#### **REVIEW**

# Mesiodistal tooth size in non-syndromic unilateral cleft lip and palate patients: a meta-analysis

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### Abstract

*Objectives* To evaluate, using meta-analysis methodology, mesiodistal tooth dimensions in non-syndromic unilateral cleft lip and palate (CLP) patients.

*Materials and methods* A literature search was conducted using PubMed, Medline, Google Scholar Beta, EMBASE Excerpta Medica, CINAHL, Web of Science, and the Cochrane Collaboration, identifying English and non-English articles reporting on mesiodistal tooth dimensions on the cleft and non-cleft side of non-syndromic unilateral CLP patients. Additional studies were identified by searching reference lists of articles consulted. Only studies with a suitable control group were included. Two examiners independently performed the literature search and data extraction. Using meta-analysis software, data extracted from each selected study were statistically combined using the fixedeffects model. Weighted mean differences, 95 % confidence intervals, and heterogeneity were calculated for each measurement.

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P. Christou Department of Orthodontics, Dental School, National and Kapodistrian University of Athens, Athens, Greece *Results* Four articles fulfilling the inclusion criteria were located and included in the meta-analysis. Maxillary incisors and first molars were found to be significantly larger on the non-cleft side while mandibular incisors and premolars were larger on the cleft side, in non-syndromic unilateral CLP patients. On the cleft side, maxillary premolars and second molars were larger in cleft than control patients while incisors were smaller, whereas all mandibular teeth were larger in cleft patients. On the non-cleft side, all maxillary teeth except for the central incisors were larger in the cleft than control patients, while all mandibular teeth were larger in the cleft patients.

*Conclusions* Non-syndromic unilateral CLP patients tend to have larger posterior but smaller anterior teeth compared with the general population. Comparing sides, unilateral CLP patients tend to have smaller maxillary but larger mandibular teeth on the cleft than on the non-cleft side.

*Clinical relevance* Given that obtaining a stable, functional, and esthetic occlusion requires a thorough evaluation of tooth size, knowledge about trends in tooth size variations in CLP patients can help with dental and orthodontic treatment planning.

**Keywords** Cleft lip and palate · Tooth size · Orthodontics · Meta-analysis

# Introduction

To obtain a stable, functional, and esthetic occlusion, dental and orthodontic treatment plans need to take into account tooth size [1]. Obtaining ideal intermaxillary relationships and occlusion, as well as post-treatment stability, requires proper alignment of the teeth in both dental arches, with adequate overjet and overbite. Tooth size is something that clinicians need to adequately consider during treatment planning, as discrepancies in tooth size between the arches can prevent the proper alignment of teeth, and thus recording these discrepancies before treatment is necessary to obtain ideal occlusion after treatment [1]. The latter is of particular challenge in cleft lip and palate (CLP) patients.

Tooth size is multifactorial in nature, determined both by genetic and environmental factors [2]. Genetics are thought to play an important role in dictating tooth size [3, 4], implying that, to a certain extent, tooth dimensions are dependent on the genetic make-up of every individual. At the same time, however, etiological factors in the prenatal and postnatal periods have been reported to cause anomalies in tooth dimensions and morphology [5]. In a study on monozygotic and dizygotic twins, Lundström [6] proposed that genetic factors affected tooth size at least as much as did environmental factors. Normal variation in tooth size is thus the result of both genetic and environmental controls [7, 8].

Permanent tooth crown size and shape are partial indicators of a person's morbidity, general well-being, and growth capacity [9, 10]. It is thus hypothesized that a compromised growth potential, such as seen in CLP individuals, might be reflected in smaller teeth [7]. The dentition is said to provide valuable retrospective information on the development of individuals with CLP, allowing a means of assessing growth at various ages, by appraising teeth that mineralized at specific intervals during growth [11]. The completed crown size of teeth is formed during a span of several years, and once formed, the crowns are readily measured and are not altered except by tooth wear and disease [7].

Dental abnormalities, such as disturbances in number, size, shape, and timing of formation, demonstrate increased frequency in children affected with CLP than in the general population [7, 11–22]. Abnormal tooth size and morphology are two of the most prevalent abnormalities observed [14].

One of the best general indicators of developmental instability is the asymmetry of bilaterally paired structures. It is assumed that the same genetic and general environmental factors control development on the two sides of the body, so that the extent to which sides differ is a measure of lack of precision of this developmental control [23]. As a consequence, apart from differences in tooth size between CLP patients and the general population, differences may also be present in unilateral CLP individuals between the side with the cleft and the side without. Even in a general population, dental asymmetry is usually present, but the differences between the left and right sides are small and may be of no statistical or clinical significance [24]. Garn et al. [25] on the other hand conclude that the same teeth on the left and right sides are of different sizes, especially the lateral incisors, first premolars, and first molars, in both upper and lower jaws.

Having recognized that, in order to achieve proper occlusion and stability, tooth dimensions of both arches must be considered [1], it was decided to concentrate on mesiodistal (MD) tooth dimensions for the purpose of the present study. Many studies have compared discrepancies in tooth size. The largest MD dimension has been reported to be the most reliable and appropriate measurement for representing the size of the crown [26]. Concerning CLP patients, the literature reveals that, although there has been a substantial amount of research into variations in tooth morphology, there are marked variations in the published results [16] as regards tooth size. Studies often tend to have small sample sizes, which can lead to bias as regards interpretation of results [16].

The aim of the present study was to systematically review the literature concerning MD tooth dimensions in nonsyndromic unilateral CLP patients and using meta-analysis methodology to specifically evaluate (1) MD tooth dimensions in non-syndromic unilateral CLP patients versus a general population and (2) MD tooth dimensions between the cleft and the non-cleft side in non-syndromic unilateral CLP patients. Our hypothesis was that differences would exist in the maxillary dentition between non-syndromic unilateral CLP patients and the general population on the cleft side, and between the cleft and the non-cleft side in non-syndromic unilateral CLP patients. No differences were expected in the mandibular dentition.

# Materials and methods

The present meta-analysis was carried out following the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement for reporting systematic reviews and meta-analyses of studies that evaluate health-care interventions [27] as best applicable to the present meta-analysis.

#### Literature search

A literature search was conducted to identify articles reporting on MD tooth dimensions on the cleft and non-cleft side of non-syndromic unilateral CLP patients in comparison to a general population, using the following databases: PubMed, Medline, Google Scholar Beta, EMBASE Excerpta Medica, CINAHL, Web of Science, and the Cochrane Collaboration. The last search was performed in the fourth week of January 2011.

The following search terms were used: cleft lip and/or cleft palate; tooth size or tooth dimensions. No language, publication date, or publication status restrictions were imposed. The search was expanded by searching reference lists of articles consulted, to identify other relevant articles.

Articles were selected for inclusion based on the following inclusion criteria:

- Human studies
- Examination of non-syndromic unilateral cleft lip and palate patients
- Sample of at least ten patients
- MD tooth measurements present
- Permanent teeth only measured
- Divided cleft side and non-cleft side
- Included a suitable control (non-cleft) group
- Number of subjects (cleft and control groups) mentioned
- Descriptive statistics with mean and standard deviation for both cleft and control groups mentioned

Articles were excluded based on the following exclusion criteria:

- Syndromic cleft lip and palate patients
- Bilateral cleft lip and palate patients
- Sample of less than ten patients, or not mentioned
- Deciduous teeth measured
- Combined data for the cleft and non-cleft sides
- No suitable control (non-cleft) group
- Insufficient statistics

In the case of more than one publication about the same patient group, the most informative and relevant article was included. Two examiners independently performed the literature search in order to maximize the number of studies retrieved. All selected articles were assessed by the two examiners for the predefined inclusion criteria, and

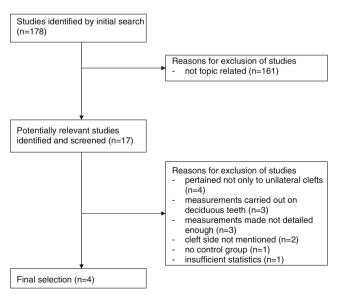


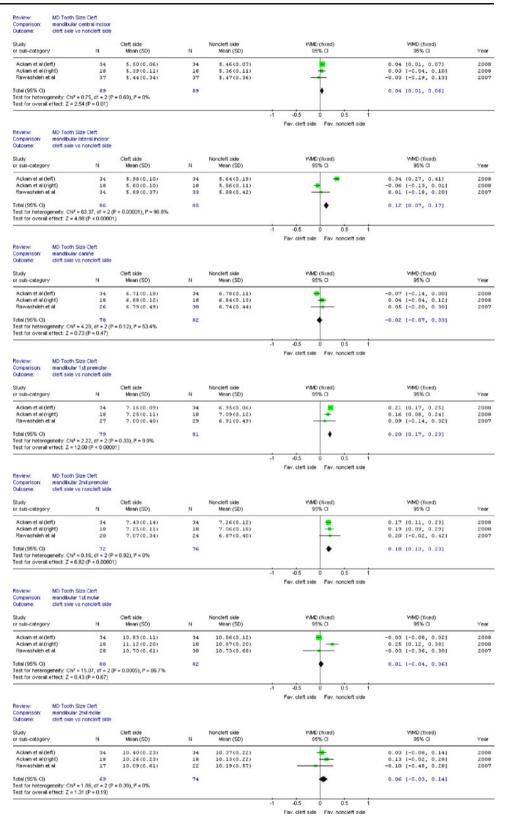
Fig. 1 Flow diagram summarizing literature search and article selection

