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Three-dimensional geometric morphometrics applied to the study of children with cleft lip and/or palate from the North East of England

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SUMMARY This prospective cross-sectional, case-controlled morphometric study investigated three-dimensional facial morphological variation among and between 8- and 12-year-old children [40 with a unilateral cleft lip and palate (UCLP), 23 with a unilateral cleft lip and alveolus (UCLA), 19 with a bilateral cleft lip and palate (BCLP), and 21 with an isolated cleft palate (ICP)]. Eighty gender- and age-matched individuals comprised the control group. The mean shape of each group was computed using generalized Procrustes analysis (GPA). Differences in shape between group means were assessed using multivariate analysis of variance and permutation tests, and shape differences were visualized for interpretation using warpings of the grand mean shape and transformation grids computed using thin plate splines (TPA).

Statistically significant differences between the mean facial shapes and forms (shape plus size) of all groups were found. The greatest difference was in the BCLP group and the second greatest in the UCLP group. The study of asymmetry indicated different degrees and differences in the nature of asymmetry that characterize different cleft lip and palate (CLP) deformities. Principal component analyses (PCA) of form space and of means, plus reflected means, were informative with respect to the differences in facial size and shape and asymmetry between these groups.

The results highlight differences in the aetiology of ICP and CLP groups and underline the potential value of statistical shape analysis in assessing the outcomes of CLP treatment.

Introduction

Oral clefts are the most common craniofacial deformity accounting for 15 per cent of all congenital abnormalities (Shapira *et al.*, 1999). The incidence of CLP in the UK is approximately 1.4 per 1000 live births (Clinical Standards Advisory Group, 1998). The aetiology of oral clefts is multifactorial involving genetic and environmental predisposing factors (World Health Organization, 2002). Two main types of clefts are recognized as being distinguished from each other, both embryologically and genetically (Fraser, 1970): a cleft lip with or without a cleft palate, and an isolated cleft palate (ICP).

Individuals with cleft lip and palate (CLP) present different facial growth patterns from those of their unaffected peers (Normando *et al.*, 1992; Semb and Shaw, 1996). However, there is debate as to how these differences arise; whether they occur as a result of intrinsic factors related to the cleft or as a consequence of cleft repair (Mars, 2004).

Surgical repair of CLP is usually carried out early in life and there is great interest in the assessment of surgical outcome (Watson, 2004; Berkowitz, 2006). It has been suggested that the causes of abnormal facial morphology may be intrinsic, iatrogenic, or functional, and there are differences of opinion regarding the relative importance of each (Capelozza Filho *et al.*, 1996; Kreiborg *et al.*, 2006). Moreover, there is debate regarding separate lip and palate repair and the timing of these in relation to subsequent facial growth (Bardach, 1990; Normando *et al.*, 1992).

Facial form in subjects with oral clefts has previously been investigated using traditional two-dimensional (2D) techniques such as radiographs (Sadowsky *et al.*, 1973; Smahel, 1984) and photographs (Asher-McDade *et al.*, 1992; Vegter *et al.*, 1997). However, these studies suffer from potential magnification errors, loss of information from the third dimension, and radiographic exposure risks. Direct facial morphometry has been undertaken on subjects with different types of oral cleft (Farkas and Lindsay, 1971; 1972; 1973), but this is time consuming and not practicable in the busy outpatient clinic. In recent years, three-dimensional (3D) imaging systems have become widely

available leading to their use in research. Duffy *et al.* (2000) reported a case-controlled 3D facial morphometric study of 8- to 11-year-old children with non-syndromic oral clefts that comprised 10 unilateral cleft lip and palate (UCLP), nine unilateral cleft lip and alveolus (UCLA), seven bilateral cleft lip and palate (BCLP), and 13 ICP and 25 matched controls. They limited their analysis to linear facial measurements and ratios in addition to subjective comparison between the group average faces. However, they experienced problems of the small sample sizes. Assessment techniques that rely on interlandmark distances and angles that produce results as tabulation of data are difficult to interpret (Bardach, 1994).

