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Title: Morphological variability of non-syndromic operated patients affected by cleft-lip and palate: A geometric morphometric study

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Abstract: Introduction: This study compares patterns of morphological variation of the craniofacial skeleton between operated affected by cleft and unaffected individuals, aiming to discuss possible morpho-functional consequences of treatment in craniofacial development. Methods: The lateral cephalograms of 76 individuals, comprising individuals with operated unilateral cleft-lip and palate (OpC) and a sex and age matched group of individuals without cleft (NonC) were used. Thirteen landmarks were used as variables in geometric morphometric tests quantifying and describing overall shape variation, differences between group means, allometry and upper-lower face covariation. Results: The OpC group showed a broader shape variation including NonC group characteristics, but mainly retrognathic maxilla, vertically elongated face, more open mandibular angle and more closed basicranial angle. Group means differed mainly in maxillomandibular relationship. Allometry differed between groups, with the smallest OpC individuals showing the most altered morphology. Upper-lower face covariation was stronger in OpC, showing mainly vertical changes in the anterior face. Conclusion: Operated individuals affected by cleft achieve a broad range of morphologies, the most altered found in individuals with skeletal Class III and small size. Furthermore, their strongest upper-lower face shape covariation suggests that a harmonic dental occlusion could be a key factor in achieving a "normal" craniofacial morphology.

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Santiago, 1st May 2014

Re-submission of manuscript

Dear Dr. David L. Turpin,

We enclose the manuscript AJODO-S-14-00153 entitled “Morphological variability of non-syndromic operated patients affected by cleft-lip and palate: A geometric morphometric study”, which has undergone the required corrections to be accepted for publication in American Journal of Orthodontics & Dentofacial Orthopedics. Please note that the current title is slightly different from the original title assigned to the given AJODO code, which was done following the suggestion of one of the reviewers.

We sincerely appreciate the comments and suggestions to our work, which have helped to substantially improve it. We enclose a separated file containing the response to each of the comments of the reviewers, plus the list of changes made to the title page and manuscript. The tables and figures have not been changed from their original, previously submitted version.

Please note that three of the authors have more than one affiliation, which need to be acknowledged in the published article. I am moving to Faculty of Odontology next month, so my current telephone number and e-mail address will change as from then.

If you have any queries please do not hesitate to contact me.

Kind regards,



Dr. Germán Manríquez Soto
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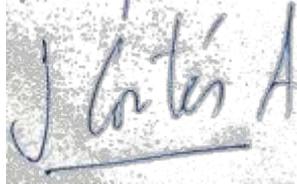
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Viviana Toro-Ibacache



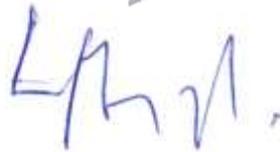
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Date: 10th February 2014

Morphologic variability of nonsyndromic operated patients affected by cleft lip and palate: A geometric morphometric study

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Introduction: In this study, we compared patterns of morphologic variations of the craniofacial skeleton between patients affected by clefts who were operated on and unaffected subjects, aiming to discuss possible morpho-functional consequences of treatment in craniofacial development. **Methods:** The lateral cephalograms of 76 subjects, comprising patients with operated unilateral cleft lip and palate (OpC) and a group matched for sex and age without cleft, were used. Thirteen landmarks were used as variables in geometric morphometric tests quantifying and describing overall shape variation, differences between group means, allometry, and upper-lower face covariation. **Results:** The OpC group showed broader shape variations including noncleft group characteristics, but mainly a retrognathic maxilla, a vertically elongated face, a more open mandibular angle, and a more closed basicranial angle. Group means differed mainly in the maxillomandibular relationships. Allometry differed between groups, with the smallest OpC patients showing the most altered morphology. Upper and lower face covariation was stronger in the OpC group, showing mainly vertical changes in the anterior face. **Conclusions:** Operated patients affected by clefts achieve a broad range of morphologies; the most altered were found in those with skeletal Class III and small size. Furthermore, their strongest upper and lower face shape covariation suggests that a harmonic dental occlusion could be a key factor in achieving “normal” craniofacial morphology. (*Am J Orthod Dentofacial Orthop* 2014;146:346-54)