Table 1 Summa	ury of the studies	Table 1         Summary of the studies included in the meta-analysis	iis					
Authors, year of publication	Origin of patients	Number of UCLP patients	Age of UCLP patients	Type of control patients	Number of control patients	Age of control patients	Method of tooth size measurements	Quality assessment
Akcam et al., 2008 [1]	Turkey	<ul> <li>53 (divided into 34 left-sided Mean 17.5 years and 18 right-sided clefts) (left-sided clefts) Mean 16.9 years (right-sided clefts)</li> </ul>	-	Non-cleft class I molar	53	Mean 15.9 years	Digital calipers on study casts	Medium
Lewis et al., 2008 UK [16]	UK	30	11–14 years	Non-cleft	30	11-14 years	11–14 years Linear measurements done electronically on standardized photographs of study casts	Medium
Peterka and Müllerová, 1983 [33]	Czechoslovakia	Czechoslovakia 63 (divided into 32 females and 31 males)	Not mentioned	Non-celft	76 where maxillary teeth were measured (41 females and 35 males) 57 where mandibuar teeth were measured (24 females and 33 males)	Not mentioned	Ocular micrometer on streneoscopic microscope with ×6 magnification of study casts	Low
Rawashdeh and Bakir, 2007 [11]	Jordan	47	Mean 15.1 years	Non-cleft	74	Mean 14.2 years	Sliding calipers on study casts	Medium

Fig. 2 Forest *plots* representing MD tooth dimensions for the maxillary arch on the cleft side and non-cleft side of unilateral CLP patients. The studies are listed in chronological order and refer to the studies summarized in Table 1. Shown for every study is the sample size (N), weighted mean difference (WMD) between the cleft and non-cleft side, as well as the 95 % confidence interval (95 % CI) for each measurement. The diamonds represent the overall WMD and 95 % CI.  $I^2$  values and  $\chi^2$  (Chi<sup>2</sup>) values (for heterogeneity) and p values (for statistical significance) are shown below each forest plot

omparison: maxillary	Size Cleft central incisor vs noncleft side						
tudy r sub-category	N	Cleft side Mean (SD)	N	Noncleft side Mean (SD)	VM/D (fixed) 95% Cl	VMD (fixed) 95% Cl	Year
Ackam et al (left) Ackam et al (right) Lewis et al	34 18 30	8.28(0.11) 8.22(0.16) 8.39(0.66)	34 18 30	8.48(0.11) 8.16(0.14) 8.86(0.51)	+	-0.20 [-0.25, -0.15] 0.06 [-0.04, 0.16] -0.47 [-0.77, -0.17]	2008 2008 2008
Rawashdeh et al stal (95% CI) est for heterogeneity: Chi	31 113 <sup>2</sup> = 27.28, df = 3 (F	8.20(0.64) 9<0.00001),P=89.0%	38 120	8.54(0.49)	•	-0.34 [-0.61, -0.07] -0.16 [-0.20, -0.11]	2007
est for overall effect: Z =	6.77 (P < 0.00001)	,			-1 -0.5 0 0.5 1		
imparison: maxillary	Size Cleft Interal Incisor vs noncleft side				Fav. cleft side Fav. noncleft side		
tudy rsub-category	N	Cleft side Mean (SD)	N	Noncelft side Mean (SD)	VMID (fixed) 95% Cl	WMD (fixed) 95% Cl	Year
Ackam et al ()eft) Ackam et al (right)	34 18	5.56(1.42) 6.94(0.57)	34 10	6.90(0.13) 7.32(0.22)	÷.	-1.34 (-1.82, -0.86) -0.38 (-0.66, -0.10)	2008
Lewis et al Ravvashdeh et al	30 24	5.84(0.92) 5.61(0.73)	30 35	7.21(0.72) 6.50(0.66)		-1.37 [-1.79, -0.95] -0.89 [-1.25, -0.53]	2008
ctal (95% CI) est for heterogeneity: Chi est for overall effect: Z =	106 <sup>2</sup> = 20.63, df = 3 (F 8.97 (P < 0.00001)	° = 0.0001), I° = 85.5% )	117		•	-0.83 (-1.02, -0.65)	
					-4 -2 0 2 4 Fav. cleft side Fav. noncleft side		
omparison: maxillary	Size Cleft canine vs noncleft side						
udy sub-category	N	Cleft side Mean (SD)	N	Noncleft side Mean (SD)	VMD (fixed) 95% Cl	WMD (fixed) 95% Cl	Year
Ackam et al ()eft) Ackam et al (right)	34 18	7.45(0.24) 7.84(0.16)	34 18	7.76(0.16) 7.69(0.11)	• •	-0.31 [-0.41, -0.21] 0.15 [0.06, 0.24]	2008 2008
Lewis et al Rawashdeh et al	30 25	8.02(0.48) 7.69(0.43)	30 27	7.88(0.44) 7.50(0.45)	<b>—</b>	0.14 [-0.09, 0.37] 0.19 [-0.05, 0.43]	2008
tal (95% CI) est for heterogeneity: Chi est for overall effect: Z =		° < 0.00001), I <sup>e</sup> = 94.3%	109		<b>†</b>	-0.03 [-0.09, 0.03]	
					-1 -0.5 0 0.5 1 Fav. cleft side Fav. noncleft side		
imparison: maxillary	Size Cleft 1st premolar vs noncleft side						
tudy r sub-category	N	Cleft side Mean (SD)	N	Noncleft side Mean (SD)	VMD (fixed) 95% CI	VMMD (fixed) 95% Cl	Year
Ackam et al (ieft) Ackam et al (right) Ravvashdeh et al	34 18 27	7.03(0.12) 6.99(0.10) 6.85(0.38)	34 18 29	7.02(0.10) 7.04(0.09) 6.78(0.43)	4	0.01 [-0.04, 0.06] -0.05 [-0.11, 0.01] 0.07 [-0.14, 0.28]	2008 2008 2007
stal (95% Cl) est for heterogeneity: Chi est for overall effect: Z =	79 <sup>a</sup> = 2.68, df = 2 (P 0.60 (P = 0.55)	= 0.26),  ² = 25.5%	81		<b>†</b>	-0.01 (-0.05, 0.03)	
					-1 -0.5 0 0.5 1 Fav. cleft side Fav. noncleft side		
omparison: maxillary	Size Cleft 2nd premoiar vs noncleft side						
tudy sub-category	N	Cleft side Mean (SD)	N	Noncelft side Mean (SD)	VMD (fixed) 95% Cl	VMMD (fixed) 95% Cl	Year
Ackam et al ()eft) Ackam et al (right)	34 18	6.63(0.14) 6.72(0.10)	34 18	6.77(0.11) 6.64(0.10)		-0.14 [-0.20, -0.08] 0.08 [0.01, 0.15]	2008 2008
Rawashdeh et al stal (95% CI)	26	6.51(0.40)	23	6.47(0.38)		0.04 [-0.18, 0.26]	2007
est for heterogeneity: Chi est for overall effect: Z =	* = 24.18, df = 2 (F	P < 0.00001), P = 91.7%					
					-1 -0.5 0 0.5 1 Fav. cleft side Fav. noncleft side		
emparison: maxillary	Size Cleft 1st molar vs noncleft side						
udy sub-category	N	Cleft side Mean (SD)	N	Noncleft side Mean (SD)	VMD (fixed) 95% Cl	WMD (fixed) 95% Cl	Year
Ackam et al ()eft) Ackam et al (right) Ravvashdeh et al	34 18 31	9.68(0.33) 9.89(0.16) 9.84(0.46)	34 18 31	10.16(0.11) 10.07(0.12) 9.92(0.54)	* <u>+</u> _	-0.48 [-0.60, -0.36] -0.18 [-0.27, -0.09] -0.08 [-0.33, 0.17]	2008 2008 2007
ctal (95% Cl) est for heterogeneity: Chi est for overall effect: Z =	83 P = 18.20, df = 2 (F 7.84 (P < 0.00001)	<sup>p</sup> = 0.0001), <sup>p</sup> = 89.0% )	83		◆	-0.28 [-0.35, -0.21]	
omparison: maxillary	Size Cleft 2nd molar vs noncieft side				-1 -0.5 0 0.5 1 Fav. cleft side Fav. noncleft side		
tudy		Cleft side		Noncleft side	WMD (fixed)	WMD (fixed)	Marc
sub-category Ackam et al (left)	N 34	Mean (SD) 9,63(0,22)	N 34	Mean (SD) 9.67(0.22)	95% CI	95% Cl	Year 2008
Ackam et al (right) Rawashdeh et al	18	9.89(0.29) 9.31(0.73)	18 20	9.81(0.27) 9.46(0.52)		0.08 [-0.10, 0.26] -0.15 [-0.57, 0.27]	2008
ctal (95% Cl) est for heterogeneity: Chi est for overall effect: Z =	69 P = 1.68, df = 2 (P 0.37 (P = 0.71)	= 0.44),   <sup>2</sup> = 0%	72		+	-0.02 (-0.11, 0.07)	
					-1 -0.5 0 0.5 1 Fav. cleft side Fav. noncleft side		

eligibility assessment was performed independently by the two examiners. Any disagreement was resolved by discussion and consensus. A quality assessment of the included studies was carried out in order to evaluate their methodological soundness. This was performed using the methods Fig. 3 Forest plots representing MD tooth dimensions for the mandibular arch on the cleft side and non-cleft side of unilateral CLP patients. The studies are listed in chronological order and refer to the studies summarized in Table 1. Shown for every study is the sample size (N), weighted mean difference (WMD) between the cleft and non-cleft side, as well as the 95 % confidence interval (95 % CI) for each measurement. The diamonds represent the overall WMD and 95 % CI.  $I^2$  values and  $\chi^2$  (Chi<sup>2</sup>) values (for heterogeneity) and p values (for statistical significance) are shown below each forest plot



described by Jadad et al. [28] and Petrén et al. [29]. The article quality was judged as low, medium, or high based on characteristics including study design, sample size, selection description, valid methods, method of error analysis, blinding in measurements, and adequate statistics. The assessment was performed by the two examiners, and in case of discrepancy, a consensus decision was taken following discussion.

