic treatment need in the permanent dentition using a prospective longitudinal approach.

MATERIAL AND METHODS

The Pelotas 1993 birth cohort is a study of a cohort of babies born in 1993 in Pelotas in southern Brazil. The study was developed to evaluate the trends in maternal and child health indicators, and to assess the associations between early life variables and later health outcomes. In 1993, all hospitals in Pelotas were monitored daily by the research team, and mothers of all 5265 newborns were invited to join a prospective study.¹³ Of these, 5249 (99.6%) agreed to take part in the study. Soon after delivery, the mothers were interviewed about demographic, socioeconomic, and health-related characteristics. The children were weighed, measured, and examined at birth by a team of doctors and medical students. For the 1-month and 3-month visits, a systematic sample of 13% of the cohort participants was randomly selected and also followed at 6 months, 1 year, and 4 years. In 1998, a sample of 1460 eligible children from the original cohort was reassessed at age 5. Of them, 87% (1270 children) were located. In 2004, all cohort members were again sought for a follow-up visit at age 11 years. The home visits included questionnaires administered to mothers and anthropometric assessments of the children. The details of the methodology have been described elsewhere.¹³

The first dental assessment of the cohort participants was carried out at age 6 in a sample of 400 children, randomly selected from a follow-up study ($n = 1270$) conducted in 1998. Because the proportion of low birth

weight children in the follow-up study was 29.7% (in the original cohort, it was 9.7%), it was necessary to calculate a weighting factor to perform the statistical analysis. Accordingly, a weighting factor of 0.34 was used for children with low birth weight, and 1.27 was applied for the others.

The sample size was calculated to estimate prevalence; the sample size calculation and the power to test associations were done a posteriori and have been shown to be sufficient to test hypotheses related to early life influences on dental emergence, dental caries, and malocclusion.¹⁴⁻¹⁶

A pilot study involving 40 children was carried out before the fieldwork. All dental examinations were performed between December 1998 and July 1999 at the children's homes by 3 dentists and 3 interviewers. Scores for the measures of agreement, calculated on a tooth-by-tooth basis,¹⁷ were high (minimum kappa value was 0.7). The 1997 World Health Organization criteria were used for diagnosing dental caries in deciduous teeth.¹⁸ In addition, the occlusion was also examined.¹⁶ Malocclusion was considered as the presence of (1) open bite (lack of contact between mandibular and maxillary central incisors when in centric occlusion), (2) unilateral or bilateral crossbite (at least 1 tooth) considered as reverse buccal overjet with or without a midline shift, and (3) bilateral deciduous canine relationships (Class I, Class II, and Class III), according to the criteria of Foster and Hamilton.¹⁹ Children who had lost their anterior teeth were excluded from the sample. The participation rate was 89.7% ($n = 359$). Nonresponses were mainly due to families having moved out of the city.

All 359 children who were assessed at age 6 were visited at their homes, dentally examined, and interviewed in 2005, when they were 12 years old. Dental caries diagnosis followed the World Health Organization criteria.¹⁸ In addition, the criteria of the DAI were adopted for the recording of malocclusion characteristics and the normative need for orthodontic treatment.¹⁸ Headlamps were used to improve visualization.

A structured interview was undertaken; this included questions about use of dental services (time since last visit, types of dental services, orthodontic treatment) and oral behaviors (toothbrushing, flossing).

A pilot study was carried out with 40 children who did not participate in the main study. The fieldwork team included 4 pairs of examiners and interviewers. Calibration was performed among the 40 children aged 11 to 13 years following methods previously described.¹⁷ Interexaminer reliability was measured using simple and weighted kappa statistics (categorical variables) and intraclass correlation coefficients (numeric variables). The minimum reliability score was 0.6 for gingival bleeding (not assessed in this study), and most values were 1.0.

Table I. Sample distribution, DAI ≥ 31 (prevalence [P 95% CI] and prevalence ratio [PR 95% CI]) according to socio-demographic, anthropometric, and dental status (N = 339)

