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ORIGINAL ARTICLE

# Dental development in patients with and without unilateral cleft lip and palate (UCLP): a case control study

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## Abstract

**Objective** To evaluate if the presence of unilateral cleft lip and palate (UCLP) causes delay in dental age and tooth development.

**Materials and methods** Panoramic radiographs of 189 non-syndromic UCLP patients, aged from 6 to 20 years, were collected. Two measures of tooth development were examined: dental maturity scale for the seven left mandibular teeth (dental age—DA) and the degree of each tooth development (developmental score—DS). All the teeth except third molars were staged according to the Demirjian's method. The data of the cleft group were compared with a control group matched for age and gender, based on the findings observed in other 189 panoramic radiographs.

**Results** At all ages, DA was lower in the UCLP group, but not always significantly; the highest difference was − 1.411 for females at 13 years old and − 0.776 for males at 12 years old. DS of all teeth was significantly lower in the UCLP group, at all ages under 17 in females, and at all ages under 18 in males. In UCLP group, tooth development was more delayed in the maxilla compared with the mandible. No evidence of a slower development at the cleft side compared with the non-cleft side was highlighted.

**Conclusions** Significant lower dental development was observed in UCLP patients compared with control ones by using DS and DA indexes.

**Clinical relevance** These findings can help the clinicians in establishing a proper orthodontic and surgical diagnosis and treatment planning in UCLP patients and for forensic age estimation's purposes.

**Keywords** Dental age · Tooth development · Cleft lip and palate · Panoramic radiograph

## Introduction

Craniofacial anomalies such as cleft lip and palate are among the most prevalent of all congenital disorders. Orofacial clefts have a worldwide frequency of 1 in 700 newborns, with a reported prevalence of 1.47/1000 in the Netherlands and Belgium [1]. Cleft patients encounter dental, hearing, speech, psychological, and esthetic problems. Moreover, a higher prevalence of severe tooth anomalies is observed. In particular, abnormal tooth formation, enamel hypoplasia, and tooth agenesis often occur in these patients. The same etiological factors inducing the formation of the cleft can also have an effect on tooth development [1–4].

In orthodontic treatment planning, dental development is of major clinical importance to accurately estimate the timing of the orthodontic intervention(s). Moreover, in cleft patients, surgical timing for alveolar bone grafting is based on dental development, not on chronological age [5–8]. An accurate evaluation of tooth development enables not only a better surgical planning, with the aim of limiting the amount of required surgeries but also the age estimations based on dental development for forensic purpose.

The staging technique described by Demirjian et al. allows to register and classify dental development of each singular tooth [9]. When multiple teeth are developing, the degree of dental development can be established by calculating a

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developmental score (DS). This procedure was described by Thevissen et al., registering and quantifying the degree of dental development of all four third molars [10]. This approach can be also adapted to specific group of developing teeth of interest.

An additional method to evaluate the dental maturity scale for the seven left mandibular teeth in a single individual is to estimate its related dental age (DA). Various methods to estimate dental age were established [9, 11–13]. The DA index can be compared between different patients (or groups of patients) to evaluate the cause-effect relationship between a specific characteristic (e.g., the presence of absence of cleft palate) and the dental development.

Previous research concerning tooth development in cleft patients suggested a delayed dental development [14–17]. However, no clear conclusions can be drawn since the methodology of these studies shows a lot of variation. Many investigations gathered different cleft types in their study sample, while the etiological factors of the different cleft severities might have varying influences on the cleft region and consequently, could affect dental maturity at different levels. To reduce these potentially disturbing factors and to allow fair comparisons in future research, the current study was limited to patients with complete unilateral cleft lip and palate (UCLP) [17]. Patients with other types of clefts (incomplete lip clefts, unilateral cleft lip and alveolus, bilateral or palatal clefts) and patients with clefts in the context of a syndrome or with relevant medical problems were excluded.

The aim of this study was to analyze the dental development and dental age in a group of non-syndromic children with complete UCLP and compare them with a control group with age- and gender-matched children without this condition.

## Materials and methods

This study was registered and approved by the Medical Ethics Committee of the University Hospitals Leuven, with the registration number S56474.

### Patient selection

Paper archives of the Dental department of the University Hospitals as well as the electronic files were retrospectively screened for all patients who had at least one consultation with the orofacial cleft care team between 1974 and 2018. In our hospital, the patient's report at intake contains complete information regarding the type of cleft. Furthermore, every patient included in the orofacial cleft care program was seen at least once by the department of human genetics. The report of this consultation was examined and screened for the presence of possible syndromes. Based on these reports, non-syndromic, Caucasian patients with complete UCLP were selected. Selected UCLP patients were included in the study when at least one panoramic radiograph of good image quality was available. If UCLP patients had multiple radiographs available, the selected one was from the age category of which, at that moment, the lowest number of subjects had been included. The retrospective screening on UCLP patients was performed by two observers independently. Disagreements during the patient selection were resolved by discussion and consensus. When disagreements remained, patients were excluded.

Data were compared with a non-cleft control group of the same Caucasian population (189 patients), matched for identical chronological age (date panoramic radiograph minus date of birth) and gender. Appendix Fig. 5 contains a case selection flowchart.

We retrospectively selected patients complying with our selection criteria for both the UCLP and control groups by analyzing the medical files of treated patients until we gather a sample big enough to obtain representative radiographic results, following the indications of previous studies (Appendix Table 5).

### Data collection methods and statistical analysis

Parameters extracted from the patient's records were gender, date of birth, number and date of panoramic radiographs taken, cleft side, agenesis of teeth, and any aberrance such as hypoplasia.

Two measures of tooth development were examined: the dental maturity scale for the seven left mandibular teeth (dental age—DA) and a degree of tooth development (developmental score—DS). Therefore, all teeth except third molars were staged according to the eight-stage technique of Demirjian et al. [9]. Both the UCLP group and the control group were staged by the same observer once, after training with an experienced operator. A tooth was not scored if it was not visualized accurately due to, e.g., overlap of other structures.

