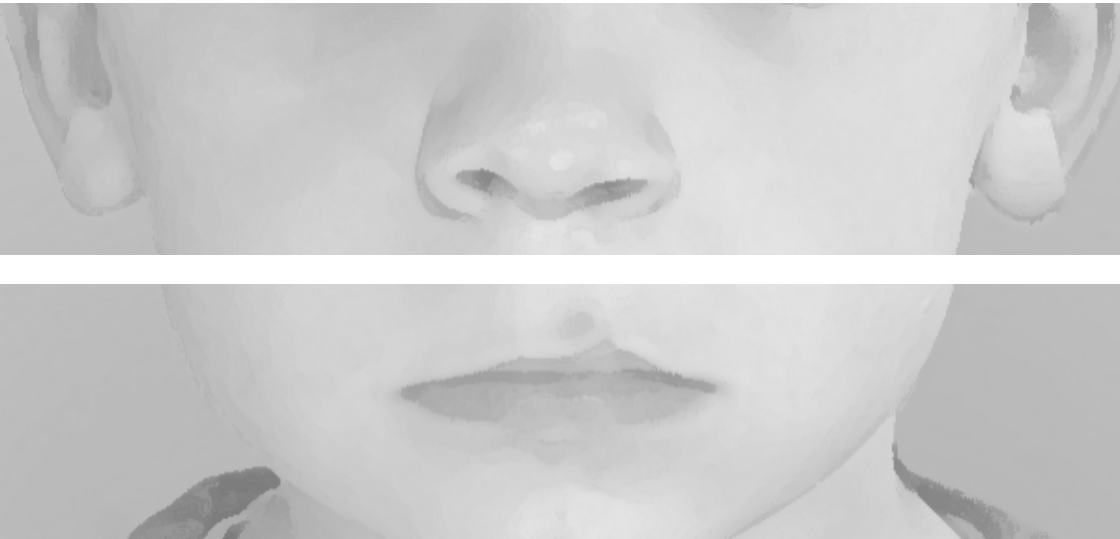




OROFACIAL CLEFTS

ASSESSMENT OF GROWTH AND TREATMENT
OUTCOME

Laurent A. M. Thierens

2020

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OUTCOME

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Thesis submitted to Ghent University and Catholic University Leuven
in partial fulfilment of the requirements for the Joint Degree of
Doctor in Health Sciences and Biomedical Sciences, respectively.

2020



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The printing of this this thesis was financially supported by: Orthotrends – Centrum voor Orthodontische Studie (COS)
Printed by: University Press

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LIST OF ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
BAMP	Bone Anchored Maxillary Protraction
BCL	Bilateral Cleft Lip
BCLP	Bilateral Cleft Lip and Palate
CA	Coefficient of Asymmetry
CI	Confidence Interval
CL	Cleft Lip
CL/P	Cleft Lip and/or Cleft Palate
CL±P	Cleft Lip with or without Cleft Palate (without isolated cleft palate)
CLP	Cleft Lip and Palate
CP	Cleft Palate
CS	Cervical Stage
CVA	Canonical Variate Analysis
CVM	Cervical Vertebral Maturation
ERN	European Reference Network
F	Female
GPA	General Procrustes Analysis
ICC	Intraclass Correlation Coefficient
ICHOM	International Consortium for Health Outcomes Measurement
IRF6	Interferon Regulatory Factor 6
M	Male
MINORS	Methodological Index for Non-Randomized Studies
N	Number
NAM	Nasoalveolar Molding
NR	Not Reported
OFC	Orofacial Cleft
PCA	Principal Component Analysis
OHRQoL	Oral Health-Related Quality of Life
RMSE	Root-Mean-Square-Error
SD	Standard Deviation
UCLA	Unilateral Cleft Lip and Alveolus

UCLP	Unilateral Cleft Lip and Palate
VAS	Visual Analogue Scale
VDWS	Van der Woude syndrome
WHO	World Health Organization

1.

GENERAL INTRODUCTION

Parts of this chapter have been published as:

Thierens LAM, Temmerman L, and De Pauw GAM. An intercenter comparison of the early treatment outcome of unilateral cleft patients. Ghent University, thesis Master in Advanced Dentistry, Department of Orthodontics, 2015:1-27.

Cleft lip, cleft palate or together occurring as cleft lip and palate are types of orofacial clefts caused by aberrant facial development during gestation. A cleft can be described as an opening in the face or a malformation of a part of the face.

Historically, many attempts have been made to classify orofacial clefts. Morian (1887) described three different types of facial clefts, depending on the relationship of the cleft to the maxillary teeth¹. Veau (1931) proposed a morphological classification based on the position and the extent of the cleft². In 2017, Allori and co-workers suggested a robust, descriptive method for cleft lip with or without cleft palate (CL±P) phenotypes that included the laterality and severity of the labial defect, the presence of an alveolar defect, and a morphological characterization of the palatal defect².

Overall, available findings indicate that orofacial clefts arise in about 1.7 per 1000 newborn babies worldwide³. A variation of prevalence at birth of cleft lip with or without cleft palate (CL±P) of 3.4-22.9 per 10 000 births (0.034%-0.23%) is suggested by international data of the World Health Organization (WHO)⁴. A higher incidence is observed in Asian (China, Japan) and Latin American populations in comparison with Israeli, South African, and southern European populations. CL±P is observed more frequently in males³. Around 66% of all unilateral CL±P cases have left-sided defects, regardless of gender, race and severity of the defect³. Based on observational studies of immigrants to the USA from Japan and China and comparison between ethnic groups in the USA and the UK, migrant groups have rates of CL±P closer to those of the area from which they originated than those in the area into which they have moved⁵⁻⁷. For 2017 and 2018, 28 and 21 newborn CL±P cases, respectively, were officially scored in Flanders by the Dutch Association of Cleft Palate and Craniofacial Anomalies.

For isolated cleft palate (CP) there is an even more pronounced variation with a prevalence of 1.3-25.3 per 10 000 births (0.013%-0.25%). This variation can possibly be explained by the different methods of data collection, because isolated cleft palate is less noticeable externally³. The prevalence is high in Canada and parts of northern Europe and low in parts of Latin America and South Africa³. In Flanders, 17 and 24 CP newborn cases were officially scored in Flanders by the Dutch Association of Cleft Palate and Craniofacial Anomalies in 2017 and 2018, respectively. CP, in contrast to CL±P, is more observed in females.

In the last decade, a downward trend can be observed in the number of newborns with an orofacial cleft in Flanders. In 2009, the Flemish Agency for Care and Health reported 87 children with a cleft lip and/or cleft palate in their annual report about perinatal activities. In 2010 a peak of 120 new cases was reported. In 2018, this number was reduced to 55 (Figure 1). It can be assumed that this downward trend is caused by technical improvements in and availability of prenatal ultrasound diagnosis, and subsequent pregnancy termination when an extensive orofacial cleft is detected.

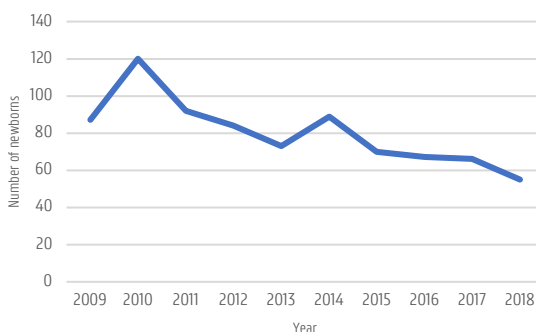


Figure 1. Newborns with cleft lip and/or cleft palate in Flanders 2009-2018 (based on *Perinatale Activiteiten in Vlaanderen 2009-2018*).

The development of the lip and the palate comprises a complex series of morphogenetic events that require close coordination of programs for cell migration, growth, progressive differentiation, morphogenetic events, and apoptosis^{3,8}. Neural crest cells are essential in the human embryonic development of the craniofacial region. They delaminate from the lateral ridges of the neural plate, contribute to and migrate through mesenchymal tissue and participate by the 4th week in formation of the frontonasal prominence, the paired maxillary processes and the paired mandibular processes. By the end of the 4th week, the formation of nasal placodes divides the lower part of the frontonasal prominence in medial and lateral nasal prominences. The upper lip and the primary palate are formed by the 6th week by aggregation of the medial nasal prominences with the maxillary processes on each side. The lateral nasal prominences show a peak of cell division before completion of the formation of the upper lip and the primary palate. This makes it susceptible to detrimental events. At this time, any disturbance in growth can lead to failure of the closure mechanism³. During the 6th week of the embryonic development, the first signs of secondary palatogenesis are seen. Initially, vertically

outgrowth down both sides of the developing tongue from the maxillary processes of the palatal shelves is observed. During week 8 post conception, the palatal shelves rotate from a vertical position and elevate into horizontal approximation⁸. After fusion, at the midline, an epithelial seam can be detected. After degenerating of the seam and continuation of the palatal mesenchyme, differentiation into muscular and bony elements can be noticed. Completion of the fusion processes is reached by the 10th week of human embryogenesis³. Failures of elevation, failures of contact and adhesion, or failures of fusion result in a cleft of the secondary palate. Wide clefts result when rotation of the palatal shelves failed. Narrow clefts can indicate rotated and elevated palatal shelves that failed to contact and fuse or failed to fuse even when contact was made⁸.

Orofacial clefts are typically classified in syndromic and non-syndromic forms. The proportion of the syndromic forms is between 5 and 7%. Syndromic forms of CL±P include more than 200 different conditions and isolated cleft palate (CP) is associated with more than 400 genetic syndromes. Syndromic clefts are characterized by the presence of a specific malformation pattern involving the presence of other associated anomalies in addition to CL/P, and is caused by monogenic diseases and chromosomal disorders⁹. The Van der Woude syndrome (VDWS) is considered as the commonest syndrome associated with the presence of a cleft. It accounts for about 2% of all cases and occurs in about 1:35000 to 1:100 000 of the Caucasian population. VDWS is characterized by congenital sinuses of the lower lip associated with CL/P. The inheritance is autosomal dominant, and the expression of the genetic condition varies from pits in the lower lip to complete CL/P. Mutations located in exons 3, 4, 7, and 9 in the interferon regulatory factor 6 (IRF6) gene on chromosome 1q are responsible for the VDWS¹⁰.

A non-syndromic cleft is a multifactorial disease derived from the interaction between genes and environmental factors. These environmental agents include maternal exposure to smoke, alcohol, diet, viral infections, drugs, and teratogen agents during early pregnancy. It has also been suggested that physical and/or emotional stress may be implicated in the development of an orofacial cleft¹¹. Genes coding for growth factors (TGFA, TGFB3), genes involved in the metabolism of xenobiotics (CYP1A1, GSTM1, NAT2), genes related to the nutritional metabolism (MTHFR, RARA), genes involved in immune response (PVLR1), and genes coding for transcription factors (MSX1, TBX22) have been identified as susceptible genes for interaction with the above described environmental agents. The IRF6 gene is also strongly associated with an increased risk of non-syndromic clefting¹⁰.

The phenotype of children with CL/P is characterized by specific hearing and speech problems, craniofacial traits, and dental anomalies. Generally, the craniofacial morphology of children with CL/P is characterized by a short, retrusive maxilla, vertical elongation of the anterior face, a retrusive mandible, reduction of the posterior facial height, a slight increase in cranial base angulation and interocular distance, and flattening of the nose at the cleft side(s)¹². Dental anomalies are observed in 96.7% of the cleft population with an increased prevalence of agenesis in the anterior (cleft) region, hyperdontia, and tooth impaction in the anterior and premolar (cleft) region^{13,14}.

Optimal management of cleft anomalies is coordinated and performed by a multidisciplinary cleft team. This team includes a designated patient care coordinator and must have, as a minimum core, a surgeon (a plastic surgeon and/or head, neck and maxillofacial surgeon), a speech therapist, and an orthodontist. The team must also have direct access to professionals in the disciplines of psychology, social work, audiology, genetics, general and paediatric dentistry, otolaryngology and paediatrics/primary care¹⁵.

The timing of the surgical and orthodontic interventions for unilateral complete oral clefts in Ghent University Hospital and University Hospitals Leuven is visualized in Table 1.

