A longitudinal three-center study of craniofacial morphology at 6 and 12 years of age in patients with complete bilateral cleft lip and palate

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Abstract In this longitudinal study, the craniofacial morphology and evaluated soft tissue profile changes, at 6 and 12 years of age in patients with complete bilateral cleft lip and palate (CBCLP) were compared. Lateral cephalograms from 148 patients with CBCLP, treated consecutively at three European cleft centers, Gothenburg (nA = 37), Nijmegen (nB = 26), and Oslo (nC = 85), were evaluated. Eighteen hard tissue and ten soft tissue landmarks were digitized. Paired t test, Pearson’s correlation coefficients, and multiple regression models were applied for statistical analysis. ANOVA and Tukey-B, as a post hoc test, were used to evaluate the increments and compare centers. Hard and soft tissue data were superimposed using the generalized Procrustes analysis. For Nijmegen, the increments of the variables SNA, ANB, SN-NL, SN-ML, NL-ML, Snss, and Snpg were significantly different than the two other centers (p = 0.041 to <0.001). SNPg increments were significantly different between Nijmegen and Oslo (p = 0.002). The three cleft centers followed different treatment protocols, but the main differences in craniofacial morphology until 12 years of age were the growth pattern and the maxillary and upper incisor variables. Follow-up of these patients until facial growth has ceased, which may elucidate components for improving treatment outcome.

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Introduction

Patients with a complete bilateral cleft lip and palate (CBCLP) are a challenge for the team involved in the interdisciplinary treatment of the condition. Longitudinal data on treatment outcome in patients with BCLP are scarce, probably due to the low incidence of the malformation [1]. Consequently, the scientific basis of the field is still weak, and hardly any evidence is available for current practices in surgery or orthodontics. Table 1 provides an overview of longitudinal studies on the craniofacial morphology of CBCLP from 6 to 12 years of age. To the best of our knowledge, only three studies have provided longitudinal data in this age range. One study [2] compared the outcome of the craniofacial treatment of CBCLP to craniofacial growth in non-cleft controls. In a Japanese study, the interest focused on specific surgical procedures, particularly one-stage versus two-stage palatoplasty [3]. In only one study, the craniofacial development of CBCLP until craniofacial growth ceased was compared between cleft centers in Oslo (Norway) and Nijmegen (the Netherlands) [4]. In addition to the few longitudinal studies, another worth mentioning is the largest mixed longitudinal data set on CBCLP to date, from the Cleft Palate Centre in Oslo (Norway), and presents facial growth from 5 to 18 or more years. The data set was compared to complete unilateral cleft lip and palate (CUCLP) patients treated in the same center [5].

In contrast to single-center studies, multicenter studies offer the possibility to collect a larger study sample, which offers the opportunity to compare different treatment protocols. Differences in the surgical and orthodontic procedures may indicate an inhibitory effect on the growth of the maxillary complex and a further result on the final treatment outcome. Following up patient samples longitudinally may identify the age at which growth starts to deviate between centers and may identify treatment procedures responsible. Therefore, the aim of the present study was to compare and longitudinally evaluate facial growth in patients with CBCLP at 6 and 12 years of age who were consecutively treated at three European cleft centers with different protocols.

Patients and methods

Patients selection

Three cleft centers participated in this study: Gothenburg, Sweden (center A); Nijmegen, the Netherlands (center B);
and Oslo, Norway (center C). Lateral cephalograms for 148 consecutively treated patients with CBCLP (Gothenburg, \( n_A = 37 \), born between 1965 and 1995; Nijmegen, \( n_B = 26 \), born between 1975 and 1995; and Oslo, \( n_C = 85 \), born between 1974 and 1995) at approximately 6 and 12 years of age were evaluated longitudinally.

The inclusion criteria were Caucasian ethnic background; no associated congenital malformations, syndromes, or mental retardation; treatment from birth onwards in the same center; cephalograms available in the age range of 5 to 7 and 11 to 13 years of age; and at least 12 years of age at the time of evaluation (born before 1996). In addition, all patients had complete BCLP with a diagnosis confirmed by the pre-operative written records, neonatal pictures of the face, and/or casts taken pre-operatively. Patients with Simonart’s band(s) were included only if no hard tissue union was present and the side of the Simonart’s band was noted.