#### Dental age

The stages of the seven left mandibular permanent teeth (except the third molar) were used to calculate dental age according to the age estimation method of Demirjian et al. [9]. A linear regression model with dental age as dependent variable and group and age as predictors was used to assess differences in dental age between UCLP and control patients. The trend of the DA over chronological age takes a rather curved or non-linear shape. To be able to flexibly model this specific curve, restricted cubic splines (with 5 knots) were used in the regression model [18–20]. Additionally, an interaction between age and group was included in the model allowing the difference between groups to depend on age. Also, in the interaction,

cubic splines were used to model age, allowing the curves for both groups to take different shapes. The analysis was performed separately for males and females.

In the UCLP group, 18 observations were missing for dental age, whereas there were no missing observations in the control group. This was due to agenesis (16 of the 18 values were lower second premolars) or lack or accurate visualization. To account for this imbalance, we used a linear regression model to predict the dental age for these patients based on the Demirjian scores for the teeth on the opposite side of the mandible, the chronological age, and group. The regression model resulted in an *R*-squared of 0.98 indicating a very good predictive quality. Hence, the analysis included all patients in both groups.

### Degree of dental development

The analysis was performed in two phases. First, we quantified on subject level the degree of development, using information from all teeth (except third molars). Second, we analyzed the difference between UCLP and control patient with respect to the degree of development.

A linear mixed model was used for the first phase, with the Demirjian stage as the outcome variable, a fixed effect for tooth and a random subject effect. For each subject, the empirical Bayes estimate of the random effect was obtained, which summarizes the developmental stages of all teeth in a single developmental score (DS), thereby also handling the presence of missing values. The DS is a normal distributed variable (*z*-score) with mean and standard deviation respectively equal to zero and one. A DS equal to zero corresponds to a subject with an average developmental level in the current study. A similar approach was used in Thevissen (2010) and Lebbe (2017) [10, 21, 22].

In the second phase, a linear regression model with the DS as dependent variable and age and group as predictors were used to evaluate differences in degree of development between UCLP and control patients. An interaction between age and group was included in the model allowing the difference between groups to depend on age. Inclusion of a quadratic term for age permitted deviations from linearity. The analysis was performed separately for males and females.

The studied tooth groups were: all teeth, maxillary teeth, mandibular teeth, teeth at the cleft side, and teeth at the non-cleft side (except third molars), which enabled to investigate the degree of dental development overall, in the maxilla, in the mandible, at the cleft side, and the non-cleft side, respectively.

All statistical analyses were performed using SAS software, version 9.4 of the SAS System for Windows. *P* values $< 0.05$ were considered statistically significant.

## Results

The descriptive data of the study sample are summarized in Table 1. Both the UCLP group and the control group consisted of 189 patients, aged from 6 to 20 years. The groups comprised 129 boys and 60 girls, with a mean chronological age of 12.7 years ± 4.32 (ranging from 5.6 to 20.7 years). The cleft was left sided in 65.61% of UCLP patients. Tooth agenesis occurred in 58.73% of UCLP patients compared with only 3.7% of control patients. Hypoplasia was seen in 24.87% of UCLP patients and in 0.53% of control patients.

### Dental age

The difference in dental age between UCLP and control patients depends on chronological age of males and females (significant interaction). Figure 1 presents the evolution of dental age over the chronological age in both groups. At almost all ages, the dental age was lower in the UCLP group. However, not at all ages the difference was statistically

**Table 1** Descriptive data of the study sample

| Variable | Statistic | Control (*N* = 189) | UCLP (*N* = 189) |
|---|---|---|---|
| Gender | | | |
| F | *n* (%) | 60 (31.75%) | 60 (31.75%) |
| M | *n* (%) | 129 (68.25%) | 129 (68.25%) |
| Chronological age | Mean | 12.7 | 12.7 |
| | Std | 4.32 | 4.32 |
| | Median | 12.2 | 12.2 |
| | IQR | (8.9; 16.6) | (8.9; 16.6) |
| | Range | (5.6; 20.7) | (5.6; 20.7) |
| Cleft side | | | |
| Right | *n* (%) | | 65 (34.39%) |
| Left | *n* (%) | | 124 (65.61%) |
| Agenesis (≥ 1 tooth missing) | | | |
| No | *n* (%) | 182 (96.30%) | 78 (41.27%) |
| Yes | *n* (%) | 7 (3.70%) | 111 (58.73%) |
| Number of missing teeth | | | |
| 0 | *n* (%) | 182 (96.30%) | 78 (41.27%) |
| 1 | *n* (%) | 5 (2.65%) | 72 (38.10%) |
| 2 | *n* (%) | 2 (1.06%) | 21 (11.11%) |
| 3 | *n* (%) | 0 (0.00%) | 7 (3.70%) |
| 4 | *n* (%) | 0 (0.00%) | 5 (2.65%) |
| 5 | *n* (%) | 0 (0.00%) | 4 (2.12%) |
| 6 | *n* (%) | 0 (0.00%) | 1 (0.53%) |
| 9 | *n* (%) | 0 (0.00%) | 1 (0.53%) |
| Hypoplasia | | | |
| No | *n* (%) | 189 (99.47%) | 142 (75.13%) |
| Yes | *n* (%) | 1 (0.53%) | 47 (24.87%) |

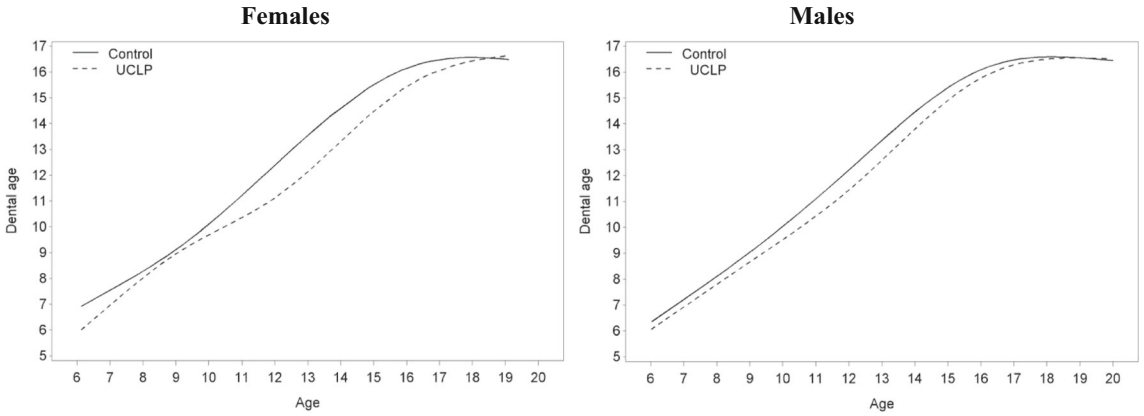


**Fig. 1** Dental age by chronological age in UCLP and control patients (seven left mandibular teeth)

significant. Table 2 presents the mean difference in dental age between the control group and the UCLP group, per age category of 1 year, separate for females and males. The highest difference in dental age was − 1.411 for females at 13 years old and − 0.776 for males at 12 years old.