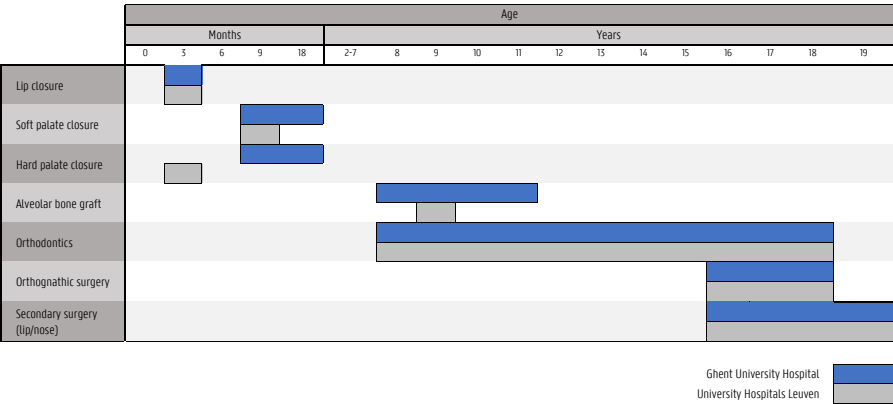


Table 1. Timing of the surgical interventions (and orthodontics) for unilateral complete clefts in Ghent University Hospital and University Hospitals Leuven.

Even though cleft management performed by a multidisciplinary team is generally accepted, treatment protocols can vary considerably between different teams¹⁶. These protocols are usually the result of scientifically acquired insights and clinical experiences.

Outcome assessment in CL/P was launched 25 years ago on European scale within the project 'Standards of Care for Cleft Lip and Palate in Europe: Eurocleft'. It was funded by the European Commission and aimed to promote a broad uplift in the quality of care and research in the area of cleft lip and palate¹⁶. After all, the potential for wider European collaboration was recognized following the publication of a European intercenter comparison study¹⁷.

The final results of the Eurocleft project included¹⁶:

- the production of a register of services in Europe, with details of professionals and teams involved in cleft care, service organization, clinical protocols and special facilities for research
- a set of common policy statements governing clinical practice for European cleft teams,
- a set of common practice guidelines describing minimum recommendations for care that all European children with clefts should be entitled to, and
- a set of common recommendations for documentation governing the minimum records that cleft teams should maintain.

The Eurocleft project and the increased awareness of cleft care served as a catalyst of numerous multicenter studies and randomized clinical trials: Scandcleft, investigating timing and surgical technique of palatal closure¹⁸, Dutchcleft, investigating infant orthopedics¹⁹, and Americleft²⁰. Flemish cleft centers have not yet been involved in (international) multicenter studies for outcome assessment. This topic is discussed in the first paper of this thesis (*Chapter 3*).

Almost two decades after Eurocleft, the Task Force Beyond Eurocleft made recommendations for initiations of local and/or participation in multinational cleft outcome studies. This Task Force also suggested that teams already active in research should: create a register for cleft professionals and teams to reach agreement of contemporary and comprehensive multidisciplinary outcome measures,

plan large multinational studies, and explore the possibilities using modern technology²¹. Concerning the latter, non-ionizing three-dimensional surface imaging is one of many modern technologies that has shown to have a big potential in cleft research.

Non-ionizing three-dimensional surface imaging enables 3D surface data acquisition in a reliable manner and works without ionizing radiation²²⁻²⁴. This group of image acquisition methods includes stereophotogrammetry, laser surface scanning, and structured light surface scanning. Stereophotogrammetry is widely used and is capable of reproducing surface geometry and mapping realistic colour and texture data by taking 2 or more photographs of the same subject from different positions. Subsequently, the photographs are stitched together by a software tool to generate a composite 3D model^{22,23}. Technical validation of several image capturing systems has shown that the stereophotogrammetry technology is sufficiently accurate for facial imaging^{25,26}. The field of application of this technique runs from cross-sectional evaluation of facial morphology, symmetry, and appearance to longitudinal evaluation of growth and (non-)surgical interventions.

For decades, craniofacial anthropometry was the method of choice in clinical practice for the assessment of facial soft tissues. Farkas and co-workers created a comprehensive measurement system that is based on the identification of anthropometric landmarks. They formalized objective means of craniofacial size and shape and created novel anthropometric procedures. They also produced anthropometric atlases of the human head and face, mainly containing projective linear measurements, arcs, angles of inclination, and deviations, each connecting anthropometric landmarks²⁷. Craniofacial anthropometry is both objective and reliable, but it requires extensive training in order to obtain reliable results^{27,28}. Since the introduction of laser surface scanning and stereophotogrammetry, the scope of anthropometry was extended to 3D surface images. This topic applied to cleft lip and palate is discussed in the second and third paper of this thesis (*Chapter 4 and 5*). The application of a landmark-independent 3D assessment method to evaluate a surgical intervention in a cleft population is discussed in the fourth paper of this thesis (*Chapter 6*).

Growth of the maxilla in patients with CL/P can be restricted in three dimensions. This can be attributed to the severity of the cleft but also to iatrogenic effects of previous surgeries such as closure of the lip and/or palate. It has been demonstrated that the magnitude of these iatrogenic effects correlates with the experience and case load of the surgeon²⁹⁻³¹. However, basal skeletal

characteristics³¹, missing lateral incisors as a sign of inherent tissue hypoplasia³¹, and altered embryonic development of the pituitary gland resulting in growth hormone deficiency^{32,33} are also considered as relevant contributing factors to this growth impairment. Clinically, cleft patients with maxillary growth impairment present with a relative Class III skeletal pattern and an anterior crossbite.

Abnormal or disturbed growth of the maxillomandibular complex can be approached in two different ways, depending on the maturational status of the patient and the extent of the anomaly. Orthognathic surgery, in combination with pre- and post-orthodontic treatment, allows three-dimensional jaw rehabilitation in a mature patient by one or two-step procedures.

On the other hand, facial growth and development during childhood or early adolescence can be guided by dentofacial orthopaedic treatment. Transverse, anteroposterior, and to a lesser extent also vertical discrepancies can be treated using appliances as maxillary expanders, headgear, functional appliances, face masks, or bone-anchored maxillary protraction with intermaxillary elastics³⁴. The latter is a more recent treatment modality for a skeletal class III that has demonstrated satisfying results in CL/P patients^{35,36}.

Success in dentofacial orthopaedics is highly dependent on the patient's maturational stage. Therefore, it is important to determine the period of accelerated growth of the relevant skeletal structure to achieve the most favourable response with the least potential morbidity³⁷. The individual skeletal maturity can be assessed using biological indicators such as increase in body height³⁸, skeletal maturation of the hand and wrist³⁹, dental calcification stages⁴⁰, and the Cervical Vertebral Maturation^{37,41}. The Cervical Vertebral Maturation (CVM) method was introduced by Lamparski and further refined by Baccetti and co-workers^{37,42,43}. It is a validated method that allows estimation of the skeletal maturation using a cephalometric radiograph. This imaging method is also routinely used for orthodontic purposes, so the radiation dose can be minimized^{44,45}.

Current literature concerning craniofacial growth assessed with the CVM method in CL/P is inconclusive, or the results cannot be extrapolated to a Caucasian population⁴⁶⁻⁴⁸. This topic is discussed in the final paper of this thesis (*Chapter 7*).

REFERENCES

1. Greenberg A. M., Schmelzeisen R. Craniomaxillofacial Reconstructive and Corrective Bone Surgery. Springer New York, **2019**.
2. Allori A. C., Mulliken J. B., Meara J. G., Shusterman S., Marcus J. R. Classification of Cleft Lip/Palate: Then and Now. *Cleft Palate Craniofac J* **2017**;54:175-88.
3. Mossey P. A., Little J., Munger R. G., Dixon M. J., Shaw W. C. Cleft lip and palate. *Lancet* **2009**;374:1773-85.
4. Mossey P., Castillia E. Global registry and database on craniofacial anomalies. Geneva: WHO, **2003**.
5. Ching G. H., Chung C. S. A genetic study of cleft lip and palate in Hawaii. I. Interracial crosses. *Am J Hum Genet* **1974**;26:162-76.
6. Croen L. A., Shaw G. M., Wasserman C. R., Tolarova M. M. Racial and ethnic variations in the prevalence of orofacial clefts in California, 1983-1992. *Am J Med Genet* **1998**;79:42-7.
7. Leck I., Lancashire R. J. Birth prevalence of malformations in members of different ethnic groups and in the offspring of matings between them, in Birmingham, England. *J Epidemiol Community Health* **1995**;49:171-9.
8. Marazita M. L., Mooney M. P. Current concepts in the embryology and genetics of cleft lip and cleft palate. *Clin Plast Surg* **2004**;31:125-40.
9. Tolarova M. M., Cervenka J. Classification and birth prevalence of orofacial clefts. *Am J Med Genet* **1998**;75:126-37.
10. Stuppia L., Capogreco M., Marzo G., La Rovere D., Antonucci I., Gatta V., et al. Genetics of syndromic and nonsyndromic cleft lip and palate. *J Craniofac Surg* **2011**;22:1722-6.
11. Carmichael S. L., Shaw G. M., Yang W., Abrams B., Lammer E. J. Maternal stressful life events and risks of birth defects. *Epidemiology* **2007**;18:356-61.
12. Semb G. A study of facial growth in patients with unilateral cleft lip and palate treated by the Oslo CLP Team. *Cleft Palate Craniofac J* **1991**;28:1-21; discussion 46-8.
13. Akcam M. O., Evirgen S., Uslu O., Memikoglu U. T. Dental anomalies in individuals with cleft lip and/or palate. *Eur J Orthod* **2010**;32:207-13.
14. Jamilian A., Jamilian M., Darnahal A., Hamed R., Mollaei M., Toopchi S. Hypodontia and supernumerary and impacted teeth in children with various types of clefts. *Am J Orthod Dentofacial Orthop* **2015**;147:221-5.

15. American Cleft Palate-Craniofacial Association "Standards of team care for cleft palate and craniofacial teams (ACPA Standards)". Retrieved 27 April 2020, from http://www.acpa-cpf.org/team_care/standards/.
16. Shaw W. C., Semb G., Nelson P., Brattstrom V., Prahl-Andersen B., et al. The Eurocleft project 1996-2000: overview. *J Craniomaxillofac Surg* **2001**;29:131-40; discussion 41-2.
17. Shaw W. C., Asher-McDade C., Brattstrom V., Dahl E., McWilliam J., Molsted K., et al. A six-center international study of treatment outcome in patients with clefts of the lip and palate: Part 1. Principles and study design. *Cleft Palate Craniofac J* **1992**;29:393-7.
18. Semb G., Enemark H., Friede H., Paulin G., Lilja J., Rautio J., et al. A Scandcleft randomised trials of primary surgery for unilateral cleft lip and palate: 1. Planning and management. *J Plast Surg Hand Surg* **2017**;51:2-13.
19. Bongaarts C. A., Kuijpers-Jagtman A. M., van 't Hof M. A., Prahl-Andersen B. The effect of infant orthopedics on the occlusion of the deciduous dentition in children with complete unilateral cleft lip and palate (Dutchcleft). *Cleft Palate Craniofac J* **2004**;41:633-41.
20. Long R. E., Jr., Hathaway R., Daskalogiannakis J., Mercado A., Russell K., Cohen M., et al. The Americleft study: an inter-center study of treatment outcomes for patients with unilateral cleft lip and palate part 1. Principles and study design. *Cleft Palate Craniofac J* **2011**;48:239-43.
21. Semb G. International confederation for cleft lip and palate and related craniofacial anomalies task force report: beyond eurocleft. *Cleft Palate Craniofac J* **2014**;51:e146-55.
22. Heike C. L., Upson K., Stuhaug E., Weinberg S. M. 3D digital stereophotogrammetry: a practical guide to facial image acquisition. *Head Face Med* **2010**;6:18.
23. Lane C., Harrell W., Jr. Completing the 3-dimensional picture. *Am J Orthod Dentofacial Orthop* **2008**;133:612-20.
24. Ayoub A., Garrahy A., Hood C., White J., Bock M., Siebert J. P., et al. Validation of a vision-based, three-dimensional facial imaging system. *Cleft Palate Craniofac J* **2003**;40:523-9.
25. Wong J. Y., Oh A. K., Ohta E., Hunt A. T., Rogers G. F., Mulliken J. B., et al. Validity and reliability of craniofacial anthropometric measurement of 3D digital photogrammetric images. *Cleft Palate Craniofac J* **2008**;45:232-9.
26. Camison L., Bykowski M., Lee W. W., Carlson J. C., Roosenboom J., Goldstein J. A., et al. Validation of the Vectra H1 portable three-dimensional photogrammetry system for facial imaging. *Int J Oral Maxillofac Surg* **2018**;47:403-10.