Clefts of the lip and palate (CLP) are common congenital anomalies. The incidence is highly variable among populations. The highest incidence is found in Asians and Native Americans, with 1 in 500 live

births, and the lowest in Africans, with 1 in 2500 births; white, Hispanic, and Latin populations (among these, Chileans) have intermediate incidence of 1 in 1000 live births.¹⁻⁴ Cleft etiology is multifactorial, comprising both genetic and environmental factors acting during intrauterine development.⁵⁻⁷

Unilateral CLP (UCLP) is the most common cleft type.^{5,8} Morphologic alterations of operated patients with UCLP have been widely reported in the literature, of which changes in maxillomandibular relationship are the most prevalent, as described below. Since unoperated subjects have the potential to develop a “normal” (ie, skeletal Class I) maxillomandibular relationship,^{9,10} it has been proposed that altered maxillomandibular relationships are caused by the effect of surgery, particularly lip closure, on the developing bone and sutures.¹¹⁻¹³ This has led to the proposal of different protocols for the surgical management of CLP that concur in the importance of reconstructing the muscular anatomy of the lip and the soft palate after the third month of age.^{12,14-16}

Despite the differences in surgical approaches and treatment protocols, the morphologic features in operated patients with UCLP tend to be uniform. In general,

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All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.

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they are described as having a retrognathic maxilla.^{11,12,16} They also show asymmetric faces¹⁷ and altered growth of the transversal^{18,19} and vertical¹⁹⁻²¹ facial dimensions. Alterations of the cranial base have also been reported, although authors do not agree about these descriptions.^{19,20}

Among the methods used to describe and compare skull morphology in individuals affected by orofacial clefts, the use of linear morphometrics and univariate statistics is common. These have some limitations related to the difficulty in assessing separately the changes in shape and size and the impossibility of capturing the geometry of all the areas of interest.²² The advances in multivariate statistics and computer technology over recent decades have led to the development of geometric morphometrics, a statistical tool widely used for the quantitative study of the shape (ie, form minus size) of organisms. Geometric morphometrics also allows visualizing the changes in morphology associated with the variables of interest.²²⁻²⁴ This statistical tool has been applied in studies of operated individuals affected by cleft to characterize their face surface^{17,25} and that of their parents.²⁶ Geometric morphometrics has also been used to study cranial morphology in affected individuals in the frontal plane²¹ and the anteroposterior changes in shape during growth.²⁷ It has been used in mice to assess developmental integration in the skull of cleft-susceptible mouse strains.²⁸

We used geometric morphometrics analyses in this study to compare the craniofacial morphologies of a group of operated patients with UCLP with a control group of unaffected subjects with normal occlusion. We tested the general null hypothesis that patients with operated UCLP and unaffected subjects show the same patterns of craniofacial shape variations. Four parameters were studied: general shape variations, differences in mean shape between groups, allometry, and shape covariation between the upper and lower face.

MATERIAL AND METHODS

Ethical approval was granted from the Scientific Ethical Committee of the Faculty of Dentistry, University of Chile (number 2013/34) for the use of image data from the faculty's clinical records.

The sample comprised the lateral radiographs of 76 persons: 38 (19 men, 19 women) patients with nonsyndromic, operated UCLP (OpC group); and 38 (19 men, 19 women) control subjects with Class I dental occlusion and with an overall harmonious skeletal and soft-tissue profile (NonC group). All the radiographs belonged to patients from the dental clinic of the University of Chile and were taken for medical reasons (diagnosis or treatment evaluation) before the beginning of this study. The radiographs had been taken according

to the institutional protocol at the time, with pano/ceph equipment (Siemens Healthcare, Erlangen Germany) operated at 75 to 80 kV and 20 to 25 mA. The position of the head was determined by the cephalostat, fixing the position of the external acoustic meatus and nasion.