## Dental development

### All teeth, except third molars

The difference in degree of dental development between UCLP and control patients depends on age: the DS was significantly lower in the UCLP group compared with the control group at all ages under 17 in females, and at all ages under 18 in males (Fig. 2 and Table 3).

### Mandible vs maxilla

Results based on upper and lower jaw separately are similar to the global results. The DS is higher in the control group compared with the UCLP group, and the difference diminishes over age. However, the differences seem to be larger in the upper jaw (Fig. 3 and Table 4).

**Table 2** Mean difference in dental age (DA) between control and UCLP patients at the different ages, with *P* value for difference between groups (seven left mandibular teeth)

| Age | Mean difference DA Control – UCLP (95% CI) | | *P* value | |
|---|---|---|---|---|
| | Females | Males | Females | Males |
| 6 | − 0.969 (− 1.942;0.004) | − 0.280 (− 0.790;0.229) | 0.0510 | 0.2797 |
| 7 | − 0.581 (− 1.149;− 0.013) | − 0.287 (− 0.597;0.024) | 0.0449* | 0.0703 |
| 8 | − 0.259 (− 0.641;0.122) | − 0.307 (− 0.595;− 0.019) | 0.1806 | 0.0369* |
| 9 | − 0.163 (− 0.603;0.277) | − 0.374 (− 0.720;− 0.029) | 0.4639 | 0.0339* |
| 10 | − 0.413 (− 0.819;− 0.007) | − 0.511 (− 0.828;− 0.195) | 0.0465* | 0.0017$^{+}$ |
| 11 | − 0.861 (− 1.213;− 0.508) | − 0.670 (− 0.972;− 0.367) | < 0.0001$^{+}$ | < 0.0001$^{+}$ |
| 12 | − 1.265 (− 1.669;− 0.860) | − 0.776 (− 1.133;− 0.418) | < 0.0001$^{+}$ | < 0.0001$^{+}$ |
| 13 | − 1.411 (− 1.824;− 0.998) | − 0.767 (− 1.117;− 0.416) | < 0.0001$^{+}$ | < 0.0001$^{+}$ |
| 14 | − 1.302 (− 1.686;− 0.917) | − 0.656 (− 0.953;− 0.359) | < 0.0001$^{+}$ | < 0.0001$^{+}$ |
| 15 | − 1.035 (− 1.459;− 0.611) | − 0.493 (− 0.803;− 0.183) | < 0.0001$^{+}$ | 0.0020$^{+}$ |
| 16 | − 0.710 (− 1.179;− 0.241) | − 0.325 (− 0.689;0.040) | 0.0033$^{+}$ | 0.0803 |
| 17 | − 0.407 (− 0.828;0.013) | − 0.191 (− 0.546;0.164) | 0.0571 | 0.2912 |
| 18 | − 0.135 (− 0.529;0.259) | − 0.089 (− 0.388;0.211) | 0.4989 | 0.5608 |
| 19 | 0.120 (− 0.474;0.713) | − 0.007 (− 0.316;0.303) | 0.6906 | 0.9663 |
| 20 | 0.366 (− 0.578;1.310) | 0.067 (− 0.378;0.512) | 0.4437 | 0.7672 |

*$P$ value < 0.05

$^{+}$ $P$ value < 0.01

Results based on post hoc tests comparing least-square means between the groups at pre-specified ages

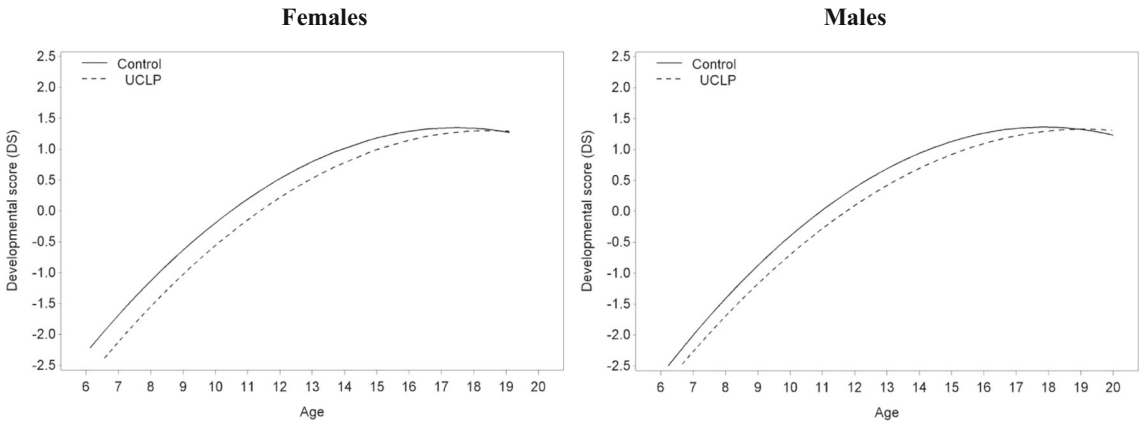


**Fig. 2** Developmental score by age in UCLP and control patients (all teeth)

### Cleft side vs non-cleft side

The difference in DS between affected and non-affected side does not depend on age (no significant interaction). There is no evidence of a slower development at the cleft side in either males or females. The mean difference in DS between cleft and non-cleft side was − 0.030 for females and − 0.041 for males. The negative difference presents a lower DS for the cleft side (Fig. 4).