## Data extraction and analysis

Information was extracted from each included study on: number of cleft patients; type and side of unilateral cleft; number of control patients; type of control patients; and means and standard deviations for MD tooth dimensions on the cleft side, non-cleft side, and control teeth of all teeth measured (central incisors to second molars for each side). The primary outcome measure was the mean difference in MD tooth dimensions.

The data were subsequently entered into the metaanalysis software of the Cochrane Collaboration (RevMan 4.2.8, released 8 July 2005). Using the fixed-effects model, forest plots were drawn and significance tests carried out (calculating P values) comparing MD tooth sizes of the cleft versus the non-cleft side in the CLP patients, the cleft side in CLP patients versus the same side in the control patients, and the non-cleft side in CLP patients versus the same side in the control patients. The results of individual studies were statistically combined into a single measure, a feature distinctive of meta-analysis. A weighted mean difference was calculated, taking into account sample size, as well as 95 % confidence intervals for each measurement.

Heterogeneity tests were also performed. If confidence intervals for the results of individual studies (depicted graphically using horizontal lines) have poor overlap, this generally indicates the presence of statistical heterogeneity. More formally, statistical tests for heterogeneity are available. These include  $\chi^2$  tests as well as calculation of  $I^2$ . The  $\chi^2$  test is based on the sum of the squared difference between the treatment effect of each individual trial and overall treatment effect, weighted by the inverse of the variance in each trial. It assesses whether observed differences in results are compatible with chance alone. A low *P* value (or a large  $\chi^2$  statistic relative to its degree of freedom) provides evidence of heterogeneity of treatment effects (variation in effect estimates beyond chance) [30].

A more useful statistic for quantifying inconsistency, and present in the forest plots, is  $I^2 = [(Q - df)/Q] \times 100\%$ , where Q is the  $\chi^2$  statistic and df is its degree of freedom [31, 32]. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50 % may be considered substantial heterogeneity [30].

# Results

# Results of literature search

The search strategy resulted in a total of 178 articles. The articles were narrowed down to 17 after the initial exclusion based on the content of the abstract. These 17 articles were read and examined in detail, and following consideration of the inclusion criteria, a total of four articles [1, 11, 16, 33] were identified for inclusion in the meta-analysis. Figure 1 provides an overview of the literature search and article selection in the form of a flow diagram. Table 1 gives a summary of the studies included in the meta-analysis. Using the quality analysis, three of the studies were classified as having medium quality [1, 11, 16] while one was classified as having low quality [33].

Cleft versus non-cleft side (Figs. 2 and 3)

When comparing MD tooth sizes of the cleft side versus the non-cleft side in the non-syndromic unilateral CLP patients, one can see several differences. In the maxillary dentition, the central incisors, lateral incisors, and first molars are significantly larger on the non-cleft than on the cleft side. All of these results however show low homogeneity. In the mandibular dentition, the central and lateral incisors, and first and second premolars are larger on the cleft than on the non-cleft side. All of these results show high homogeneity except for the lateral incisors.

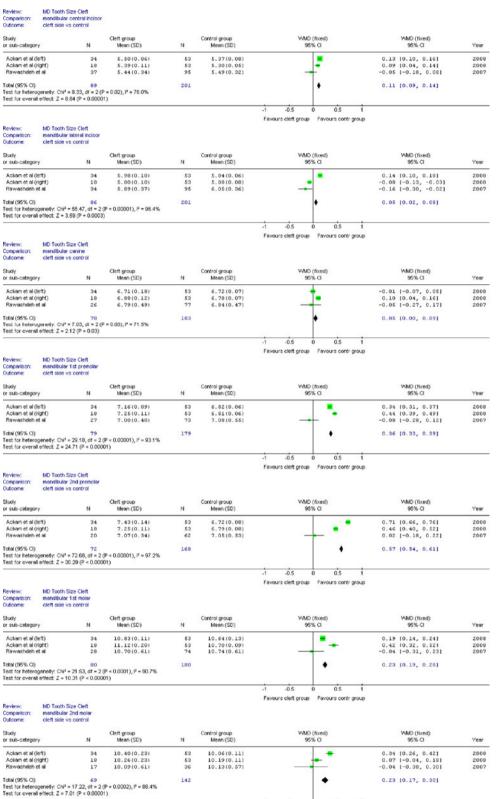
Cleft side versus control (Figs. 4 and 5)

When comparing MD tooth sizes of the cleft side in the nonsyndromic unilateral CLP patients versus the same side in the control patients, one can see the following differences. Maxillary second molars and first and second premolars of the cleft side in non-syndromic unilateral CLP patients are larger than in control patients, while the maxillary central and lateral incisors are smaller. As regards the mandibular dentition, all of the mandibular teeth are larger on the cleft side in non-syndromic unilateral CLP patients than in control patients. These results present low homogeneity.

Non-cleft side versus control (Figs. 6 and 7)

When comparing MD tooth sizes of the non-cleft side in the non-syndromic unilateral CLP patients versus the same side in the control patients, a similar trend is seen as for the cleft side versus the control patients. In the maxillary arch, all teeth except for the central incisors are larger in the nonsyndromic unilateral CLP patients than in the control patients but with a low homogeneity seen in the results. The central incisors are larger in the control patients, again with a low homogeneity. In the mandibular arch, all teeth are larger in the non-syndromic unilateral CLP patients than in the control patients, except for the mandibular lateral incisors which are larger in the control patients. Low homogeneity is again seen here apart from the results for the mandibular first molars.

Fig. 4 Forest plots representing MD tooth dimensions for the maxillary arch on the cleft side in unilateral CLP patients and the same side in control patients. The studies are listed in chronological order and refer to the studies summarized in Table 1. Shown for every study is the sample size (N), weighted mean difference (WMD) between the cleft and non-cleft side, as well as the 95 % confidence interval (95 % CI) for each measurement. The diamonds represent the overall WMD and 95 % CI.  $I^2$  values and  $\chi^2$  (Chi<sup>2</sup>) values (for heterogeneity) and p values (for statistical significance) are shown below each forest plot



0 Favours cleft group Favours contr group

0.5

-0.5

Fig. 5 Forest *plots* representing MD tooth dimensions for the mandibular arch on the cleft side in unilateral CLP patients and the same side in control patients. The studies are listed in chronological order and refer to the studies summarized in Table 1. Shown for every study is the sample size (N), weighted mean difference (WMD) between the cleft and non-cleft side, as well as the 95 % confidence interval (95 % CI) for each measurement. The diamonds represent the overall WMD and 95 % CI.  $I^2$  values and  $\chi^2$  (Chi<sup>2</sup>) values (for heterogeneity) and p values (for statistical significance) are shown below each forest plot

