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The Slav-cleft: A three-center study of the outcome of treatment of cleft lip and palate. Part 1: Craniofacial morphology

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A B S T R A C T

Results of a comparison of the outcomes of treatment of cleft lip and palate can be affected by growth characteristics of populations from which subjects with the clefts are derived. Moreover, conventional cephalometric techniques used in cleft studies for analysis of facial morphology provide only a partial description of shape and are confounded by biases regarding the reference structures. In this retrospective comparison, craniofacial morphology of preadolescent patients with unilateral cleft lip and palate treated in Warsaw (n = 35, age = 10.6 years, SD = 1.2), Prague (n = 38, age = 11.6 years, SD = 1.4), and Bratislava (n = 26, age = 10.5 years, SD = 1.6) were evaluated on cephalograms with the cephalometric method used in the Eurocleft study and geometric morphometrics. We found that patients treated in Warsaw showed slightly more favorable outcomes than in Prague and Bratislava. The differences were related primarily to the position of maxillary alveolar process, cranial base, mandibular angle, and soft tissues. Although no association between a component of treatment protocol and the outcome was found, it is possible that organizational factors such as participation of high-volume, experienced surgeons contributed to these results.

1. Introduction

An evaluation of craniofacial morphology in patients with orofacial clefts is part of a comprehensive assessment of treatment outcomes. Usually, it is carried out comparing the effectiveness of different methods of treatment. However, problems can arise when the comparison is performed in an international setting and patients treated in different cleft centers have also different ethnic backgrounds. In such situations, morphological differences between background populations can affect the findings. This issue was discussed in relation to the Eurocleft study, a large intercenter comparison of treatment outcomes for cleft lip and palate in northern and western Europe (Trenouth et al., 1999). Trenouth et al. (1999) compared facial growth of 9- and 12-year-olds without any cleft from several countries including Norway and England. They found that for both ages, the maxillary convexity described by the sn-ss (SNA) angle, increased by 1.7° for young persons from Norway, whereas it decreased by 2.6° for boys from Manchester, England. Thus, the maxilla was considerably more prominent in 12-year-old Norwegians than for their English peers. This finding, in turn, could affect the outcome of comparing Norwegian and English patients with clefts, because any difference in maxillary prominence detected in children with the cleft could be partly a result of distinctive craniofacial growth in background populations. A similar challenge was encountered while interpreting the results of the comparison between cleft centers in Warsaw and Oslo (Fudalej et al., 2015); a more prominent maxilla found in Norwegians could have resulted from differences in facial growth trajectories between

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the two populations or from more favorable treatment in the case of the Oslo group. A comparison of samples with the same ethnic background can overcome this problem to a certain degree.

The neighboring countries of Poland, the Czech Republic, and Slovakia, are predominantly Slavic. The term *Slavic* describes the largest Indo-European ethno-linguistic group in Europe that shares a long-term cultural continuity and speaks a set of related languages. Present-day Slavs are classified as West, East, or South Slavs, with Poles, Czechs, and Slovaks belonging to the West Slavic group (http://www.britannica.com/topic/Slav). Although the common ethno-linguistic origin of Poles, Czechs, and Slovaks does not guarantee that the craniofacial morphology of these populations is identical, the anthropometric research has revealed some differences between Slavs and other ethnic groups (e.g., Anglo-Saxons, Latinos, etc.) (Kolar, 1987). For example, despite a large within-group variability of the cephalic index, it has been demonstrated that Anglo-Saxons are significantly more scaphocephalic than Slavs. Other studies also imply that the craniofacial morphology of Slavs is different than for those from other ethno-linguistic groups. Ross (2004) evaluated craniofacial variation in Croatians, Bosnians, Macedonians, Greeks, and white Americans living in the 20th century. She found a marked differentiation among Balkan groups, which was ordered relative to ethno-linguistic ancestry – The Mahalanobis distance (D^2) between mean craniofacial shapes of Bosnians and Croats (both groups are relatively homogenous and historically to originate from the same Slavic ancestry) was 4.5, whereas D^2 between Bosnians and white Americans was 11.1, and between Bosnians and Greeks was 19.2. This indicates that ethno-linguistic *distance* is associated with the degree of differences in craniofacial shapes. Furthermore, genetic differences between European populations can be related to ethno-linguistic background. For example, Barbujani and Sokal (1990) found that out of 33 gen-frequency boundaries in Europe, 31 were coincident with linguistic boundaries. Although no direct evidence is available, it seems sensible to assume that craniofacial morphology of Poles, Czechs, and Slovaks is quite comparable.

Of the three cleft centers participating in this study, the Prague center did not compare the effects of its treatment protocol with the outcomes achieved in other centers, whereas the Bratislava center participated in one comparative investigation (Koželj et al., 2012). In contrast, the cleft team from Warsaw Institute of Mother and Child had participated in several international comparisons (Fudalej et al., 2009a, 2009b, 2015) and its outcome was found to be relatively advantageous. Assuming similarity of facial form in Polish, Czech, and Slovak populations, it seems appropriate to evaluate morphology of the craniofacial region in patients with orofacial clefts treated in Warsaw, Prague, and Bratislava. In such a comparison, the Warsaw group would serve as a reference sample. Therefore, the objective of this study was to compare facial morphology in a sample of patients with complete unilateral cleft lip and palate treated in three centers (Warsaw, Prague, and Bratislava) using different surgical protocols. The H_0 hypothesis is that facial morphology in all groups is comparable.

2. Materials and methods

2.1. Subjects

Preadolescent children with cleft lip and palate (CLP) from three Central European cleft centers – Warsaw (Poland), Prague (Czech Republic), and Bratislava (Slovakia) – were selected for this retrospective study of facial morphology. The inclusion criteria were complete unilateral cleft lip and palate (CUCLP) operated on at the respective center, and lateral cephalograms taken at about 10 years of age. The exclusion criterion was CUCLP associated with other syndromes.

The Warsaw (W) group comprised 35 subjects (25 boys and 10 girls) born between July 1993 and January 1996. They were consecutively operated on by a single experienced surgeon at the Warsaw Institute of Mother and Child between May 1994 and August 1996. In all subjects, the CUCLP was corrected with a one-stage surgical protocol. The details of the protocol were described by Fudalej et al. (2009a). Radiographic assessment was carried out at a mean age of 10.6 years (SD = 1.2, range = 8–13.6).