27. Deutsch C. K., Shell A. R., Francis R. W., Bird B. D. The Farkas System of Craniofacial Anthropometry: Methodology and Normative Databases. In: V. Preedy (eds) Handbook of Anthropometry. **2012**; Springer, New York, NY
28. Farkas L. G., Deutsch C. K. Anthropometric determination of craniofacial morphology. *Am J Med Genet* **1996**;65:1-4.
29. Ross R. B. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. *Cleft Palate J* **1987**;24:5-77.
30. Kapucu M. R., Gursu K. G., Enacar A., Aras S. The effect of cleft lip repair on maxillary morphology in patients with unilateral complete cleft lip and palate. *Plast Reconstr Surg* **1996**;97:1371-5; discussion 6-8.
31. Meazzini M. C., Tortora C., Morabito A., Garattini G., Brusati R. Factors that affect variability in impairment of maxillary growth in patients with cleft lip and palate treated using the same surgical protocol. *J Plast Surg Hand Surg* **2011**;45:188-93.
32. Roitman A, Laron Z. Hypothalamo-pituitary hormone insufficiency associated with cleft lip and palate. *Arch Dis Child* **1978**;53:952-5.
33. Rudman D., Davis T., Priest J. H., Patterson J. H., Kutner M. H., Heymsfield S. B., et al. Prevalence of growth hormone deficiency in children with cleft lip or palate. *J Pediatr* **1978**;93:378-82.
34. De Clerck H. J., Proffit W. R. Growth modification of the face: A current perspective with emphasis on Class III treatment. *Am J Orthod Dentofacial Orthop* **2015**;148:37-46.
35. Garib D., Yatabe M., de Souza Faco R. A., Gregorio L., Cevdanes L., de Clerck H. Bone-anchored maxillary protraction in a patient with complete cleft lip and palate: A case report. *Am J Orthod Dentofacial Orthop* **2018**;153:290-7.
36. Yatabe M., Garib D. G., Faco R. A. S., de Clerck H., Janson G., Nguyen T., et al. Bone-anchored maxillary protraction therapy in patients with unilateral complete cleft lip and palate: 3-dimensional assessment of maxillary effects. *Am J Orthod Dentofacial Orthop* **2017**;152:327-35.
37. Baccetti T., Franchi L., McNamara J. J. The Cervical Vertebral Maturation (CVM) Method for the Assessment of Optimal Treatment Timing in Dentofacial Orthopedics. *Semin Orthod* **2005**;11:119-29.
38. Bjork A. Variations in the growth pattern of the human mandible: longitudinal radiographic study by the implant method. *J Dent Res* **1963**;42(1)Pt 2:400-11.
39. Bjork A., Helm S. Prediction of the age of maximum puberal growth in body height. *Angle Orthod* **1967**;37:134-43.

40. Demirjian A, Goldstein H, Tanner J. M. A new system of dental age assessment. *Hum Biol* **1973**;45:211-27.
41. O'Reilly M. T., Yanniello G. J. Mandibular growth changes and maturation of cervical vertebrae--a longitudinal cephalometric study. *Angle Orthod* **1988**;58:179-84.
42. Baccetti T., Franchi L., McNamara J. A., Jr. An improved version of the cervical vertebral maturation (CVM) method for the assessment of mandibular growth. *Angle Orthod* **2002**;72:316-23.
43. Lamparski D. G. Skeletal age assessment utilizing cervical vertebrae. *Am J Orthod Dentofacial Orthop* **1972**;67:458-9.
44. Szemraj A., Wojtaszek-Slominska A., Racka-Pilszak B. Is the cervical vertebral maturation (CVM) method effective enough to replace the hand-wrist maturation (HWM) method in determining skeletal maturation?-A systematic review. *Eur J Radiol* **2018**;102:125-8.
45. Cericato G. O., Bittencourt M. A., Paranhos L. R. Validity of the assessment method of skeletal maturation by cervical vertebrae: a systematic review and meta-analysis. *Dentomaxillofac Radiol* **2015**;44:20140270.
46. Sun L., Li W. R. Cervical vertebral maturation of female children with orofacial clefts. *Cleft Palate Craniofac J* **2013**;50:535-41.
47. Sun L., Li W. R. Cervical vertebral maturation of children with orofacial clefts. *Cleft Palate Craniofac J* **2012**;49:683-8.
48. Ravi M., Ravikala S. Assessment of skeletal age in children with unilateral cleft lip and palate. *Int J Clin Pediatr Dent* **2013**;6:151-5.

OBJECTIVES AND METHODOLOGY

2.

The following **general hypotheses** were postulated:

- The early surgical outcome of Flemish cleft lip and palate patients meets the international standards.
- Non-ionizing 3D imaging technologies allow objective evaluation of cross-sectional and longitudinal facial surface data
- Patients with cleft lip and/or palate have an increased risk for delayed skeletal maturation.

The following **specific aims** with according **methodology** were determined:

AIM 1

To assess the dentoalveolar relationship of 5- to 6-year-old cleft patients in two university-based cleft centers in order to evaluate the early surgical treatment outcome and to compare these results with the international standards.

METHODS

The early surgical outcome of unilateral cleft lip and palate patients was investigated using a retrospective study design. Plaster casts of 5- to 6-year-old unilateral cleft patients were prospectively collected in Ghent University Hospital and University Hospitals Leuven. The dentoalveolar relationship was assessed using 2 validated indices (5-Year-Olds' Index and the modified Huddart/Bodenham scoring system) in order to evaluate the surgical closure of the lip and palate.

AIM 2

To explore the modalities of state-of-the-art non-ionizing 3D surface imaging technologies for longitudinal and cross-sectional evaluation of facial morphological characteristics in patients with orofacial clefts.

METHODS

This aim has been addressed with two systematic reviews. The first systematic review focused on the assessment modalities of non-invasive 3D images for the quantification of facial morphology, symmetry, and appearance (cross-sectional measurements). The second systematic review focused on the quantification of soft tissue changes using non-invasive 3D images (longitudinal measurements).

CHAPTER
4&5

AIM 3

To assess the influence of an alveolar bone graft on the nasolabial asymmetry of unilateral cleft patients.

METHODS

The effects of an alveolar bone graft on nasolabial asymmetry in 8- to 10-year-old unilateral cleft patients was investigated using a prospective study design. Three-dimensional surface images of the face were collected pre- and postoperatively in the collaborating hospitals (Ghent University Hospital, AZ Monica Antwerp, and AZ Sint-Jan Bruges). Image processing and analysis was performed by using a 3D anthropometric mask and superimposition of the facial structures and their mirror image.

CHAPTER
6

AIM 4

To determine if patients with CL/P have an increased risk for a delayed skeletal maturation in order to optimize the timing of dentofacial orthopedics

METHODS

The timing of the skeletal maturation in cleft patients was investigated on lateral skull radiographs, previously recorded for diagnostic (orthodontic) purposes in Ghent University Hospital and University Hospitals Leuven. Skeletal maturational status was determined by using the Cervical Vertebral Maturation (CVM) method. The CVM method allows classification into six cervical stages (CS 1-6) based on a visual appraisal of two morphological characteristics of the cervical vertebrae C2, C3, and C4.

CHAPTER

7

3.

A RETROSPECTIVE INTERCENTER COMPARISON OF TWO SURGICAL PROTOCOLS THROUGH THE DENTAL ARCH RELATIONSHIP OF 5- TO 6-YEAR-OLD UNILATERAL CLEFT PATIENTS.

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Pauw GAM. *Clin Oral Invest* **2019** Apr;23(4):1777-84

ABSTRACT

Objectives: The objectives of this retrospective equivalence trial were to assess the dental arch relationship of 5- to 6-year-old patients with unilateral cleft lip and palate (UCLP) treated in two specialized cleft centers with a different surgical protocol using the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system, and to determine the correlation between these two scoring indices.

Materials and Methods: The dental arch relationship of seventy-three 5- to 6-year-old patients with complete UCLP was evaluated on plaster casts using the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system. The sagittal occlusion, overbite, and overjet were also recorded. Inter- and intra-examiner agreement were determined using Intraclass Correlation Coefficients.

Results: A good to very good inter- and intra-examiner agreement was found. No significant mean difference in outcome based on the 5-Year-Olds' Index, the modified Huddart/Bodenham scoring system, overjet, or overbite was detected. For mean difference in sagittal occlusion the hypothesis that both centers are clinically equivalent was confirmed. A strong negative correlation ($r_s = -0.832$) between the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system was found.

Conclusions: The dental arch relationship of 5- to 6-year-old unilateral cleft patients treated in two Belgian cleft centers are clinically equivalent based on sagittal occlusion, despite substantial differences in their treatment protocol. Clinical equivalence for other parameters was not confirmed. There is a strong correlation between the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system.

Clinical relevance: A well implemented treatment protocol for cleft patients is of the utmost importance, but case load and skill of the surgeon are also important factors for the quality of the results.

Keywords: cleft lip and palate, early treatment outcome, modified Huddart/Bodenham scoring system, 5-Year-Olds' Index

INTRODUCTION

Patients with cleft lip and palate (CLP) receive specialized care from professionals during an intensive treatment pathway from birth until the age of 18 and older. Ideally, the activities of these specialists are coordinated by a cleft team. The affected anatomical structures of the lip, jaw, and palate are reconstructed to restore the function and the esthetics of the child.

The dental arch relationship can be used as an indicator of the surgical outcome of cleft lip and palate repair as poorly performed primary surgery is likely to compromise dental development and facial growth¹. A wide range of indices has been developed to assess malocclusions in patients with CLP². The Goslon (Great Ormond Street, London and Oslo) Yardstick is a categorical scoring system for the late mixed or early permanent dentition². The 5-Year-Olds' Index is a Goslon Yardstick-like index that can be performed at an earlier moment to measure the surgical outcome by evaluating the dentoalveolar relationship in dental casts³. The Huddart/Bodenham scoring system rates the deciduous dentition numerically based on the presence and severity of crossbites in the anterior segment and the two buccal segments^{2,3}. The modified Huddart/Bodenham scoring system also allows scoring in the mixed and permanent dentition⁴. The latter shows a high intra- and inter-examiner reliability⁵. The 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system are the two recommended indices as an outcome measure for the early treatment of UCLP⁶ and there is a high degree of correlation between the 5-Year-Olds' Index, the Goslon Yardstick, and the modified Huddart/Bodenham scoring system^{7,8}.

Care for children with CLP is often scattered across different centers with a limited case load and their own preferences concerning the treatment protocol. During the last two decades, great efforts have been made on an international level to define minimum standards. These efforts aimed to increase the quality of care and recent results confirmed this^{6,9-13}.

The objectives of this study are to assess if two centers with a different surgical protocol for 5 to 6-year old patients with UCLP can be considered clinically equivalent with respect to the dental arch relationship, and to determine the correlation between the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system for this sample.

MATERIALS AND METHODS

The study was a retrospective equivalence trial between two centers' outcome assessment of the early treatment of UCLP patients. Patients were included using following criteria: (1) repaired, complete UCLP, (2) 5 to 6 years of age, (3) no syndromes or soft tissue bands, and (4) all primary surgical interventions exclusively performed in the cleft centers of the Ghent University Hospital (Belgium, center 1) or Leuven University Hospitals (Belgium, center 2).

In center 1, lip repair was performed at 3 months using a modified rotation-advancement flap technique (Millard)¹⁰. The soft and hard palate repair was performed at 12 to 18 months in a one-stage intervention. The soft palate was closed using an intravelar palatoplasty (Sommerlad)¹⁴. The hard

palate was closed using a Bardach flap with Langenbeck extension. In center 2, lip repair was performed at 3 months using a modified Tennison-Randall technique (using a supra-vermillion triangle and – on indication – a Millard C flap to the midcollumella)¹². The soft palate and the distal part of the hard palate were repaired at 12 months using a staged suprapariosteal repositioning approach and the hard palate was closed at the age of 5 to 6 years old using hemipalatinal flaps according to von Langenbeck, with a two layered (nasal and oral) closure⁴. In case of crossbite a presurgical expansion was done using a removable expansion appliance. In each center, the respective surgical procedures were performed by the same surgeon for all patients.