All patients were Chileans living in Santiago de Chile or the surrounding areas, representing a dihybrid sample of Amerindian-Spanish admixture with varying levels of the Amerindian component. Those with a greater Amerindian component have been associated with a higher susceptibility to clefts compared with subpopulations of white origins.²⁹ The mean ages were 13.1 ± 2.67 years in the OpC group and 12.68 ± 2.28 years in the NonC group. Patients in the OpC group had undergone cosmetic surgery of the soft tissues and orthodontic treatment without orthognathic surgery or orthopedic treatment with a maxillary-traction facial mask. The primary cleft closure of the patients in the OpC group was performed at a few clinical institutions by various surgeons in Chile. When these patients were operated on, most surgeons in Chile used an approach based on the Tennison-Randall, Skoog, and Millard techniques, with the primary lip closure performed at 3 months of age, the primary soft-palate closure at 12 months, and the hard-palate closure performed simultaneously at one of these times.³⁰

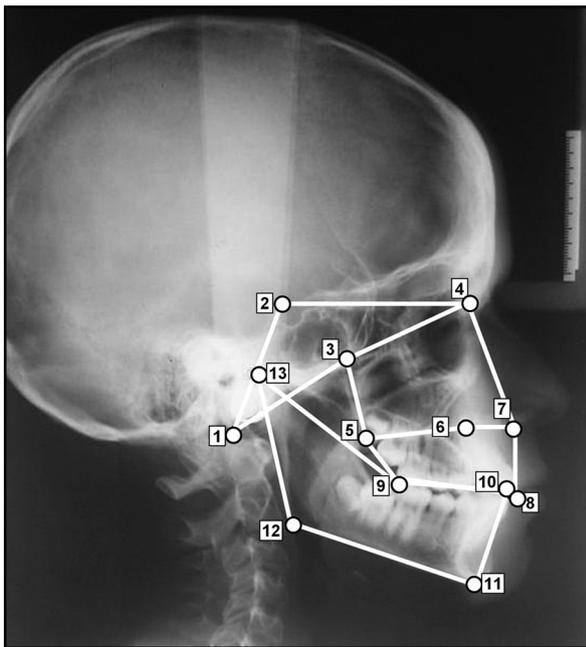
The 2-dimensional geometry of the cranial base, upper face, and mandible was captured using 13 landmarks (Table 1, Fig 1). They were selected according to the criteria of Bookstein³¹ and Dryden and Mardia³² for biologic landmark data. To improve the comparability with other studies in the field, most of the selected landmarks were based on those of Delaire et al.³³ The number of landmarks used was considered sufficient to capture key anatomic features and appropriate to increase the statistical power of analyses (see the studies of Bookstein³⁴ and Monteiro et al³⁵ for recommendations about the optimal number of landmarks and sample size). The landmarks were marked by 1 observer (A.D.M.) on a transparent acetate sheet placed on each radiograph and revised by a second observer (J.C.A.). Raw data in the format of x and y coordinates representing each landmark were digitized by 1 observer (V.T.-I.) using a mechanical digitizing system (MicroScribe; Immersion, Palo Alto, Calif). Landmark coordinates were exported as text files to be used in subsequent analyses. To assess the effect of measurement error, 16 subjects (4 men and 4 women from each of the 2 groups) were redigitized on 6 different days.

Statistical analysis

The geometric morphometric analyses were performed on shape variables. These were obtained by Procrustes fit, which consists of translation, rotation, and

Table I. Selected landmarks (a subset of landmarks was assigned to upper face [UF] and lower face [LF] for covariation analysis)

Landmark		Abbreviation	Description
1	Basion	Ba	Most anterior point of the foramen magnum
2	Clinoid posterior	CIP	Apex of the posterior clinoid process
3	Pterygoid superior (UF)	PtS	Most superior point of the pterygopalatine fossa
4	Enlow (UF)	M	Intersection between the frontonasal and the nasomaxillary sutures
5	Posterior nasal spine (UF)	PNS	Most posterior point of the bony palate
6	Nasopalatine (UF)	Np	Most superior point of the anterior wall of the nasopalatine canal
7	Anterior nasal spine (UF)	ANS	Most anterior point of the anterior nasal spine
8	Upper incisor	UI	Incisal edge of the central incisors
9	Occlusal posterior (LF)	OcP	Most posterior point of contact between both dental arches
10	Lower incisor (LF)	LI	Incisal edge of the central incisors
11	Menton (LF)	Me	Most inferior point of the menton
12	Gonion (LF)	Go	Point of maximum curvature at the gonial angle
13	Condyle posterior (LF)	CoP	Most posterior point of the head of the condyle