Variable	n (%)	P (95% CI)	PR (95% CI)*
All	339 (100.0)	18.5 (14.0-23.1)	-
Sex			
Male	182 (54.8)	18.1 (12.5-23.8)	1
Female	157 (55.2)	19.1 (12.9-25.3)	1.0 (0.6-1.6)
Skin color			
White	270 (80.0)	17.0 (12.5-21.6)	1
Black	69 (20.0)	24.6 (14.2-35.1)	1.3 (1.1-1.5)
Head circumference at birth (percentile)			
>10	230 (79.6)	18.7 (13.6-23.8)	1
≤ 10	104 (20.4)	19.2 (11.5-26.9)	1.0 (0.6-1.8)
Maternal schooling level at childbirth (y)			
>4	260 (74.1)	17.9 (9.2-26.7)	1
≤ 4	78 (25.9)	18.8 (14.1-23.6)	1.0 (0.5-1.6)
Untreated carious teeth at age 12 (n)			
0	200 (61.1)	17.0 (11.7-22.3)	1
1	64 (17.8)	23.4 (12.8-34.1)	1.6 (0.9-3.0)
2	33 (9.1)	12.1 (0.4-23.9)	1.1 (0.4-2.8)
3 or more	42 (12.0)	23.8 (10.4-37.2)	1.6 (0.8-3.1)
Dental visit in the last year at age 12			
Yes	157 (46.8)	19.1 (12.9-25.3)	1
No	182 (56.2)	18.1 (12.5-23.8)	0.9 (0.6-1.5)
Orthodontic treatment by age 11			
Yes	23 (7.3)	19.1 (12.9-25.3)	1
No	316 (92.7)	18.1 (12.5-23.8)	3.0 (0.6-14.6)
Malocclusion in deciduous dentition [†]			
Any malocclusion	203 (61.1)	22.2 (15.9-28.4)	1.1 (1.0-2.9)
Only open bite	109 (43.7)	27.7 (18.3-37.1)	2.1 (1.2-3.8)
Only crossbite	17 (12.8)	-	-
Only canine malocclusion [‡]	15 (10.2)	9.8 (7.3-27.0)	0.8 (0.1-3.8)
Open bite + crossbite	23 (15.0)	17.6 (0.6-35.7)	1.3 (0.5-4.0)
Open bite + canine	18 (10.8)	32.3 (5.5-57.5)	2.4 (1.0-5.9)
Canine + crossbite	8 (4.6)	-	-
Open bite + crossbite + canine	13 (8.1)	32.3 (1.6-66.2)	2.5 (0.9-7.0)

*Bivariate analysis; [†]reference categories: absence of the analyzed malocclusion; [‡]canine relationships on the right and left sides (Class II and Class III).

Intraexaminer reliability was not assessed because of logistical and ethical constraints, as described in detail elsewhere.²⁰

Statistical analysis

Poisson regression models were performed, and prevalence ratios were estimated using the dichotomized DAI as the outcome according to 2 criteria: highly desirable/mandatory orthodontic treatment (DAI ≥ 31) and only mandatory orthodontic treatment (DAI ≥ 36).¹⁸ We tested the association between both outcomes and the various combinations of deciduous-dentition malocclusions: (1) any malocclusion; (2) open bite only; (3) crossbite only; (4) Class II and Class III canine malocclusion only; (5) open bite and crossbite; (6) open bite and canine malocclusion; (7) crossbite and canine malocclusion; and (8) open bite, crossbite, and canine

malocclusion. The reference category for all combinations investigated was no malocclusion. Sex, skin color, head circumference at birth (>10th or ≤ 10 th percentile), maternal schooling (<4 or ≥ 4 years of schooling), number of untreated carious teeth (using the index of decayed, missing, and filled permanent teeth: 0, 1, 2, ≥ 3) at age 12, dental visit in the last year at age 12 (yes, no), and history of orthodontic treatment (no, yes) were controlled for in the analyses. The independent variables were included in the model, assuming that more distal factors (anthropometric and socioeconomic conditions) determined intermediate (dental caries) and proximal (dental visit and orthodontic treatment) conditions.²¹ Poisson regression is recommended in cross-sectional studies when the frequency of the binary outcome measured is higher than 20%; in such cases, the odds ratio estimated using logistic regression tends to overestimate the prevalence ratio.²²

Table II. DAI ≥ 36 (prevalence [P 95% CI] and prevalence ratio [PR 95% CI]) according to sociodemographic, anthropometric, and dental status (n = 339)