## Discussion

### Staging method and radiographic evaluation

Assessing dental mineralization on radiographs is an accurate way to determine tooth development and dental age. Many authors have reported various techniques for staging tooth development. These techniques divide the whole dental maturity track

**Table 3** Mean difference in development score (DS) between control and UCLP patients at the different ages, with p value for difference between groups (all teeth)

| Age | Mean difference DS Control – UCLP (95% CI) | | *P* value | |
|---|---|---|---|---|
| | Females | Males | Females | Males |
| 6 | − 0.449 (− 0.721;− 0.178) | − 0.235 (− 0.390;− 0.080) | 0.0014$^{+}$ | 0.0032$^{+}$ |
| 7 | − 0.434 (− 0.633;− 0.235) | − 0.263 (− 0.380;− 0.146) | < 0.0001$^{+}$ | < 0.0001$^{+}$ |
| 8 | − 0.415 (− 0.561;− 0.269) | − 0.284 (− 0.375;− 0.192) | < 0.0001$^{+}$ | < 0.0001$^{+}$ |
| 9 | − 0.393 (− 0.509;− 0.276) | − 0.297 (− 0.378;− 0.216) | < 0.0001$^{+}$ | < 0.0001$^{+}$ |
| 10 | − 0.367 (− 0.477;− 0.257) | − 0.302 (− 0.384;− 0.220) | < 0.0001$^{+}$ | < 0.0001$^{+}$ |
| 11 | − 0.338 (− 0.455;− 0.221) | − 0.299 (− 0.387;− 0.211) | < 0.0001$^{+}$ | < 0.0001$^{+}$ |
| 12 | − 0.306 (− 0.431;− 0.181) | − 0.289 (− 0.382;− 0.195) | < 0.0001$^{+}$ | < 0.0001$^{+}$ |
| 13 | − 0.270 (− 0.399;− 0.141) | − 0.270 (− 0.367;− 0.174) | < 0.0001$^{+}$ | < 0.0001$^{+}$ |
| 14 | − 0.231 (− 0.359;− 0.104) | − 0.244 (− 0.340;− 0.149) | 0.0005$^{+}$ | < 0.0001$^{+}$ |
| 15 | − 0.189 (−0.311;− 0.067) | − 0.211 (− 0.303;− 0.119) | 0.0027$^{+}$ | < 0.0001$^{+}$ |
| 16 | − 0.144 (− 0.263;− 0.025) | − 0.169 (− 0.257;− 0.081) | 0.0183* | 0.0002$^{+}$ |
| 17 | − 0.095 (− 0.223;0.033) | − 0.120 (− 0.207;− 0.033) | 0.1444 | 0.0073$^{+}$ |
| 18 | − 0.043 (− 0.201;0.115) | − 0.063 (− 0.159;0.034) | 0.5919 | 0.2007 |
| 19 | 0.012 (− 0.199;0.223) | 0.002 (− 0.117;0.121) | 0.9074 | 0.9753 |
| 20 | 0.071 (− 0.212;0.354) | 0.074 (− 0.081;0.229) | 0.6197 | 0.3451 |

*$P$ value < 0.05

$^{+}$ $P$ value < 0.01

Results based on post hoc tests comparing least-square means between the groups at pre-specified ages

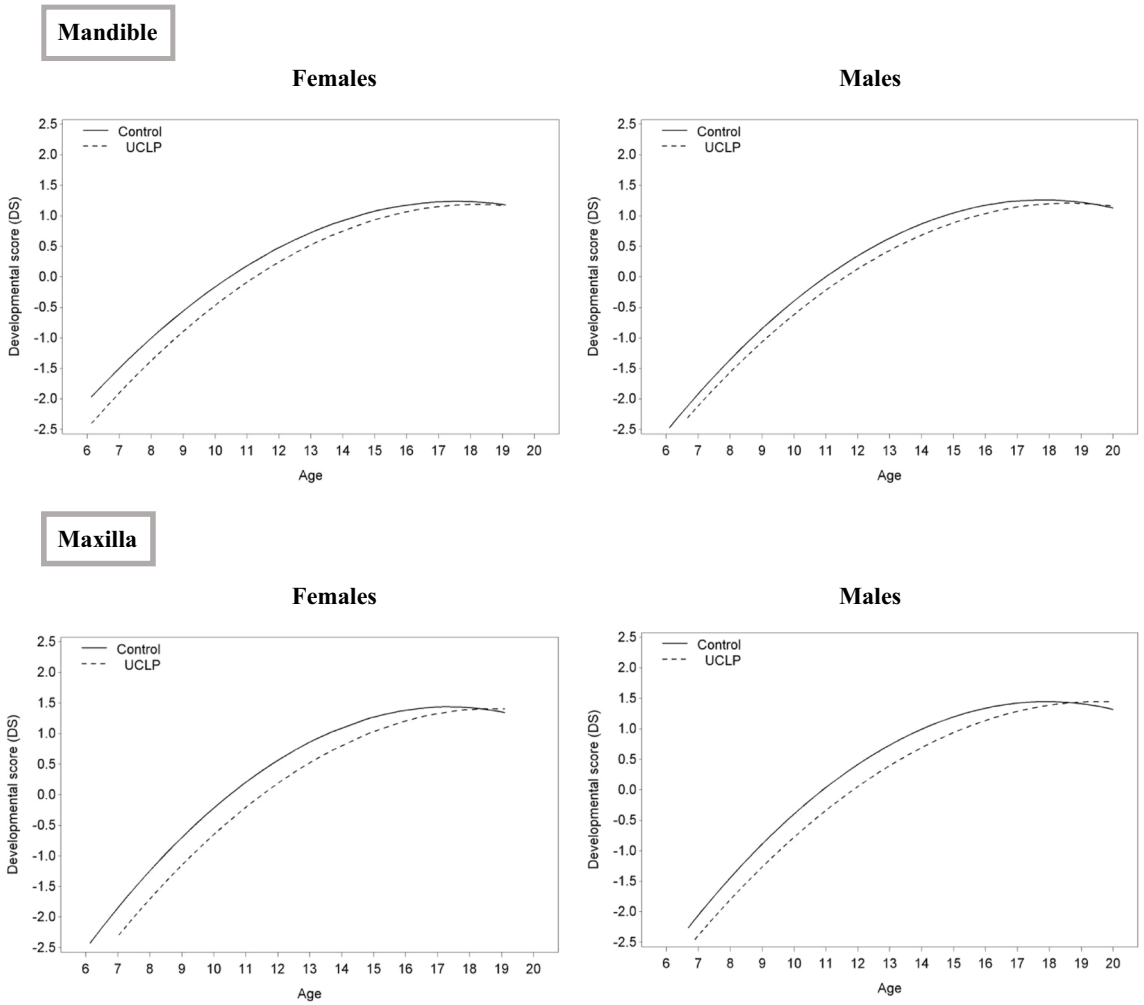


**Fig. 3** Developmental score by age in UCLP and control patients (mandible and maxilla)

into consecutive developmental stages. The length and number of stages vary depending on a particular technique.