Emerging technologies in computer graphics have led to readily available imaging and visualization tools. Furthermore, the development of statistical tools for evaluating variations in shape and form (shape plus size) offers great potential in objective evaluation of CLP and of management outcome. Thus the aim of this study was to use these tools to investigate 3D facial variation including asymmetry among and between groups of 8- to 12-year-old children with UCLP, UCLA, BCLP, and ICP and a gender- and age-matched control group. This was achieved using 3D surface scans of the face from which 3D co-ordinate landmark data were taken. Variations between group means were then explored using statistical tools from the field of geometric morphometrics. These allow correct statistical evaluation of differences between group means and the exploration of asymmetry (O'Higgins and Jones, 1998; Zelditch *et al.*, 2004).

Subjects and methods

Ethical approval was granted from the Northumberland Local Research Ethics Committee (06/Q0902/36) and consent was obtained from the parents/guardians and children.

The sample comprised 103 children aged 8–12 years: 40 non-syndromic, operated subjects with UCLP; 23 with UCLA; 19 with BCLP; 21 with ICP; and 80 gender- and age-matched controls. All subjects were Caucasian and living in the North East of England. Children with non-syndromic CLP were recruited from the cleft multidisciplinary clinics at the Royal Victoria Infirmary co-ordinated clinics in the North East of England. Children with UCLP were included only if the cleft was complete. None of the affected children had undergone alveolar bone grafting at the time of data collection. The children in the control group were recruited from the Child Dental Health Department at Newcastle Dental Hospital. Care was taken to ensure that the children in the control group had harmonious balanced faces with a Class I dental occlusion, competent lips, and no craniofacial abnormalities, including hypodontia, and that none had undergone orthodontic treatment. The large sample size of the control group was intended to increase the power of the analysis between it and the various cleft subgroups (Field, 2005). This sample size has a 90 per cent power to detect an effect size (standardized difference) of 0.85 assuming a type I error rate of 5 per cent. Unfortunately, separate analyses of males and females could not be undertaken due to the small number of subjects in all cleft subgroups.

3D facial scans were captured using stereophotogrammetry (V3.0 3dMD, Atlanta, Georgia, USA). The subjects were seated 95 cm in front of the unit with the Frankfort plane raised anteriorly by 10 degrees to the horizontal to ensure a clearer picture of the nose. The capture time was 2 milliseconds that minimized changes in position or facial expression. The scan resolution was 2 megapixels. 3D scans were reflected if necessary to ensure all unilateral clefts were on the left. Further analyses used only these left and reflected, right-sided clefts. Thirty-nine anthropometric homologous landmarks were used to characterize facial and nasiolabial form. The landmarks were defined according to Farkas (1994) and Hajeer (2003). An additional paired landmark, sbal'R and sbal'L, was defined to obtain more information about the effect of the cleft and surgery on alae insertions (Table 1). The landmarks were recorded using MorphAnalyser software V 2.07. MorphAnalyser software is a 3D software package originally developed by Tiddeman *et al.* (2000) and is used in the Child Dental Health Department, Newcastle University. This software allows 3D visualization of faces, interactive placement of landmarks, and extraction of the x, y and z co-ordinates of each landmark. From these, linear and angular measurements are constructed, 3D landmark symmetry assessed, and average faces constructed by matching corresponding surfaces between specified landmarks.

The software was validated by an error assessment study carried out as part of this research. The results revealed that the software was reliable and accurate (0.15 mm or less) and compared favourably with other software employed in 3D data analysis, e.g. software-based analysis tool FAT in Glasgow with a reported error of 0.28 mm or less. Overall error from image acquisition, MorphAnalyser software, and operator error was, on average, 0.5 mm. This value was comparable with that of other 3D morphometric validation studies (Garrahy 2002; Hajeer, 2003).

The x, y and z co-ordinates of each of the recorded landmarks were extracted and saved in a text file to be submitted for further shape analysis.