**Fig 1.** Selected landmarks. The wire frame used for visualization is represented as white lines.

scaling to unit size of the landmark configurations.^{32,36} These new rotated, translated, and scaled configurations lie in a manifold-like shape space from where they are orthogonally projected to a tangent Euclidian space to obtain shape variables (Procrustes coordinates) that are suitable for traditional multivariate statistics. As a result of this stage, a consensus configuration was obtained that is the reference for quantifying the shape changes of the subjects in the sample (see Fig 3 in the study of O'Higgins and Jones³⁶).

An analysis of variance (Procrustes ANOVA) was performed on the redigitized sample to assess the general

effect of sex, condition, and measurement error on shape variation^{37,38} In this subsample, there was no significant effect of sex or repeated landmark placing (Table II). The nonsignificant effect of sex was corroborated by repeating the analysis in the groups in the entire sample (data not shown). Subsequently, the subjects were not pooled by sex in the rest of the analyses (except for allometry, as explained below).

General shape variations were studied using principal component analysis.^{24,36} The differences between average landmark configurations of each group were assessed using discriminant analysis and estimating the Mahalanobis distances between group means in the original shape space.³⁸ The strength of the classification of the subjects in each group based solely on their morphology was estimated through leave-1-out cross-validation.³⁸

The effect of size on shape variation or allometry^{27,39} within groups was evaluated by multivariate regression of Procrustes coordinates on centroid size^{36,39}: ie, the square root of the sum of the squared distance of each landmark from the configuration geometric centroid.⁴⁰ Since an ANOVA of centroid size yielded a significant effect of sex (Table III), the sexes were studied separately in the control and experimental groups. To improve the visualization of the dependence of shape on centroid size, the approach of Drake and Klingenberg⁴¹ was used. According to this approach, shape scores for each group are computed by projecting the shape variables onto a line in the direction of the regression vector. The directions of the allometric vectors representing the pattern of shape changes with the size of each group were compared to assess differences in shape-size relationships.⁴²

The shape covariation between the upper and lower face within groups was assessed using 2-block partial

Table II. Procrustes ANOVA for sources of general variation in a subsample of 16 subjects

Effect	SS	MS	df	F	P value
Sex	0.019974	0.000908	22	0.64	0.8946
Condition	0.180671	0.008212	22	5.78	<0.0001
Individual	0.406597	0.001422	286	18	<0.0001
Measurement error	0.139006	0.000079	1760		

SS, Sum of squares; MS, mean square; df, degrees of freedom; F, value of the F statistic.

Table III. Two-way ANOVA of centroid size and the effects of condition and sex

Effect	SS	MS	df	F	P value
Condition	173.2	173.2	1	2.178	0.144
Sex	2992	2992	1	37.620	<0.0001
Condition and sex interaction	3.459	3.459	1	0.0435	0.835
Error	5726	79.53	72		

SS, Sum of squares; MS, mean square; df, degrees of freedom; F, value of the F statistic.

least square (PLS) analysis. This analysis estimates the extent of covariation between 2 sets of data.⁴³ To evaluate the strength of the association between the main axes of covariation, the RV coefficient (Escoufier's multivariate analog of the squared correlation⁴⁴) was calculated. Since the graphic output of the PLS analysis shows shape changes in separate and independent blocks (1 for each upper and lower face), interpretations of relative sizes and positions between blocks were not possible.

The statistical significance of differences between mean shapes, the allometric effect, and upper and lower face covariation were calculated using permutation tests with a significance level of 0.05. All geometric morphometric analyses were performed with the software MorphoJ version 1.05.⁴⁵ The main trend of shape changes was inferred using wire frames connecting landmark points, warped from the mean shape in each case to fit the configuration of the target.