Study	rs control	Cleft group	1000	Control group	WMD (fixed)	VMD (fixed)	12.20-0
or sub-category Ackam et al (left)	N 34	Mean (SD) 8.28(0.11)	N 53	Mean (SD) 8.46(0.07)	95% CI	95% Cl	Year 2008
Ackam et al (right) Lewis et al Rawashdeh et al	10 30 31	8.22(0.16) 8.39(0.66) 8.20(0.64)	53 30 105	8.43(0.07) 9.33(0.53) 8.68(0.55)		-0.21 [-0.29, -0.13] -0.94 [-1.24, -0.64] -0.48 [-0.73, -0.23]	200
otal (95% CI)	113		241			-0.20 [-0.24, -0.17]	
est for heterogeneity: Chi <sup>a</sup> est for overall effect Z = 1	= 28.72, df = 3 ( 1.13 (P < 0.000	(P < 0.00001), P = 89.6% 01)					
					-4 -2 0 2 4 Favours cleft group Favours contr group		
Review: MD Tooth S Comparison: maxillary la Dutcome: cleft side v	teral incisor						
Study vr sub-category	N	Cleft group Mean (SD)	N	Control group Mean (SD)	VAMD (fixed) 95% CI	VMD (fixed) 95% Cl	Year
Ackam et al (left) Ackam et al (right)	34 18	5.56(1.42) 6.94(0.57)	53 53	6.60(0.07) 6.65(0.07)	<u>-</u>	-1.04 [-1.52, -0.56] 0.29 [0.03, 0.55]	2008
Lewis et al Rawashdeh et al	30 24	5.84(0.92) 5.61(0.73)	30 92	7.45(0.50) 6.85(0.56)	<b>-</b>	-1.61 [-1.98, -1.24] -1.24 [-1.55, -0.93]	2008 2007
otal (95% Cl) est for heterogeneity: Chi*	106 = 89.95, df = 3 (	(P < 0.00001), P = 96.7%	228		٠	-0.68 [-0.85, -0.51]	
est for overall effect Z = 7	.99 (P < 0.0000	1)			4 -2 0 2 4		
					Favours cleft group Favours contr group		
Review: MD Tooth S Comparison: maxillary c Outcome: cleft side v	anine						
Study or sub-category	N	Cleft group Mean (SD)	N	Control group Mean (SD)	VM/D (fixed) 95% Cl	VAMD (fixed) 95% Cl	Year
Ackam et al (left) Ackam et al (right)	34 19	7.45(0.24) 7.84(0.16)	53	7.64(0.07) 7.65(0.06)	+ _	-0.19 [-0.27, -0.11]	2008
Ackam et al (right) Lewis et al Rawashdeh et al	19 30 25	7.84(0.16) 8.02(0.48) 7.69(0.43)	53 30 65	7.65(0.06) 8.31(0.45) 7.86(0.51)		0.19 [0.11, 0.27] -0.29 [-0.53, -0.05] -0.17 [-0.38, 0.04]	2008
Total (95% CI)	107		201		•	-0.01 [-0.06, 0.04]	
Test for heterogeneity: Chi <sup>2</sup> Test for overall effect Z = 0	= 52.66, df = 31 1.37 (P = 0.71)	(P < 0.00001), P = 94.3%					
					-1 -0.5 0 0.5 1 Favours cleft group Favours contr group		
Review: MD Tooth S Comparison: maxillary 1 Outcome: cleft side v	st premolar						
Study or sub-category	N	Cleft group Mean (SD)	N	Control group Mean (SD)	WMD (fixed) 95% Cl	VMD (fixed) 95% Cl	Year
Ackam et al (left) Ackam et al (right) Rawashdeh et al	34 18 27	7.03(0.12) 6.99(0.10) 6.85(0.38)	53 53 41	6.80(0.08) 6.74(0.07) 7.00(0.40)	-	0.23 [0.18, 0.28] 0.25 [0.20, 0.30] -0.15 [-0.34, 0.04]	2008 2008 2007
Total (95% CI) Test for heterogeneity: Chi?	79 = 16 20, df = 21	(P = 0.0003), I <sup>2</sup> = 87.7%	147		•	0.23 (0.19, 0.26)	
Test for overall effect Z = 1					-i -us u us i		
					Favours cleft group Favours contr group		
Review: MD Tooth S Comparison: maxiliary 2 Outcome: cleft side v	nd premolar						
Study or sub-category	N	Cleft group Mean (SD)	N	Control group Mean (SD)	WMD (fixed) 95% CI	VMMD (fixed) 95% Cl	Year
Ackam et al (left) Ackam et al (right)	34 18	6.63(0.14) 6.72(0.10)	\$3 53	6.40(0.07) 6.32(0.07)	•.	0.23 [0.18, 0.28] 0.40 [0.35, 0.45]	2008
Rawashdeh et al	26	6.51(0.40)	63	6.62(0.41)	-	-0.11 [-0.29, 0.07]	2007
Total (95% CI) Test for heterogeneity: Chi <sup>2</sup> Test for overall effect: Z = 1			169			0.30 [0.27, 0.34]	
		0.5			-1 -0.5 0 0.5 1		
					Favours cleft group Favours contr group		
Review: MD Tooth S	st molar						
Review: MD Tooth S Comparison: maxillary 1 Outcome: cleff side v	/s control						
Comparison: maxillary 1 Outcome: cleft side v Study	vs control N	Cleft group Mean (SD)	N	Control group Mean (SD)	WMD (fixed) 95% Cl	VMMD (fixed) 95% Cl	Year
Comparison: maxiliary 1 Outcome: cleft side v Study or sub-category Ackam et al (left)		Cleft group Mean (SD) 9.68 (0.33) 9.89 (0.16)	53	Mean (SD) 9.72(0.11)		95% Cl -0.04 [-0.15, 0.07]	2008
Comparison: maxiliary 1 Dutcome: cleft side v Study or sub-category Ackam et al (left) Ackam et al (right) Rowoshdeh et al	N 34 18 31	Mean (SD) 9.68(0.33)	53 53 79	Mean (SD)		95% Cl -0.04 [-0.15, 0.07] 0.01 [-0.07, 0.09] -0.25 [-0.44, -0.06]	
Comparison: mealliny 1 Outcome: cleft side v Study or sub-category Ackan et al (left) Ackan et al (left) Rawashdeh et al Iotal (95% CI) Test for heterogeneity. Chi <sup>2</sup>	N 34 19 31 83 = 6.11, df = 2 (f	Mean (SD) 9.68(0.33) 9.89(0.16) 9.84(0.46)	53 53	Mean (SD) 9.72(0.11) 9.88(0.10)		95% Cl -0.04 [-0.15, 0.07] 0.01 [-0.07, 0.09]	2008
Comparison: mealliny 1 Outcome: cleft side v Study or sub-category Ackan et al (left) Ackan et al (left) Rawashdeh et al Iotal (95% CI) Test for heterogeneity. Chi <sup>2</sup>	N 34 19 31 83 = 6.11, df = 2 (f	Mean (SD) 9.68(0.33) 9.89(0.16) 9.84(0.46)	53 53 79	Mean (SD) 9.72(0.11) 9.88(0.10)	95% CI	95% Cl -0.04 [-0.15, 0.07] 0.01 [-0.07, 0.09] -0.25 [-0.44, -0.06]	2008
Comparison: maxiliary 1 Outcome: cleft side v Study or sub-category Ackam et al (6#) Ackam et al (right)	N 34 16 31 83 = 6.11, df = 2 (f 00 (P = 0.32) Size Cleft nd noler	Mean (SD) 9.68(0.33) 9.89(0.16) 9.84(0.46)	53 53 79	Mean (SD) 9.72(0.11) 9.88(0.10)		95% Cl -0.04 [-0.15, 0.07] 0.01 [-0.07, 0.09] -0.25 [-0.44, -0.06]	2008
Comparison: maxiliary 1 Outcome: cleft side v Study or sub-category Ackan et al (GH) Ackan et al (GH) Rawashdeh et al Iotal (1975-CU) Test for heterogenety: Chi <sup>2</sup> Test for heterogenety: Chi <sup>2</sup>	N 34 16 31 83 = 6.11, df = 2 (f 00 (P = 0.32) Size Cleft nd noler	Mean (SD) 9.68(0.33) 9.89(0.16) 9.84(0.46)	53 53 79	Mean (SD) 9.72(0.11) 9.88(0.10)	95% CI	95% Cl -0.04 [-0.15, 0.07] 0.01 [-0.07, 0.09] -0.25 [-0.44, -0.06]	2008
Comparison: maxiliary 1 Dutoome: cleft side v Study or sub-category Ackam et al (left) Ackam et al (left) Rawadshich et al Iotal (1976-01) Fest for heterogeneits: Chi <sup>10</sup> Fest for heterogene	N 34 16 31 93 = 6.11, dt = 2 (f 00 (P = 0.32) Size Cleft nd molar s control N 34	Mean (SD) 9.68 (0.33) 9.69 (0.16) 9.04 (0.46) 2 = 0.05), P = 67.3% Cleft group Mean (SD) 9.63 (0.22)	53 53 79 185 N 53	Mean (SD) 9.72 (0.11) 9.98 (0.10) 10.09 (0.46) 0.09 (0.46) Control group Mean (SD) 9.33 (0.22)	sers ci	95% Cl -0.04 [-0.15, 0.07] 0.01 [-0.07, 0.09] -0.25 [-0.44, -0.06] -0.03 [-0.09, 0.03] WMD (fixed) 95% Cl 0.30 [0.21, 0.39]	2008 2009 2007 2007 Year 2009
Comparison: maxiliary 1 Outcome: cleft side v Study or sub-category Ackan et al (GH) Ackan et al (GH) Rawashdeh et al Iotal (1975 CU) Test for heterogenety: Chi <sup>2</sup> Test for heterogenety: Chi <sup>2</sup> Test for heterogenety: Chi <sup>2</sup> Test for overall effect Z = 1 MC Tocht 5 Comparison: MC Tocht 5 Comparison: cleft side v Study or sub-category	N 34 18 31 83 85 86.11, df = 2 (f 00 (P = 0.32) Size Cleft nd molar s control N	Mean (SD) 9.68 (0.33) 9.69 (0.16) 9.04 (0.46) P = 0.05), P = 67.3% Cleft group Mean (SD)	\$3 \$3 79 185	Mean (SD) 9.9(0.10) 9.9(0.46) 10.09(0.46) Control group Mean (SD)	sers ci	95% Cl -0.04 [-0.15, 0.07] 0.01 [-0.07, 0.09] -0.25 [-0.44, -0.06] -0.03 [-0.09, 0.03] VMD (fixed) 95% Cl	2008 2009 2007 2007

Fig. 6 Forest *plots* representing MD tooth dimensions for the maxillary arch on the non-cleft side in unilateral CLP patients and the same side in control patients. The studies are listed in chronological order and refer to the studies summarized in Table 1. Shown for every study is the sample size (N), weighted mean difference (WMD) between the cleft and non-cleft side, as well as the 95 % confidence interval (95 % CI) for each measurement. The diamonds represent the overall WMD and 95 % CI.  $I^2$  values and  $\chi^2$  (Chi<sup>2</sup>) values (for heterogeneity) and p values (for statistical significance) are shown below each forest plot