Morphologika software was used to carry out shape analysis. It is an integrated software package developed by (O'Higgins and Jones, 1998) that allows geometric morphometric analysis of landmark configurations using either 2D or 3D landmark co-ordinates. Differences in shape and size between and within groups can be explored using generalized Procrustes analyses (GPA) and principal components' analyses (PCA). In addition, thin-plate spline (TPS) analysis allows interactive visualization of these differences.

The landmark co-ordinates of subjects were submitted to GPA to register (best fit) them by standardizing translational and rotational differences and scaling them to unit centroid size (O'Higgins and Jones, 1998). The resulting shape co-ordinates

were tangent projected [to minimize the deformation of the distributions following GPA (O'Higgins and Jones, 1998)] and used to explore within- and between-group variability. multivariate analysis of variance (MANOVA) and permutation analysis were used to assess between-group differences. PCA, which summarizes variation in many correlated variables in a few uncorrelated axes of shape and form (Mitteroecker *et al.*, 2004), have been carried out using a validated program, Morphologika software2v2.5 (O'Higgins and Jones, 1998). Since then it has been employed widely in shape analysis (Cardini, 2006; Marroig, 2007; Rivera, 2008). Patterns of variation were explored using the resulting principal component (PC) scores, warped mean shapes, and transformation grids from TPS. Asymmetry in each group was assessed by the Procrustes distance between group means and their reflections (Mardia *et al.*, 2000), and visualized using warping and transformation grids.

Results

Group means and differences between means

Figure 1 shows the mean faces of each group with the same texture map overlaid. Table 2 presents Procrustes and form

Table 1 Anthropometric landmarks employed in the study.

Upper facial landmarks	
Endocanthion (enR, enL)	Right and left, located at the inner commissure of the eye fissure
Exocanthion (exR, exL)	Located at the outer commissure of the eye fissure
Nasion (n)	Point in the midline of the nasal root identical to hard tissue nasion
Nasolabial landmarks	
Alare curvature (acR, acL)	Most lateral point in the curved base line of each ala
Alare (alR, alL)	Most lateral point on each alar contour where the nostril starts to be curved laterally
Columellar high point (cR, cL)	Highest point on the columella crest
Inner alare (ali'R, ali'L)	Inner marking level at the midportion of the alae where the thickness of each ala is measured
Outer alare (alo'R, alo'L)	Outer marking level at the midportion of the alae where the thickness of each ala is measured
Pronasale (prn)	Most protruded point of the apex of the nose
Subalare (sbalR, sbalL)	Point at the lower limit of each alar base where it joins the skin of the upper lip
Subalare' (sbali'R, sbali'L)	Point at the inner lower limit of each alar base
Subnasale (sn)	Midpoint of maximum concavity where the upper lip skin meets columella base
Subnasale inner (sniR, sniL)	Midpoint of columella on each side at the bottom line where the thickness of the columella is measured
Cheilion (chR–chL)	Point located at each labial commissure
Christa philtri (cphR, cphL)	Point on each elevated margin of the upper lip at the junction of the vermillion line of the upper lip and white roll line
Laberale superiorus (ls)	Midpoint of upper vermilion line
Laberale inferiorus (li)	Midpoint of the lower vermilion line
Superior labial sulcus (sls)	Deepest midline point between the mouth and the nose
Stomion Superiorus (stos)	Most inferior midpoint of the vermilion border of the upper lip
Stomion inferiorus (stoi)	Most superior midpoint of the vermilion border of the lower lip
Lower facial landmarks	
Sublabialis (sl)	Determines the lower border of the lower lip and the upper border of the chin
Pogonion (pog)	The most anterior midpoint of the chin
Menton (me)	The lowest median point on the lower border of the mandible
Aural landmarks	
Subtragion (sbtrR, sbtrL)	Most inferior point on the anterior inferior margin of the helix attachment of the face
Otobasion inferiorus (otbiR, otbiL)	Most inferior point on the ear lobe at the attachment to the cheek

The landmarks characterize the facial form but mainly the nasolabial region.