The Prague (P) group comprised 38 subjects (27 boys and 11 girls) taken from a series of 77 patients born between the years 2000 and 2003. They were treated consecutively by the cleft team at the Center for Treatment of Craniofacial Anomalies in Prague. The CUCLP was closed in 2 stages; closure of the lip was done at 7.3 months (SD = 5.5, range = 3.9–35.2) using the Tennison–Randall technique, whereas closure of the hard and soft palate was performed at 35.5 months (SD = 6.4, range = 18.4–54) using the Wardill–Kilner method (in some patients, the Wardill–Kilner method was combined with vomerplasty).

Five surgeons were involved in the closure of the CUCLP. No infant orthopedics (IO) was carried out.

Radiographic assessment was carried out at mean age of 11.6 years (SD = 1.4, range = 8.8 to 14.4).

The Bratislava group (B) comprised 26 subjects (19 boys and 7 girls) taken from a series of 44 patients born between the years 2000 and 2005. They were consecutively treated by the cleft team at the Clinic of Plastic and Reconstructive Surgery, Comenius University in Bratislava. The CUCLP was closed in 2 stages; closure of the lip was done using the Millard technique at 4.6 months (SD = 1.8, range = 2.4–8.5), whereas closure of the palate was performed using the Wardill–Kilner method (in some patients, the Wardill–Kilner method was combined with vomerplasty) at 12.4 months (SD = 6.4, range = 7.6–42.7). Five surgeons were involved in the treatment; a single surgeon operated on 18 patients, and 4 surgeons operated on the remaining 8 patients. Infant orthopedic treatment was performed on 23 patients (3 patients did not receive IO). Radiographic assessment was carried out at mean age of 10.5 years (SD = 1.6, range = 7.6–13.8).

A summary of the Warsaw, Prague, and Bratislava protocols is provided in Table 1.

2.2. Methods

Craniofacial morphology was analyzed on lateral cephalograms taken in centric occlusion using two methods: (1) the cephalometric protocol applied previously in the Eurocleft study (Brattström et al., 2005), and (2) geometric morphometrics (GM). In both methods, scans of cephalograms (or digital cephalograms) were downloaded into the Viewbox software, version 4 (dHAL software, Kifissia, Greece), and 27 landmarks (15 for hard tissues and 12 for soft tissues; Fig. 1) were identified by one investigator (P.F.). In line with the Eurocleft cephalometric protocol, 13 angular and 2 ratio variables were calculated to compare groups. In contrast to the cephalometric protocol, geometric morphometrics used generalized partial least-square Procrustes superimposition of the same sets of landmarks to extract coordinates of craniofacial shape, which were subsequently analyzed (Halazonetis, 2004).

2.3. Statistical analysis and method error

Descriptive statistics (means and standard deviation) were computed for each group. One-way analysis of variance (ANOVA) with Tukey–Kramer post-hoc pairwise tests was carried out to identify intergroup differences for angular and ratio variables. To

Table 1
Summary of treatment protocols in three groups.

Procedure	Warsaw (n = 35)	Prague (n = 38)	Bratislava (n = 26)
Infant orthopedics	No	No	Yes (in 23 patients)
Lip closure	9 months	7 months	4 months
Palatal closure		36 months	12 months
Alveolar bone grafting	8–11 years	8–11 years	8–11 years

investigate whether there was any relationship between facial morphology and age and treatment type, regression models were built with cephalometric variables as dependent variables and age and group as independent variables.

Principal component analysis (PCA) was carried out on Procrustes coordinates to identify patterns of craniofacial shape variation in the sample. The broken-stick criterion was used to determine the number of principal components (PCs) with statistical and biological significance. Sexual dimorphism in shape space was evaluated with permutation tests (10,000 permutations without replacement). Multivariate regression analysis was performed to investigate the relationship of shape variables (dependent variables: PCs) with age, sex, and treatment type (independent variables: age, sex, and group).

To determine the method reliability, 18 cephalograms were selected at random and digitized twice within 2 weeks. The error of cephalometric analysis was assessed with Bland–Altman plots. For geometric morphometrics, method error was expressed as the distance between duplicate digitizations in shape space compared with the total variance of the sample in shape space. Statistical analyses were done with Stata software (version 13).

3. Results

3.1. Groups

The sex proportion was comparable in the groups (males formed between 71% and 73% of each group). However, the subjects treated in Bratislava were almost 1 year younger than those treated in Prague, and the difference was statistically significant (Table 2).

3.2. Method error

Bland–Altman plots (Fig. 2a and b) demonstrated good reliability of cephalometric measurements. The mean error of the 18 duplicated digitizations, expressed as a percentage of total shape variance, was 5.02%.

3.3. Cephalometric analysis

Several differences between groups were found (Table 2). They concerned mostly hard tissues: the maxilla was more convex in the W group than in the B group (difference = 3°, p = 0.032, Fig. 3). The maxillo-mandibular relationship was more favorable in the W than P group (the ss-n-sm angle was 2.6° larger in the W group than in the P group, p = 0.003, Fig. 3). The inter-incisal angle was more obtuse in the Prague group than either the W or B group ($p < 0.001$), while maxillary incisors were less proclined in the P group than in the W group ($p < 0.001$). The only difference between the groups regarding morphology of soft tissues was the inclination of the nasal dorsum relative to Sella-Nasion line, which was less inclined in the P group than in the B group (p = 0.012).