The eight-stage technique developed by Demirjian et al. [9] is one of the most widely used developmental staging methods in children. This technique classifies the distinct dental developmental stages based on objective observations and the threshold between the different stages is well described, hence avoiding the need to involve tooth measurements of, e.g., root length.

Anatomic factors, such as superimposition of hard and soft tissues on the teeth in the upper jaw, can cause challenging radiographic analysis [23, 24]. However, the effect of the cleft, which is situated in the maxilla, cannot be fully reflected when only scoring the mandibular teeth. Therefore, maxillary teeth were scored as well in the present study. Nevertheless, all subjects were staged by the same observer on panoramic radiographs using the same technique, meaning that the possible shortcoming of scoring teeth in the maxilla was equal for each of the included patients.

When using panoramic radiographs, problems of distortion, enlargement, positioning problems, and overlap often occur. Even though these problems may cause a level of unreliability for linear and angular measurements, they may be acceptable for ratio calculations [25, 26]. The Demirjian method uses developmental stages based on tooth shape and the ratio of crown height to root length, rather than on the absolute length, so that elongated or shorted projections of developing teeth will not affect the accuracy of evaluation [27]. Although the Demirijan method does present some limitations, such as overestimation of chronological age in certain age groups [28], it was decided to use it in the present study to enable comparison with most available studies investigating similar conditions.

Nowadays, CBCT's are often taken in CLP patients since it has been proven that 3D imaging improves diagnosis, treatment planning, and treatment outcomes in these subjects. Teeth can be observed in all angles without image superimposition, which makes analysis more accurate. De Mulder et al. 2018 introduced an optimized imaging protocol for CLP patients based on European guidelines to achieve the concepts of optimization and justification, which can be employed as an international reference for CLP care programs. Uncontrolled radiological exposures (either 2D or

**Table 4** Mean difference in development score (DS) between control and UCLP patients at the different ages, with *P* value for difference between groups (mandible and maxilla separately)

| Age | Mean difference DS Control – UCLP (95% CI) | | *P* value | |
|---|---|---|---|---|
| | Females | Males | Females | Males |
| Mandible | | | | |
| 6 | − 0.440 (− 0.688;− 0.192) | − 0.175 (− 0.321;− 0.028) | 0.0006+ | 0.0199* |
| 7 | − 0.405 (− 0.586;− 0.223) | − 0.194 (− 0.305;− 0.084) | < 0.0001+ | 0.0006+ |
| 8 | − 0.370 (− 0.503;− 0.237) | − 0.209 (− 0.295;− 0.122) | < 0.0001+ | < 0.0001+ |
| 9 | − 0.336 (− 0.442;− 0.230) | − 0.218 (− 0.294;− 0.141) | < 0.0001+ | < 0.0001+ |
| 10 | − 0.302 (− 0.403;− 0.201) | − 0.222 (− 0.299;− 0.144) | < 0.0001+ | < 0.0001+ |
| 11 | − 0.269 (− 0.375;− 0.162) | − 0.220 (− 0.303;− 0.137) | < 0.0001+ | < 0.0001+ |
| 12 | − 0.235 (− 0.349;− 0.122) | − 0.213 (− 0.302;− 0.125) | < 0.0001+ | < 0.0001+ |
| 13 | − 0.203 (− 0.321;− 0.085) | − 0.201 (− 0.293;− 0.110) | 0.0009+ | < 0.0001+ |
| 14 | − 0.171 (− 0.287;− 0.055) | − 0.184 (− 0.275;− 0.094) | 0.0043+ | < 0.0001+ |
| 15 | − 0.139 (− 0.251;− 0.028) | − 0.162 (− 0.249;− 0.075) | 0.0149* | 0.0003+ |
| 16 | − 0.108 (− 0.216;0.001) | − 0.134 (− 0.217;− 0.051) | 0.0516 | 0.0017+ |
| 17 | − 0.077 (− 0.194;0.040) | − 0.101 (− 0.183;− 0.018) | 0.1945 | 0.0168* |
| 18 | − 0.047 (− 0.191;0.098) | − 0.063 (− 0.154;0.029) | 0.5239 | 0.1781 |
| 19 | − 0.017 (− 0.209;0.176) | − 0.019 (− 0.132;0.094) | 0.8640 | 0.7398 |
| 20 | 0.013 (− 0.245;0.271) | 0.030 (− 0.117;0.176) | 0.9219 | 0.6889 |
| Maxilla | | | | |
| 6 | − 0.462 (− 0.790;− 0.134) | − 0.295 (− 0.479;− 0.112) | 0.0062+ | 0.0017+ |
| 7 | − 0.466 (− 0.706;− 0.226) | − 0.332 (− 0.470;− 0.194) | 0.0002+ | < 0.0001+ |
| 8 | − 0.462 (− 0.638;− 0.286) | − 0.359 (− 0.467;− 0.250) | < 0.0001+ | < 0.0001+ |
| 9 | − 0.451 (− 0.592;− 0.311) | − 0.375 (− 0.471;− 0.279) | < 0.0001+ | < 0.0001+ |
| 10 | − 0.434 (− 0.567;− 0.300) | − 0.381 (− 0.478;− 0.284) | < 0.0001+ | < 0.0001+ |
| 11 | − 0.408 (− 0.549;− 0.267) | − 0.376 (− 0.480;− 0.272) | < 0.0001+ | < 0.0001+ |
| 12 | − 0.376 (− 0.527;− 0.225) | − 0.362 (− 0.472;− 0.251) | < 0.0001+ | < 0.0001+ |
| 13 | − 0.337 (− 0.492;− 0.181) | − 0.337 (− 0.451;− 0.223) | < 0.0001+ | < 0.0001+ |
| 14 | − 0.290 (− 0.444;− 0.136) | − 0.302 (− 0.415;− 0.189) | 0.0003+ | < 0.0001+ |
| 15 | − 0.236 (− 0.384;− 0.089) | − 0.256 (− 0.365;− 0.148) | 0.0019+ | < 0.0001+ |
| 16 | − 0.175 (− 0.319;− 0.031) | − 0.201 (− 0.304;− 0.097) | 0.0173* | 0.0002+ |
| 17 | − 0.107 (− 0.262;0.048) | − 0.135 (− 0.238;− 0.031) | 0.1732 | 0.0108* |
| 18 | − 0.032 (− 0.223;0.160) | − 0.058 (− 0.173;0.056) | 0.7436 | 0.3149 |
| 19 | 0.051 (− 0.204;0.306) | 0.028 (− 0.113;0.169) | 0.6930 | 0.6945 |
| 20 | 0.141 (− 0.201;0.482) | 0.125 (− 0.058;0.308) | 0.4167 | 0.1805 |