Treatment protocols

Table 2 shows the treatment protocols of the three centers. In the Gothenburg center, two surgeons were involved in the primary surgical procedures, in Nijmegen three, and in Oslo two. One basic difference among the centers is that Oslo does not employ infant orthopedics, whereas Nijmegen, and at that time Gothenburg, applied different infant orthopedic techniques. The surgical concepts of the lip closure procedure are also different among the centers; a one-stage procedure is performed at Nijmegen, whereas the other two centers finalize the lip closure in two operations. Soft palate closure varied among the centers between 6 and 18 months of age. The surgical soft palate closure technique is comparable in Nijmegen and Oslo, whereas Gothenburg has developed its own technique. Another important difference among the centers is early versus late hard palate closure. Oslo completes the hard palate closure between the ages of 3 and 6 months in two separate surgical procedures. In Gothenburg and Nijmegen, the hard palate is closed at a later stage, at approximately 9 years of age. In Nijmegen this is combined with a premaxillary osteotomy at roughly 9 years of age. Secondary procedures are performed in all centers, mainly consisting of columellaplasty at 6 to 7 years of age (Nijmegen and Oslo) and lip/nose revisions from the age of 6 years (all centers).

Radiographic assessment

Lateral cephalograms were available that had been taken in centric occlusion and oriented to the Frankfurt horizontal plane. The cephalograms from all centers were scanned on a 12-bit scanner (R2 ImageChecker M5000 DM, R2 Technology, Inc., Sunnyvale, CA, USA) at 150 dpi. For the cephalometric analysis, all cephalograms were digitized with a commercially available software program (Viewbox 3/dHAL Software, Kifissia, Greece) by one operator (TB) blinded to the center at which the patient was treated.

Table 2  Treatment protocols (primary procedures for lip, alveolus, and palate) for patients with complete bilateral cleft lip and palate from birth until 12 years of age at the cleft palate centers in this study

| Timing  | Center A \( ^a \) | Center B \( ^b \) | Center C \( ^c \) |
|---------|----------------|----------------|----------------|
| Birth   | Infant orthopedics (duration, 1.5 years) Nose plugs (duration, 2.5 years) | Infant orthopedics with extra-oral strapping (mean duration, 9.2 months) | Straight-line lip closure and hard palate closure on one side (mean age, 3.4 months) |
| 3 months | Bilateral lip adhesion (mean age, 3.3 months) | One-stage lip closure (modified Manchester; mean age, 7.2 months) | Straight-line lip closure and hard palate closure on the other side (mean age, 4.9 months) |
| 6 months | Soft palate closure (center’s own technique; mean age, 8.5 months) | Modified Von Langenbeck soft palate closure (mean age, 13.8 months) | Modified von Langenbeck soft palate closure (mean age, 19 months) |
| 12 months | Definitive bilateral lip and nose repair (mean age, 18 months; center’s own technique) | | Bilateral alveolar bone grafting (iliac crest) (mean age, 9.9 years) |
| 18 months | One-side alveolar bone grafting (tibia) (mean age, 8.0 years) Hard palate closure with alveolar bone grafting of second side (mean age, 8.5 years) | Hard palate closure and bilateral alveolar bone grafting (chin) (after 1975) and osteotomy of the premaxilla (mean age, 9.9 years) | |

\( ^a \) Gothenburg

\( ^b \) Nijmegen

\( ^c \) Oslo
Figure 1 shows the cephalometric reference points (18 hard and ten soft tissue landmarks) used in this study. Twenty cephalometric variables were calculated from these landmarks. Only angular measurements were used in order to avoid errors due to magnification differences between the centers. To determine the measurement error, 20 cephalograms for age 6 and 20 cephalograms for age 12 were randomly selected and digitized twice by the same operator (TB) at an interval of 1 month.

The generalized Procrustes analysis was used to superimpose the tracings in order to visualize the craniofacial morphology of patients at each center. This analysis was based on minimizing the square distances between corresponding points and scaling all tracings to a common