The dental arch relationship was scored on plaster casts. Impressions were taken with an irreversible hydrocolloid (Orthotrace, Cavex Holland, Haarlem, The Netherlands) and bite registration was performed in maximum intercuspitation with bite registration wax (Tenatex Red, Kemdent, Swindon, UK). The study models were fabricated in white dental plaster. A number was randomly assigned to each model. Two assessors were trained and calibrated to score the study models. The assessors were both orthodontic residents familiar with determination of dental occlusion, dental relationships, and cleft anatomy. A standardization exercise on 10 casts with subsequent discussion. If this discussion was inconclusive, an experienced supervisor was consulted to achieve final agreement. Twenty randomly selected models were reassessed 3 months after the initial measurements to determine the inter- and intra-examiner agreement.

The dental arch relationship of the study models was assessed using following outcome parameters: the modified Huddart/Bodenham scoring system, the 5-Year-Olds' Index, overjet, overbite, and the sagittal occlusion of deciduous canines and (deciduous) molars. The 5-Year-Olds' Index is a subjective scoring system with 5 reference groups. Malocclusions are assessed and scored on a scale of 1 to 5 (best to worst prognosis) on a value judgement in terms of sagittal, vertical, and transversal dentoalveolar discrepancies¹⁵. The modified Huddart/Bodenham scoring system rates the position of every tooth, with exception of the lateral incisors, relative to its opponent in the lower jaw. The modified Huddart/Bodenham scoring system divides the maxillary arch into three segments: the labial, the buccal cleft, and the buccal non-cleft segment. The anteroposterior relationship of the central incisors is scored on a scale of -3 to +1. The buccopalatal relationship of the canines, premolars, and (deciduous) molars is scored on a scale of -2 to 0. Before the age of 6, the first permanent molars are not scored, even when erupted. The score of an absent or non-erupted tooth is determined by the midpoint of the maxillary alveolar ridge at the location of that particular tooth. A maximum range of

scores is between -18 and +2 before the age of 6 and between -22 and +2 after and including the age of 6⁷. For the scoring of the 5-Year-Olds' Index a written description, reference images and the original reference paper were provided. Written instructions and the original reference paper were provided for the scoring of the Modified Huddart/Bodenham scoring system. The overjet and overbite were determined to the nearest half millimeter using an orthodontic diagnostic instrument by Korkhaus (Dentaurum, Ispringen, Germany). The sagittal occlusion was quantified for the deciduous canines and second deciduous molars using the Angle classification method. Class I relationship was scored as zero. A deviation with respect to a Class I relationship of a quarter premolar width was scored as 1, a half premolar width as 2, three quarter premolar width as 3, and a full premolar width as 4. A Class II relationship was given a positive sign; a Class III relationship was given a negative sign^{16,17}.

Statistical analysis was performed with SPSS 24 (IBM, Armonk, New York, USA). Intraclass Correlation Coefficients (ICC's) were calculated for all continuous surgical outcomes to evaluate inter- and intra-examiner agreement. The Kappa coefficient with bootstrapped 95% confidence interval was calculated for the proportion of patients with good to excellent outcome on the 5-Year-Old's Index and for the proportion of patients with poor to very poor outcome to evaluate inter- and intra-examiner agreement. Distributions of the modified Huddart/Bodenham scoring system, overjet (mm), overbite (mm), and sagittal occlusion were compared between centers by means of independent samples Mann-Whitney U tests. The 95% confidence intervals for the mean differences were constructed by bootstrapping (10 000 samples), because the data were not normally distributed, and the sample size was too low for asymptotic approximations. The hypothesis of clinical equivalence between the two centers was accepted if the 95% confidence interval of the mean differences between the centers lied within predefined equivalence limits. These equivalence limits are considered to be the largest difference between centers in surgical outcome that is clinically acceptable. The equivalence margin for difference in modified Huddart/Bodenham scoring system was set at 2 points (-2 to + 2), for difference in overjet and overbite at 1 mm (-1 to +1), and for difference in sagittal occlusion at 2 points (-2 to +2).

The proportion of patients with good to excellent outcome on the 5-Year-Old's Index was compared between centers by means of a two-sided Fisher's exact test. A 95% confidence interval for the difference between these two independent proportions was constructed with Newcomb's method, which is based on the Wilson score confidence interval. The same approach was used to compare the proportion of patients with poor to very poor outcome on the 5-Year-Old's Index. The hypothesis of clinical equivalence between the two centers with respect to outcome on the 5-Year-Old's Index was

accepted if the 95% confidence interval of the difference in proportion between the centers lied within the predefined equivalence limits of 20% (-20% to +20%).

The correlation between outcome on the 5-Year-Olds' Index and outcome on the modified Huddart/Bodenham scoring system was investigated with the Spearman's rank correlation coefficient. The study design was evaluated and approved by the Ethical Committees of the Ghent University Hospital (21 August 2014) and the University Hospitals Leuven (14 November 2014) under registration number B670201420725 and is in accordance with the Declaration of Helsinki.

	Center 1	Center 2	Total
Patients (n)	23	50	73
Cleft type			
UCLP Left (n)	11	30	41
UCLP Right (n)	12	20	32
Sex (m/f)	11/12	22/28	33/40
Mean age at time of data collection (years ($\pm$ SD))	5.73 ($\pm$ 0.85)	6.06 ($\pm$ 0.94)	5.96 ($\pm$ 0.92)
N, number; UCLP, unilateral cleft lip and palate; m, male; f, female; SD, Standard Deviation.			

Table 1. Sample characteristics

RESULTS

A total of 73 patients (23 in center 1, 50 in center 2), born between 2006 and 2010, were included in this study. The proportion of boys/girls was almost 1:1. The characteristics of the studied sample are shown in Table 1.

ICC's and Kappa coefficients for inter- and intra-examiner agreement are shown in Table 2. ICC's and Kappa coefficients for agreement between assessors were good to very good, ranging from 0.77 to 0.92. ICC's and Kappa coefficients for agreement within one assessor also were good to very good, ranging from 0.64 to 0.93¹⁸.

Table 3 shows the outcomes for each center, together with the mean difference or difference in proportion between centers and its 95% CI. For the mean difference in sagittal occlusion, the 95% confidence interval falls entirely within the range of equivalency and the hypothesis that both centers are clinically equivalent with respect to sagittal occlusion can be confirmed.

	Inter-examiner agreement			Intra-examiner agreement		
	Kappa / ICC	Lower-upper bound	p	Kappa / ICC	Lower-upper bound	p
5-Year-Olds' Index, good or excellent outcome	0.77	0.41-1.00	0.001	0.77	0.42-1.00	0.001
5-Year-Olds' Index, poor or very poor outcome	1	/	<0.001	0.64	0.00-1.00	0.003
Modified Huddart/Bodenham scoring system	0.92	0.79-0.97	< 0.001	0.93	0.83-0.97	< 0.001
Overjet (mm)	0.91	0.78-0.96	< 0.001	0.91	0.77-0.96	< 0.001
Overbite (mm)	0.80	0.55-0.92	< 0.001	0.75	0.46-0.90	< 0.001
Sagittal occlusion	0.91	0.78-0.96	< 0.001	0.91	0.79-0.97	< 0.001
ICC, Intraclass Correlation Coefficient; lower-upper bound, lower and upper confidence interval limits, p, level of significance.						

Table 2. Inter- and Intra-examiner agreement

		Center 2					
		Center 1					
		Mean	SD	Mean	SD	Mean difference	P
Modified Huddart/Bodenham scoring system		-4.96	4.51	-6.38	6.02	1.78	0.214
	Overjet (mm)	0.13	2.28	-0.12	2.19	0.25	0.393
	Overbite (mm)	1.96	2.10	1.40	1.71	0.59	0.295
	Sagittal occlusion	1.74	3.08	1.88	4.65	-0.14	0.928
		%	n/N	%	n/N	% difference	p
5-Year-Olds' Index, good or excellent outcome		52.2	12/23	46.0	23/50	6.2	0.801
	5-Year-Olds' Index, poor or very poor outcome	8.7	2/23	22.0	11/50	-13.3	0.206
Abbreviations: SD, Standard Deviation; CI, Confidence Interval; n, number of units in a subgroup; N, total number of units.							
P values correspond to those from the independent samples Mann-Whitney U test for continuous outcomes and to those from the Fisher's exact test for proportions. 95% CI's for the mean difference in continuous outcomes were obtained with bootstrapping, 95% CI's for differences in proportions were obtained with Newcomb's method.							

Table 3. Differences in surgical outcomes between centers with 95% confidence interval and predefined equivalence bounds.

No significant mean difference in outcome on both predefined groups of the 5-Year-Olds' Index, the modified Huddart/Bodenham scoring system, overjet (mm), and overbite (mm), could be found. However, uncertainty exists about the clinical equivalence of both centers with respect to these outcomes, because the 95% CI's do not lie entirely within the predefined equivalence margins.

The Spearman's rank correlation coefficient indicated a strong negative correlation ($r_s = -0.832$) between the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system. This correlation is visualized with box plots in Figure 1.

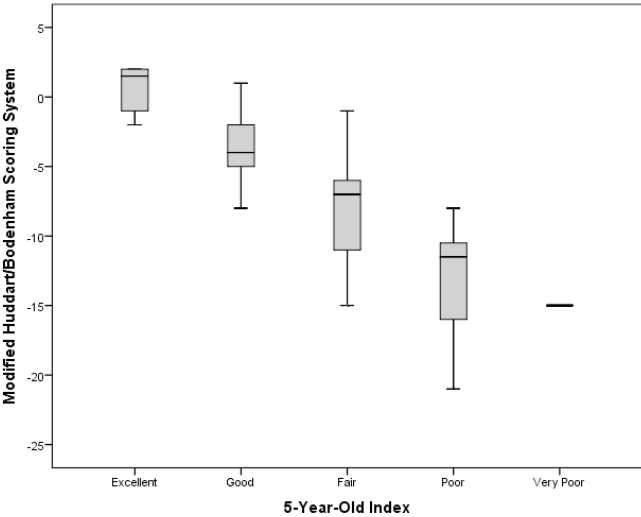


Figure 1. Box plots visualizing the correlation between the 5-Year-Olds' Index and the Modified Huddart/Bodenham scoring system

DISCUSSION

Cleft management protocols are designed by experiences of practitioners and their colleagues, and by using the literature available at that time. This can explain why in two Belgian cleft centers substantive differences in cleft management protocols can be observed. Despite these different

protocols, no significant differences in dental arch relationship were found. Nevertheless, clinical equivalence could only be accepted for sagittal occlusion and was uncertain for the other outcomes. The equivalence bounds as used in this paper represent a consensus, in that particular circumstance and for that particular claim, in what small potential difference can be considered clinically insignificant, to allow the treatments to be considered clinically equivalent¹⁹. Therefore, the equivalence bounds as stated in Table 3 are merely based on both statistical reasoning and clinical judgement.

The strong negative correlation between the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system indicates that a low score for the 5-Year-Olds' Index (a good dental arch relationship) coincides very well with a high score for the modified Huddart/Bodenham scoring system (also a good dental arch relationship). These results can only be obtained if the observers have been calibrated accurately for the 5-Year-Olds' Index. These results are in accordance with previous research⁸.

Several indices for the assessment of malocclusion in UCLP patients are available. According to the WHO, the ideal index should meet following requirements: reliability, validity and acceptance by the profession; requires minimal judgment; lends itself to statistical analysis; and to be administratively simple^{2,20}. A recent systematic review studied the available indices and concluded that the modified Huddart/Bodenham scoring system equaled or outperformed the rest of the indices in all of the WHO requirements². Although this index does not have the highest prevalence, it shows an acceptable reliability and validity, a high statistical power, and does not require calibration. The point scale used in the modified Huddart/Bodenham scoring system only relies on dental measurements, making this index simple and objective, and explains why similar rates of reliability are seen among trained and non-trained individuals. The weakness of the modified Huddart/Bodenham scoring system is the limited or even lacking assessment of the skeletal component of a malocclusion. In contrast to the modified Huddart/Bodenham scoring system, the Goslon Yardstick and 5-Year-Olds' Index use clinical measurements and are able to differentiate between a generalized mild malocclusion and a localized severe malocclusion, and can assess vertical discrepancies. This requires a calculated judgment by the assessor, which adds to its subjectivity and requires calibration². Both indices showed to be highly negatively correlated with $r_s = -0.832$ ($P < 0.001$). Similar conclusions were drawn concerning the Goslon Yardstick, the 5-Year-Olds' Index, and the modified Huddart/Bodenham scoring system^{7,8}.