*$P$ value < 0.05

+ $P$ value < 0.01

Results based on post hoc tests comparing least-square means between the groups at pre-specified ages

3D) by various disciplines lead to high cumulative doses, a matter that was taken into account in this protocol [29]. To our knowledge, only one study used CBCT to evaluate tooth development in CLP patients [30]. In our study, insufficient CBCT's were available since the protocol suggested by De Mulder et al. was implemented in our hospital only since

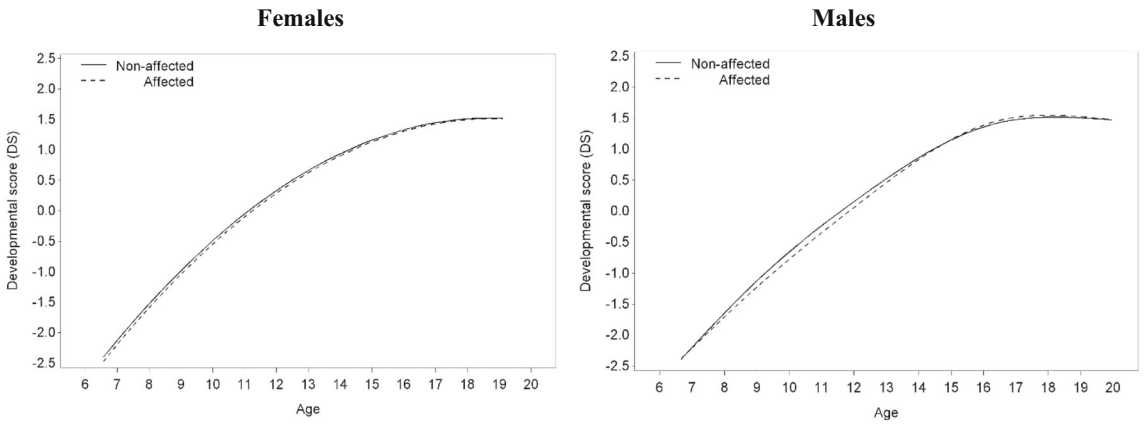


**Fig. 4** Developmental score by age in affected and non-affected side

2016. In future research, it is recommended to evaluate dental development on CBCT.

### Overview of the related literature (Appendix Table 5)

A systematic literature search, including all studies related to this topic published until the end of 2018, revealed 36 studies with a large heterogeneity in study groups and staging methods. A delay in tooth development or dental age was observed in almost all these studies (32/36). However, establishing appropriate comparisons was difficult since the methodology of these studies showed a big variation. Many studies on this topic combined patients with different cleft types in one study group. In our study, we only included patients with complete unilateral cleft lip and palate, since it has been reported that isolated cleft palate and other types of clefts are etiologically different. This may influence tooth development in different ways [31].

In consistency with our findings, most research on this topic found that UCLP is more common in boys and that the left side is significantly more affected than the right side. Both the male-female ratio and left side-right side ratio in patients with UCLP were approximately 2:1 [14, 32–37].

We found a delay in tooth development both in the upper and lower jaw, not only at the level of the cleft. This is in accordance with previous studies [38–41].

### Dental agenesis

Developmental tooth abnormalities, such as hypoplasia and agenesis of teeth, are frequently seen in cleft patients. In this study, 58.73% of UCLP patients had agenesis of at least one tooth and hypoplasia was seen in 24.87% of the cleft patients.

Diagnosis of tooth agenesis was based on interpretation of a panoramic radiograph, together with examination of clinical records. It has been reported that all permanent teeth except third molars have started their mineralization on average at the age of 6. In this study, all patients were at least 6 years old [42]. The panoramic radiographs were selected from a patient group followed longitudinally by the orofacial cleft care program. This aspect tended to guarantee that the diagnosis of tooth agenesis was made even more reliable. Nevertheless, very late development of the mandibular second premolar has been described in some patients. To prevent a false-positive diagnosis of this tooth, the method suggested by Sharma et al. was used [43]. This method proposes that the mandibular second premolar is highly unlikely to develop if the adjacent first molar is beyond stage "root one half" and the first premolar is beyond stage "crown complete." This was checked in patients with agenesis.

Lebbe et al. 2017 showed a delayed tooth development in non-cleft patients with dental agenesis, so the presence of tooth agenesis is an important factor to take into account when evaluating tooth development [22]. In our study, more significant differences between UCLP and control patients were found when evaluating the degree of dental development (DS) compared with estimation of dental age.

In fact, DS enables us to include also patients with dental agenesis thanks to the method's characteristics.

On the other hand, by using DA estimation, when missing teeth were present, a linear regression model was used to predict dental age based on the Demirjian scores of the teeth on the opposite side of the mandible, the age, and group. This could support the finding of Lebbe et al. 2017, namely that dental development is more delayed in patients with agenesis of teeth. In addition, for the estimation of dental age, only the left lower permanent teeth were scored, while the upper lateral incisor in UCLP patients was the most agenetic. Dental agenesis in UCLP patients was more frequently seen in the upper jaw; this could explain why dental maturity in UCLP patients was more delayed in the maxilla compared with the mandible.