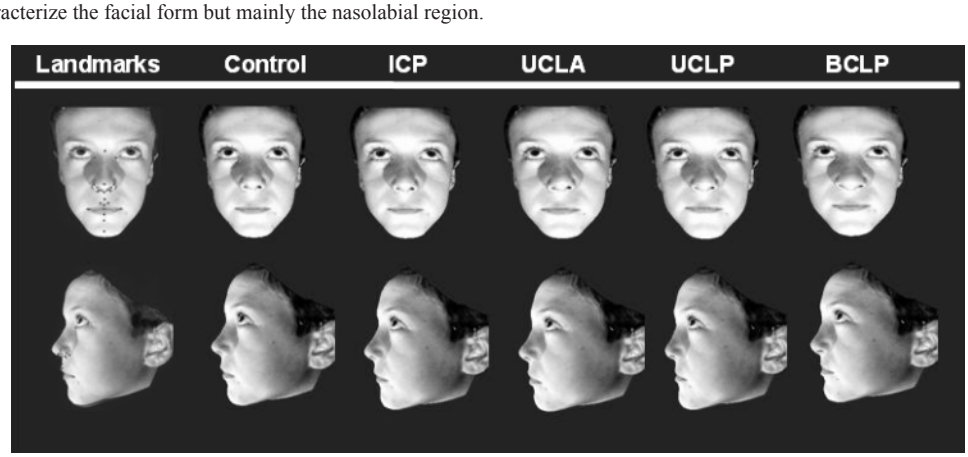

Figure 1 Landmarks and group mean shapes with warped surfaces and the same texture map.

distances between the control and cleft group means. They were all highly significant as estimated by permutation tests and MANOVA. With regard to shape, BCLP and UCLP were the most different from the controls. However, when the logarithm (ln) of the centroid size (the square root of the squared Euclidean distances from each landmark to the centroid; mean of landmark co-ordinates) was included, ICP was also different from the control mean.

The differences between group means obscure the fact that there was a considerable overlap between some groups (Figure 2). Thus, PC1 of shape from GPA/PCA of the control and UCLP groups (Figure 2A) that have a large Procrustes distance between their means, almost completely separates the scatters of individuals, while the control and ICP groups with a smaller Procrustes distance between means were less clearly distinguished (Figure 2B).

Table 2 Differences in means among the control and cleft groups; unilateral cleft lip and palate (UCLP), unilateral cleft lip and alveolus (UCLA), bilateral cleft lip and palate (BCLP), and isolated cleft palate (ICP).

	Control	UCLP	UCLA	BCLP	ICP
Control	0	0.0662	0.0375	0.0744	**0.0551**
UCLP	0.0585	0	0.0460	0.0421	0.0536
UCLA	0.0360	0.0413	0	0.0578	**0.0501**
BCLP	0.0695	0.0419	0.0556	0	0.0668
ICP	0.0273	0.0509	0.0334	0.0634	0

The diagonal line of zeros separates the results of the analysis: Procrustes distances below, and form distances above (*P* value for Procrustes distances <0.001 except for UCLA versus ICP = 0.005). Bold indicates form distances that are ~0.0015 > Procrustes distances.

PCA of tangent projected mean shape co-ordinates plus ln centroid size resulted in the plots shown in Figure 3. In Figure 3A, PC1 separates the cleft lip group means (UCLA, UCLP, and BCLP) according to severity of the defect while PC2 distinguishes the ICP mean from the rest. From Figure 4, the shape variability, represented by increasingly positive