RESULTS

In terms of general shape variation, the principal component analysis results show some overlap between groups (Fig 2). About a third of the patients in the OpC group showed a craniofacial variation similar to that of the NonC subjects. However, because of the much larger variability in the OpC group compared with the NonC group, 2 main clusters of subjects can be distinguished. The main axes of shape variation depict changes in the anteroposterior facial projection in relation to the cranial

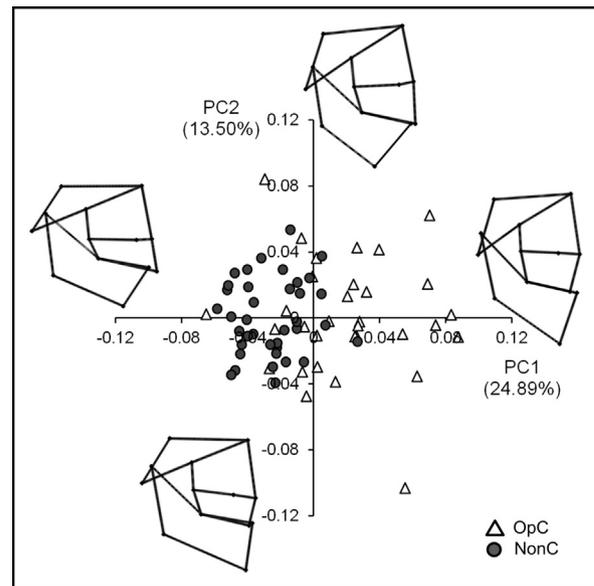


Fig 2. Principal component analysis of shape variables. The wire frames show the associated shape features at the extreme of each axis. Proportions of variance are explained in parentheses

base, the anteroposterior relationship between the maxilla and the mandible, and the vertical dimensions of the anterior portion (Na, ANS, UI; see Table 1 for abbreviations) relative to the posterior portion of the upper face (PtS, PNS, and OcP).

The discriminant analysis resulted in significant differences between the mean shape configurations of each group (Mahalanobis distance, 2.95; $P < 0.0001$). The cross-validation of the linear discriminant classification showed that 7 patients in the OpC and 5 in the NonC groups had a craniofacial shape that could have been found in the opposite group (corresponding to 18.42% and 13.15% of mismatching, respectively). The OpC group mean had a slightly more closed cranial base, an anterior crossbite, a more open mandibular angle, and a more elongated anterior face compared with the control group (Fig 3).

None of the groups showed a significant allometric effect (Table IV). The vector directions representing the shape-size relationship pattern did not differ significantly between groups either, but among the male subjects the relationship was close to the threshold value for statistical significance. Despite the P values we obtained, the plots of the regression scores against centroid size depict a different size-shape relationship between the OpC group and the controls (Fig 4), irrespective of sex. The largest subjects in both groups showed a similar maxillomandibular relationship and anterior dental occlusion, but the OpC group had

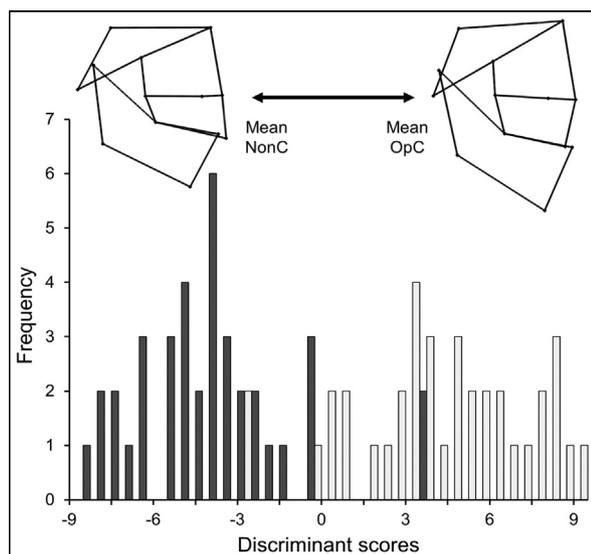


Fig 3. Cross-validated discriminant analysis results. The OpC group is represented by *light bars* and the NonC group by *dark bars*. *Wire frames* represent the mean group shape.