Variable	P (95% CI)	PR (95% CI)*
All	9.1 (8.8-9.4)	-
Sex		
Male	9.3 (5.1-13.6)	1
Female	8.39 (4.4-13.4)	0.9 (0.5-2.1)
Skin color		
White	8.5 (5.2-11.9)	1
Black	11.6 (3.8-19.3)	1.2 (0.9-1.7)
Head circumference at birth (percentile)		
>10	9.1 (5.4-12.9)	1
≤ 10	9.6 (3.9-15.4)	1.0 (0.4-2.4)
Maternal schooling level at childbirth (y)		
>4	9.0 (2.5-15.5)	1
≤ 4	9.2 (5.7-12.8)	1.0 (0.4-2.2)
Untreated carious teeth at age 12 (n)		
0	9.5 (5.4-13.6)	1
1	6.3 (0.2-12.3)	1.1 (0.4-3.2)
2	6.1 (0.1-14.7)	1.1 (0.3-4.5)
3 or more	14.3 (3.2-25.3)	1.9 (0.7-4.9)
Dental visit in the last year at age 12		
Yes	10.2 (5.4-15.0)	1
No	8.2 (4.2-12.3)	0.8 (0.4-1.6)
Orthodontic treatment by age 11		
Yes	8.7 (0.1-21.1)	1
No	9.2 (6.0-12.4)	1.4 (0.3-6.8)
Malocclusion in deciduous dentition [†]		
Any malocclusion	12.4 (7.4-17.3)	4.4 (1.3-12.4)
Only open bite	14.7 (6.9-21.5)	4.6 (1.4-14.6)
Only crossbite	-	-
Only canine malocclusion [‡]	7.8 (0.1-24.5)	2.5 (0.3-22.2)
Open bite + crossbite	12.2 (3.2-27.6)	4.3 (1.0-19.2)
Open bite + canine	29.5 (3.7-55.2)	9.5 (2.5-35.6)
Canine + crossbite	-	-
Open bite + crossbite + canine	10.8 (0.1-33.7)	3.5 (0.4-29.5)

*Bivariate analysis; [†]Reference categories: absence of the analyzed malocclusion; [‡]Canine relationships on the right and left sides (Class II and Class III).

Ethical issues

Consent for the interviews and the examinations was obtained, and both projects were approved by the Pelotas Federal University Ethics Committee. Adolescents with dental treatment needs were referred to the dental clinic of the postgraduate dentistry program of Pelotas Federal University. This study followed the guidelines for strengthening the reporting of observational studies in epidemiology.²³

RESULTS

A total of 339 adolescents (age, 12 years) were examined and interviewed in 2005, representing 94.4% of those investigated at aged 6. Over half of the adolescents were male, and one-fifth were classified as having black

skin. About three-quarters of the mothers had received a school education longer than 4 years. More than half of the adolescents were free of caries, and 1 in 8 had 3 or more untreated dental caries lesions. Only a small proportion had had previous orthodontic treatment. More than half had some type of malocclusion in the deciduous dentition. The presence of only open bite was the most prevalent occlusal condition in the deciduous teeth, whereas concurrent crossbite and canine malocclusion had the lowest prevalence (Table I). The presence of any malocclusion, only open bite, and concurrent open bite and canine malocclusion in the deciduous dentition were positively associated with highly desirable/mandatory treatment need (DAI ≥ 31) (Table I) and only mandatory treatment need (DAI ≥ 36) (Table II). The presence of concurrent open bite and crossbite was associated with only mandatory treatment need (Table II).

Unadjusted and adjusted Poisson regression analyses for the association between open bite in the deciduous dentition and highly desirable/mandatory need as well as only mandatory treatment need are presented in Table III. A positive association was found between only open bite and both outcomes after controlling for potential confounders. The prevalence of highly desirable orthodontic treatment need in children with only open bite in the deciduous dentition was 2 times higher than in children with no malocclusion. Children with only open bite in the deciduous dentition were almost 5 times more likely to need mandatory orthodontic treatment than children with no malocclusion. The association between open bite and canine malocclusion in the deciduous dentition with need for highly desirable/mandatory treatment need persisted after controlling for demographic characteristics, socioeconomic status, untreated dental caries, dental visits, and past orthodontic treatment by age 12. The amount of variance in the outcomes explained by the final models ranged from 3.5% (open bite \times DAI ≥ 31) to 25.9% (open bite and canine malocclusion \times DAI ≥ 36) (Table III).