Review: MD Tooth Size Comparison: maxillary centri Outcome: noncleft side v	al incisor						
Study or sub-category	N	Cleft group Mean (SD)	N	Control group Mean (SD)	VMMD (fixed) 95% Cl	VMD (fixed) 95% Cl	Vear
Ackam et al (left) Ackam et al (right) Lewis et al Peterka et al (fem) Peterka et al (maie) Rawashdeh et al	34 18 30 32 30 38	8.48(0.11) 8.16(0.14) 8.86(0.51) 8.60(0.20) 8.60(0.40) 8.54(0.49)	53 53 30 41 34 105	8.43(0.07) 8.46(0.07) 9.33(0.53) 8.70(0.50) 9.00(0.60) 8.68(0.55)		0.05 [0.01, 0.09] -0.30 [-0.37, -0.23] -0.47 [-0.73, -0.21] -0.10 [-0.27, 0.07] -0.40 [-0.65, -0.15] -0.14 [-0.33, 0.05]	2008 2009 2000 1983 1983 2007
Total (95% Cl) Test for heterogeneity: Chi <sup>a</sup> = 93 Test for overall effect: Z = 3.79	182 1.17, dt = 5 (P = 0.0001	(P < 0.00001), P = 94.6% )	316		•	-0.06 [-0.10, -0.03]	
					-1 -0.5 0 0.5 1 Favours cleft group Favours contr group		
Review: MD Tooth Size Comparison: maxillary latera Outcome: noncleft side v	l incisor						
Study or sub-category	N	Cleft group Mean (SD)	N	Control group Mean (SD)	VMD (fixed) 95% Cl	WMD (fixed) 95% CI	Year
Ackam et al (left) Ackam et al (right)	34 18	6.90(0.13) 7.32(0.22)	53 53	6.65(0.07)		0.25 [0.20, 0.30] 0.72 [0.62, 0.82]	2008
Lewis et al Peterka et al (fem) Peterka et al (male) Rawashdeh et al	30 25 17 35	7.21(0.72) 7.00(0.50) 7.00(0.60) 6.50(0.66)	30 41 35 92	7.45(0.50) 6.60(0.60) 6.90(0.50) 6.85(0.56)		-0.24 [-0.55, 0.07] 0.40 [0.13, 0.67] 0.10 [-0.23, 0.43] -0.35 [-0.60, -0.10]	2008 1983 1983 2007
Total (95% Cl) Test for heterogeneity: Chi <sup>2</sup> = 10	159 17.64, df = 5	5 (P < 0.00001), P = 95.4%	304		•	0.30 (0.26, 0.34)	
Test for overall effect: Z = 14.27	r (P < 0.000	101)			-1 -0.5 0 0.5 1		
Review: MD Tooth Size	Cleft				Favours cleft group Favours contr group		
Comparison: maxillary canin Outcome: noncleft side v							
Study or sub-category	N	Cleft group Mean (SD)	N	Control group Mean (SD)	VMD (fixed) 95% Cl	VMMD (fixed) 95% Cl	Year
Ackam et al (left) Ackam et al (right)	34 10	7.76(0.16) 7.69(0.11)	\$3 50	7.65(0.06) 7.64(0.07)		0.11 [0.05, 0.17] 0.05 [0.00, 0.10]	2008 2009
Lewis et al Peterka et al (tem)	30 31	7.88(0.44) 7.80(0.30)	30 41	8.31(0.45) 7.70(0.40)		-0.43 [-0.66, -0.20] 0.10 [-0.06, 0.26]	2008
Peterka et al (maie) Rawashdeh et al	26 27	0.10(0.30) 7.50(0.45)	35 65	8.10(0.50) 7.86(0.51)		0.00 [-0.20, 0.20] -0.36 [-0.57, -0.15]	1983 2007
Total (95% Cl) Test for heterogeneity: Chi <sup>a</sup> = 37			277		•	0.05 [0.02, 0.09]	
Test for overall effect: Z = 2.78	(P = 0.006)				-1 -0.5 0 0.5 1		
Review: MD Tooth Size	Cleft				Favours cleft group Favours contr group		
Comparison: maxillary 1st pr Outcome: noncleft side v	remolar						
Study or sub-category	N	Cleft group Mean (SD)	N	Control group Mean (SD)	VMD (fixed) 95% Cl	VMID (fixed) 95% Cl	Year
Ackam et al (left) Ackam et al (right)	34 18	7.02(0.10)	53 53	6.74(0.07)		0.28 [0.24, 0.32] 0.24 [0.19, 0.29]	2008
Peterka et al (fem) Peterka et al (maie) Rawashdeh et al	32 28 29	7.00(0.10) 7.10(0.30) 6.78(0.43)	70 35 41	7.04(0.47) 7.30(0.50) 7.00(0.40)		-0.04 [-0.16, 0.08] -0.20 [-0.40, 0.00] -0.22 [-0.42, -0.02]	1983 1983 2007
Total (95% Cl) Test for heterogeneity: Chi <sup>a</sup> = 65	141		252	110010.007	•	0.23 (0.20, 0.25)	
Test for overall effect: Z = 15.74	(P < 0.000	(F 4 6 6 6 6 6 7 ), F 4 6 5 3 10 (01)			-1 -0.5 0 0.5 1		
					Favours cleft group Favours contr group		
Review: MD Tooth Size Comparison: maxillary 2nd p Outcome: noncleft side v	remola:						
Study or sub-category	N	Cleft group Mean (SD)	N	Control group Mean (SD)	VMD (fixed) 95% Cl	VMID (fixed) 95% Cl	Vear
Ackam et al (left)	34	6.77(0.11)	53	6.32(0.07)	-	0.45 [0.41, 0.49]	2008
Ackam et al (right) Peterka et al (fem) Peterka et al (maie)	18 24 18	6.65(0.10) 6.60(0.20) 6.90(0.50)	53 41 35	6.40(0.07) 6.70(0.40) 6.90(0.50)	_ <b>_</b>	0.25 [0.20, 0.30] -0.10 [-0.25, 0.05] 0.00 [-0.28, 0.28]	2008 1983 1983
Rawashdeh et al	23	6.47(0.38)	63	6.62(0.41)		-0.15 [-0.34, 0.04]	2007
Total (95% CI) Test for heterogeneity: Chi <sup>a</sup> = 10 Test for overall effect: Z = 21.13	117 6.13, df = 4 8 (P < 0.000	4 (P < 0.00001), P = 96.2% 101)	245		•	0.33 [0.30, 0.36]	
					-1 -0.5 0 0.5 1 Favours cleft group Favours contr group		
Review: MD Tooth Size Comparison: maxiliary 1 st m Outcome: noncleft side v	olar				Favours cleft group Favours contr group		
Study or sub-category	N	Cleft group Mean (SD)	N	Control group Mean (SD)	VMD (fixed) 95% Cl	WMD (fixed) 95% Cl	Year
Ackam et al (left) Ackam et al (right)	34 18	10.16(0.11) 10.07(0.12)	53 53	9.88(0.10) 9.72(0.11)		0.28 [0.23, 0.33] 0.35 [0.29, 0.41]	2008
Peterka et al (fem) Peterka et al (maie)	32 30	10.50(0.70) 10.60(0.60)	41 35	10.20(0.60) 10.50(0.50)		0.30 [0.00, 0.60] 0.10 [-0.17, 0.37]	1983 1983
Rawashdeh et al Total (95% CI)	31 145	9.92(0.54)	79	10.09(0.45)		-0.17 [-0.39, 0.05]	2007
Test for heterogeneity: Chi <sup>2</sup> = 23 Test for overall effect: Z = 15.71					5. <sup>1</sup> 0		
					-1 -0.5 0 0.5 1 Favours cleft group Favours contr group		
Review: MD Tooth Size Comparison: maxillary 2nd m Outcome: noncleft side v	nolar				naradine do Cantonata - Patropatranesi - 201		
Study or sub-category	N	Cleft group Mean (SD)	N	Control group Mean (SD)	WMD (fixed) 95% Cl	WMD (fixed) 95% CI	Year
Ackam et al (left) Ackam et al (right)	34 18	9.67(0.22) 9.81(0.27)	53 53	9.44(0.14) 9.33(0.22)	*	0.23 [0.15, 0.31] 0.48 [0.34, 0.62]	2008 2008
Peterka et al (fem) Peterka et al (male)	19 19	8.90(0.70) 9.90(0.90)	39 28	9.40(0.50) 9.70(0.70)		-0.50 [-0.85, -0.15] 0.20 [-0.28, 0.68]	1983 1983
Rawashdeh et al Total (95% CI)	20	9.46(0.52)	26 199	9,60(0.55)		-0.14 [-0.45, 0.17] 0.24 [0.18, 0.31]	2007
Test for heterogeneity: Chi <sup>a</sup> = 34 Test for overall effect: Z = 7.12	.42, df = 4	(P < 0.00001), I <sup>z</sup> = 88.4% H)					
					-1 -0.5 0 0.5 1		

-1 -0.5 0 0.5 1 Favours cleft group Favours contr group

Fig. 7 Forest *plots* representing MD tooth dimensions for the mandibular arch on the noncleft side in unilateral CLP patients and the same side in control patients. The studies are listed in chronological order and refer to the studies summarized in Table 1. Shown for every study is the sample size (N), weighted mean difference (WMD) between the cleft and non-cleft side, as well as the 95 % confidence interval (95 % CI) for each measurement. The diamonds represent the overall WMD and 95 % CI.  $I^2$  values and  $\chi^2$  (Chi<sup>2</sup>) values (for heterogeneity) and p values (for statistical significance) are shown below each forest plot