Regression analysis showed that some intergroup differences such as the maxillomandibular relationship (ss-n-sm angle), mandibular convexity (s-n-pg angle), inclination of maxillary base (NSL/NL angle), and nasal shape (gs-prn-pgs, ns-prn-sn, and ns-

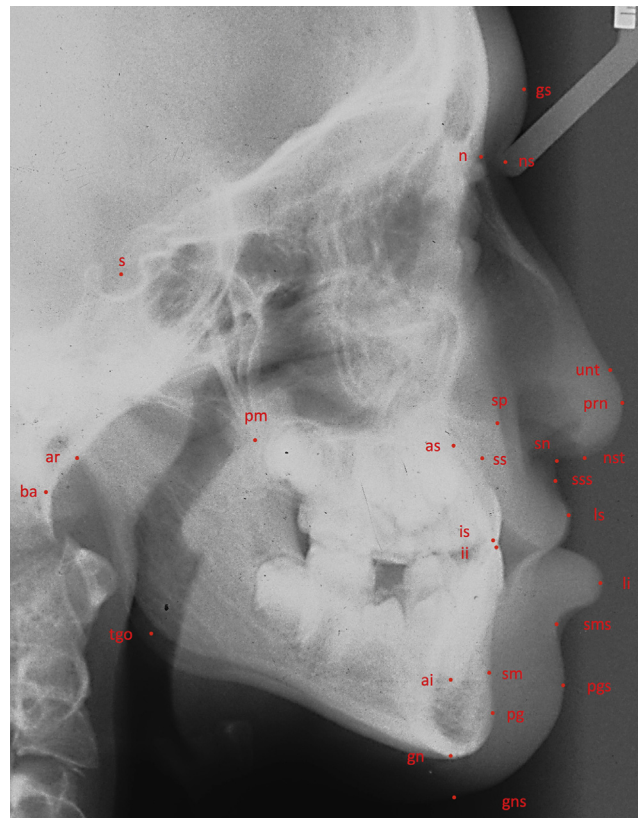

Fig. 1. Reference points and lines on lateral cephalometric radiograph. *Hard tissue reference points*: ai, apex inferius (the apex of the root of the most prominent lower central incisor); ar, articulare (the point at the intersection between the contours of the mandibular ramus and the occipital bone); as, apex superius (the apex of the root of the most prominent upper central incisors); ba, basion (the most posterior–inferior point on the clivus bone); gn, gnathion (the most inferior point on the mandibular symphysis); ii, incision inferius (the incisal edge of the lower most prominent incisor); is, incision superius (the incisal edge of the most prominent upper incisor); n, nasion (the most anterior point of the frontonasal suture); pg, pogonion (the most anterior point on the mandibular symphysis); pm, pterygo-maxillare (the intersection of the nasal floor and the posterior contour of the maxilla); s, sella (the center of the sella turcica); sm, supramentale (B-point; the deepest point on the anterior contour of the lower anterior process); sp, spina nasalis anterior (the apex of the anterior nasal spine); ss, subspinale (A-point; the deepest point on the anterior contour of the upper alveolar arch); tgo, gonion tangent point (the point of intersection between the mandibular line and the ramus line). *Soft tissue reference points*: gs, soft tissue glabella (the most anterior point on the soft tissue glabella); gns, soft tissue gnathion (the soft tissue point overlying gn); li, labrale inferius (the most prominent point on the prolabium of the upper lip); ls, labrale superius (the most prominent point on the prolabium of the upper lip); ns, soft tissue nasion (the deepest point on the frontonasal curvature); nst, nasal septum tangent point (the anterior tangent point to the tangent to the nasal septum through sn); pgs, soft tissue pogonion (the most prominent point on the chin); prn, pronasale (the most prominent point on the apex of the nose); sms, soft tissue supramentale (the point of the greatest concavity in the midline of the lower lip); sn, subnasale (the deepest point in the nasolabial curvature); sss, soft tissue subspinale (the point of greatest concavity or convexity in the midline of the upper lip); unt, upper nasal tangent point from ns. *Skeletal reference lines*: Ili, axis of lower incisors (a line from ii to ai); Ils, axis of upper incisors (a line from is to as); ML, mandibular line (the tangent to the lower border of the mandible through gn); NL, nasal line (the line through sp and pm); NSL, nasion-sella-line (the line through n and s).
(From Brattström et al., 2005; modified.)

Table 2
Results of cephalometric analysis in three groups.

Variables	Warsaw		Prague		Bratislava		p value	Differences
	Mean	SD	Mean	SD	Mean	SD		
Age	11.07	1.10	11.67	1.49	10.72	1.74	**0.032**	B–P
s-n-ss (SNA)	75.66	3.61	73.91	3.84	72.72	4.59	**0.016**	W–B
ss-n-sm (ANB)	1.33	2.76	−1.30	3.66	0.10	2.99	**0.003**	W–P
s-n-pg	75.41	4.03	76.37	3.18	73.70	2.88	**0.013**	P–B
NSL/NL	11.24	4.31	7.90	5.04	9.43	3.90	**0.009**	W–P
NSL/ML	37.30	5.59	37.63	4.83	39.68	4.50	0.157	
n-sp/n-gn × 100%	43.13	3.37	43.69	2.94	43.58	2.87	0.727	
Ils/Ili	143.03	10.89	151.82	11.07	142.33	8.61	**<0.001**	W–P, P–B
Ils/NL	105.02	8.17	96.64	9.54	101.05	5.93	**<0.001**	W–P
sss-ns-sms	5.87	2.70	5.08	3.39	4.52	2.97	0.271	
sss-ns-pgs	4.48	3.11	3.48	3.78	3.21	3.30	0.369	
gs-prn-pgs	147.77	5.79	144.88	6.22	146.39	5.74	0.157	
gs-sn-pgs	173.54	6.80	173.54	7.63	175.50	7.70	0.535	
ns-prn-sn	104.52	5.94	103.01	5.51	101.14	4.82	0.080	
nst-sn-ls	101.64	12.78	102.69	14.68	95.80	13.96	0.145	
ns-sn/ns-gns × 100%	43.31	2.40	44.26	2.81	43.94	2.51	0.365	
ns-unt/NSL	105.91	4.68	108.44	5.47	104.37	5.68	**0.012**	P–B

SD, standard deviation; W, Warsaw; P, Prague; B, Bratislava.
Bold denotes statistically significant difference.

unt/NSL angles) were related to the age of the subjects (Table 3). However, the low values of the coefficients of determination (adjusted R^2 were 0.14 or less), suggesting that age and group were relatively weakly influencing values of cephalometric measurements, should be noted.