Fig. 1 Reference points on the lateral cephalometric radiographs. **Skeletal reference points:** S sella—the geometric center of the sella turcica, N nasion—the most anterior point at the frontonasal suture, ANS anterior nasal spine, A the deepest point on the anterior contour of the upper alveolar process, As apex superius—the apex of the root of the upper central incisor, Ls incision superius—the incisal edge of the most prominent upper incisor, Li incision inferius—the incisal edge of the most prominent lower incisor, Ai apex inferius—the apex of the root of lower central incisor, B the deepest point of the anterior contour of the lower alveolar process, Pg pagonion—the most anterior point of the mandibular symphysis. Gn gnaethion—the most anterior inferior point of the bone chin, Me menton—the most inferior point of the mandibular symphysis, Go gonion point—the most posterior inferior point on the angle of the mandible, Mtp mandibular tangent posterior—the most posterior inferior point on the outline of the mandibular body, R ramus point—the most posterior—inferior point of the mandibular ramus, Ar artiiculare—the constructed point at the intersection of the images of the posterior margin of the ramus and the outer margin of the cranial base, Ba basin—the lowest point on the anterior margin of the foramen magnum in the median plane, Pm pterygo-maxillare—the intersection of the nasal floor and the apex of the pterygoid fissure. **Soft tissue reference points:** n soft tissue nasion—the deepest point on the frontonasal curvature, an anterior nasalis—the most prominent point on the nose tip, sn soft tissue subnasale—the point of intersection between the base of the nose and upper lip of soft tissue, ss soft tissue subspinale—the point of greatest concavity in the midline of the upper lip, ls labrale superius—the most prominent point of the upper lip, li labrale inferius—the most prominent point of the lower lip, sm soft tissue supramentale—the point of greatest concavity in the midline of the lower lip, pg soft tissue pogonion—the most prominent point on the soft tissue of the chin, gn soft tissue gnaethion—the most anterior inferior point of the soft tissue chin, me soft tissue menton—the lowest point on the lower border of the mandible. **Reference lines:** SN sella–nasion line, NL nasal line—through Pm and ANS, ILs axis of upper incisors, ILi axis of lower incisors, ML mandibular line—the tangent of the lower border of the mandible through Me and Mtp, RL ramus line—through Ar and R, E-line esthetic line—through an and pg. **Hard tissue angles:** SNA, SNB, ANB, SNPg, ILs-NL, ILs-SN, ILi-ML, ILs-ILi inter-incisal angle, SN-NL, SN-ML, NL-ML, RL-ML gonial angle, and NSGa. **Soft tissue angles:** S-n-an, S-n-ss, S-n-sm, S-n-pg, n-an-pg, an-sn-ss nasolabial angle, and n-sn-pg
size. According to this method, no reference structures (such as the cranial base) are used for the superimposition. First, the tracings at 6 and 12 years were superimposed for each center. Next, a cross-sectional figure of all three centers at 6 years or 12 years was made [6–8].

Statistical analysis

Statistical analyses were performed using SPSS 16.0 software (Chicago, IL, USA). Paired t tests were used for calculating systematic differences between the first and second digitization. The reliability between the two measurements was calculated as Pearson’s correlation coefficients. In the multiple regression model, center and gender were included as independent variables. Oslo was used as the reference center. The p values for the comparison of increments between the centers were calculated using ANOVA, and the Tukey-B test was used as the post hoc test.

Results

Sample characteristics for each center are shown in Table 3. The intra-observer duplicate measurement error for all

| Table 3 Characteristics of the centers at which the cephalograms were taken |
|---------------------------------|-----------------|------------------|-----------------|------------------|
|                                  | N   | Male | Female | Mean age±SD | Mean age±SD |
|---------------------------------|-----|------|--------|-------------|-------------|
| Center A*                        | 37  | 26   | 11     | 6.8±0.59    | 12.9±0.35   |
| Center B**                       | 26  | 21   | 5      | 6.1±0.34    | 12.2±0.64   |
| Center C**                       | 85  | 57   | 28     | 6.0±0.64    | 12.3±0.73   |
| Total                            | 148 | 104  | 44     |             |             |