vr sub-category	22	Cleft group	55	Control grcup	VMD (fixed)	WMD (fixed)	121010-0
Ackam et al (left)	N 34	Mean (SD) 5.46(0.07)	N 53	Mean (SD) 5.30(0.05)	95% CI	95% Cl 0.16 (0.13, 0.19)	Year 2008
Ackam et al (right) Peterka et al (fen)	18	5.36(0.11) 5.50(0.20)	53	5.37(0.08)	±7	-0.01 [-0.07, 0.05] 0.00 [-0.14, 0.14]	2008
Peterka et al (male) Rawashdeh et al	30 37	5.50(0.10) 5.47(0.36)	32 95	5.50(0.40) 5.49(0.32)	±	0.00 [-0.14, 0.14] -0.02 [-0.15, 0.11]	198:
tal (95% CI)	150	3.47(0.36)	257	5.45(0.32)		0.12 [0.09, 0.14]	200
est for heterogeneity: Chi <sup>2</sup> = 3 est for overall effect: Z = 9.73	9.37, df = 4 (		201			0.12 (0.09, 0.14)	
					-1 -0.5 0 0.5 1		
eview: MD Tooth Size omparison: mandibular lat utcome: noncleft side	eral incisor				Favours cleft group Favours contr group		
tudy r sub-category	N	Cleft group Mean (SD)	N	Control grcup Mean (SD)	WMD (fixed) 95% Cl	VMD (fixed) 95% Cl	Year
Ackam et al (left)	34	5.64(0.19)	53	5,88(0,08)	-	-0.24 [-0.31, -0.17]	200
Ackam et al (right) Peterka et al (fen)	18	5.86(0.11) 5.90(0.20)	53 24	5.84(0.06) 6.00(0.40)	-	0.02 [-0.03, 0.07] -0.10 [-0.27, 0.07]	2000
Peterka et al (male) Rawashdeh et al	30 33	6.10(0.20) 5.88(0.42)	32 95	5.50(0.40) 6.05(0.36)	_	0.60 [0.44, 0.76] -0.17 [-0.33, -0.01]	198
tal (95% CI)	147	0.00(0.42)	257	6.00(0.36)		-0.05 [-0.09, -0.01]	200
est for heterogeneity: Chi <sup>2</sup> = 1 est for overall effect: Z = 2.32	06.26, df = 4	(P < 0.00001), P = 96.2%	207		1	-0.05 (-0.05, -0.01)	
					-1 -0.5 0 0.5 1 Favours cleft group Favours contr group		
eview: MD Tooth Size omparison: mandibular ca utcome: noncleft side	nine				Favours cleft group Favours contr group		
tudy rsub-category	N	Cleft group Mean (SD)	N	Control grcup Mean (SD)	WMD (fixed) 95% Cl	WMD (fixed) 95% Cl	Year
Ackam et al (left)	34	6.78(0.19)	53	6.78(0.07)	+	0.00 [-0.07, 0.07]	2008
Ackam et al (right) Peterka et al (fen)	18 32	6.84(0.13) 6.60(0.10)	53 23	6.72(0.07) 6.60(0.50)		0.12 [0.06, 0.18] 0.00 [-0.21, 0.21]	2008
Peterka et al (male) Rawashdeh et al	31 30	7.00(0.30) 6.74(0.44)	32 77	7.00(0.40) 6.84(0.47)	_ <b>+</b>	0.00 [-0.17, 0.17] -0.10 [-0.29, 0.09]	198
stal (95% CI)	145		238		•	0.05 [0.01, 0.09]	.525
est for heterogeneity: Chi <sup>2</sup> = 9 est for overall effect: Z = 2.27	.87, df = 4 (F (P = 0.02)	P = 0.04), P = 59.5%					
					-1 -0.5 0 0.5 1		
eview: MD Tooth Size omparison: mandibular 1s alcome, nuncteft side	t premolar				Favours cleft group Favours contr group		
tudy r sub-category	N	Cleft group Mean (SD)	N	Control grcup Mean (SD)	VMMD (fixed) 95% Cl	WMD (fixed) 95% Cl	Year
Ackam et al (left) Ackam et al (right)	34 19	6.95(0.06)	53 53	6.81(0.06) 6.82(0.06)		0.14 (0.11, 0.17) 0.27 [0.21, 0.33]	200
Peterka et al (fen) Peterka et al (male)	29	7.10(0.20) 7.30(0.30)	24 31	7.20(0.50) 7.20(0.40)	+	-0.10 [-0.31, 0.11] 0.10 [-0.08, 0.28]	1983
Rawashdeh et al	29	6.91(0.49)	73	7.08(0.55)		-0.17 [-0.39, 0.05]	2001
otal (95% CI)	138	(P < 0.00001), P = 87.1%	234		+	0.15 (0.13, 0.18)	
rest for heterogeneity: Chi <sup>2</sup> = 3 rest for overall effect: Z = 13.0	0.90, df = 4 (	01)					
lest for heterogeneity: Chi <sup>2</sup> = 3	0.90, df = 4 (	01)			-1 -0.5 0 0.5 1 Favours cleft aroup Favours contr aroup		
est for heterogeneity: Chi <sup>2</sup> = 3 est for overall effect: Z = 13.0 teview: MD Tooth Size comperison: mandibular 2m	0.90, df = 4 ( 15 (P < 0.000 e Cleft id premolar	01)			-1 -0.5 0 0.5 1 Favours cleft group Favours contr group		
est for heterogeneity: Chill = 3 est for overall effect: Z = 13.0 teview: MD Tooth Size comparison: mandibular 2n fulcome: noncieft side tudy	0.90, df = 4 ( 15 (P < 0.000 e Cleft id premolar	Ot) Cleft group Mean (SD)	N	Control grcup Mean (SD)		WMD (fixed) 95% Cl	Year
est for heterogenetty: Ch <sup>2</sup> = 3 est for overall effect: Z = 13.0 teview: MD Tooth Size comparison: moncleft side tudy e sub-category Ackam et al (left)	0.90, df = 4 ( 15 (P < 0.000 e Cleft id premolar vs control N 34	Cleft group Mean (SD) 7. 26 (0.12)	53	Mean (SD) 6.79(0.08)	Favours cleft group Favours contr group VMMD (fixed)	95% Cl 0.47 [0.42, 0.52]	2008
extern heterogenety: Ch <sup>2</sup> = 3 est for overall effect: Z = 13.0 to both Sizz ducome: MD Tooth Sizz mandBudar 2m nuncleft side: tudy sub-ottegory Ackam et al (left) Ackam et al (right) Peters at el (right)	0.90, df = 4 ( 15 (P < 0.000 e Cleft di premolar vs control N 34 18 30	Cleft group Mean (SD) 7. 26 (0.12) 7. 06 (0.10) 7. 10 (0.10)	53 53 24	Mean (SD) 6.79(0.08) 6.72(0.08) 7.00(0.50)	Favours cleft group Favours contr group VMMD (fixed)	95% Cl 0.47 [0.42, 0.52] 0.34 [0.25, 0.43] 0.10 [-0.10, 0.30]	2000 2000 1983
est for heterogenety. Ch <sup>2</sup> = 3 est for overall effect. Z = 13.0 est for overall effect. Z = 13.0 verwer: MD Tooth Size unductore: noncleft side uudy sub-oategory Ackan et al (Pet) Ackan et al (Pet) Peteria et al (Pet) Peteria et al (Pet)	0.90, df = 4 ( 15 (P < 0.000 e Cleft di premolar vs control N 34 18	Cleft group Mean (SD) 7. 26 (0.12) 7. 06 (0.19)	53 53	Mean (SD) 6.79(0.08) 6.72(0.08)	Favours cleft group Favours contr group VMMD (fixed)	95% CI 0.47 [0.42, 0.52] 0.34 [0.25, 0.43]	2000 2000 1983 1983
extern heterogenety: Ch <sup>2</sup> = 3 ext for overall effect: Z = 13.0 weiew: MD Tooth Size utcome: monoleuta size tudow: noncleff side hudy sub-category Ackam et al (leff) Ackam et al (leff) Ackam et al (leff) Peters at et al (mae) Rewastade et al	0.90, df = 4 ( 15 (P < 0.000 e Cleft xd premolar vs control N 34 18 30 27 24 133	Of) Cett group Mean (SD) 7. 26 (0.12) 7. 26 (0.13) 7. 20 (0.10) 7. 30 (0.20) 6. 87 (0.40)	53 53 24 30	Mean (SD) 6.79(0.08) 6.72(0.08) 7.00(0.50) 7.20(0.40)	Favours cleft group Favours contr group VMMD (fixed)	95% CI 0.47 [0.42, 0.52] 0.34 [0.25, 0.43] 0.10 [-0.10, 0.30] 0.10 [-0.06, 0.26]	2000 2000 1983 1983
extern chererogenety. Ch <sup>2</sup> = 3 est for overall effect: Z = 13.0 every. MD Tooth Size unandbuder 2n utcome: noncleft side tudy sub-category Ackam et al (Pet) Ackam et al (Pet) Ackam et al (Pet) Peteria et al (Pet) Peteria et al (Pet) Rawashdeh et al catel (SS CI)	0.90, df = 4 ( 15 (P < 0.000 e Cleft ki premolar vs control N 34 18 90 27 27 133 2.24, df = 4 (	Cleft group Mean (SD) 7, 56 (6, 1.2) 7, 56 (6, 1.8) 7, 10 (6, 1.8) 7, 10 (6, 1.8) 7, 10 (6, 1.8) 6, 87 (8, 40) (P < 0,00001), P = 93.6%	53 53 24 30 62	Mean (SD) 6.79(0.08) 6.72(0.08) 7.00(0.50) 7.20(0.40)	Pavours cleft group Pavours contr group VMD (tixed) 95% Cl	95% CI 0.47 [0.42, 0.52] 0.34 [0.25, 0.43] 0.10 [-0.10, 0.30] 0.10 [-0.10, 0.30] 0.10 [-0.05, 0.25] -0.18 [-0.39, 0.03]	2008 2008 1983 1983
extern for heterogenety: Ch <sup>2</sup> = 3 ext for overall effect: Z = 13.0 eview: 8D Tooth Size omparison: noncleft side udcome: noncleft side tudy r sub-category Ackam et al (left) Ackam et	0.90, dt = 4 ( 15 (P < 0.000 e Cleft id premolar vs control N 34 18 30 27 24 133 (2.24, dt = 4 ( 13 (P < 0.000)	Cleft group Mean (SD) 7, 56 (6, 1.2) 7, 56 (6, 1.8) 7, 10 (6, 1.8) 7, 10 (6, 1.8) 7, 10 (6, 1.8) 6, 87 (8, 40) (P < 0,00001), P = 93.6%	53 53 24 30 62	Mean (SD) 6.79(0.08) 6.72(0.08) 7.00(0.50) 7.20(0.40)	Favours cleft group Favours contr group VMMD (fixed)	95% CI 0.47 [0.42, 0.52] 0.34 [0.25, 0.43] 0.10 [-0.10, 0.30] 0.10 [-0.10, 0.30] 0.10 [-0.05, 0.25] -0.18 [-0.39, 0.03]	2008 2008 1983 1983