The same modeling was repeated for any malocclusion in the deciduous dentition and the outcomes; in each case, there was a strong association: ie, those with any malocclusion in the deciduous dentition were significantly more likely to require mandatory treatment in the permanent dentition (Table IV). When concurrent open bite and crossbite in the deciduous dentition and need for mandatory treatment in the permanent dentition were evaluated, we observed a strong association, which remained after adjusting for confounding; the need for mandatory treatment was almost 4 times greater than among those without concurrent open bite and crossbite in the deciduous dentition (Table IV). The amount of

Table III. Multivariable models (prevalence ratio [PR]) between only open bite and open bite and canine malocclusion in deciduous dentitions and highly desirable/mandatory orthodontic treatment (DAI ≥31) and only mandatory orthodontic treatment (DAI ≥36)

Model	Variable	DAI ≥31		DAI ≥36	
		PR (95% CI)	Pseudo R ²	PR (95% CI)	Pseudo R ²
Only open bite					
1	Only open bite	2.1 (1.2-3.8)	0.0304	4.6 (1.4-14.6)	0.0730
2	Model 1 + head circumference at birth	2.1 (1.2-3.8)	0.0324	4.6 (1.5-14.6)	0.0762
3	Model 2 + sex	2.1 (1.2-3.8)	0.0333	4.6 (1.5-14.4)	0.0772
4	Model 3 + maternal schooling	2.1 (1.2-3.9)	0.0338	4.7 (1.5-14.9)	0.0777
5	Model 4 + untreated carious teeth at age 12	2.0 (1.1-3.6)	0.0352	4.5 (1.4-14.0)	0.0779
6	Model 5 + dental visit	2.0 (1.1-3.6)	0.0354	4.5 (1.5-14.0)	0.0789
7	Model 6 + orthodontic treatment	2.0 (1.1-3.6)	0.0355	4.6 (1.5-14.2)	0.0840
Open bite and canine malocclusion					
1	Open bite and canine malocclusion	2.4 (1.0-5.9)	0.0549	9.5 (2.5-35.6)	0.1754
2	Model 1 + head circumference at birth	2.5 (1.0-6.1)	0.1463	9.6 (2.5-37.9)	0.1841
3	Model 2 + sex	2.5 (1.0-6.2)	0.2344	9.2 (2.3-37.3)	0.1855
4	Model 3 + maternal schooling	2.6 (1.0-6.4)	0.3375	9.1 (2.3-36.0)	0.1860
5	Model 4 + untreated carious teeth at age 12	2.6 (1.1-6.5)	0.4180	10.2 (2.7-38.3)	0.2225
6	Model 5 + dental visit	2.6 (1.0-6.6)	0.5519	10.9 (2.8-41.5)	0.2285
7	Model 5 + orthodontic treatment	2.8 (1.1-6.8)	0.0776	12.0 (3.4-45.3)	0.2592

Table IV. Multivariable models (prevalence ratio [PR]) between prevalence of any malocclusion (open bite, crossbite, or canine malocclusion) and open bite and crossbite in deciduous dentition and highly desirable/mandatory orthodontic treatment (DAI ≥31) and only mandatory orthodontic treatment (DAI ≥36)

Model	Variable	DAI ≥31		DAI ≥36	
		PR (95% CI)	Pseudo R ²	PR (95% CI)	Pseudo R ²
Any malocclusion					
1	Any malocclusion	1.7 (1.0-2.9)	0.0152	4.1 (1.3-12.4)	0.0509
2	Model 1 + head circumference at birth	1.7 (1.0-2.9)	0.0157	4.1 (1.3-12.4)	0.0517
3	Model 2 + sex	1.7 (1.0-2.9)	0.0157	4.1 (1.3-12.4)	0.0519
4	Model 3 + maternal schooling	1.7 (1.0-3.0)	0.0157	4.1 (1.4-12.7)	0.0520
5	Model 4 + untreated carious teeth at age 12	1.6 (1.0-2.9)	0.0158	4.0 (1.3-12.0)	0.0522
6	Model 5 + dental visit	1.6 (0.9-2.9)	0.0160	4.1 (1.4-12.2)	0.0549
7	Model 6 + orthodontic treatment	1.7 (0.9-2.9)	0.0205	4.1 (1.4-12.2)	0.0551
Open bite and crossbite					
1	Open bite and crossbite malocclusion	1.4 (0.5-3.9)*	-	4.3 (1.0-18.1)	0.0553
2	Model 1 + head circumference at birth	-	-	4.4 (1.0-18.1)	0.0692
3	Model 2 + sex	-	-	3.9 (0.9-17.3)	0.0988
4	Model 3 + maternal schooling	-	-	3.7 (1.0-14.0)	0.1043
5	Model 4 + untreated carious teeth at age 12	-	-	4.6 (1.4-15.5)	0.1157
6	Model 5 + dental visit	-	-	3.8 (1.3-11.5)	0.1795
7	Model 6 + orthodontic treatment	-	-	4.7 (1.5-14.1)	0.2207

*P = 0.482 (Wald test: not statistically significant).

variance in the outcomes explained by the final models ranged from 2.1% (any malocclusion × DAI ≥31) to 22.1% (open bite and crossbite × DAI ≥36) (Table III).