Table IV. Analysis of size effect on shape (allometry) within and between groups

Subjects		Regression		Allometric vector comparison	
Sex	Condition	R ²	P value	Vector angle (°)	P value
Women	OpC	0.083	0.121	94.661	0.644
	NonC	0.062	0.329		
Men	OpC	0.071	0.204	70.647	0.061
	NonC	0.088	0.087		

relatively less anteroposteriorly developed cranial base and upper face. The palate segment between Np and PNS was less developed in relation to the ANS-Np portion, and the angle LI-Me-Go was more acute. The smallest subjects, on the other hand, showed different maxillomandibular relationships, with an anterior crossbite in the OpC group. This group also had a less vertically developed posterior portion of the upper face compared with the NonC group (Fig 4).

The PLS analysis of both groups showed that the first 2 axes (ie, PLS1 and PLS2) explain more than 80% of the total covariation between the upper and lower face. Although it was not significantly strong in any group, upper and lower face shape covariation was higher in the OpC group than in the control group (Table V). Consistent with the principal component and discriminant analysis results, the patients in the OpC group showed a more vertically elongated upper face particularly in the anterior portion and a relatively

less elongated post-Np palate (Fig 5). These upper-face features are associated with a more vertically elongated midbody of the mandible and a more anteriorly positioned Me relative to LI. Compared with the OpC group, the control group showed a more antero-posteriorly developed face and post-Np palate. The associated mandibular changes keep the overall “normal” relationship between landmarks; ie, Me position is kept posterior to LI. Covariation patterns in PLS2 depict the same shape patterns in terms of vertical and anteroposterior expansion as in PLS1. The OpC group showed a less anteroposteriorly developed post-Np palate and a lower dental arch. In both groups, the main differences with PLS1 can be observed in the position of ANS with respect to the rest of the upper face (Fig 5).

DISCUSSION

In this study, we compared patterns of morphologic variation between operated patients with UCLP and a control group. Geometric morphometric tools were used to quantify, characterize, and compare craniofacial morphology in terms of general shape variation, difference between mean shapes, allometric effect, and shape covariation between the upper and lower face. The general hypothesis that operated patients with UCLP and unaffected subjects show the same pattern of shape variation was not supported by our findings. However, our results show both similarities and differences between the control and experimental groups; the causes are discussed further below.

General shape variations in the OpC group were widely spread, incorporating several combinations of features such as normal occlusion or anterior crossbite, anteroposteriorly vertically elongated or shortened face, convex or concave profile, and open or closed mandibular angle (Fig 3). In comparison, the control group showed less extreme combinations of features, several of which were shared with the OpC group. Although an overlap between groups was found, the mean shapes were significantly different between the groups. This is likely to occur because of the effect of the most distinctive feature between groups: the anterior occlusion—ie, an anterior crossbite in the OpC group. As was previously mentioned, this is the most common finding in studies.^{11,12,16,20} In terms of shape variation, our results agree with those obtained by Cortés Araya and Granic Marinov.²⁰ These authors, in a detailed cephalometric study of operated individuals with UCLP from the same geographic region as in our study, found them to have a retrusive maxilla, an anterior crossbite, and a reduced height of the posterior region of the upper face as well as posteroanteriorly more inclined palates