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exterv: to Tooth Size to overall effect: Z = 13.0 tooth Size tooth Size tooth Size noncleft side tooth Size tooth Size noncleft side tooth Size no	0.90, df = 4, 1 15 (P < 0.000 e Cleft k dipremolar vs control N 34 18 30 27 24 133 (24, df = 4, 1 3 (P < 0.000 e Cleft t molar	Cleft group Mean (SD) 7, 56 (6, 1.2) 7, 56 (6, 1.8) 7, 10 (6, 1.8) 7, 10 (6, 1.8) 7, 10 (6, 1.8) 6, 87 (8, 40) (P < 0,00001), P = 93.6%	53 53 24 30 62	Mean (SD) 6.79(0.08) 6.72(0.08) 7.00(0.50) 7.20(0.40)	Pavours cleft group Pavours contr group VMD (fored) 95% Cl -1 -0.5 0 0.5 1	95% CI 0.47 [0.42, 0.52] 0.34 [0.25, 0.43] 0.10 [-0.10, 0.30] 0.10 [-0.10, 0.30] 0.10 [-0.05, 0.25] -0.18 [-0.39, 0.03]	2008 2008 1983 1983
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ext for heterogenety: $CH^2 = 3$ ext for overall effect: Z = 13.0       eview:     MD Tooth Size       omparison:     mandibular 2n       ukcome:     moncleft side       tudy     sub-ottegory       Ackam et al (left)     Ackam et al (left)       Rawashdeh et al     (me)	0.90, drf = 4, 1 5 (P < 0.000 e Cleft id premoler vs control N 34 18 32 2, 24, df = 4, 13 (P < 0.000 e Cleft it moler vs control N 34 19 2, 24, df = 4, 10 e Cleft it moler vs control N 34 19 2, 24, 35 2, 24, 35 3, 26, 35 3, 36 3, 36	Cleft group Mean (SD) 7, 26 (0, 12) 7, 06 (0, 18) 7, 10 (0, 10) 6, 67 (0, 40) (P < 0.00001), P = 93.6% 01) (Cleft group Mean (SD) 10, 66 (0, 12) 10, 67 (0, 20) 11, 20 (0, 40)	53 53 24 30 62 222 822 8 8 8 8 8 8 8 3 8 3 8 3 24	Mean (SD) 6. 79(0.08) 6. 72(0.09) 7. 00(0.50) 7. 05(0.53) 7. 05(0.53) 0.5(0.53) 10. 70(0.09) 10. 70(0.09) 11. 00(0.70)	Favours cleft group Favours contr group WMD (funed) 55% Cl 55% Cl 4 55% Cl 55% C	95% Cl 0.47 [0.42, 0.52] 0.34 [0.28, 0.43] 0.10 [-0.10, 0.30] 0.10 [-0.39, 0.03] 0.39 [0.35, 0.43] VMO (fixed) 95% Cl 0.16 [0.11, 0.21] 0.23 [0.12, 0.33]	2001 2001 198: 2007 2007 2007 2001 2001 198: 198:
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extern contrained and the set of the release of the contrained and the set of	0.90, drt = 4 (1 5 (P < 0.000) e Cleft id premolar vs control N 34 18 224, dt = 4 (1 32 224, dt = 4 (1 32 30 145 32 30 145 30	Cleft group Mean (SD) 7.26 (0.12) 7.06 (0.18) 7.10 (0.10) 7.30 (0.10) 7.30 (0.10) 7.30 (0.10) 7.30 (0.10) 7.30 (0.10) 7.30 (0.10) (P < 0.0001),P = 93.6% 01) Cleft group Mean (SD) 10.96 (0.12) 10.97 (0.20) 11.70 (0.40) 10.73 (0.68) P = 051), P = 0%	53 53 24 30 62 222 222 N N 53 53 24 32 74	Mean (SD) 6. 79(0.08) 6. 72(0.09) 7. 00(0.50) 7. 00(0.50) 7. 05(0.53) 0. 50(0.53) 10. 70(0.09) 10. 70(0.09) 11. 50(0.60)	Favours cleft group Favours contr group WMD (funed) 55% Cl 55% Cl 4 55% Cl 55% C	95% Cl 0.47 [0.42, 0.52] 0.34 [0.28, 0.43] 0.10 [-0.10, 0.30] 0.10 [-0.39, 0.03] 0.39 [0.35, 0.43] WMD (fixed) 95% Cl 0.16 [0.11, 0.21] 0.21 [-0.55, 0.45] -0.01 [-0.29, 0.27]	2008 2008 1983 1983 2007
extern beterogenety: Ch <sup>2</sup> = 2 ext for overall effect: Z = 13.0 eview: 8D Tooth Size comparisor: noncleft side uccome: noncleft side uccome: noncleft side uccome: noncleft side uccome: noncleft side data (5% Cf) ext for heterogenety: Ch <sup>2</sup> = 6 ext for overall effect: Z = 20.2 eview: 8D Tooth Size wiew: 8D Tooth Size wiew: 8D Tooth Size uccome: noncleft side uccome: noncleft side uccome: noncleft side uccome: noncleft side uccome: noncleft side	0.90, drt = 4 (1 5 (P < 0.000) e Cleft id premolar vs control N 34 18 224, drt = 4 (1 3 (P < 0.000) e Cleft t molar N 34 18 22 2, drt = 4 (P 2, 0.000) e Cleft t dial 22 30 14 22 30 14 30 22 30 14 30 22 30 30 14 30 30 30 30 30 30 30 30 30 30 30 30 30	Cleft group Mean (SD) 7.26 (0.12) 7.06 (0.18) 7.10 (0.10) 7.30 (0.10) 7.30 (0.10) 7.30 (0.10) 7.30 (0.10) 7.30 (0.10) 7.30 (0.10) (P < 0.0001),P = 93.6% 01) Cleft group Mean (SD) 10.96 (0.12) 10.97 (0.20) 11.70 (0.40) 10.73 (0.68) P = 051), P = 0%	53 53 24 30 62 222 222 N N 53 53 24 32 74	Mean (SD) 6. 79(0.08) 6. 72(0.09) 7. 00(0.50) 7. 00(0.50) 7. 05(0.53) 0. 50(0.53) 10. 70(0.09) 10. 70(0.09) 11. 50(0.60)	Pavours cleft group Favours contr group VMD (6xed) 35% Cl -1 -0.5 Favours contr group VMD (6xed) 56% Cl 95% Cl 4 4 4 4 4 4 4 4 4 4 4 4 4	95% Cl 0.47 [0.42, 0.52] 0.34 [0.28, 0.43] 0.10 [-0.10, 0.30] 0.10 [-0.39, 0.03] 0.39 [0.35, 0.43] WMD (fixed) 95% Cl 0.16 [0.11, 0.21] 0.21 [-0.55, 0.45] -0.01 [-0.29, 0.27]	2003 2000 1993 2007 2007 2007 2006 2006 2006 1993
extern: to Tooth Size and the advector of the advector and the advector and the advector and the advector and the advector advecto	0.90, drt = 4 (1 5 (P < 0.000) e Cleft id premolar vs control N 34 18 224, drt = 4 (1 3 (P < 0.000) e Cleft t molar N 34 18 22 2, drt = 4 (P 2, 0.000) e Cleft t dial 22 30 14 22 30 14 30 22 30 14 30 22 30 30 14 30 30 30 30 30 30 30 30 30 30 30 30 30	Cleft group Mean (SD) 7, 26 (0, 12) 7, 06 (0, 18) 7, 10 (0, 10) 7, 30 (0, 20) 6, 67 (0, 40) (P < 0.00001), P = 93.6% 01) (P < 0.00001), P = 93.6% 01) (Cleft group Cleft group Cleft group	53 53 24 30 62 222 222 N N 53 53 24 32 74	Mean (SD) 6. 79(0.08) 7. 00(0.50) 7. 00(0.53) 7. 05(0.53) Control group Mean (SD) 10. 70(0.09) 10. 64(0.13) 11. 00(0.60) 10. 74(0.61)	Pavours cleft group Pavours contr group VMD (bod) 35% Cl Favours cleft group Pavours contr group VMD (tod) 35% Cl Favours cleft group Pavours contr group VMD (tod) 400 (bod) 50% Cl	95% Cl 0.47 [0.42, 0.52] 0.34 [0.28, 0.43] 0.10 [-0.10, 0.30] 0.10 [-0.39, 0.03] 0.39 [0.35, 0.43] WMD (fixed) 95% Cl 0.16 [0.11, 0.21] 0.21 [-0.55, 0.45] -0.01 [-0.29, 0.27]	2006 2006 1993 2007 2007 2007 2006 2006 1993 1993
extern thereingenety: Ch <sup>2</sup> = 3 ext for overall effect: Z = 13.0 view: MD Tooth Size uccome: mandbudar 2n uccome: mandbudar 2n uccome: mandbudar 2n uccome: MD Tooth Size mandbudar 2n uccome: MD Tooth Size to Ackam et al (left) Ackam et al (l	0.90, drf = 4 (1 5 (P < 0.000) e Cleft id premoler vs control N 34 18 32 2,24, drf = 4 13 (P < 0.000) e Cleft 18 32 2,24, drf = 4 (F (P < 0.000) 145 2,27, drf = 4 (F (P < 0.000) 145 2,27, drf = 4 (F	O1) Cleft group Mean (SD) 7, 26 (0, 12) 7, 06 (0, 18) 7, 10 (0, 10) 7, 30 (0, 10) (P < 0.0001), P = 93.6% O1) Cleft group Mean (SD) 10, 96 (0, 12) 10, 97 (0, 20) 11, 20 (0, 40) 10, 73 (0, 68) 20 (51), P = 0% 1)	53 53 24 30 62 222 222 85 85 85 85 82 4 32 24 236	Mean (SD) 6. 79(0.08) 6. 72(0.09) 7. 00(0.50) 7. 00(0.50) 7. 05(0.53) 0. 05(0.53) 10. 70(0.09) 10. 70(0.09) 11. 50(0.60) 11. 50(0.61)	Pavours cleft group Favours contr group VMD (6xed) 35% Cl -1 -0.5 Favours contr group VMD (6xed) 35% Cl -1 -1 -1 -0.5 -1 -1 -0.5 -1 -1 -0.5 -1 -1 -0.5 -1 -1 -0.5 -1 -1 -1 -0.5 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1	95% Cl 0.47 [0.42, 0.52] 0.34 [0.25, 0.43] 0.10 [-0.10, 0.30] 0.10 [-0.10, 0.30] 0.39 [0.35, 0.43] WMD (fixed) 95% Cl 0.16 [0.11, 0.21] 0.23 [0.13, 0.33] 0.20 [-0.11, 0.51] 0.20 [-0.29, 0.45] 0.17 [0.13, 0.21] 0.17 [0.13, 0.21]	2000 2000 1963 2007 2007 2000 2000 2000 2000 2000 200
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## Discussion