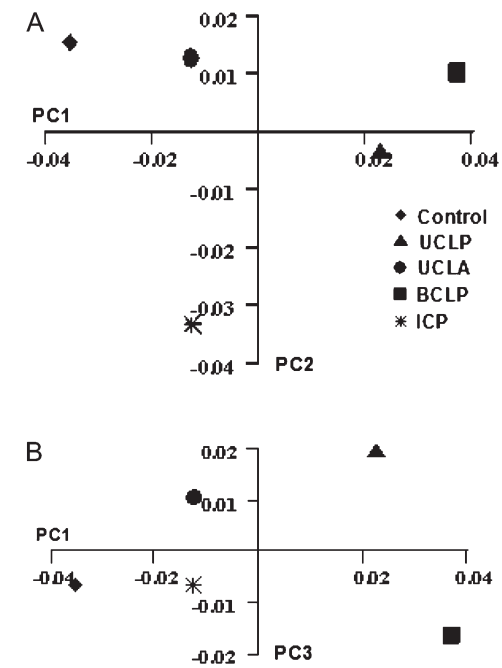

Figure 3 Principal component analysis of form space. First principal component (PC1) accounts for 55 per cent; PC2, 26 per cent; and PC3, 13 per cent of total variance. PC2 has a significant regression with the logarithm of centroid size, *P* = 0.038 and multivariate regression of shape on size accounts for 33 per cent of total variance in this analysis (Wilks' lambda *P* = 0.0715)

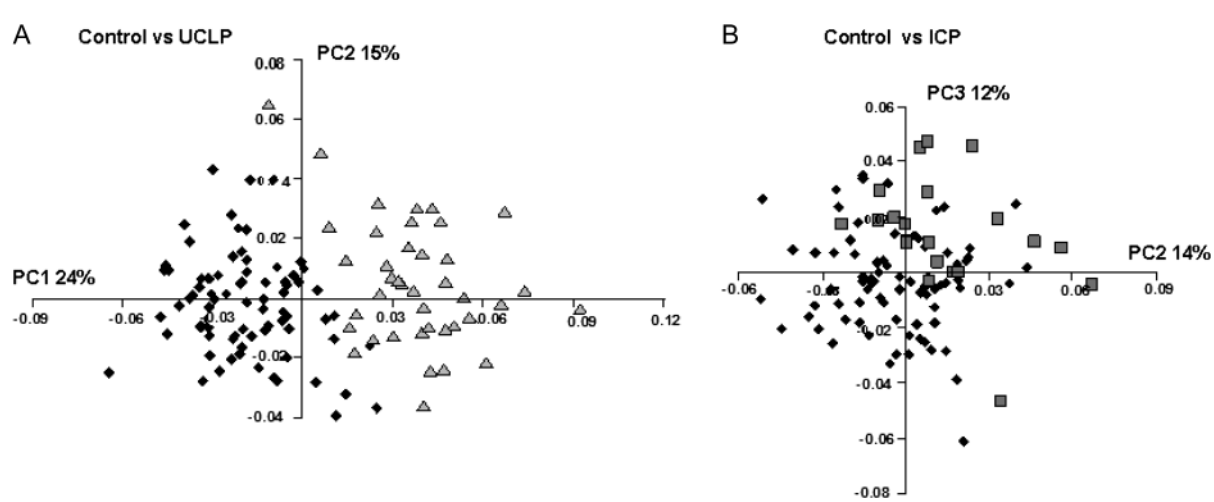

Figure 2 Variability within and between groups. (A) First principal component (PC1) from generalized Procrustes analysis and principal component analysis of shape space of the control versus the unilateral cleft lip and palate group (UCLP) separates these to a considerable degree; (B) analysis of the controls versus the isolated cleft palate group (ICP) results in scatters that are less clearly separated, most evident on the combination of PC2 versus PC3; there is a clear difference in means but overlap in distributions. Diamonds, controls; triangles, UCLP; rectangles, ICP.