3.4. Geometric morphometric analysis

A scatter plot of the sample in shape space is presented in Fig. 4. The broken-stick criterion showed that PC1 through PC8 were nontrivial, i.e., had statistical and biological significance (Table 4). In total, they explained 70.9% of sample variability. The first two PCs (PC1 and PC2) describe the variation of the maxilla and mandible in antero-posterior and vertical directions; PC1 refers to the variation in the combined antero-posterior and vertical direction, while PC2 referred to variation mainly in antero-posterior direction (Fig. 5). Additionally, PC1 and PC2 describe the variation of the soft tissue profile, particularly the nose and chin. Both PC1 and PC2 explain >38% of the variability of the sample. PC3 describes the variation in the cranial base, maxillary alveolus, and nose regions, while PC4 refers mainly to the variation of soft tissues below the nose. PC3 and PC4 explain >14% variability of the sample.

Permutation tests demonstrated statistically significant differences in shape space between males and females in the whole sample ($p = 0.009$), as well as in group P ($p = 0.028$). In groups W and B, no sexual dimorphism in shape space was found ($p = 0.681$ and $p = 0.092$, for W and B, respectively). Fig. 6 demonstrates consensus male and female shapes superimposed using a Procrustes fit. The largest differences are related to facial height (male faces were longer than female faces) and soft tissue convexity of the subnasal region and chin.

Intergroup differences in shape space in males and females are presented in Fig. 7. In males, permutation tests demonstrated statistically significant differences between the Warsaw and Prague groups ($p = 0.031$) and P and B groups ($p = 0.033$). In females, the difference was only between the Warsaw and Prague groups ($p = 0.044$). When males and females were pooled together, intergroup differences were found between the Warsaw and Prague groups and between the Prague and Bratislava groups ($p = 0.004$ and 0.008, for W vs. P and P vs. B comparisons, respectively; Table 5).

Multivariate regression analysis with PC1 through PC8 as dependent variables and age, group, and sex as independent variables demonstrated that the age variable affected the craniofacial variability described by PC5 and PC7, the type of treatment of the cleft (i.e. group) influenced the variability described by PC3, PC6, and PC8, and sex affected the variability described by PC1 and PC4 (Table 6). For most of the 8 PCs, coefficients of determination (R^2) were <0.2. For PC7, R^2 was 0.32. However, PC7 described only 4.2% variance in the sample in shape space.

4. Discussion

The aim of this study was to initiate an international collaboration between countries sharing a similar ethnic background. It was proposed that similarities in ethnicity would reduce differences in craniofacial morphology between background populations. Furthermore, we wished to compare the morphology of the faces of children with CUCLP treated with 3 different surgical protocols, i.e., one-stage repair (W group), two-stage repair with palatoplasty performed at 12 months (B group), and two-stage repair with palatoplasty performed at 36 months (P group).

Our results show that the H_0 hypothesis was rejected – morphology of the craniofacial region in groups is different. The cephalometric part of our investigation suggests that the maxillary prominence and maxillo-mandibular relationship are slightly more favorable in patients treated in Warsaw than at the other two centers. This is also apparent when the age of patients is accounted for. The GM supplements the cephalometric analysis by showing that fairly good maxillary prominence in the Warsaw group is accompanied by positive overbite and overjet. However, the GM has revealed a more detailed picture of morphological differences between patients treated at the three centers. First of all, contrary to expectations based on cephalometric findings, multivariate regression models show that differences in shape space are *not* related to PC1 and PC2. In CUCLP, it is common to classify treatment results as “poor” when a patient needs orthognathic surgery. It is also widely accepted that the necessity for orthognathic operation results from significant inhibition in maxillofacial growth in antero-posterior and vertical directions. Because PC1 and PC2 describe a considerable part of craniofacial variation in the antero-posterior and vertical directions, the fact that they do not discriminate well the W, P, and B groups implies that patients from Warsaw, Prague, and Bratislava are quite comparable in terms of the amount of inhibition of vertical and anterior growth of the body of the maxilla. Multivariate regression analysis demonstrates that only PC3, PC6,