Cleft lip and palate research is difficult for various practical reasons. First, there is the fragmented pattern of patient care. In Belgium, recognition of cleft teams is not organized by the federal Ministry of Health. In most university hospitals, cleft teams are organized by the hospitals themselves, each of one end up having their own protocol and composition. As a result of this situation, the number of

treated patients per center can be very variable. Therefore, it takes a considerable amount of time in order to obtain a sufficiently large sample and to detect significant differences. Secondly, there are often ethical objections to examine the effect of an intervention on an evidence-based manner. The drafting and implementation of prospective, randomized clinical trials have, in this regard, many obstacles.

Thirdly, due to the slow and subtle effects of various procedures on dentofacial growth and development, it can take up to 10 years until the influence of a particular intervention reflects in craniofacial morphology²¹. Finally, there is a great phenotypic variability of cleft lip and palate patients, which hampers the demonstration of causality and decision-making.

The Leuven Cleft Lip and Palate Team and the Centre of Congenital Facial Anomalies of the Ghent University Hospital agreed to follow the protocol for data collection of CLP patients drawn by the WHO and the Dutch Association for Cleft Lip and Palate and Related Craniofacial Anomalies. Every new cleft patient is registered and at certain ages data are collected. On the long-term, it will be possible to evaluate the quality of the interventions and to compare results with other cleft teams, also in other countries.

The proportion of boys and girls with UCLP is ca. 2:1²². This is in contrast with the proportions of ca 1:1 for both groups in our study. However, bias due to this deviant proportion might be marginal and might be explained by a 2004 study suggesting that increased paternal age inverts the ratio of UCLP from male to female²³.

The results of previously performed studies with the 5-Year-Olds' Index as outcome are shown in Table 4. Generally, the results of our study are in line with the results found in the available literature. Flinn and co-workers compared the dental arch relationship of 5-year-old patients from three different centers and found means of 2.05 (± 0.95), 2.12 (± 0.86) and 2.42 (± 1.07)²¹. Bongaarts and co-workers compared the effect of infant orthopedics and obtained averages of 2.23 (± 0.84) in patients treated with infant orthopedics and 2.16 (± 0.85) in patients treated without infant orthopedics at the age of 6¹⁷. Both centers in this study showed slightly higher means. Williams and co-workers subdivided 18% and 19% of the patients in category 4 and category 5 respectively²⁴. These results differ from the patient distribution of center 1 (9% in category 4 and 0% in category 5) and center 2 (19% and 2% respectively) in our study. The mean scores for the modified Huddart/Bodenham scoring system were -4.96 (± 4.51) for center 1 and -6.38 (± 6.02) for center 2. These results are in line with results of studies performed in Bangladesh (-8.26 ± 7.12) and Japan (-6.43 ± 3.34 and -8.01 ± 4.29)^{25,26}.

Plaster study models are susceptible to damage, loss, and misplacement and demand for physical storage space²⁷. Three-dimensional digital models are shown as a reproducible and reliable alternative to plaster casts for rating dental arch relationships with the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system²⁸⁻³⁰. Recently, an automated method for scoring dental arch relationships using the modified Huddart/Bodenham scoring system was developed. It showed to be a valid, reproducible, and objective method to evaluate maxillary arch constriction³¹.

Researchers	n	Excellent (%)	Good (%)	Fair (%)	Poor (%)	Very poor (%)	Mean
Atack et al. ³²							
Center A	46	35		24		44	3.13
Center B	54	57		28		15	2.35
Johnson et al. ³³	54	4	24	49	19	4	2.95
Williams et al. ³⁴	223	5	24	34	38	19	3.21
DiBiase et al. ³⁵	44	16	41	30	9	5	2.45
Bongaarts et al. ¹⁷							
With infant orthopedics	22	27	41	27	5	0	1.90
Without infant orthopedics	23	26	26	48	0	0	2.22
Flinn et al. ²¹							
Center A	41	33	39	22	3	3	2.05
Center B	33	30	33	30	7	0	2.12
Center C	44	22	38	25	10	6	2.42
Suzuki et al. ³⁶	136	11	18	40	25	5	2.95
Clark et al. ³⁷	30	20	37	27	13	3	2.43
Al-Ghatam et al. ⁹	198	53		28		19	NR
Mikoya et al. ²⁵							
One-stage palatoplasty	31	1	22	45	25	7	3.13
Two-stage palatoplasty	37	6	17	56	19	2	2.94
(Current study)							
Center 1	23	13	39	39	9	0	2.43
Center 2	50	13	30	30	19	2	2.64
n, number of patients.							

Table 4. Previous results of the 5-Year-Olds' Index: means and breakdown into the 5 categories

Collection of study models in 5- to 6- year old children has an intrinsic difficulty. Dental impression taking often encounters resistance of children³⁷. The use of intra-oral 3D scanning has shown to have advantages in terms of patient acceptance and in reliability of scoring dental arch relationships^{38,39}.

Studies using assessors with similar calibration have shown to obtain valid and reliable results for both indices. The modified Huddart/Bodenham scoring system has been promoted as not requiring any form of calibration prior to use due to its objectivity. This in contrast with the 5-Year-Olds' Index requiring more calibration⁴⁰. The latter might have had influence on the final results.

Although we failed to find significant differences in outcomes between center 1 and 2, the treatment protocols showed differences, especially in timing of the hard palate closure. Kuijpers-Jagtman and co-workers described the advantages of delayed hard palate closure. The detrimental effect of scar tissue on the maxillary growth would be smaller if the closure is delayed. Disadvantages of this procedure are the possibility of worse speech performance and the need of obturation of the palatal defect for several years before repair⁴¹. Nollet and co-workers concluded that protocols with closure of the hard palate at 18 months, 22 months and 9 years old showed the best dental arch relationships. Caseload and skill of the surgeon might be more important factors for the quality of the results⁴².

CONCLUSIONS

The dental arch relationship of 5- to 6-year-old unilateral cleft patients treated in two Belgian cleft centers are clinically equivalent based on sagittal occlusion, despite substantial differences in their treatment protocol. Clinical equivalence for other parameters was not confirmed. There is a strong correlation between the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system.

ACKNOWLEDGEMENTS

The authors wish to thank Ms V. Thienpont for the data collection and support in this study; Dr K. Bonte, Dr N. Roche, Dr J. Schoenaers, Dr V. Vander Poorten, and Dr G. Hens for their contribution in the surgical interventions; Dr. Stefanie De Buyser for the statistical analyses; and in extent all the members of the cleft teams of Ghent University Hospital and University Hospitals Leuven.

REFERENCES

1. Mars M., Asher-McDade C., Brattstrom V., Dahl E., McWilliam J., Molsted K., et al. A six-center international study of treatment outcome in patients with clefts of the lip and palate: Part 3. Dental arch relationships. *Cleft Palate Craniofac J* **1992**;29:405-8.
2. Altalibi M., Saltaji H., Edwards R., Major P. W., Flores-Mir C. Indices to assess malocclusions in patients with cleft lip and palate. *Eur J Orthod* **2013**;35:772-82.
3. Atack N., Hathorn I., Mars M., Sandy J. Study models of 5 year old children as predictors of surgical outcome in unilateral cleft lip and palate. *Eur J Orthod* **1997**;19:165-70.
4. Vander Poorten V., Ostyn F., Van Kerckhoven W., Wellens W., Breuls M., Verdonck A., et al. The Leuven staged suprapariosteal repositioning repair: long-term velopharyngeal function in non-syndromic cleft palate. *B-ENT* **2006**;2 Suppl 4:35-43.
5. Dobbyn L., Gillgrass T., McIntyre G., Macfarlane T., Mossey P. Validating the Clinical Use of the Modified Huddart and Bodenham Scoring System for Outcome in Cleft Lip and/or Palate. *Cleft Palate Craniofac J* **2015**;52:671-5.
6. Smallridge J., Hall A. J., Chorbachi R., Parfect V., Persson M., Ireland A. J., et al. Functional outcomes in the Cleft Care UK study--Part 3: oral health and audiology. *Orthod Craniofac Res* **2015**;18 Suppl 2:25-35.
7. Gray D., Mossey P. A. Evaluation of a modified Huddart/Bodenham scoring system for assessment of maxillary arch constriction in unilateral cleft lip and palate subjects. *Eur J Orthod* **2005**;27:507-11.
8. Dobbyn L. M., Weir J. T., Macfarlane T. V., Mossey P. A. Calibration of the modified Huddart and Bodenham scoring system against the GOSLON/5-year-olds' index for unilateral cleft lip and palate. *Eur J Orthod* **2012**;34:762-7.
9. Al-Ghatam R., Jones T. E., Ireland A. J., Atack N. E., Chawla O., Deacon S., et al. Structural outcomes in the Cleft Care UK study. Part 2: dento-facial outcomes. *Orthod Craniofac Res* **2015**;18 Suppl 2:14-24.
10. Millard D. R. Extensions of Rotation-Advancement Principle for Wide Unilateral Cleft Lips. *Plastic and Reconstructive Surgery* **1968**;42:535-6.
11. Persson M., Sandy J. R., Waylen A., Wills A. K., Al-Ghatam R., Ireland A. J., et al. A cross-sectional survey of 5-year-old children with non-syndromic unilateral cleft lip and palate: the Cleft Care UK study. Part 1: background and methodology. *Orthod Craniofac Res* **2015**;18 Suppl 2:1-13.
12. Brauer R. O., Cronin T. D. The Tennison Lip Repair Revisited. *Plastic and Reconstructive Surgery* **1983**;71:633-40.

13. Waylen A, Ness A. R., Wills A. K., Persson M., Rumsey N., Sandy J. R. Cleft Care UK study. Part 5: child psychosocial outcomes and satisfaction with cleft services. *Orthod Craniofac Res* **2015**;18 Suppl 2:47-55.
14. Sommerlad B. C. A technique for cleft palate repair. *Plastic and Reconstructive Surgery* **2003**;112:1542-8.
15. Atack N., Hathorn I. S., Semb G., Dowell T., Sandy J. R. A new index for assessing surgical outcome in unilateral cleft lip and palate subjects aged five: reproducibility and validity. *Cleft Palate Craniofac J* **1997**;34:242-6.
16. Heidbuchel K. L., Kuijpers-Jagtman A. M. Maxillary and mandibular dental-arch dimensions and occlusion in bilateral cleft lip and palate patients from 3 to 17 years of age. *Cleft Palate Craniofac J* **1997**;34:21-6.
17. Bongaarts C. A., Kuijpers-Jagtman A. M., van 't Hof M. A., Prahl-Andersen B. The effect of infant orthopedics on the occlusion of the deciduous dentition in children with complete unilateral cleft lip and palate (Dutchcleft). *Cleft Palate Craniofac J* **2004**;41:633-41.
18. Altman D. G. *Practical Statistics for Medical Research*. Chapman and Hall, London: **1991**.
19. Wiens B. L. Choosing an equivalence limit for noninferiority or equivalence studies. *Control Clin Trials* **2002**;23:2-14.
20. Weinberg S. M., Leslie E. J., Hecht J. T., Wehby G. L., Deleyiannis F. W. B., Moreno L. M., et al. Hypertelorism and Orofacial Clefting Revisited: An Anthropometric Investigation. *Cleft Palate-Craniofacial Journal* **2017**;54:631-8.
21. Flinn W., Long R. E., Garattini G., Semb G. A multicenter outcomes assessment of five-year-old patients with unilateral cleft lip and palate. *Cleft Palate Craniofac J* **2006**;43:253-8.
22. Mossey P. A., Little J., Munger R. G., Dixon M. J., Shaw W. C. Cleft lip and palate. *Lancet* **2009**;374:1773-85.
23. Rittler M., Lopez-Camelo J., Castilla E. E. Sex ratio and associated risk factors for 50 congenital anomaly types: clues for causal heterogeneity. *Birth Defects Res A Clin Mol Teratol* **2004**;70:13-9.
24. Bugaighis I., O'Higgins P., Tiddeman B., Mattick C., Ben Ali O., Hobson R. Three-dimensional geometric morphometrics applied to the study of children with cleft lip and/or palate from the North East of England. *Eur J Orthod* **2010**;32:514-21.
25. Mikoya T., Shibukawa T., Susami T., Sato Y., Tengan T., Katashima H., et al. Dental arch relationship outcomes in one- and two-stage palatoplasty for Japanese patients with complete unilateral cleft lip and palate. *Cleft Palate Craniofac J* **2015**;52:277-86.