N number of patients per center, SD standard deviation

*Gothenburg

**Nijmegen

*Oslo

| Table 4 Intra-observer reliability for hard and soft tissue cephalometric measurements |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                  | Reliability | DME | Mean difference | 95% CI | p value | Reliability | DME | Mean difference | 95% CI | p value |
|---------------------------------|-------------|-----|-----------------|--------|---------|-------------|-----|-----------------|--------|---------|
| Hard tissue variables           |             |     |                 |        |         |             |     |                 |        |         |
| SNA                             | 0.796       | 2.02| 0.66            | [-0.65–1.96] | 0.305   | 0.928       | 0.88 | 0.04            | [-0.48–0.57] | 0.868   |
| SNB                             | 0.786       | 1.33| -0.39           | [-1.25–0.47] | 0.355   | 0.966       | 0.58 | -0.25           | [-0.59–0.10] | 0.149   |
| ANB                             | 0.74        | 1.75| 1.05            | [-0.08–2.17] | 0.067   | 0.94        | 0.76 | 0.29            | [-0.16–0.75] | 0.198   |
| SNPg                            | 0.706       | 1.52| -0.37           | [-1.35–0.61] | 0.435   | 0.962       | 0.66 | -0.34           | [-0.73–0.06] | 0.089   |
| SN-NL                           | 0.543       | 2.70| -0.03           | [-1.77–1.71] | 0.971   | 0.918       | 1.16 | -0.32           | [-1.00–0.38] | 0.354   |
| SN-ML                           | 0.417       | 4.55| 2.02            | [-0.91–4.95] | 0.166   | 0.925       | 1.39 | -0.08           | [-0.91–0.75] | 0.850   |
| NL-ML                           | 0.457       | 3.30| -0.43           | [-2.60–1.69] | 0.679   | 0.926       | 1.31 | 0.24            | [-0.54–1.02] | 0.531   |
| ILs-SN                          | 0.497       | 8.90| -4.07           | [-9.80–1.66] | 0.154   | 0.967       | 1.78 | 0.99            | [-0.07–2.06] | 0.065   |
| ILs-NL                          | 0.583       | 8.03| -4.10           | [-9.27–1.07] | 0.114   | 0.967       | 1.85 | 0.64            | [-0.47–1.74] | 0.244   |
| Interincisal                    | 0.673       | 7.56| 3.69            | [-2.61–9.99] | 0.236   | 0.975       | 1.75 | 0.01            | [-1.04–1.05] | 0.992   |
| ILI-ML                          | 0.817       | 2.76| 0.84            | [-0.94–2.61] | 0.336   | 0.882       | 1.88 | -1.08           | [-2.20–0.04] | 0.058   |
| RL-ML*                          | 0.46*       | 4.74*| 3.78*          | [0.73–6.82]*    | 0.018*  | 0.815       | 2.84 | -0.91           | [-2.60–0.79] | 0.280   |
| NSBa                            | 0.615       | 2.88| 1.53            | [-0.32–3.39] | 0.100   | 0.834*      | 2.13*| 1.62*           | [0.34–2.89]*    | 0.015*  |
| Soft tissue variables           |             |     |                 |        |         |             |     |                 |        |         |
| Snan                            | 0.676       | 3.370| -0.23          | [-2.40–1.94] | 0.828   | 0.767       | 2.30 | -0.03           | [-1.40–1.35] | 0.968   |
| Snss                            | 0.47        | 3.389| 0.05           | [-2.13–2.23] | 0.963   | 0.921       | 1.31 | 0.18            | [-0.58–0.74] | 0.649   |
| Snsm                            | 0.459       | 2.676| 0.10           | [-1.62–1.82] | 0.906   | 0.879       | 1.11 | 0.08            | [-0.61–0.96] | 0.800   |
| Snpg                            | 0.409       | 2.593| 0.02           | [-1.65–1.69] | 0.984   | 0.895       | 0.99 | 0.13            | [-0.46–0.73] | 0.650   |
| nanpg                           | 0.695       | 3.785| -0.95          | [-3.39–1.48] | 0.424   | 0.927       | 1.75 | -0.07           | [-1.11–0.97] | 0.891   |
| nnsnp                           | 0.757       | 3.753| 0.96           | [-1.46–3.37] | 0.418   | 0.947       | 1.77 | 0.18            | [-0.87–1.24] | 0.725   |
| Nasolabial                      | 0.721       | 10.72| -2.66          | [-9.56–4.24] | 0.431   | 0.887       | 4.97 | 0.22            | [-2.75–3.19] | 0.880   |

*p≤0.05, variables that are reaching significance

DME duplicate measurements error, CI confidence interval
cephalometric variables at 6 and 12 years of age is presented in Table 4. Significant differences were observed in the variable RL-ML (p = 0.018) at 6 years old and NSBa at 12 years old (p = 0.015). These variables were excluded from further evaluation in both age groups. For all other variables, the reliability coefficients ranged from 0.409 to 0.817 for the 6-year-old group, and from 0.767 to 0.975 for the 12-year-old group. Hard and soft tissue cephalometric variables for both age groups and the three centers are presented in Table 5.