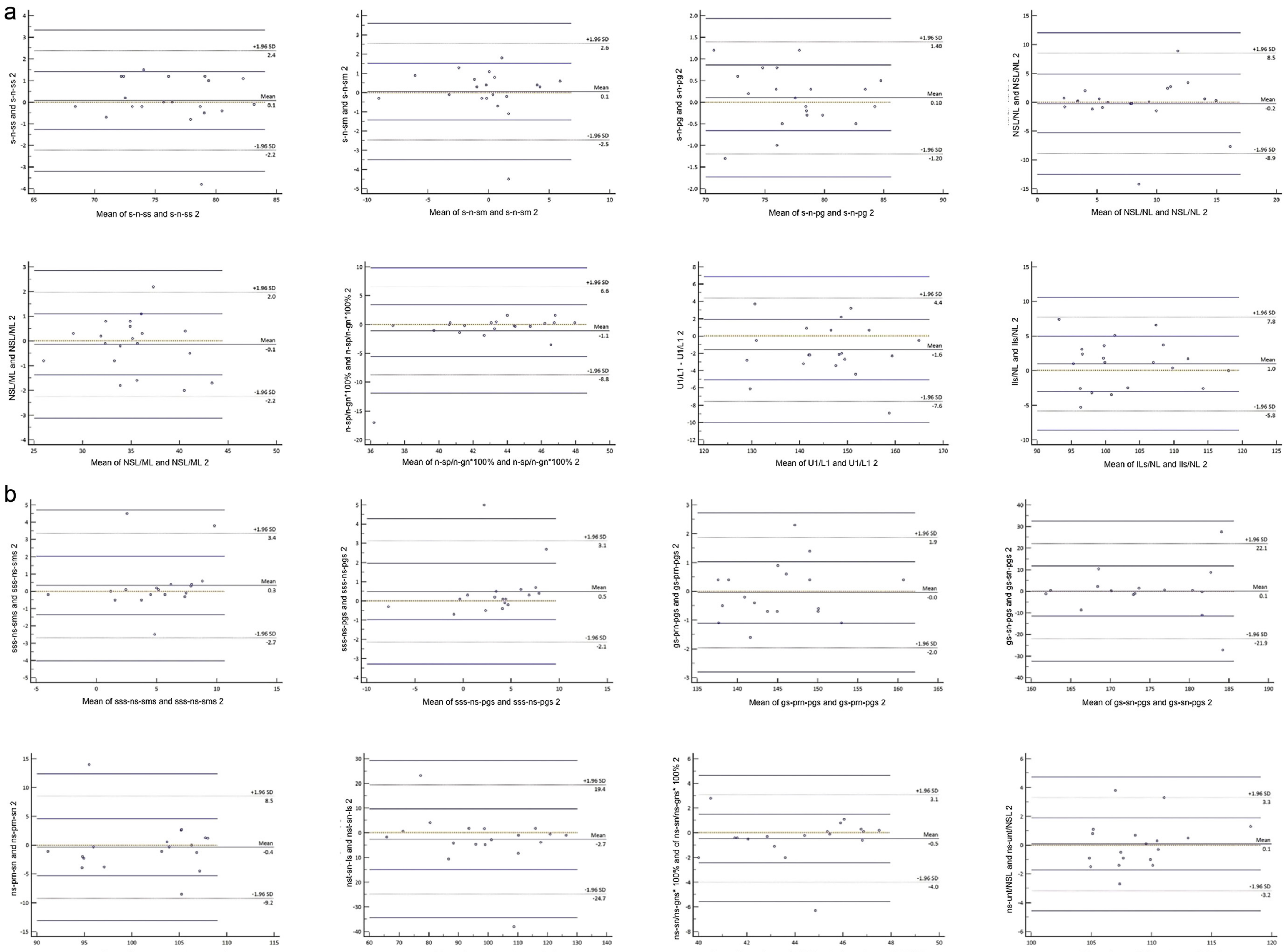

Fig. 2. Bland–Altman plots demonstrating the bias for (a) hard tissue and (b) soft tissue cephalometric variables.

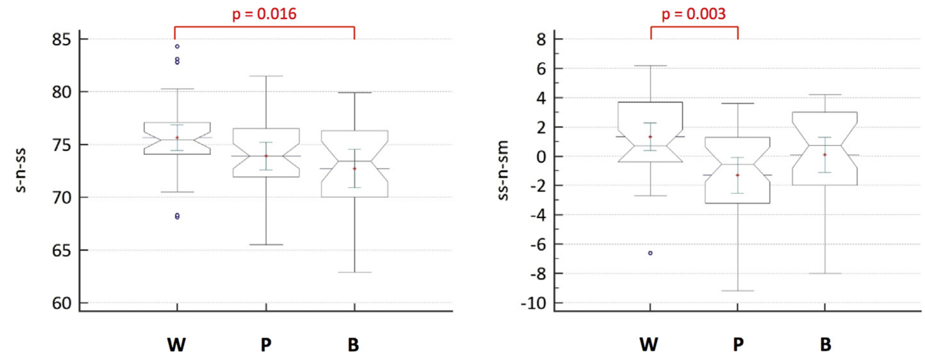

Fig. 3. Differences among Warsaw (W), Prague (P), and Bratislava (B) groups regarding maxillary prominence (s-n-ss angle) and maxilla-mandibular relationship (ss-n-sm).

Table 3
Results of regression analysis.

Dependent variables	Independent variables	Coefficient	Standard error	p	R^2 adjusted
s-n-ss (SNA)	(Constant)	76.72			0.07
	Age	0.04	0.28	0.886	
	Group (1-W, 2-P, 3-B)	−1.57	0.51	**0.003**	
ss-n-sm (ANB)	(Constant)	7.64			0.07
	Age	−0.54	0.22	**0.019**	
	Group (1-W, 2-P, 3-B)	−0.85	0.42	**0.046**	
s-n-pg	(Constant)	69.31			0.08
	Age	0.65	0.24	**0.008**	
	Group (1-W, 2-P, 3-B)	−0.69	0.45	0.127	
NSL/NL	(Constant)	23.71			0.13
	Age	−1.06	0.30	**0.001**	
	Group (1-W, 2-P, 3-B)	−1.27	0.57	**0.028**	
NSL/ML	(Constant)	43.27			0.04
	Age	−0.64	0.35	0.067	
	Group (1-W, 2-P, 3-B)	1.04	0.65	0.112	
n-sp/n-gn × 100%	(Constant)	45.68			0.01
	Age	−0.23	0.21	0.286	
	Group (1-W, 2-P, 3-B)	0.18	0.40	0.659	
Ils/Ili (U1/L1)	(Constant)	159.69			0.00
	Age	−1.20	0.78	0.128	
	Group (1-W, 2-P, 3-B)	−0.10	1.46	0.946	
ILs/NL	(Constant)	97.73			0.03
	Age	0.66	0.61	0.286	
	Group (1-W, 2-P, 3-B)	−2.21	1.14	0.056	
sss-ns-sms	(Constant)	5.11			0.01
	Age	0.12	0.22	0.580	
	Group (1-W, 2-P, 3-B)	−0.67	0.42	0.120	
sss-ns-pgs	(Constant)	4.49			0.00
	Age	0.04	0.25	0.860	
	Group (1-W, 2-P, 3-B)	−0.65	0.49	0.188	
gs-prn-pgs	(Constant)	165.40			0.14
	Age	−1.56	0.41	**0.000**	
	Group (1-W, 2-P, 3-B)	−0.81	0.79	0.305	
gs-sn-pgs	(Constant)	182.22			0.02
	Age	−0.90	0.53	0.094	
	Group (1-W, 2-P, 3-B)	1.01	1.03	0.327	
ns-prn-sn	(Constant)	118.47			0.12
	Age	−1.08	0.38	**0.005**	
	Group (1-W, 2-P, 3-B)	−1.76	0.72	**0.017**	
nst-sn-ls	(Constant)	109.56			0.01
	Age	−0.30	1.01	0.768	
	Group (1-W, 2-P, 3-B)	−3.01	1.94	0.124	
ns-sn/ns-gns × 100%	(Constant)	42.30			0.01
	Age	0.08	0.19	0.681	
	Group (1-W, 2-P, 3-B)	0.36	0.37	0.333	
ns-unt/NSL	(Constant)	91.90			0.13
	Age	1.41	0.37	**0.000**	
	Group (1-W, 2-P, 3-B)	−0.63	0.70	0.369	

Bold denotes statistical significance.

and PC8 are associated with differences in shape space between groups. These three PCs refer mainly to variation of the cranial base, maxillary alveolus, mandibular angle, and soft tissues (nose and lips). Of these structures, only growth of the alveolar process, nose, and upper lip are directly affected by the cleft and/or its surgical treatment. Second, there is significant variation within the cranial base, which includes key landmarks for cephalometric analysis, i.e., the basion and sella. In particular, large positional variation of the