26. Haque S., Alam M. K., Khamis M. F. Treatment Outcome of Bangladeshi UCLP Patients Based on Both Phenotype and Postnatal Treatment Factors Using Modified Huddart Bodenham (mHB) Index. *Cleft Palate Craniofac J* **2016**;
27. Desmedt D. J., Maal T. J., Kuijpers M. A., Bronkhorst E. M., Kuijpers-Jagtman A. M., Fudalej P. S. Nasolabial symmetry and esthetics in cleft lip and palate: analysis of 3D facial images. *Clin Oral Investig* **2015**;19:1833-42.
28. Djordjevic J., Lewis B. M., Donaghy C. E., Zhurov A. I., Knox J., Hunter L., et al. Facial shape and asymmetry in 5-year-old children with repaired unilateral cleft lip and/or palate: an exploratory study using laser scanning. *Eur J Orthod* **2014**;36:497-505.
29. Duffy S., Noar J. H., Evans R. D., Sanders F. Three-dimensional analysis of the child cleft face. *Cleft Palate-Craniofacial Journal* **2000**;37:137-44.
30. Chawla O., Deacon S. A., Attack N. E., Ireland A. J., Sandy J. R. The 5-year-olds' Index: determining the optimal format for rating dental arch relationships in unilateral cleft lip and palate. *Eur J Orthod* **2012**;34:768-72.
31. Martin C. B., Ma X., McIntyre G. T., Wang W., Lin P., Chalmers E. V., et al. The validity and reliability of an automated method of scoring dental arch relationships in unilateral cleft lip and palate using the modified Huddart-Bodenham scoring system. *Eur J Orthod* **2016**;38:353-8.
32. Attack N., Hathorn I., Dowell T., Sandy J., Semb G., Leach A. Early detection of differences in surgical outcome for cleft lip and palate. *Br J Orthod* **1998**;25:181-5.
33. Johnson N., Williams A. C., Singer S., Southall P., Attack N., Sandy J. R. Dentoalveolar relations in children born with a unilateral cleft lip and palate (UCLP) in Western Australia. *Cleft Palate Craniofac J* **2000**;37:12-6.
34. Mosmuller D. G. M., Maal T. J., Prahl C., Tan R. A., Mulder F. J., Schwartz R. M. F., et al. Comparison of two- and three-dimensional assessment methods of nasolabial appearance in cleft lip and palate patients: Do the assessment methods measure the same outcome? *J Craniomaxillofac Surg* **2017**;45:1220-6.
35. DiBiase A. T., DiBiase D. D., Hay N. J., Sommerlad B. C. The relationship between arch dimensions and the 5-year index in the primary dentition of patients with complete UCLP. *Cleft Palate Craniofac J* **2002**;39:635-40.
36. Suzuki A., Yoshizaki K., Honda Y., Sasaguri M., Kubota Y., Nakamura N., et al. Retrospective evaluation of treatment outcome in Japanese children with complete unilateral cleft lip and palate. Part 1: Five-year-olds' index for dental arch relationships. *Cleft Palate Craniofac J* **2007**;44:434-43.

37. Clark S. A., Attack N. E., Ewings P., Hathorn I. S., Mercer N. S. Early surgical outcomes in 5-year-old patients with repaired unilateral cleft lip and palate. *Cleft Palate Craniofac J* **2007**;44:235-8.
38. Burhardt L, Livas C, Kerdijk W, van der Meer W. J., Ren Y. Treatment comfort, time perception, and preference for conventional and digital impression techniques: A comparative study in young patients. *Am J Orthod Dentofacial Orthop* **2016**;150:261-7.
39. Chalmers E. V., McIntyre G. T., Wang W., Gillgrass T., Martin C. B., Mossey P. A. Intraoral 3D Scanning or Dental Impressions for the Assessment of Dental Arch Relationships in Cleft Care: Which is Superior? *Cleft Palate Craniofac J* **2016**;53:568-77.
40. Jones T., Leary S., Attack N., Ireland T., Sandy J. Which index should be used to measure primary surgical outcome for unilateral cleft lip and palate patients? *Eur J Orthod* **2016**;38:345-52.
41. Manyama M., Larson J. R., Liberton D. K., Rolian C., Smith F. J., Kimwaga E., et al. Facial morphometrics of children with non-syndromic orofacial clefts in Tanzania. *BMC Oral Health* **2014**;14:93.
42. Meyer-Marcotty P., Alpers G. W., Gerdes A. B., Stellzig-Eisenhauer A. Impact of facial asymmetry in visual perception: a 3-dimensional data analysis. *Am J Orthod Dentofacial Orthop* **2010**;137:168.e1-8; discussion -9.

4.

ASSESSMENT MODALITIES OF NON-IONIZING THREE-DIMENSIONAL SURFACE IMAGES FOR THE QUANTIFICATION OF FACIAL MORPHOLOGY, SYMMETRY, AND APPEARANCE IN CLEFT LIP AND PALATE: A SYSTEMATIC REVIEW.

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N. *Int J Oral Maxillofac Surg* **2018** Sep;47(9):1095-105.

ABSTRACT

The use of non-ionizing three-dimensional surface imaging in cleft lip and palate is emerging, but methodologically properly designed assessment methods of the images are not well established. Therefore, the aim of this study was to review the current literature relating to the assessment modalities of non-ionizing three-dimensional surface images for the quantification of facial morphology, symmetry, and appearance in cleft lip and palate, and to assess the precision and accuracy of these modalities. A systematic literature search was performed using MEDLINE (via PubMed), CENTRAL, Web of Science, and EMBASE. Cross-sectional studies with prospective or retrospective data collection, using 3D non-ionizing surface imaging, with a subjective or objective outcome assessment, and at least 10 cleft lip and/or palate patients were considered eligible. Overall, 1767 unique studies were identified and 33 met the inclusion criteria. The images were objectively assessed using elementary measurements and comprehensive statistical methods for superimposition, shape description, and structuring. Subjective assessment was performed using a Likert-type scale or a Visual Analog Scale. It can be concluded that non-ionizing 3D surface images are widely used in cleft research, but 3D analysis of the images is often methodologically sub-optimal. Researchers must fully utilize the content of 3D images to quantify morphology, symmetry, and appearance.

INTRODUCTION

Orofacial clefts (OFCs) comprise a range of disorders affecting facial bony structures and soft tissues during gestation. These malformations are located in the mid facial area and the lips, nose, alveolar process, and palate are primarily affected¹. Although rehabilitation is possible with good quality care, OFCs inevitably have a lifelong effect on speech, hearing, cognition, and facial morphology to a certain extent².

The face plays an important role in social recognition. Therefore, unfavorable facial appearance in patients with OFCs can be a source of social and emotional distress³. The unfavorable morphology of these faces deviates to a certain degree from the norm (the non-affected “average” faces)⁴, and can primarily, but not solely, be explained by the residual asymmetry⁵.

Various assessment methods have been described for quantitative or qualitative evaluation of faces in OFCs, such as direct clinical assessment^{6,7}, radiographic cephalometric assessment^{8,9}, clinical photographic assessment¹⁰⁻¹², and clinical videographic assessment^{13,14}. Over the last decade, non-

ionizing three-dimensional (3D) surface imaging gained remarkable interest. This can be explained by the non-ionizing character, the fast capture time, the simplicity of application, and the reliable storage and archiving of data¹⁵⁻¹⁹. Although the use of non-ionizing 3D surface images is well established, processing and quantitative assessment are often confronted with operator bias. No (systematic) reviews reporting about this topic have been made up to now. Therefore, the aim of this study was 1) to review the current literature relating to the assessment modalities of non-ionizing three-dimensional surface images for the quantification of facial morphology, symmetry, and appearance in cleft lip and palate, 2) and to assess the accuracy and precision of these modalities.

MATERIALS AND METHODS

The results are reported in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses)²⁰. The search aimed to identify all original articles reporting diagnostic methods with a quantitative outcome.

Eligibility criteria

A systematic review was performed to investigate the assessment modalities of non-ionizing three-dimensional surface images for the quantitative assessment of facial morphology, symmetry, and appearance in cleft lip and palate. According to these criteria, the population comprised patients with repaired or unrepaired cleft lip and/or palate without age restriction. Morphology, symmetry, or appearance should be evaluated in an objective or subjective manner on non-ionizing three-dimensional images acquired with 3D surface scanning or 3D digital stereophotogrammetry. Methods relying on measurements with or without superimposition were identified as objective methods. Methods requiring judgement to some extent without strict criteria and allowing a degree of interpretation were identified as subjective methods.

Eligible studies should present the following characteristics: (1) cross-sectional studies with prospective or retrospective data collection; (2) studies with at least 10 patients per study group; (3) studies containing original data concerning humans; and (4) studies published in English. The exclusion criteria were: (1) abstracts, (2) conference summaries; (3) case series or case reports; (4) studies without a quantitative outcome; (5) reliability studies; and (6) method development studies.

Data sources and search methods

Studies were identified using the electronic databases MEDLINE (provided by PubMed, 1966-present), Web of Science (1955-present), EMBASE (1980-present), and CENTRAL (Cochrane Central Register of Controlled Trials) (1988-present). The following search terms were combined to create an appropriate search string: cleft lip, cleft palate, three-dimensional imaging, anthropometry, (stereo)photogrammetry, surface scanning, and morphometry. The electronic search strings in the selected databases are shown in Table 1. Backward and forward citation tracking (snowballing) was also performed, using reference lists and the Science Citation Index of all the articles eligible for inclusion in this paper.

Study selection, data extraction and quality assessment

The search strategy was established a priori by all authors, and eligibility assessment was performed by two independent reviewers (LT & NDR) in a non-blinded standardized manner. The titles and abstracts of retrieved studies were independently reviewed, and subsequently full-text articles, corresponding to the selected titles and abstracts, were retrieved. Disagreements between the two reviewers concerning article selection were resolved by consensus after rereading and discussion with the other authors.

The methodological quality of the included studies was analyzed according to an adapted version of MINORS²¹. The items 'follow-up period appropriate to the aim of the study' and 'loss to follow-up less than 5%' of the MINORS checklist were not used because they are not applicable to cross-sectional studies. Disagreements concerning the quality control between the two reviewers were resolved by consensus after rereading and discussion with the other authors.

The following data were collected: (1) basic study characteristics: author(s), year and country of publication; (2) population characteristics: sample size, age at data collection, cleft type, and studied facial region; (3) characteristics of the imaging and assessment method: image acquisition method, image capturing system, measurement methods, outcome measures, accuracy and precision, and reliability coefficient.

Electronic database	Search string
MEDLINE	(cleft lip[MeSH Terms] OR cleft lip[Tiab] OR cleft palate[MeSH Terms] OR cleft palate[Tiab]) AND (morphometr*[Tiab] OR photogrammetry[Mesh] OR photogrammetr*[Tiab] OR stereophotogrammetr*[Tiab] OR anthropometr*[Tiab] OR Imaging, Three-Dimensional[Mesh] OR 3D[Tiab] OR three-dimensional[Tiab])
Web of Science	(TS=("cleft lip") OR TS=("cleft palate") OR TS=("cleft lip and palate")) AND (TS=(morphometr*) OR TS=(stereophotogrammetr*) OR TS=(photogrammetr*) OR TS=("three dimensional imag*") OR TS=(anthropometr*))
EMBASE	"cleft lip"/exp OR 'cleft lip':ab OR 'cleft palate'/exp OR 'cleft palate':ab OR 'cleft lip palate'/exp OR 'cleft lip palate':ab AND ('morphometry'/exp OR 'morphometry':ab OR 'stereophotogrammetry'/exp OR 'stereophotogrammetry':ab OR 'photogrammetry'/exp OR 'photogrammetry':ab OR 'three dimensional imaging'/exp OR 'three dimensional imaging':ab OR 'anthropometry'/exp OR 'anthropometry':ab) AND [embase]/lim
Cochrane Central Register of Controlled Trials (CENTRAL)	("cleft lip" OR "cleft palate" OR "cleft lip and palate") AND (morphometr* OR stereophotogrammetr* OR photogrammetr* OR three dimensional imag* OR anthropometr*)

Table 1. Electronic search strategies in the selected databases

RESULTS

General description of the included studies

The search in the electronic databases was finalized on September 1, 2017. The schematic diagram of the literature search and screening process is shown in Figure 1.