Seo et al. 2013 recently found that the same genes whose mutations cause tooth agenesis, such as PAX9 and MSX1, frequently also contain SNPs as genetic risk factors for non-syndromic orofacial clefts [44, 45]. Moreover, it has been reported that these genetic factors could also induce a delay in tooth development [46, 47]. This genetic association may possibly play a role in the etiology of the delay in dental development in cleft patients and this might also explain why the delay is not only found at the level of the cleft. It could be interesting to further investigate this potential relationship in future research.

### Clinical implications

Considering the determinant role of dental development in establishing the proper treatment timing in orthodontics, our results can help the clinicians in better planning the orthodontic therapy, the secondary bone graft augmentation, and understanding the reduces growth rate in UCLP patients. Some studies have already highlighted a relationship between dental maturation stages and skeletal maturity [27, 48–50].

Moreover, the results of this study could be important for forensic age estimation leading to different legal consequences. UCLP patients could falsely be a minor when applying the existing reference tables for persons without this condition.

## Conclusions

Dental age and tooth development in UCLP patients were delayed compared with subjects without this condition. Within UCLP patients, a slightly more delayed dental maturation in the upper jaw was observed compared with the lower jaw. There is no evidence of a slower dental development at

the cleft side compared with the non-cleft side. These findings are relevant for forensic age estimation outcomes and for orthodontic and surgical treatment planning in UCLP patients.

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**Authors' contribution** All authors contributed to the study conception and design. Material preparation and data collection were performed by Julie Van Dyck and Maria Cadenas de Llano-Pérula. Analysis was performed by Annouschka Laenen. The first draft of the manuscript was written by Julie Van Dyck and Maria Cadenas de Llano-Pérula and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** For this type of study, formal consent is not required.