The increments for all cephalometric variables between 6 and 12 years of age are different among the three centers and are presented in Table 6. For Nijmegen, the increments of the variables SNA, ANB, SN-NL, SN-ML, NL-ML, Sns, and Snpg were significantly different from those of the other two centers (p = 0.041 to <0.001). Snpg increments were significantly different between Nijmegen and Oslo (p = 0.002). The sagittal position of the maxilla diminished during growth for all three centers, which was represented by the hard tissue variable SNA and the soft tissue variable Sns. The variables decreased significantly more at Nijmegen than the other two centers (Fig. 2a, b). The SNA angle also has an effect on the ANB angle, which decreased significantly more in the Nijmegen group than in the other two. The Snpg variable increased significantly more in the Oslo group than the Nijmegen group, and the corresponding soft tissue variable (Snpg) was significantly different in the Nijmegen group compared with the other centers (Fig. 3a, b). The increments for the vertical growth pattern (SN-NL and NL-ML) were significantly different for Nijmegen compared with the other two centers. In the Nijmegen group, SN-NL significantly decreased and NL-ML increased between 6 and 12 years, and SN-ML was significantly different between the centers (p = 0.041). However, none of the differences reached significance in the post hoc test.

The results of the multiple regression model are presented in Table 7. The cephalometric variables at

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**Table 5** Hard and soft tissue cephalometric measurements at the three centers

|                      | Center A<sup>a</sup> (n<sub>A</sub>=37) | Center B<sup>b</sup> (n<sub>B</sub>=26) | Center C<sup>c</sup> (n<sub>C</sub>=85) |
|----------------------|----------------------------------------|----------------------------------------|----------------------------------------|
|                      | 6 years  | 12 years | 6 years  | 12 years | 6 years  | 12 years | 6 years  | 12 years | 6 years  | 12 years | 6 years  | 12 years |
| Hard tissue variables|          |          |          |          |          |          |          |          |          |          |          |          |
| SNA                  | 85.38    | 4.16     | 79.88    | 3.50     | 85.03    | 5.54     | 77.25    | 4.62     | 84.75    | 4.28     | 80.00    | 3.38     |
| SNB                  | 75.32    | 3.66     | 75.43    | 3.77     | 72.92    | 4.15     | 72.80    | 4.08     | 74.65    | 3.61     | 75.60    | 3.83     |
| ANB                  | 10.06    | 3.49     | 4.44     | 2.61     | 12.12    | 3.80     | 4.46     | 3.20     | 10.09    | 3.33     | 4.40     | 3.18     |
| SNpg                 | 75.61    | 3.65     | 76.72    | 3.89     | 72.70    | 3.82     | 73.00    | 4.17     | 74.72    | 3.80     | 76.9     | 4.10     |
| SN-NL                | 12.90    | 3.78     | 13.13    | 3.55     | 13.02    | 5.86     | 9.21     | 4.53     | 9.62     | 4.50     | 8.27     | 3.62     |
| SN-ML                | 36.24    | 4.68     | 36.23    | 4.83     | 39.93    | 5.50     | 39.86    | 5.83     | 35.94    | 5.66     | 34.09    | 6.40     |
| NL-ML                | 23.33    | 5.17     | 23.10    | 4.64     | 26.91    | 6.95     | 30.66    | 4.84     | 26.79    | 5.80     | 25.95    | 5.98     |
| ILs-SN               | 63.62    | 13.45    | 86.56    | 11.00    | 57.71    | 15.13    | 76.79    | 13.57    | 61.67    | 12.25    | 85.30    | 10.92    |
| ILs-NL               | 76.53    | 12.58    | 99.70    | 10.83    | 70.72    | 16.10    | 86.00    | 12.19    | 71.30    | 11.99    | 93.58    | 11.00    |
| Interincisal angle   | 172.58   | 14.13    | 148.61   | 11.71    | 177.43   | 18.74    | 154.80   | 15.64    | 175.66   | 16.06    | 151.24   | 13.07    |
| ILi-ML               | 87.55    | 9.40     | 88.60    | 7.80     | 84.94    | 7.18     | 88.55    | 7.13     | 86.30    | 7.01     | 93.58    | 11.00    |
| Soft tissue variables|          |          |          |          |          |          |          |          |          |          |          |          |
| Snan                 | 106.63   | 5.17     | 108.96   | 6.12     | 105.84   | 3.40     | 106.20   | 5.56     | 108.85   | 5.63     | 111.29   | 4.93     |
| Snss                 | 90.62    | 4.50     | 89.01    | 4.86     | 90.86    | 4.68     | 85.20    | 4.73     | 89.44    | 3.92     | 88.18    | 3.91     |
| Snsm                 | 80.37    | 4.39     | 82.16    | 5.42     | 78.79    | 3.66     | 79.25    | 4.50     | 79.60    | 3.78     | 81.74    | 3.95     |
| Snpg                 | 81.66    | 4.61     | 83.81    | 5.65     | 80.06    | 3.45     | 80.40    | 4.42     | 81.04    | 3.82     | 83.28    | 4.10     |
| nanpg                | 140.02   | 4.90     | 139.13   | 5.34     | 139.50   | 5.08     | 138.47   | 5.20     | 136.51   | 5.75     | 135.01   | 5.56     |
| nsnpg                | 159.97   | 6.09     | 167.40   | 6.77     | 157.62   | 7.33     | 167.68   | 7.91     | 161.36   | 7.26     | 168.92   | 7.92     |
| Nasolabial angle     | 126.88   | 11.88    | 116.93   | 15.32    | 133.45   | 12.11    | 120.92   | 13.68    | 119.37   | 13.80    | 107.96   | 15.75    |