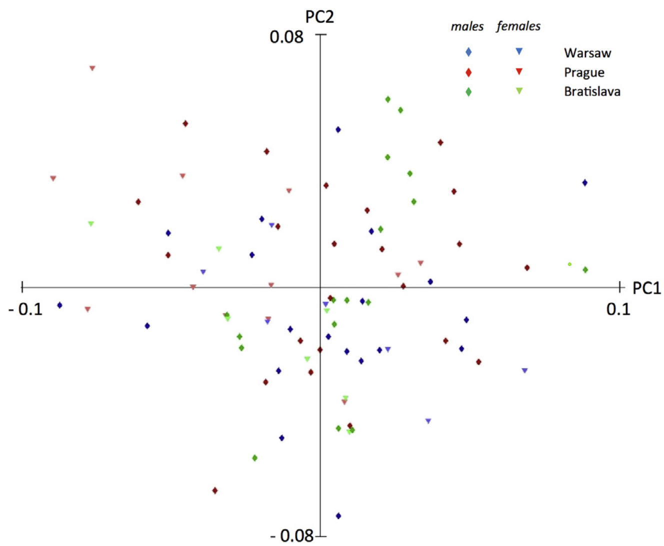

Fig. 4. Scatter plot of the sample in shape space.

Table 4
Percent variance in shape space described by the principal components that were considered to be statistically meaningful.

	Variance	% variance	% cumulative variance
PC1	0.001533	24.3%	24.3%
PC2	0.000881	13.9%	38.2%
PC3	0.000491	7.8%	46.0%
PC4	0.000411	6.5%	52.5%
PC5	0.000361	5.7%	58.2%
PC6	0.000302	4.8%	62.9%
PC7	0.000267	4.2%	67.2%
PC8	0.000234	3.7%	70.9%

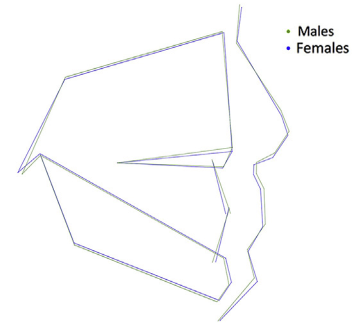

Fig. 6. Consensus male and female shapes superimposed using Procrustes fit.

sella can affect cephalometric measurements used to assess maxillary position (e.g. s s-n-ss, NSL/NL). To a certain degree, this weakens our initial assumption regarding craniofacial similarity in Slavic populations from Warsaw, Prague, and Bratislava. Third, the variation of the soft tissues was higher than the variation of underlying hard tissues. For example, PC3 showed that the tip and base of the nose were more variable in shape space than the anterior nasal spine (sp), which creates a bony foundation for the basal part of the nose; PC5 showed, in turn, that the antero-posterior variation of the nose and lips is considerably higher than the corresponding variation of the anterior contour of the maxilla, mandible and incisors.

Determining which factors are responsible for favorable outcomes is challenging. The Eurocleft study implied that participation of experienced surgeons might be a key factor in achieving optimal treatment outcomes. Poor results were, in turn, attributed to decentralized cleft care with less experienced surgeons performing cleft repairs (Shaw et al., 2005). This relationship was confirmed subsequently in other studies. An evaluation of treatment

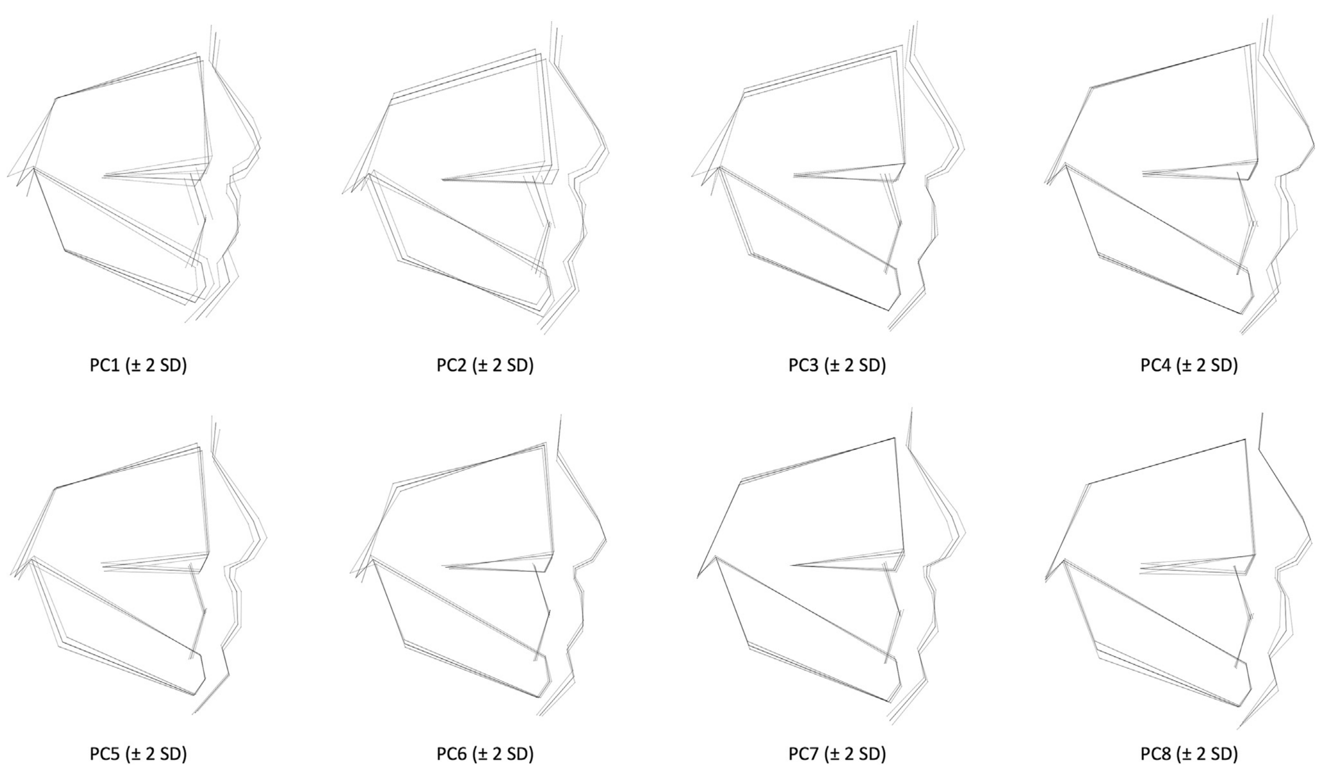

Fig. 5. Variation in the sample comprising all subjects treated in Warsaw, Prague, and Bratislava along eight first principal components (PC).