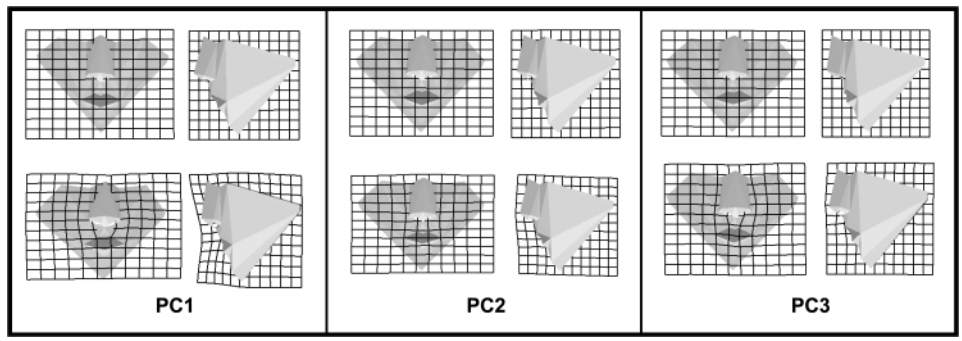

Figure 4 Shape variability in form space. First principal component analysis PC1 top = reference, PC1 score −0.04, bottom = target, PC1 score 0.04; PC2 top = 0.02, bottom = −0.04; PC3 top = 0.02, bottom = −0.02. All transformation grids are deformed ×2 and are approximately sited in the plane that shows greatest deformation. Note symmetry of deformation on PC1 and PC2 and asymmetry on PC3

PC1 scores due to a symmetric broadening and indrawing of the nasal tip and subnasal region, can be seen. In contrast, increasingly negative PC2 scores (Figure 4) represent a reduction in mid and lower face height with symmetric narrowing and projection of the nasal and subnasal region. On PC3 (Figure 3B), the control and ICP group scores shows the least asymmetry. The UCLA and UCLP groups had increasingly greater positive scores indicating progressively more asymmetry, while the BLCP group had a slightly more negative score. This represents asymmetric widening of the nose (Figure 4).

Asymmetry

The Procrustes distances between group means and their reflections indicate that the control and ICP groups at 0.0063 and 0.0090 mm, respectively, were the least, and the UCLP and UCLA groups at 0.0418 and 0.0354 mm, respectively, the most asymmetric. The BCLP group at 0.0140 mm was moderately asymmetric. The UCLP (0.042) and UCLA (0.035) group means were six times more asymmetric than the control (0.0063). GPA/PCA results in PCs 1, 3, 4, and 5 (84 per cent total variance) representing symmetric shape differences (see below) among groups, while PCs 2, 6, 7, 8, and 9 (16 per cent) represent asymmetry within groups (Figure 5). PC2 (13 per cent variance) represents an aspect of nasolabial asymmetry shared only by the UCLA and UCLP groups (Figure 5). Its influence on between-group differences (Procrustes distances, Table 2) is shown in Table 3, a comparison of Procrustes distances from GPA of symmetric and asymmetric means. The largest differences were in the distances between UCLA and UCLP and the other groups but the scale of these differences was small (approximately 10 per cent) compared with the distances between either symmetric or asymmetric means. Finally, analyses using UCLP and UCLA means derived just from left-sided clefts were virtually identical to the results from the reflected right- and left-sided clefts.

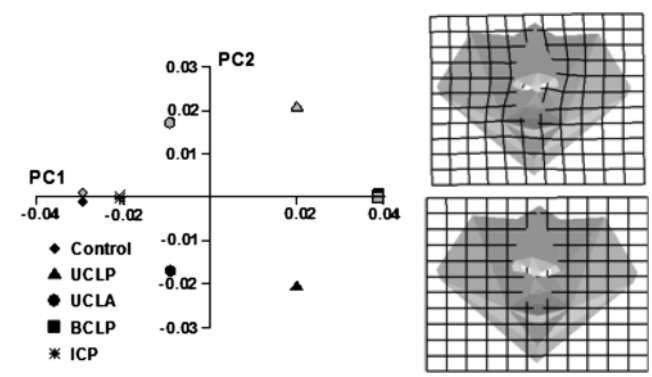

Figure 5 Asymmetry analysis. Plot of first principal component PC1 (62% total variance) versus PC2 (13%). Note that means are (black) and reflected means are (grey) for unilateral cleft lip and alveolus (UCLA) and unilateral cleft lip and palate (UCLP). Groups are separated by PC2. Reference (lower) and target (upper) Cartesian transformation grid indicates the shape variability represented by PC2 scores −0.03 to 0.03, ×2.