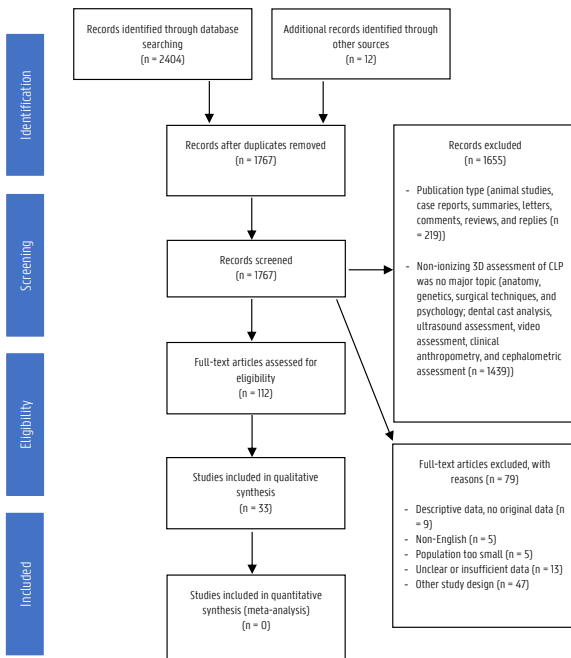


Figure 1. Schematic diagram of the literature search and screening process conform the PRISMA guidelines

Overall, 1767 unique studies were identified after removal of duplicates, of which 33 met the inclusion criteria. The study characteristics are presented in Table 2. The age of the included patients was heterogeneous and ranged from 2 months to 49 years old. The observed patients had unilateral cleft lip (UCL; 14 studies^{16,22-34}), unilateral cleft lip and alveolus (UCLA; 8 studies^{25,27,33,35-39}), unilateral cleft lip and palate (UCLP; 30 studies^{16,22-29,33-53}), isolated cleft palate (CP; 8 studies^{16,34-39,53}), bilateral cleft lip (BCL; 2 studies^{31,34}), or bilateral cleft lip and palate (BCLP; 10 studies^{24,28,34-39,44,53}). The anatomical regions considered for three-dimensional assessment were the nose, lips, mid face, lower face, cheeks, orbital region, chin, and full face. The included studies showed substantial methodological and clinical heterogeneity, so data of these studies could not be pooled by means of meta-analysis.

Author	Year of publication	Country	Number of patients	Age (years)	Anatomical region assessed	Cleft type(s)
Ayoub et al. ²²	2011	United Kingdom	94	10	lips and nose	UCL, UCLP
Ayoub et al. ⁴⁰	2011	United Kingdom	21	3	nose	UCLP
Ayoub et al. ⁴¹	2011	United Kingdom			lips	
Bell et al. ²³	2014	United Kingdom	95	10	lips, nose, and full face	UCL, UCLP
Bennett et al. ⁵³	2017	United States of America	24	NR	cheeks	UCLP, BCLP, CP
Billwatsch et al. ⁴²	2006	Germany	22	10	lips, nose and mid face	UCLP
Bugaighis et al. ³⁶	2014	United Kingdom	103	8-12	full face	UCLP, UCLA, BCLP, CP
Bugaighis et al. ³⁷	2014					
Bugaighis et al. ³⁸	2010					
Bugaighis et al. ³⁹	2014					
Dadáková et al. ²⁴	2016	Czech Republic	72	3 (2.5-3.7) 4.5 (4.0-5.0)	full face	UCL, UCLP, BCLP
Desmedt et al. ²⁵	2015	The Netherlands	84	10 [8.6-12.3]	lips and nose	UCL, UCLA, UCLP
Djordjevic et al. ¹⁶	2014	United Kingdom	12	5.3 (±0.5)	full face	UCL, UCLP, CP
Duffy et al. ³⁵	2000	United Kingdom	39	(8-11)	full face	UCLP, UCLA, BCLP, CP
Hood et al. ²⁶	2004	United Kingdom	23	0.25	full face	UCL, UCLP
Kishi et al. ⁴³	2012	Japan	15	2 to 4 months	lips and nose	UCLP
Krimmel et al. ⁴⁴	2006	Germany	50	5 to 7 months	lips and nose	UCLP, BCLP
Kuijpers et al. ²⁷	2015	The Netherlands	58	8.6-12.3	lips, nose, cheek, chin, and full face	UCL, UCLA, UCLP
Linden et al. ⁴⁵	2016	United States of America	38	5.3 (±2.2) 8.5 (±3.8)	nose	UCLP
Manyama et al. ²⁸	2014	Tanzania	42	29.4 (± 31.8) months	full face	UCL, UCLP, BCLP
Meyer-Marcotty et al. ⁴⁶	2010	Germany	18	17-35 (21.6)	full face	UCLP

Table 2. Characteristics of the Included studies. (1/2)

Meyer-Marcotty et al. ⁴⁷	2011	Germany	30	17-39 (25.4)	full face	UCLP
Meyer-Marcotty and Stellzig-Eisenhauer ²⁹	2009	Germany	30	25.4±6.6	full face, mid face, and lower face	UCL, UCLP
Mosmuller et al. ³³	2017	The Netherlands	79	10 (8.6-12.3)	lips and nose	UCL, UCLA, UCLP
Oh et al. ³⁰	2011	South Korea	30	1-20	lips	UCL
Othman et al. ⁴⁸	2014	Malaysia	15	18-25	full face	UCLP
Othman and Koay ⁴⁹	2016	Malaysia	20	7-12 (10.22±1.81)	lips, nose, full face	UCLP
Russell et al. ³²	2015	United States of America	90	NR	lips	UCL
Stauber et al. ⁵⁰	2008	Germany	40	10	lips, nose, and mid face	UCLP
Stebel et al. ⁵¹	2016	The Netherlands	40	10 (8.8-12)	lips and nose	UCLP
Tanikawa et al. ³¹	2010	United States of America	57	12.5±4.1	lips	UCL, BCL
Van Loon et al. ⁵²	2011	India	44	3.1 (12-96 months)	lip and nose	UCLP
Weinberg et al. ⁵⁴	2017	United States of America	287	3-49	orbital region	UCL, UCLP, BCL, BCLP, CP
Abbreviations: NR, Not Reported; UCL, unilateral cleft lip; UCLA, unilateral cleft lip and alveolus, UCLP, unilateral cleft lip and palate; CP, isolated cleft palate; BCL, bilateral cleft lip; BCLP, bilateral cleft lip and palate.						

Table 2. Characteristics of the included studies. (2/2)

Quality assessment

The results of the quality assessment using the adapted version of the MINORS checklist are shown in Figure 2. Generally, the items concerning the study aim, the study endpoints, and the control group achieved score 1 (reported, but not adequate) or score 2 (reported and adequate). The items 'inclusion of consecutive patients', 'prospective collection of data', 'unbiased assessment of the study endpoint', and 'prospective calculation of the study size' were not or not adequately reported in the included studies.

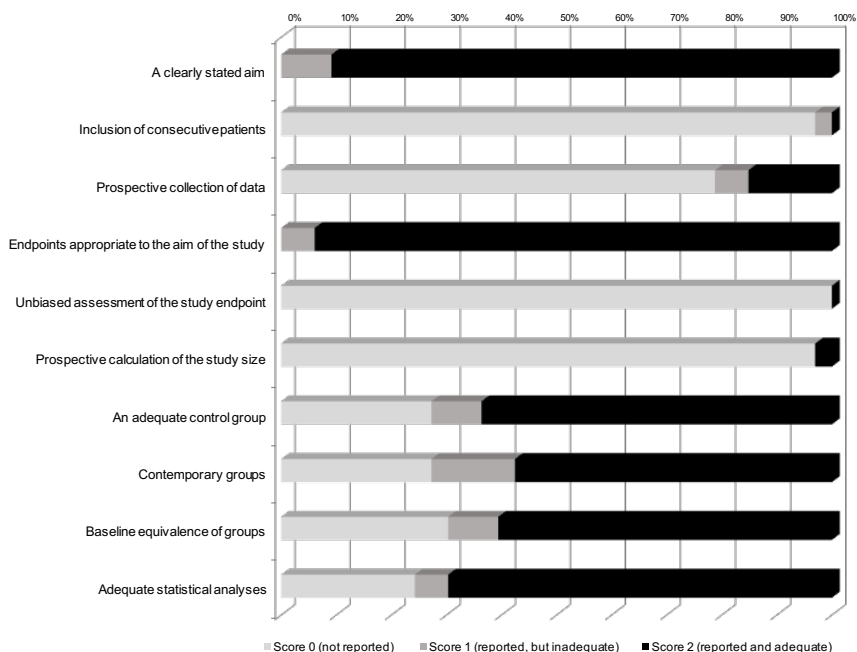


Figure 2. Characteristics of the included studies

Image acquisition methods and image capturing systems

The image acquisition methods and image capturing systems are shown in Table 3. Stereophotogrammetry was the most commonly used method for image acquisition (25 studies^{22-28,30-34,36-41,44,45,48,49,51-53}). The stereophotogrammetry technique is capable of reproducing surface geometry and map realistic color and texture data by taking 2 or more photographs of the same subject from different positions. Subsequently, the photographs are stitched together by a software tool to generate a composite 3D model^{18,19}. The stereophotogrammetric imaging systems used were 3dMD face (3dMD Technologies Ltd; 10 studies^{25,33,34,36-39,51-53}), Vectra H1 or M5 360 (Canfield Scientific; 5 studies^{24,30,45,48,49}), Di3D (Dimensional Imaging Limited; 4 studies^{22,23,40,41}), DSP 400 3D Imaging System

[3dMD Ltd.]⁴⁴, MU-4 Imaging System [3dMD Ltd.]³¹, C3D [3D Matic Faraday Partnership]²⁶, and InSpeck 3D MegaCapturor [Creaform Inc.]²⁸, in order of the most reported use.

Structured light-based imaging technologies were used by 6 studies^{29,31,42,46,47,50}. Imaging capturing systems using this technology were the FaceScan optical 3D sensor (3D-Shape GmbH; 3 studies^{29,46,47}), CAM^{3D} (3D-Shape GmbH; 2 studies^{42,50}), and Rainbow 3D camera model 250 system (Genex Technologies Inc)³¹. The structured light technique is based on projection of a pattern of white light (grids, dots, or stripes) onto the subject and simultaneously recording of the distorted light pattern with a calibrated camera¹⁸.

In three papers, laser-based imaging technologies were used (3 studies^{16,35,43}). Reported imaging capturing systems using laser surface scanning were Vivid 900¹⁶ and Vivid 910⁴³ (Konica Minolta Sensing Europe). This technique is based on a laser beam scanning the surface area of the target subject. This beam is scattered by the subject and collected at a known distance by a camera. The x, y, and z coordinates of a surface point are then calculated by using trigonometry^{18,54}.

Objective assessment methods

The assessment methods and outcome measures are shown in Table 3. A clear distinction can be made between objective and subjective assessment methods. Within the objective methods linear, angular, and volumetric measurements (16 studies^{22,26,30-32,34,37,40,42-45,48,49,52,53}) and linear, angular, or volumetric measurements, and/or distance mapping using superimposed original and mirrored scans (9 studies^{16,25,27,29,33,36,46,47,50}) were the most commonly used. Following methods were also reported: linear measurements and/or distance mapping using superimposed original and control group scans (2 studies^{16,41}), distance mapping after superimposition of original cleft faces and average healthy faces (1 study¹⁶), and linear measurements and/or distance mapping after superimposition of average cleft faces and average healthy faces (3 studies^{24,35,39}).