Using meta-analyses methodology, which consists of a clearly formulated question and explicit methods to identify, select, and analyze relevant research [34], the present study demonstrates that non-syndromic unilateral CLP patients tend to have larger posterior teeth both on the cleft and the non-cleft side, when compared with the general population. This is an unexpected finding as it seems to contradict the widely held belief that CLP patients have smaller teeth than control subjects. Most articles in the literature report a tooth size reduction in CLP patients [1, 7, 11, 14, 16, 17, 19, 20, 35], although they tend to generalize results. This inconsistency of the present finding with the results of other studies may be due to the bias arising from small sample sizes of individual studies as Lewis et al. [16] have reported and an overgeneralization when it comes to interpretation of results.

Despite the general reports that teeth in CLP patients are smaller than in controls, some studies maintain that certain teeth in CLP patients are larger than in the general population, while others find no difference. Akcam et al. [1], for example, state that maxillary and mandibular premolar MD dimensions are larger in CLP than in control patients, which is in agreement with the present results. Peterka and Mullerova [33], on the other hand, report that there are no remarkable differences in the MD widths between individuals with CPL and a control group.

Although, on the whole, teeth of non-syndromic unilateral CLP patients tend to be larger than those of the general population, the present study also found that the cleft side central and lateral maxillary incisors are smaller mesiodistally than in the general population. The canines, however, noted for their developmental stability [36], do not show important differences. The finding concerning the maxillary incisors was expected and consistent with previous findings in the literature showing the central and lateral maxillary incisors to be the most affected teeth in the cleft region [1, 7, ]14, 16, 17, 19, 35]. Maxillary lateral incisors with abnormal morphology have been reported in up to 94 % of patients with cleft lip with or without cleft palate, on the cleft side [14]. Abnormal morphology of the maxillary central incisor on the cleft side has also been reported [37]. The significant size reduction in the maxillary central and lateral incisors on the cleft side of non-syndromic unilateral CLP patients could be explained on the basis that both are emerging from the medial nasal process that is claimed to be deficient [11]. In addition, direct damage during surgical repair on the permanent teeth cannot be ruled out [13, 38].

As far as the comparison between the cleft and non-cleft side is concerned, the results of the present study reveal that non-syndromic unilateral CLP patients show a trend towards smaller maxillary but larger mandibular teeth on the cleft than the non-cleft side. More specifically, it was found that central incisors, lateral incisors, and first molars in the maxilla are smaller in the cleft than in the non-cleft region. Previous studies have also cited that maxillary central and lateral incisors are smaller on the cleft side [11, 16, 19]. Sofaer [23] and Werner and Harris [7] report high levels of tooth size asymmetry between the cleft and non-cleft sides. In the mandible, analysis of the present data shows that incisors and premolars are larger on the cleft side, while the other teeth do not demonstrate any differences. Raw-ashdeh and Bakir [11] similarly found that in the mandibular arch, lateral incisor, and premolars were larger on the cleft than the non-cleft side.

An indisputable explanation as to why there are differences between tooth sizes in CLP patients and the general population has yet to be published. Several authors have suggested various propositions. Some claim that an underlying genetic link may exist between clefting and tooth size, while others maintain that there is likely to be a direct local effect on the developing tooth germs where the cleft involves the alveolus, rather than a genetic effect [19]. A hypothesis states that the underlying embryonic disturbance which leads to clefts is widely spread and can affect other tissues and organs of the body in various unpredictable ways. It may thus be expected that the influence on various units of the dentition, which are in various phases of morphogenesis and morphodifferentiation throughout the late embryonic and fetal periods, may be reflected by variations in tooth size and morphology [38]. Morphological and size irregularities of the dental crowns in individuals affected with CLP occur throughout the entire dentition and not merely in the maxillary units in the immediate area of the cleft [39]. The mandibular dentition is also affected. Whereas the most extreme dental abnormalities are almost always limited to the vicinity of the cleft, less severe abnormalities either appear in other regions or are generalized throughout the dentition [23]. If clefting was an isolated phenomenon incurred during early fetal development, the permanent teeth that form much later (especially those teeth away from the cleft site and in the mandible) should be unaffected. If, on the other hand, clefting is simply one of the more overt sequelae of a compromised growth potential, it would follow that the whole dentition would in some way be affected [7].

The results suggest that isolated CLP is not just a localized transient disruption in development. The systemic compromised growth potential is expressed in these data as alterations in tooth size and amplified asymmetry in both dental arches. It cannot be ruled out however that the cleft itself, which interferes with feeding, respiration, and many other physical and psychological functions, is not in part responsible for the observed alterations in tooth size [7].

Abnormally high levels of tooth-size asymmetry have been found in children with oral clefts. The asymmetry may be to some extent under genetic control [23]. Asymmetric development of contralateral teeth in both jaws is far more common in these children. This asymmetry has been suggested to be a milder expression of hypodontia [14]. Increased fluctuating dental asymmetry is proposed to be an indication of amplified developmental instability, such as that occurring in CLP [40]. Considering all tooth types, maxillary teeth are not inherently more asymmetric than their mandibular counterparts, even though the cleft is limited to the maxillary arch [7].

The actual differences in MD tooth size between CLP patients and the general population, although statistically significant, was on average less than 0.5 mm. Where measurement errors and reliability were evaluated by duplicate measurements, both systematic error and random error were found to be very low in each of the individual studies. A reduction in tooth size of less than 0.5 mm however was considered clinically insignificant. The only clinical significant differences seen are for the maxillary lateral incisor (cleft vs. non-cleft; cleft side vs. control) and the mandibular second premolars (cleft side vs. control).

Individual tooth dimensions are important in the clinical assessment of proportions and ratios [16]. Orthodontists aim to achieve a stable, functional, and esthetic occlusion. In order to accomplish this, the dentition has to be in proportion; this is important not only from an aesthetic standpoint but also occlusally [41]. If teeth in CLP patients were universally smaller or larger in a systematic way, then no serious complications would arise because, aesthetically, the teeth would all look in proportion and, occlusally, would articulate properly [16]. However, according to the results of this study, the degree of difference between tooth dimensions in CLP patients and in the general population varies according to tooth type.

The present meta-analysis, following the application of the inclusion criteria, only located four suitable articles. This is unfortunately a rather low number and may suggest that results should be taken with caution. Ideally, a meta-analysis with a larger number of good quality studies would be able to provide more reliable results. However, given the state of the existing literature, the present results accurately represent the data that is currently available. The quality analysis used in the present study identified three medium-quality studies and one low-quality study. Certain limitations are however present when judging quality. Firstly, the quality assessment method used was designed for randomized clinical trials while the present study does not require a randomized clinical trial design but a case-control design, which is adequate to investigate the hypothesis. Furthermore, there are limitations in carrying out blinded measurements when comparing clefts and controls because the cleft case will mostly always be recognizable. These limitations must be taken into consideration when judging the quality of the included studies.

Further research into tooth size in cleft patients is necessary as many aspects of this still remain unclear. This should involve determination of tooth sizes in bilateral and other types of cleft cases. Different tooth size patterns may be observed in these patients assuming that the bilateral condition reflects less developmental control on average than in the unilateral [7]. Other tooth size parameters should also be investigated, apart from MD tooth dimensions, which are equally as important for optimal occlusal relationships. Finally, looking into tooth sizes of the deciduous dentition would also be valuable in order to help in the understanding of clefting and tooth size differences.

# Conclusions

Non-syndromic unilateral CLP patients tend to have larger posterior teeth both on the cleft side and on the non-cleft side, when compared with the general population. Central and lateral maxillary incisors of the cleft side, however, are smaller in non-syndromic unilateral CLP patients than in the general population. The non-cleft side maxillary central and mandibular lateral incisors are also smaller in non-syndromic unilateral CLP patients than in the general population. Non-syndromic unilateral CLP patients tend to have smaller maxillary teeth on the cleft than the non-cleft side but larger mandibular teeth.

**Conflicts of interest** The authors declare that they have no conflicts of interest.

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