Table 3 Differences among symmetric means for the control and cleft subgroups; unilateral cleft lip and palate (UCLP), unilateral cleft lip and alveolus (UCLA), bilateral cleft lip and palate (BCLP), and isolated cleft palate (ICP).

	Control	UCLP	UCLA	BCLP	ICP
Control	0	0.0549	0.0319	0.0691	0.0271
UCLP	**0.0036**	0	0.04	0.0356	0.0463
UCLA	**0.0041**	**0.0012**	0	0.0518	0.0283
BCLP	0.0004	**0.0063**	**0.0038**	0	0.0630
ICP	0.0002	**0.0046**	**0.0051**	0.0004	0

Procrustes distances above and differences from Procrustes distances among asymmetric means below the diagonal cells including values of zero. Bold indicates differences <0.001.

Discussion

In this study, a 3D acquisition system was employed to capture 3D images of facial surfaces. Shape analyses of landmarks from these images provide insights into the impact of cleft aetiology on facial morphology. Use of a

control group of the same ethnicity minimized the influence of factors such as ethnicity and environment that might otherwise influence facial growth and development. Several 2D non-controlled retrospective studies have compared the treatment outcomes of subjects with UCLP in the UK with matched children with oral clefts from other European centres. These studies showed that the UK centres have poorer results (Mars *et al.*, 1987; Williams *et al.*, 1994; Grunwell *et al.*, 2000). However, different craniofacial morphologies across Europe might have influenced the outcome (Kerr and Ford, 1986).

Shaw *et al.* (1992) examined 151 British children with UCLP of a similar age to those in the current research (8–11 years) in a retrospective cross-sectional non-controlled cohort study to compare cleft repair surgical outcome between six British centres. The number of subjects included ranged between 23 and 26 from each centre. They compared craniofacial form, dental arch relationships, and nasolabial appearance. However, that study used 2D radiographs and photographs for data recording, losing the third dimension. In the present study, the implementation of shape analysis provides greater 3D detail of the impact of aetiology on facial morphology. The birth age group was extended to include five birth years to reduce the problems arising from small sample size, commonly associated with studies of oral clefts (Mars, 2004). This research can be considered to be a continuation of prior UK-based studies that extends these by examining more CLP groups, controlling data acquisition, using advanced 3D technology, and more comprehensive analyses while focusing on one centre.

The findings of the present study show differences in the aetiology and growth pattern of ICP compared with CLP groups. All affected group means differed significantly from each other and from the controls. The most severely affected groups in terms of form (Table 2) were those with defects involving the lip, alveolus, and palate (UCLP and BCLP).

Generally a small size, especially of the mandible relative to the mean, seems to be a feature of ICP (Table 2; Figures 2–3) since it results in less disruption of the nasal and subnasal regions. It has been suggested that an ICP may be secondary to a small retruded mandible, which does not allow the tongue to descend prior to secondary palate fusion during the eighth week of intrauterine life (Kreiborg and Hermann, 2002; Watson, 2004; Berkowitz, 2006; Kreiborg, *et al.*, 2006).

Dahl *et al.* (1982) demonstrated, in their cross-sectional study on unoperated Danish infants with clefts using three-projection cephalometry, that infants with ICP presented a more retrusive mandible compared with other cleft groups. The maxilla was also more retrusive but not to the same extent as the mandible. The present study showed that compared with controls and other cleft groups a small mandible (and mid face) was present in ICP. Is this a consequence of the cleft or its cause? More studies of younger and foetal cases are needed. These plus biomechanical modelling studies of facial growth secondary to ICP may eventually lead to resolution of the question.