DISCUSSION

The findings from this prospective cohort study underpin the hypothesis that after controlling for confounders, malocclusion in the deciduous teeth at age 6

is a risk factor for orthodontic treatment need in the permanent dentition. Children with only open bite and those with concurrent open bite and canine malocclusion in the deciduous dentition had a greater need for both highly desirable and mandatory orthodontic treatment by age 12 than did children with no malocclusion at age 6. Moreover, the combination of crossbite and open bite in the deciduous teeth was associated with mandatory orthodontic treatment need by age 12.

Previous research has suggested that the type of dentition is associated with the severity of malocclusion in the permanent teeth,²⁴ whereas other authors have suggested that occlusal pattern in the deciduous dentition is related to occlusal relationship in the mixed dentition.^{25,26} Only a few studies have investigated the relationship between malocclusion in the deciduous dentition as a risk factor for malocclusion in the permanent dentition with a prospective design.^{10,11} Of those, most neither performed multivariable regression modeling to control the role of confounders nor evaluated the influence of the different types of malocclusion in the deciduous dentition on the later malocclusion.

We observed no association of socioeconomic status with malocclusion. This reinforces the findings from several studies that have emphasized the role of genetics, sucking habits, and dental caries as the main determinants of malocclusion.^{16,27} The final model of the association between open bite and canine malocclusion and DAI ≥ 36 explained 25.9% of the outcomes, and the association between open bite and crossbite and DAI ≥ 36 explained 22.1%; these should be considered high.

Orthodontic interventions normally take less time and are less expensive the earlier they are done in life; however, the effectiveness of early orthodontic intervention in the deciduous and mixed dentitions is not well established. No systematic review has investigated simultaneous orthodontic intervention in several types of malocclusion in the deciduous or mixed dentition on malocclusion in the permanent dentition. Systematic reviews report only weak evidence that early orthodontic or orthopedic interventions are effective in correcting open bite²⁸ and posterior crossbite.²⁹ Therefore, there is no clear recommendation that early intervention would be beneficial. On the other hand, there is a clear indication that those with a malocclusion in the deciduous dentition should be monitored during their adolescence.

This study highlights an important relationship between open bite in the deciduous dentition and subsequent orthodontic treatment need in the permanent dentition, with a stronger association when open bite and canine malocclusion are concurrent, suggesting a skeletal developmental etiology. Further investigation on the effectiveness of early orthodontic or orthopedic intervention in several types of malocclusion in the deciduous and mixed dentitions may improve our understanding of this complex association.

This study had some limitations. The sample size was relatively small, making the detection of relatively small differences difficult. Another issue was that the DAI is more a socially derived esthetic index than an index of malocclusion; however, the DAI has long been

recommended by the World Health Organization as a tool for estimating orthodontic treatment needs at the population level, reflecting the mainly social imperative that underlies most orthodontic-treatment seeking and provision.¹⁸ On the other hand, this is one of the few studies in oral health that have followed a sample of a multidisciplinary population-based birth cohort. Several waves of this cohort were undertaken, all with high participation rates; international standardized methodologic procedures were adopted, and the examiners had a high diagnostic reliability and were blinded to the research question under study. We also estimated the association between deciduous-dentition malocclusion and DAI using Poisson regression analysis to prevent overestimation. For example, the overestimation of the measures of association when logistic regression was run varied from 10% (full model of any malocclusion and DAI ≥ 31) to 35% (full model of open bite and canine malocclusion and DAI ≥ 31). Therefore, recall, selection, and interview biases have been minimized. Finally, the low access to orthodontic treatment in the studied population allowed us to identify the “natural history” of malocclusion from ages 6 to 12 years.

CONCLUSIONS

Children with a malocclusion that is apparent at a young age should be monitored more frequently as their permanent teeth emerge, so that parents or caregivers can better prepare for possible orthodontic treatment. Also, further studies are necessary to better understand the relationship of each type of malocclusion to orthodontic need. The changes in malocclusion from the deciduous to the permanent dentition highlight the need for longitudinal tracking. Since it is difficult to prevent malocclusion, more effort should be directed toward early effective treatment.

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