## Appendix 1

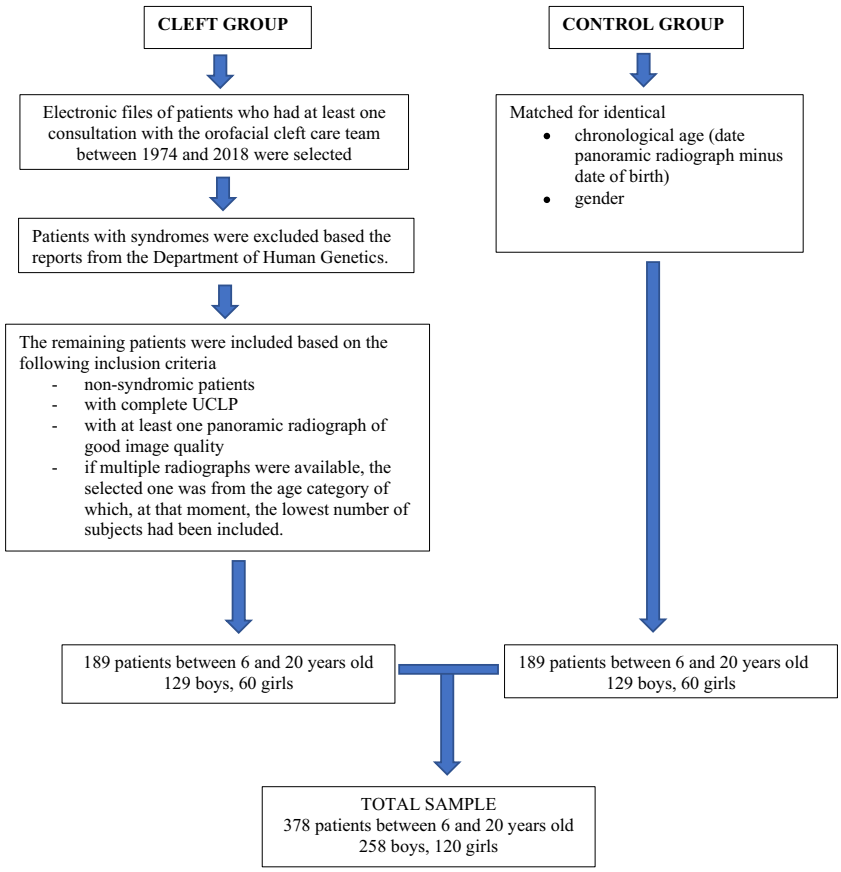


**Fig. 5.** Case selection flowchart

## Appendix 2

**Table 5** Overview of the existing literature

| First author, year | | Study sample | Cleft type | Control group | Data used | Method for determination dental development | Variation in tooth development |
|---|---|---|---|---|---|---|---|
| Almotairy, 2017 | 108 | 69M/39F | UCLP | Non-CLP (age matched) | OPG | Demirjian's and Willems' methods | Delay compared with control group |
| Tan, 2017 | 60 | 36M/24F 33M/22F | UCLP | Non-CLP (age, gender, and race matched) | OPG | Demirjian, asymmetric tooth development | 5–9 years: mean delay = 0.55 years<br>9–13 years: no sig delay<br>sig asymmetrical tooth development in both groups |
| Zhang, 2016 | 40 | 30M/10F | 31 UCLP, 9 ULCA | Non-cleft side | CBCT | Crown height, root length, and full length | Asymmetrical tooth development in UJ and LJ |
| Topolski, 2014 | 107 | 68M/39F | 73 (B)CLP, 27 UCL(A), 2 CP, 5 UCL(P) | Non-CLP (age and gender matched) | OPG | Demirjian | No sig delay |
| Bindayel, 2014 | 51 | 34M/17F | 47 UCLP, 4 BCLP | No | OPG | Demirjian | Mean delay of 0.7 years |
| Tan, 2012 | 60 | 36M/24F | UCLP | Non-CLP (age, gender, and race matched) | OPG | Demirjian | Mean delay of 0.55 years |
| Heliövaara, 2009 | 73 | 34M/39F | SMCP | CP (age and gender matched) | OPG | Demirjian | SMCP: no delay; CP: mean delay of 0.2 years |
| Hazza'a, 2009 | 80 | 20M/20F | 40 UCLP, 40 BCLP | Non-CLP (age and gender matched) | OPG | Demirjian | UCLP: mean delay of 0.34 years; BCLP: mean delay of 0.61 years |
| Gonzalez-Carrera, 2009 | 53 | 59%M/40%F | 37 UCLP, 16 BCLP | Non-CLP | OPG | Nolla | sig delay for tooth pairs in UCLP (right side) group |
| Lai, 2008 | 231 | 123M/108F | 156 UCLP, 39 BCLP, 8 UCLA, 28 CP | Non-CLP (age and gender matched) | OPG | Demirjian | Mean delay of 0.4 years, sig delay in UJ and LJ |
| Borodkin, 2008 | 49 | NM | UCLP and BCLP | Non-CLP (age and gender matched) | OPG | Demirjian | Mean delay of 0.52 years |
| Huyskens, 2006 | 70 | 45M/25F | UCLP | Non-CLP (age and race matched) | OPG | Demirjian | Mean delay of 0.64 years |
| Pioto, 2005 | 95 | 46M/49F | 32 UCLP, 28 UCLA, 35 CL | Non-cleft side | OPG | Nolla | Delay I2 cleft side = 0.5–1.6 years |
| Carrara, 2004 | 477 | 311M/166F | UCLP | Non-cleft side | Clinical and RX | Karber's method, modified by Hayes and Mantal (eruption) | sig delay compared with non-cleft side |
| Ribeiro, 2002 | 98 | 63M/35F | UCLP | Non-cleft side | OPG | Nolla and Solis | Delay of 1 stadium (Nolla) or 2 stadia (Solis) compared with non-cleft side |
| Heidbüchel, 2002 | 74 | 54M/20F | BCLP | Non-CLP (age and gender matched) | OPG | Demirjian | sig delay at 5 years; no delay at 9.5 and 14 years |
| Mitsea, 2001 | 34 | 22M/12F | CL(P) | Non-CLP (age and gender matched) | OPG | Nolla | sig delay PM in cleft group |
| Eerens, 2001 | 54 | 34M/20F | 38 UCLP, 10 CP, 2 UCLA | | OPG | Demirjian and Goldstein | No sig delay |

**Table 5** (continued)

| First author, year | | Study sample | Cleft type | Control group | Data used | Method for determination dental development | Variation in tooth development |
|---|---|---|---|---|---|---|---|
| | | | | Non-CLP siblings and non-CLP control (age and gender matched) | | | |
| Solis, 1998 | 79 | 47M/32F | UCLP and UCLA | Non-CLP (race matched) | OPG | Gleiser and Hunt | sig delay: compared with non-cleft side: 1.02 year; compared with control group: 1.59 year |
| Pham, 1997 | 53 | 30M/23F | 39 CLP, 3 UCLA, 7 incompl. UCLA, 4 mixed | Non-CLP (age, gender, and race matched) | OPG | Demirjian | Mean delay of 0.6 years |
| Peterka, 1996 | 342 | 342M/0F | 163 UCLP, 82 BCLP, 97 CP | Non-CLP (age, gender, and race matched) | Dental plaster casts | Tooth eruption | sig delay/acceleration eruption |
| Prahl-Andersen and Souren, 1994 | 106 | 66M/40F | UCLP | No | OPG | Demirjian | Mean delay of 0.7 years |
| Peterka, 1993 | 30 | 30M/0F | UCLP | Non-cleft side | Dental plaster casts | Tooth eruption | sig delay I2, C, PM1, PM2 |
| Brouwers, 1991 | 88 | 64M/24F | UCLP | Non-CLP (age matched) | OPG | Tooth length measurement | No sig delay compared with non-cleft side, sig delay compared with control group |
| Harris, 1990 | 54 | NM | 35 UCLP, 19 BCLP | Non-CLP (age and gender matched) | OPG | Moorrees, Fanning, and Hunt; Harris and McKee | Mean delay of 0.9 years |
| Pöyry, 1989 | 131 | 89M/42F | 87 UCLP, 30 BCLP, 14 CL | No | Occlusal RX and OPG | Haavikko/Nyström, Demirjian | sig delay |
| Nyström, 1988 | 47 | 31M/16F | CL(P), CP | Twins and non-CLP | OPG | Demirjian and Goldstein | Mean delay of 0.3 years in CLP group |
| Loevy, 1988 | 109 | 66M/43F | 48 UCLP, 34 BCLP, 27 CP | Non-CLP (age matched) | OPG | Demirjian | sig acceleration compared with control group |
| Fuchslocher, 1988 | 187 | NM | 125 UCLP, 62 BCLP | Non-CLP | Dental plaster casts | Tooth eruption | General delay |
| Ranta, 1984 | 251 | 88M/163F | CP | No | OPG | Haavikko | Mean delay of 0.7 years (sig greater delay when hypodontia) |
| Ranta, 1983 | 95 | 37M/58F | CP | Non-CLP, CLP without hypodontia | OPG | Haavikko | sig delay in hypodontia group |
| Ranta, 1982 | 475 | 250M/225F | UCL(A), UCLP, BCLP, and CP | Non-CLP | OPG | Haavikko | sig delay of 0.3–0.7 years |
| Haring, 1976 | 18 | 14M/4F | 10 BCLP, 8 UCLP | Non-CLP | Dental plaster casts, cephalometric x-rays | Previous studies: Fels Research Institute and Nolla | No sig delay in eruption and tooth development |
| Ranta, 1971 | 37 | 25M/12F | UCLP | Non-cleft side | OPG, dental plaster casts, clinical data | Moorrees, tooth eruption | Delay |
| Fishman, 1970 | 68 | NM | 33 UCLP, 13 BCLP, 14 UCL(A), 7 CP | No | Dental plaster casts, RX | Hurme's tooth emergence chart | Delayed tooth eruption in all groups |
| Bailit, 1967 | 39 | 22M/17F | CP | Non-CLP | OPG | Moorrees | Mean delay of 0.74 years |

*sig*, significant; *UCLP*, unilateral cleft lip and palate; *UCLA*, unilateral cleft lip and alveolar; *BCLP*, bilateral cleft lip and palate; *CP*, cleft palate; *CL*, cleft lip; *NM*, not mentioned; *I1*, central incisor; *I2*, lateral incisor; *C*, canine; *PM*, premolar; *M1*, first molar; *M2*, second molar; *UJ*, upper jaw; *LJ*, lower jaw

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