Clefting of the lip and alveolus, with or without cleft palate, whether unilateral or bilateral, results in common symmetrical aspects of deformity of the nasal and subnasal regions represented by PC1 (Figures 3–4) and variably expressed, according to severity. The common aspects of shape differences from the control in the anterior cleft group (UCLA, UCLP, and BCLP) means reflect their common aetiology; failure of fusion of the frontal and maxillary processes, possibly due to hypoplasia of one or more processes. Alternatively, hypoplasia of processes beyond the foetal stage may be secondary to the initial defect and subsequent surgical repair and scarring, or because of altered loading secondary to a disrupted anatomy with consequent impact on facial growth. In resolving whether hypoplasia is the cause or the effect, genetic studies that examine and characterize changes in form with time relative to controls as well as functional modelling studies using finite element analysis (e.g. Kupczik *et al.*, 2007) would be informative.

Asymmetry of group mean form in this study was estimated by calculating the difference between group mean shapes and their reflection (Mardia *et al.*, 2000). Asymmetry represented a rather small aspect of the overall differences between groups (approximately 10–15 per cent) and was most pronounced in the UCLP and UCLA groups (Table 3; Figure 5). In these groups, the ala and the lateral crus of the alar cartilage on the affected side and the columella were displaced laterally with lengthening of the affected side of the nose and displacement of the dome of the crura leading to deformation of the nostril. This agrees with the 3D analysis of Garrahy (2002); however, asymmetry was not entirely confined to the nasolabial region. This study also demonstrated that facial asymmetry was present even in aesthetically pleasing faces. Therefore, the use of the midfacial plane to assess facial asymmetry is not possible since it is not usually a plane. This is important in relation to craniofacial deformities where assessment of facial asymmetry is one of the challenges faced by surgeons and orthodontists.

These present findings are in accordance with other 3D morphometric studies reported in the literature (Farkas and Cheung, 1981; Ras *et al.*, 1994; Garrahy, 2002). However, asymmetry represented a rather small aspect of the overall difference between the unilateral cleft groups (UCLP and UCLA) and the other groups (controls, BCLP, and ICP). This is a rather surprising finding given that asymmetry is a feature that is a major concern for both patients and clinicians. It likely reflects the sensitivity of our visual systems to facial form and asymmetry. Asymmetry in the cleft lip groups was not entirely confined to the nasolabial region; this implies a more generalized consequence of clefting on facial development, possibly due to tissue deficiency and biomechanical sequelae of asymmetric loading on bone growth within the functional matrix. One concern is that the UCLA and UCLP means were calculated by first reflecting

all right-sided clefts to the left, thus increasing sample size for mean estimation. This could have obscured significant directional asymmetry but the fact that the results using left-sided clefts only were virtually identical to those combining right and left strongly suggest that this is not the case.

The findings reflect differences in the aetiology and growth of ICP subjects compared with CLP groups and underlines the potential value of statistical shape analysis in assessing the outcomes of CLP treatment. Moreover, the findings highlight that post-repair, cleft lip and soft tissue defects have a greater effect on facial shape than an ICP.

It would be ideal to compare these findings with results obtained from other centres in the UK and the tools described in this study show promise in this regard. Recent changes in cleft care delivery in the UK whereby this is undertaken only in large, more centralized centres using fewer management protocols should eventually facilitate larger scale studies and provide a better understanding of surgical and orthodontic treatment outcomes. It should be noted that five surgeons using different techniques operated on the subjects in the study. However, because of the small sample size of subgroups, it was not possible to examine the effect of surgeon or technique on outcome.

Conclusions

1. All affected cleft group means differed significantly from each other and the controls, and their form reflects aetiology.
2. The most severely affected groups in terms of form were those with defects involving the lip, alveolus, and palate (UCLP and BCLP).
3. The small size of, especially, the mandible relative to the mean seems to be a feature of ICP.
4. Asymmetry accounts for approximately 10–15 per cent of the variance among the control and cleft groups.
5. Geometric morphometric methods show promise in clinical evaluation of oral clefts and the results of surgery and other interventions aimed at correcting developmental anomalies of the craniofacial complex.

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