All variables are in degrees

<sup>a</sup>Gothenburg  
<sup>b</sup>Nijmegen  
<sup>c</sup>Oslo
12 years were the dependent variables, and the cephalometric variables at 6 years, gender, and center (Gothenburg or Nijmegen) were the independent variables. Oslo is the reference category center. All cephalometric variables except the ones related to the upper incisors could be explained by the cephalometric variables at 6 years of age. Gender did not play a significant role in predicting the values of the cephalometric variables at 12 years of age. A center effect was present for Gothenburg for SNPg, Snpg, and SN-NL, which were predictive values for the 12-year results. The center effect for Nijmegen, which is marked in bold in Table 7, was found for the prediction of a number of cephalometric variables (SNA, SNB, SNPg, SN-ML, and NL-ML) at 12 years of age.

For every cephalometric variable, a prediction model can be extracted using the following equation, which estimates, for example, the SNA angle at age 12 to be:

\[
\text{SNA}_{12} = 32.27 + 0.564 \text{SNA}_6 - 0.29 - 0.48 \text{Gothenburg} - 2.94 \text{Nijmegen}
\]

For instance a girl (boy=0 and girl=1), from Gothenburg (Nijmegen=0 and Gothenburg=1), with an SNA angle of 88° at 6 years is estimated to have a SNA angle at 12 years of: \(32.27 + 0.564 \times 88 - 0.29 - 0.48 = 81.13°\).

The results of superimposition using the generalized Procrustes analysis of the 6- and 12-year-old group means are shown in Fig. 4a–c. Figure 5 visualizes the superimpositions of the mean tracings of all three centers at 6 (Fig. 5a) and 12 years (Fig. 5b).

**Discussion**

An intercenter comparison allows access to adequate samples for investigating clinical outcomes and international variations in treatment outcomes and growth adaptation [9]. However, intercenter studies cannot eliminate susceptibility or proficiency bias as the patients are drawn from different populations and the surgeons are inevitably different, but the patients from the three centers in the present study were treated by a limited number of surgeons according to a strictly defined and consistent protocol (see Table 2). Nevertheless, intercenter studies are not easy to perform. The variability in record taking and treatment protocol, even within the same center, as well as many co-factors such as clinician skill, proficiency, and the possibility of adapting a treatment procedure to the expected prognosis, make intercenter studies difficult. Even if the research evidence for retrospective longitudinal studies is considered to be rather weak, it has the advantage of recruiting consecutive cases for consistent evaluation [10, 11]. For the present study, we were able to include 148 patients with CBCLP who were followed...
longitudinally over a 6-year period, which is the largest sample reported in the literature to date. Only a few studies with very small samples cover the same age period longitudinally (Table 1).

In order to reach a consensus on data collection for further research purposes, the Eurocleft project has specified the ages for recording cleft lip and palate patients. Cephalometric radiographs were recommended at the age of 10 years [12]. In the present study, the CBCLP patients were born before 1996 in order to have radiographs at the two target ages and is the reason why our age groups were not in accordance with the Eurocleft recommendations published later [12].