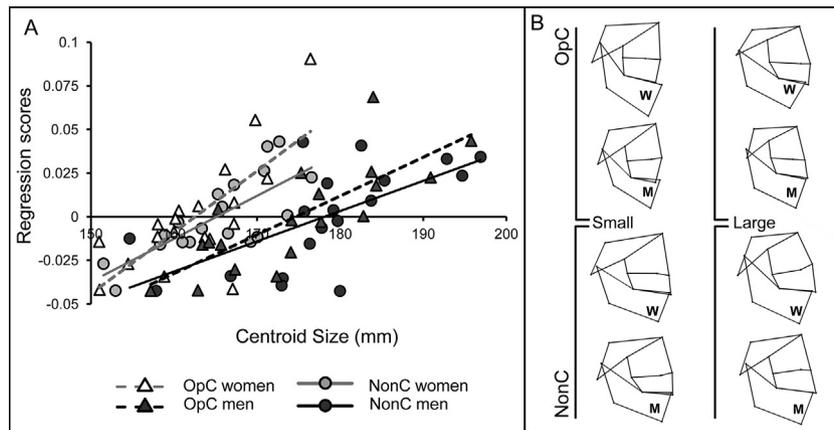


Fig 4. Allometric effect: **A**, regression of shape components against centroid size, showing the different relationships between shape and size of each group; **B**, shape changes per 30 mm of decrease (small subjects) or increase (large subjects) in centroid size. *W*, Women; *M*, men.

Table V. PLS values of upper and lower face shape covariations

Group	PLS	Singular value	P value	Total covariation (%)	Correlation	P value	RV	P value
OpC	PLS1	0.000847	0.180	51.619	0.537	0.252	0.172	0.058
	PLS2	0.000677	0.016	32.947	0.519	0.087		
	PLS3	0.000390	0.142	10.949	0.372	0.319		
	PLS4	0.000241	0.209	4.191	0.398	0.034		
	PLS5	0.000056	0.915	0.223	0.081	0.900		
	PLS6	0.000032	0.429	0.072	0.057	0.375		
NonC	PLS1	0.000549	0.617	54.644	0.536	0.248	0.103	0.593
	PLS2	0.000437	0.241	34.545	0.489	0.098		
	PLS3	0.000182	0.903	6.020	0.282	0.672		
	PLS4	0.000153	0.458	4.258	0.226	0.589		
	PLS5	0.000054	0.800	0.526	0.058	0.965		
	PLS6	0.000006	0.849	0.006	0.014	0.822		

RV, Esoufier's coefficient.

relative to the anterior portion of the cranial base. However, we found different combinations of cranial base morphology, with the UCLP patients showing a relatively more closed basicranial angle compared with the more open one found by the mentioned authors. This difference between studies and the broader range of basicranial morphology that we found can be related to the different methods used. Geometric morphometrics analyzes differences in the complete geometry of a structure, whereas traditional cephalometric approaches use linear measurements and angles as separate variables describing the form of the structure.

Allometry, or shape changes with size, was not significantly different between groups. However, differences were found in the shape of the smallest subjects, who were not necessarily the youngest ones. The patients in the OpC group showed the shape features characteristic of the mean group shape. Overall size did not vary

significantly between groups; this differs from the results of Horswell and Levant,¹⁹ who in a cephalometric study found a retarded growth pattern in operated individuals with UCLP. We found that the largest patients in the OpC group had a “normal” morphology, thus supporting the idea that the altered shape in operated individuals with UCLP is due to altered growth.²⁷ The altered growth of the upper face has been proposed to be caused mainly by an inappropriate reconstruction of facial and palatal musculature, depriving the maxilla of a key developmental factor.^{13,16} The altered growth of the upper face has also been related to an individual, genetically based tendency of individuals with cleft to a relatively less developed upper face.^{26,27} Whether the altered shape in small cleft patients is due to an individual tendency cannot be fully elucidated in our study. However, it is likely that the broad shape variations and hence allometric patterns in the OpC