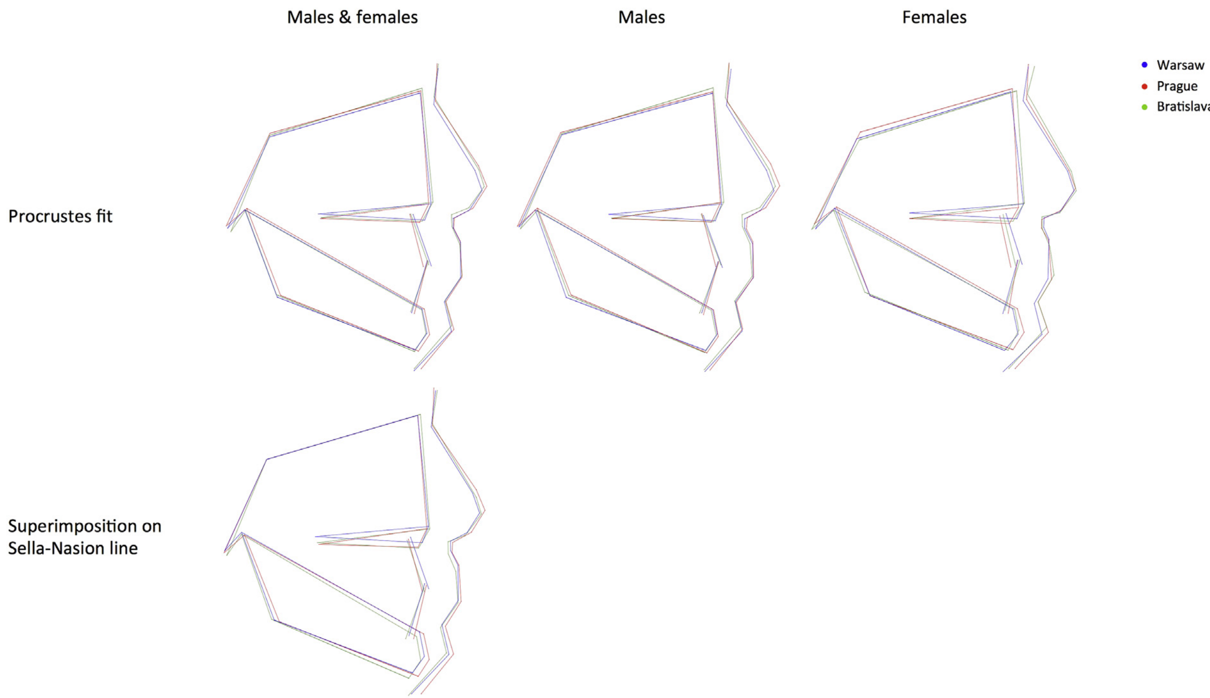

Fig. 7. Differences among Warsaw, Prague, and Bratislava groups in shape space in males and females using Procrustes fit. Additionally, conventional superimposition on sella-nasion line for a pooled sample of males and females was performed to visualize differences between Procrustes fit and sella-nasion superimpositions.

outcomes in five Turkish cleft centers demonstrated that decentralized cleft services and participation of low-volume surgeons were related to poor results of treatment and an increased need for orthognathic surgery (Dogan et al., 2014). On the other hand, centralization of cleft care with participation of high-volume surgeons can significantly improve treatment outcomes. This situation occurred after an overhaul of the cleft care system in the United Kingdom. In the 1980s and 1990s, there were 57 cleft centers in the UK, and only one surgeon operated annually on at least 40 infants with clefts (i.e. a high-volume surgeon). Average outcomes were significantly worse compared to the best European centers (Clinical Standards Advisory Group [CSAG] study, Bearn et al., 2001). After a reduction in the number of cleft centers to 11, almost all cleft surgeons were considered high-volume. As a result, the outcome of treatment of orofacial clefts improved significantly (Cleft Care UK [CCUK] study, Ness et al., 2015; Al-Ghatam et al., 2015). In the current project, the Warsaw, Prague, and Bratislava centers differed regarding the number of surgeons involved in cleft surgery; in Warsaw, a single high-volume surgeon operated on all patients, while five surgeons with different levels of experience operated on children with clefts in Prague and Bratislava. Thus our findings seem to agree with conclusions of the Eurocleft and CCUK studies. However, Ness et al. (2015) emphasized that it was not clear which element(s) of centralization of cleft care led to an improvement in outcomes. They suggested that improvements in surgical training, an increase in number of operations per surgeon, creation of multidisciplinary teams, and the creation of an audit culture could be associated with improved results of treatment of orofacial clefts.

Table 5
Differences in shape space between mean shapes of patients treated in Warsaw, Prague, and Bratislava.

	Males	Females	Both sexes
		p value	
Warsaw vs Prague	0.031	0.044	0.004
Warsaw vs Bratislava	0.081	0.177	0.064
Prague vs Bratislava	0.033	0.069	0.008

Although the experience of the surgeon is deemed as a key factor associated with good outcomes, the surgical technique can also contribute to the results of therapy of orofacial clefts (Karsten et al., 2003; Liao et al., 2014). For example, Karsten et al. (2003) found better development of the maxilla, better occlusion, and less palatal scarring following the so-called “minimal incision technique” compared to the Wardill–Kilner method. In a recent publication, Liao et al. (2014) evaluated the effect of vomerplasty on maxillofacial growth. In vomerplasty, vomerine soft tissues are used for closure of the cleft palate. It has been asserted that vomerplasty results in a less denuded surface of the palatal bone after surgery; hence, less scar tissue develops in growth-sensitive areas of the maxilla. Liao et al. found that, in fact, vomerplasty was related to more favorable maxillary growth in patients with non-syndromic CUCLP. The vomerplasty for cleft palate repair was used only in Warsaw; neither the cleft team from Prague nor the team from Bratislava used this technique. It is likely that the use of vomerplasty as a part of surgical protocol contributed to the outcomes achieved in Warsaw. It should be emphasized, however, that the precise identification of which component(s) of the surgical protocol is responsible for a good (or poor) result is impossible using the current research design. Only randomized controlled clinical trials (RCTs) allow the determination of causative factors; however, RCTs in the cleft research field are very rare due to the length of follow-up and the challenging organization required.