Three-dimensional cephalometry is the latest tool, but 2D cephalometric analysis is still the classic tool for describing facial growth and development in patients with cleft lip and palate. Because of concerns about the radiation dose of multislice or cone-beam computer tomography, it will probably continue to be the evaluation tool for longitudinal studies on facial growth and treatment outcome. However, in addition to the fact that 2D cephalometry is a two-dimensional representation of three-dimensional structures, cephalometric measurements have an inherent method error that varies depending on the radiographic projection, measuring system, type of landmark, and observer. Differences in the magnitude of the measurement error are caused by the precision of landmark

Fig. 2 Box plot distribution of a angles SNA and b Sns (in degrees) at 6 (blue) and 12 (green) years of age. (Centers: A Gothenburg, B Nijmegen, and C Oslo)

Fig. 3 Box plot distribution of a angles SNPg and b Snpg (in degrees) at 6 (blue) and 12 (green) years of age. (Centers: A Gothenburg, B Nijmegen, and C Oslo)
### Table 7  Multiple regression model using cephalometric variables as dependent variables and cephalometric variables at 6 years, gender, and center as the independent variables

|                    | Value at 6 years | Gender (m=0; f=1) | Center A | Center B |
|--------------------|------------------|-------------------|----------|----------|
|                    | R²               | Const             | Beta     | p value  | 95% CI   | Beta     | p value  | 95% CI   | Beta     | p value  | 95% CI   |
| Hard tissue variables |                  |                   |          |          |          |          |          |          |          |          |          |
| SNA                | 0.526            | 32.27             | 0.564*   | <0.001* | [0.468–0.661]* | -0.29    | 0.545    | [-1.23–0.65] | -0.48    | 0.353    | [-1.51–0.54] | -2.94*   | <0.001* | [-4.12–1.77]* |
| SNB                | 0.670            | 13.33             | 0.836*   | <0.001* | [0.733–0.939]* | -0.41    | 0.332    | [-1.24–0.42] | -0.73    | 0.112    | [-1.64–0.17] | -1.41*   | 0.009* | [-2.45–0.36]* |
| ANB                | 0.274            | -0.10             | 0.454*   | <0.001* | [0.328–0.581]* | -0.27    | 0.584    | [-1.22–0.69] | 0.05     | 0.919    | [-0.97–1.07] | -0.89    | 0.14    | [-2.09–0.30] |
| SNPg               | 0.682            | 12.26             | 0.868*   | <0.001* | [0.760–0.976]* | -0.61    | 0.176    | [-1.49–0.28] | -1.00    | 0.041*   | [-1.97–0.04]* | -2.27*   | <0.001* | [-3.38–1.15]* |
| SN-NL              | 0.369            | 5.00              | 0.349*   | <0.001* | [0.226–0.472]* | -0.25    | 0.685    | [-1.49–0.98] | 3.71*    | <0.001* | [2.31–5.11]* | -0.28    | 0.726   | [-1.87–1.31] |
| SN-ML              | 0.580            | 5.12              | 0.796*   | <0.001* | [0.671–0.922]* | 1.08     | 0.153    | [–0.40–2.56] | 1.93*    | 0.019*   | [0.33–3.54]* | 2.74*    | 0.005* | [0.84–4.65]* |
| NL-ML              | 0.419            | 11.82             | 0.514*   | <0.001* | [0.385–0.643]* | 1.09     | 0.196    | [–0.57–2.74] | -1.05    | 0.267    | [–2.90–0.81] | 4.79*    | <0.001* | [2.73–6.85]* |
| ILs-SN             | 0.100            | 78.31             | 0.106    | 0.144   | [-0.037–0.250] | 1.30     | 0.531    | [–2.79–5.38] | 1.09     | 0.629    | [–3.37–5.55] | -7.92*   | 0.003* | [–13.04–2.79]* |
| ILs-NL             | 0.144            | 88.48             | 0.066    | 0.358   | [–0.076–0.209] | 1.12     | 0.582    | [–2.89–5.13] | 5.81*    | 0.011*   | [1.38–10.24]* | -7.39*   | 0.004* | [–12.38–2.39]* |
| Interincisal angle | 0.071            | 119.22            | 0.184*   | 0.007*  | [0.051–0.317]* | -0.79    | 0.737    | [–5.46–3.87] | -2.09    | 0.417    | [–7.16–2.99] | 3.12     | 0.289   | [–2.68–8.92] |
| ILIML              | 0.288            | 46.63             | 0.496*   | <0.001* | [0.365–0.627]* | -0.41    | 0.712    | [–2.61–1.79] | -1.34    | 0.269    | [–3.73–1.03] | -0.13    | 0.925   | [–2.86–2.60] |
| Soft tissue variables |                  |                   |          |          |          |          |          |          |          |          |          |          |
| Snan               | 0.330            | 56.96             | 0.501*   | <0.001* | [0.353–0.650]* | -0.69    | 0.419    | [–2.37–0.99] | -1.24    | 0.191    | [–3.10–0.62] | -3.67*   | 0.001* | [–5.81–1.53]* |
| Snss               | 0.548            | 25.55             | 0.705*   | <0.001* | [0.586–0.824]* | -1.42*   | 0.011*   | [–2.51–0.32] | -0.05    | 0.937    | [–1.24–1.15] | -4.19*   | <0.001* | [–5.56–2.82]* |
| Ssnm               | 0.551            | 16.50             | 0.824*   | <0.001* | [0.694–0.953]* | -0.98    | 0.08     | [–2.09–0.12] | -0.25    | 0.679    | [–1.46–0.95] | -1.95*   | 0.006* | [–3.33–0.58]* |
| Snpg               | 0.593            | 13.15             | 0.869*   | <0.001* | [0.743–0.995]* | -0.92    | 0.097    | [–2.02–0.17] | -0.03    | 0.954    | [–1.22–1.15] | -2.16*   | 0.002* | [–3.52–0.80]* |
| nanpg              | 0.363            | 62.42             | 0.533*   | <0.001* | [0.393–0.673]* | -0.51    | 0.546    | [–2.17–1.15] | 2.24*    | 0.020*   | [0.36–4.11]* | 1.80     | 0.095   | [–0.32–3.91] |
| nsnpg              | 0.486            | 47.90             | 0.748*   | <0.001* | [0.617–0.878]* | 1.12     | 0.267    | [–0.87–3.11] | -0.45    | 0.680    | [–2.62–1.71] | 1.71     | 0.181   | [–0.80–4.22] |
| Nasolubial angle   | 0.320            | 44.79             | 0.542*   | <0.001* | [0.373–0.712]* | -4.81    | 0.051    | [–9.64–0.01] | 4.75     | 0.085    | [–0.66–10.15] | 4.66     | 0.157   | [–1.81–11.14] |