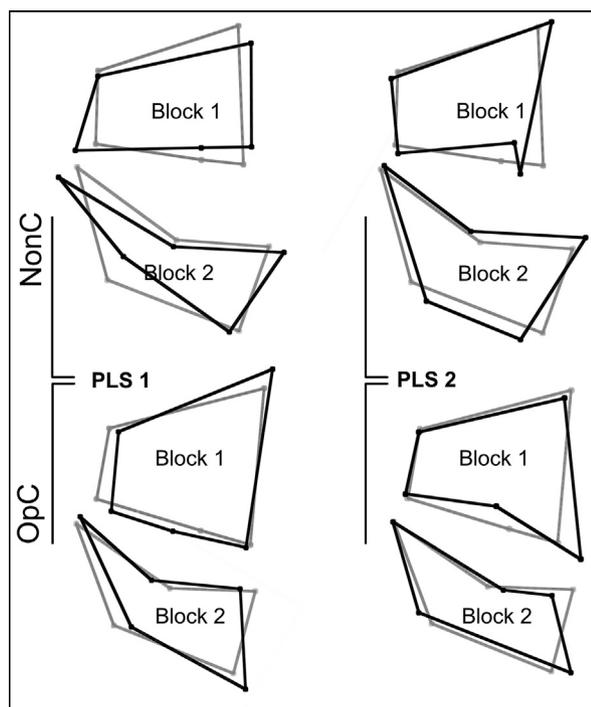


Fig 5. PLS analysis of upper and lower face covariation. Gray wire frames represent each group's mean maxillary (*Block 1*) and mandibular (*Block 2*) shapes. Magnitudes of shape changes were increased twice to improve visualization.

group relate to differences in treatment approaches, for which we did not have detailed information and hence did not control for.

The upper and lower face covariation pattern was stronger in the OpC group than in the control group, although in both cases the relationship was not significant. The almost, but not statistically, significant covariation in the OpC group was not surprising given the observed pattern of shape variation, where an important part of the sample (about a third) showed “normal” morphology. The strongest upper and lower face covariations in the OpC group were in relation to their altered shape features— anterior crossbite, retruded position of the upper face, increased anterior facial height, posteroanteriorly inclined palate, and increased mandibular angle. This suggests that the altered facial profile is the product of the integrated development of facial features in which a less developed and small upper face and possibly the cranial base are leading mandibular development.⁴⁶ The importance of the functional loading in bone morphology, by bone remodeling processes reacting to external loads, is widely acknowledged.⁴⁷⁻⁵¹ In the cranium, mastication is perhaps the main source of high, repetitive loads that act on the cranium, which develops over a long time (at

least until the end of skeletal growth). In subjects without a cleft, it has been shown that the shape of the mandible correlates with diet and at the same time with the shape of the maxilla. However, the mandible does not covary with the rest of the upper face, whose morphology correlates more to nonfunctional factors such as population history, showing that these 3 structures have a modular behavior.^{52,53} Therefore, we propose that dental occlusion plays a key role in the correlated changes between the upper and lower face. An altered occlusion could lead to limited ranges of maxillomandibular relationships in space during mastication,⁵⁴ altered dental load distributions, and thus an enhanced effect of mastication on craniofacial development, either by increasing or by decreasing the magnitude of loads being transmitted to the cranium during mastication.^{49,55} On the other hand, a normal occlusion and normal mandibular dynamics allow for a somewhat independent development of the different parts, which would achieve a harmonic relationship with each other under normal ranges of masticatory loading. Furthermore, a diminished masticatory muscle force is seen in long-faced, noncleft subjects,^{56,57} thus reducing the masticatory force input in bone development and perhaps enhancing the effect of parafunctions during feeding and speech.^{58,59} For esthetic as well as developmental reasons, the effect of an early, functional reconstruction of the labial and palatal musculature is irreplaceable. In addition, it would be worthwhile to investigate further how dental occlusion and perhaps masticatory muscle forces constrain facial development and growth, and how they can be used to improve treatment with orthopedics or physiotherapy.

CONCLUSIONS

The results of our study show that differences and also similarities can be found in the patterns of shape variations of operated patients affected by UCLP and unaffected subjects. The affected group showed a broader range of craniofacial features and a different relationship with size compared with the control group. With the control group as a reference, the main differences in the anatomy of the mandible, cranial base, and, most markedly, the upper face were found in the patients affected by clefts with a Class III maxillomandibular relationship and the smallest size. In addition to this, the strengths of covariation (greater in the study group) between the upper and lower face are the mean factors explaining the differences between the groups. These results might reflect the importance of a normal dental occlusion, in addition to a correct reconstruction of the soft tissues, in the resulting craniofacial development.

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