Although well established in many scientific disciplines (e.g., paleontology, evolution, systematics), has been rarely been used in cleft research. Until now, researchers used it to investigate relationships between the shape of the face of parents and children with clefts (Weinberg et al., 2009), to study shape variability in patients with different types of clefts (Bugaighis et al., 2010; Toro-Ibacache et al., 2014) or in individuals with unoperated cleft lip and palate (Manyama et al., 2014). This present study is probably the first in which GM was used to compare craniofacial morphology in

Table 6
Results of multivariate regression analysis with eight principal components (PC1 through PC8) as dependent variables and age, type of treatment (i.e., group), and sex as independent variables.

		Coefficient	SE	t	p value	95% confidence interval	
						Lower limit	Upper limit
PC1	$R^2 = 0.07$						
	Age	−0.0028	0.0026	−1.100	0.273	−0.008	0.002
	Group (1-W, 2-P, 3-B)	−0.0003	0.0050	−0.060	0.949	−0.010	0.010
	Sex	−0.0202	0.0084	−2.410	**0.018**	−0.037	−0.004
	Constant	0.0368	0.0312	1.180	0.242	−0.025	0.099
PC2	$R^2 = 0.02$						
	Age	0.0019	0.0021	0.910	0.367	−0.002	0.006
	Group (1-W, 2-P, 3-B)	0.0032	0.0041	0.780	0.438	−0.005	0.011
	Sex	−0.0009	0.0070	−0.130	0.897	−0.015	0.013
	Constant	−0.0283	0.0259	−1.090	0.277	−0.080	0.023
PC3	$R^2 = 0.08$						
	Age	0.0003	0.0013	0.210	0.835	−0.002	0.003
	Group (1-W, 2-P, 3-B)	0.0065	0.0025	2.570	**0.012**	0.001	0.011
	Sex	−0.0026	0.0043	−0.610	0.546	−0.011	0.006
	Constant	−0.0163	0.0159	−1.030	0.306	−0.048	0.015
PC4	$R^2 = 0.09$						
	Age	0.0008	0.0015	0.550	0.581	−0.002	0.004
	Group (1-W, 2-P, 3-B)	0.0024	0.0029	0.810	0.418	−0.003	0.008
	Sex	0.0130	0.0049	2.660	**0.009**	0.003	0.023
	Constant	−0.0176	0.0182	−0.970	0.335	−0.054	0.019
PC5	$R^2 = 0.10$						
	Age	−0.0035	0.0013	−2.670	**0.009**	−0.006	−0.001
	Group (1-W, 2-P, 3-B)	−0.0035	0.0025	−1.400	0.165	−0.009	0.001
	Sex	−0.0035	0.0043	−0.830	0.409	−0.012	0.005
	Constant	0.0471	0.0159	2.960	0.004	0.015	0.079
PC6	$R^2 = 0.16$						
	Age	−0.0014	0.0010	−1.340	0.184	−0.003	0.001
	Group (1-W, 2-P, 3-B)	0.0064	0.0020	3.180	**0.002**	0.002	0.010
	Sex	−0.0075	0.0034	−2.210	**0.030**	−0.014	−0.001
	Constant	0.0062	0.0126	0.490	0.622	−0.019	0.031
PC7	$R^2 = 0.32$						
	Age	0.0055	0.0010	5.600	**0.000**	0.004	0.007
	Group (1-W, 2-P, 3-B)	−0.0018	0.0019	−0.940	0.349	−0.006	0.002
	Sex	−0.0061	0.0032	−1.880	0.063	−0.012	0.000
	Constant	−0.0568	0.0120	−4.730	0.000	−0.081	−0.033
PC8	$R^2 = 0.06$						
	Age	0.0010	0.0011	0.960	0.342	−0.001	0.003
	Group (1-W, 2-P, 3-B)	−0.0043	0.0021	−2.050	**0.044**	−0.008	0.000
	Sex	0.0008	0.0035	0.240	0.813	−0.006	0.008
	Constant	−0.0032	0.0131	−0.250	0.805	−0.029	0.023

Bold denotes statistical significance.

patients with orofacial clefts treated by different cleft teams. In our opinion, it allows more detailed analysis of the differences in facial morphology between groups and a better visualization of morphological variability. Therefore we recommend the use of GM in similar studies.

In the cephalometric part of this study, we compared groups comprising boys and girls pooled together. The rationale for this was that in patients with CUCLP angular measurements and ratios are comparable for both sexes before adolescence (Semb, 1991). A similar approach was also applied in the Eurocleft (Brattström et al., 2005) and Americleft (Daskalogiannakis et al., 2011) studies. Furthermore the Warsaw, Prague and Bratislava groups were well-balanced regarding sex. As a result, even if some between-sex differences were present but impossible to detect because of insufficient power, it seems unlikely that they would have affected the results of the comparison among the Warsaw, Prague, and Bratislava groups.

This study does have some limitations. Neither the Prague group nor the Bratislava group consisted of consecutively treated patients. The 40–50% dropout rate, although common in studies in the cleft field, could have led to bias. Initial cleft size was not known, hence it was not included in the analysis. We compared patients before completion of craniofacial growth and orthodontic treatment. It is possible that if the comparison were performed during adulthood, additional intergroup differences would be identified. As a result, our findings should be considered preliminary.

5. Conclusion

In this study, craniofacial morphology was slightly more favorable in patients treated in Warsaw and less favorable in patients treated in Prague. It is possible that organizational factors such as participation of high-volume, experienced surgeons contributed to these results.

Conflict of interest

The authors declare no conflicts of interest.

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