*p<0.05, variables that are reaching significance

m male, f female, CI confidence interval

a Gothenburg

b Nijmegen
definition and the amount of noise from adjacent structures. In young patients with cleft lip and palate, the identification of cephalometric landmarks is even more difficult due to abnormal anatomy, especially for the localization of the landmarks point A, anterior nasal spine, and posterior nasal spine [13]. As described by Hotz and Gnoinski [14], point A is difficult to locate in young individuals because of the tooth germs molding the anterior contour of the maxilla. The most difficult age for examining radiographs in patients with a cleft is the period before shedding of the incisors, as all of the above-mentioned problems occur in this period of time. In our study, the intra-observer measurement error showed a systematic difference for one of 20 variables in the 6-year group and one in the 12-year-old group (see Table 4).

At 6 years of age, all patients (at all centers) with CBCLP showed a large SNA angle with retroclined upper incisors. This finding should not be interpreted as a prognathism of the entire maxilla, but the large SNA angle is the result of a forward positioning of the premaxilla in bilateral cleft lip and palate. Cephalometric findings at an even earlier age than examined in our study have shown an extremely protruding premaxilla with a short maxilla of reduced posterior height, a short mandible, and bimaxillary retrognathia with a more vertical facial growth pattern [15].

The protrusion of the premaxilla in the 6-year olds from all
In the present study, we also noticed that the Dutch children had a significantly more retrusive mandibular growth pattern than the Scandinavian children.

Conclusions

Even though the three cleft centers followed different treatment protocols, the craniofacial morphology of their patients with CBCLP was not very different until the age of 12. However, the growth pattern differed, especially with respect to maxillary and upper incisor variables. The premaxillary osteotomy performed around 10 years of age in Nijmegen seems to inhibit sagittal and vertical maxillary development. Further evaluation of the group until growth has ceased is needed to solve the controversy about the long-term effect of premaxillary osteotomy.

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Conflict of interest  Demetrios Halazonetis has a financial interest in the Viewbox software used for cephalometric analysis.

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