Author	Image capturing system	Assessment methods	Outcome measures
Stereophotogrammetry			
Avoub et al. ²²	Di3D (Dimensional Imaging Limited)	Linear measurements Shape quantification using Generalized Procrustes Analysis and Principal Component Analysis	Distances Principal Components Scores
Avoub et al. ⁴⁰	Di3D (Dimensional Imaging Limited)	Linear and angular measurements Bookstein analysis	Distances and angles 3D coordinate differences
Avoub et al. ⁴¹	Di3D (Dimensional Imaging Limited)	Linear measurements after Generalized Procrustes Analysis of original and control group scans	Distances
Bell et al. ²³	Di3D (Dimensional Imaging Limited)	Landmark-based asymmetry analysis and facial curve analysis	Asymmetry scores
Bennett et al. ⁵³	3dMDface (3dMD Ltd.)	Volumetric measurements	Volumes
Bugaighis et al. ³⁶	3dMDface (3dMD Ltd.)	Linear measurements after Generalized Procrustes Analysis of the original and mirrored facial scans	Distances
Bugaighis et al. ³⁷	3dMDface (3dMD Ltd.)	Linear and angular measurements	Distances and angles
Bugaighis et al. ³⁸	3dMDface (3dMD Ltd.)	Shape quantification using Generalized Procrustes Analysis and Principal Component Analysis	Principal Components Scores
Bugaighis et al. ³⁹	3dMDface (3dMD Ltd.)	Linear measurements and distance mapping after construction of averages faces using Generalized Procrustes Analysis	Distances; subjective description of color-coded distance maps

Table 3. Image capturing systems, assessment methods, and outcome measures sorted by image acquisition method (1/4)

Dadáková et al. ²⁴	Vectra (Canfield Scientific)	Shape quantification using Generalized Procrustes Analysis and Principal Component Analysis Distance mapping after construction of averages faces using Generalized Procrustes Analysis	Principal Components Scores	Color-coded distance maps and shell distance significance maps
Desmedt et al. ²⁵	3dMDface (3dMD Ltd.)	Linear measurements and distance mapping after superimposition of the original and mirrored facial scans (method of Verhoeven et al.) Subjective rating (VAS)	Color-coded distance maps; mean absolute asymmetry scores VAS score	Color-coded distance maps; mean absolute asymmetry scores VAS score
Hood et al. ²⁶	C30 (3D Matic Faraday Partnership)	Linear and angular measurements	Distances, ratios, and angles	Distances, ratios, and angles
Krimmel et al. ⁴⁴	DSP 400 3D Imaging System (3dMD Ltd.)	Linear measurements	Distances	Distances
Kuijpers et al. ²⁷	3dMDface (3dMD Ltd.)	Linear measurements and distance mapping after superimposition of the original and mirrored facial scans (method of Verhoeven et al.)	Color-coded distance maps; mean absolute asymmetry scores	Color-coded distance maps; mean absolute asymmetry scores
Linden et al. ⁴⁵	Vectra H1 (Canfield Scientific)	Linear measurements	Root-mean square scores	Root-mean square scores
Manyama et al. ²⁸	InSpeck 3D MegaCapturor (Creaform Inc.)	Shape quantification using Generalized Procrustes Analysis, Principal Component Analysis, and Canonical Variate Analysis	Principal Components Scores and Canonical Variate Scores	Principal Components Scores and Canonical Variate Scores
Mosmuller et al. ³⁵	3dMDface (3dMD Ltd.)	Linear measurements and distance mapping after superimposition of the original and mirrored facial scans (method of Verhoeven et al.) Subjective rating (VAS)	Color-coded distance maps; mean absolute asymmetry scores VAS score	Color-coded distance maps; mean absolute asymmetry scores VAS score

Table 3. Image capturing systems, assessment methods, and outcome measures sorted by image acquisition method (2/4)

Oh et al. ³⁰	Vectra H1 (Canfield Scientific)	Linear measurements Subjective rating (VAS)	Distances and ratios VAS score
Othman et al. ⁴⁸	Vectra M5 360 (Canfield Scientific)	Linear measurements	Distances and ratios
Othman and Koay ⁴⁹	Vectra M5 360 (Canfield Scientific)	Linear measurements	Distances and ratios
Russell et al. ³²	NR (3dMD Ltd.)	Linear measurements	Distances, asymmetry scores
Stebel et al. ⁵¹	3dMDFace (3dMD Ltd.)	Subjective rating (VAS)	VAS score
Tanikawa et al. ³¹	MU-4 (3dMD Ltd.)	Linear and angular measurements	Angles and ratios
van Loon et al. ⁵²	3dMDFace (3dMD Ltd.)	Linear and volumetric measurements	Distances, volumes, and asymmetry scores
Weinberg et al. ³⁴	3dMDFace (3dMD Ltd.)	Linear measurements	Distances and ratios
Structured-light surface scanning			
Blüwatsch et al. ⁴²	CAM ³⁰ (3D-Shape GmbH)	Linear, angular, and volume measurements after establishing a plane of symmetry	Distances, areas, and volumes
Meyer-Marcotty et al. ⁴⁶	FaceScan optical 3D sensor (3D-Shape GmbH)	Linear measurements after superimposition of the original and mirrored facial scans to determine a plane of symmetry (method of Benz. et al) Subjective rating (9-point ordinal scale)	Index of facial asymmetry Ordinal scores for facial attractiveness

Table 3. Image capturing systems, assessment methods, and outcome measures sorted by image acquisition method (3/4)

Meyer-Marcotty et al. ⁴⁷	FaceScan optical 3D sensor (3D-Shape GmbH)	Linear measurements after superimposition of the original and mirrored facial scans to determine a plane of symmetry (method of Benz, et al) Subjective rating (9-point ordinal scale)	Index of facial asymmetry Ordinal scores for facial attractiveness
Meyer-Marcotty and Stelzig-Eisenhauer ²⁸	FaceScan optical 3D sensor (3D-Shape GmbH)	Linear measurements after superimposition of the original and mirrored facial scans to determine a plane of symmetry (method of Benz, et al) Subjective rating (9-point ordinal scale)	Index of facial asymmetry Ordinal scores for facial attractiveness
Stauber et al. ⁵⁰	CAM ^{3D} (3D-Shape GmbH)	Linear, angular, and volumetric measurements after superimposition of the original and mirrored facial scans to determine a plane of symmetry	Distances, angles, and volumes
Tanikawa et al. ³¹	Rainbow 3D camera model 250 system (Genex Technologies Inc)	Linear and angular measurements	Angles and ratios
Laser surface scanning			
Djordjevic et al. ¹⁶	Vivid 900 (Konica Minolta Sensing Europe)	Distance mapping after superimposition of the individual cleft faces with average healthy faces of boys and girls, and after superimposition of the original and mirrored facial scans	Color-coded distance maps and histograms (with average distances and coincidence level)
Duffy et al. ³⁵	NR	Linear measurements and distance mapping after superimposition of average cleft faces and average healthy faces	Distances and ratios; subjective description of color-coded distance maps
Kishi et al. ⁴³	Vivid 910 (Konica Minolta Sensing Europe)	Linear and angular measurements	Distances and angles
Abbreviations: NR, Not Reported; VAS, Visual Analog Scale			

Table 3. Image capturing systems, assessment methods, and outcome measures sorted by image acquisition method (4/4)

Facial shape analysis was statistically performed using Generalized Procrustes Analysis (GPA), Bookstein Analysis, Principle Component Analysis (PCA), and/or Canonical Variate Analysis (CVA)^{22,24,28,37,38,40}. Generalized Procrustes Analysis compares the shape of subjects by superimposition after translation, rotation, and scaling using an arbitrarily chosen reference shape. Bookstein Analysis also uses superimposition by translation, rotation, and scaling, but with 2 landmarks as reference landmarks^{55,56}. Principle Component Analysis (PCA) and Canonical Variate Analysis (CVA) are both multivariate analyses. Principle Component Analysis explains the variance in a dataset with a small number of relevant variables (the principal components) by describing a new orthogonal coordinate system. In addition, Canonical Variate Analysis determines the relationships between groups of variables in a dataset by defining coordinate systems that optimally describe the cross-covariance between two datasets.

Subjective assessment methods

Subjective methods for quantitative assessment included rating using a Visual Analog Scale (VAS) (4 studies^{25,30,33,51}) and rating using a 9-point ordinal scale (3 studies^{29,46,47}).

Precision and accuracy

The precision and/or accuracy of the used methods are shown in Table 4. Precision can be defined as a measure of the extent to which repeated observations conform. Accuracy is the way in which an observed value of a quantity agrees with the true value⁵⁷. In the majority of the papers this was investigated by the authors themselves. Others reported the results of a previous reliability or validation study using the same methodology. Four studies did not report any information concerning precision or accuracy^{24,34,45,53}.

Twelve studies^{22,23,26,28,31,40,41,43,44,48,49,58} reported the precision of their method using the reproducibility of landmark identification (range: 0.008-2mm). Reproducibility refers to the variation in measurements made on a subject under changing conditions. These changing conditions may be due to measurements being made by different observers, or measurements being made over a period of time, within which the 'error-free' level of the variable could undergo non-negligible change⁵⁹. Precision as reliability of the registration method was reported in 12 studies^{25,27,29,30,32,33,42,46,47,50-52}, and relates the magnitude of the measurement error in observed measurements to the inherent variability in the 'error-free', 'true', or underlying level of the quantity between subjects. Accuracy of

the method was reported in one study as the error of the imaging system. Therefore, this study investigated the relationship between digital measurements and true (anthropometric) measurements¹⁶. In addition, the error of the digitization and error of software were reported in combination with reproducibility of landmark identification in four studies³⁶⁻³⁹. A reliability coefficient was missing in the majority of the studies.

Author	Precision and/or accuracy of the method		Reliability coefficient
Ayoub et al. ²²	Reproducibility of landmark identification	NR (landmark identification duplicated when <0.5 mm)	NR
Ayoub et al. ⁴⁰			
Ayoub et al. ⁴¹			
Bell et al. ²³	Reproducibility of landmark identification	0.5 to 2 mm*,**	NR
Bilwatsch et al. ⁴²	Reliability of distance, area, and volume measurements	<1 mm and < 1.5°	NR
Bugaighis et al. ³⁶	Reproducibility of landmark identification Error of the software (MorphAnalyser software) Error of the imaging system	0.5 mm	NR
Bugaighis et al. ³⁷			
Bugaighis et al. ³⁸			
Bugaighis et al. ³⁹			
Desmedt et al. ²⁵	Reliability of absolute nasolabial asymmetry registration	0.008 mm* 0.05 mm*,***	0.99*
	Reliability of nasolabial esthetics registration	-2.69 to 2.76*,**** 4.57 to 5.32*,****,*****	0.76 to 0.83**
Djordjevic et al. ¹⁶	Error of the imaging system	<0.75 mm	NR
Duffy et al. ³⁵	Reproducibility of landmark identification	0.47% to 5.5% of difference*,**	NR
Hood et al. ²⁶	Reproducibility of landmark identification	0.81 mm* 0.5 mm**	NR
Kishi et al. ⁴³	Reproducibility of landmark identification	0.008 mm	NR
Krimmel et al. ⁴⁴	Reproducibility of landmark identification	5.3% of difference**	NR
Kuijpers et al. ²⁷	Reliability of absolute nasolabial asymmetry registration	0.05 mm*,***	0.99*
Manyama et al. ²⁸	Reproducibility of landmark identification	0.338 mm**	NR

Table 4. Precision and/or accuracy of the assessment modalities for the quantification of facial morphology, symmetry, and appearance in cleft lip and palate. (1/2)

Meyer-Marcotty et al. ⁴⁶	Reliability of facial asymmetry registration	< 0.006 mm	NR
Meyer-Marcotty et al. ⁴⁷	Reliability of facial asymmetry registration	< 0.005 mm	NR
Meyer-Marcotty and Stellzig-Eisenhauer ²⁹	Reliability of facial asymmetry registration	< 0.006 mm	NR
Mosmuller et al. ³³	Reliability absolute nasolabial asymmetry registration	NR	0.99*
	Reliability of nasolabial esthetics registration	NR	0.56*
Oh et al. ³⁰	Reliability of nasolabial esthetics registration	0.51 to 0.55*,**** 0.65 to 0.93**, ****	NR NR
Othman et al. ⁴⁸	Reproducibility of landmark identification	NR	0.66 to 0.97
Othman and Koay ⁴⁹	Reproducibility of landmark identification	0.05 to 1.55 mm* 0.02 to 0.79 mm**	0.54 to 0.99* 0.76 to 0.99**
Russell et al. ³²	Reliability of lip height asymmetry registration	NR	0.98**
Stauber et al. ⁵⁰	Reliability of distance, area, and volume measurements	<1 mm and < 1.5°	NR
Stebel et al. ⁵¹	Reliability of nasolabial esthetics registration	-4.43 to 2.43*,**** 4.78 to 6.09*,****, ****	0.73 to 0.86*
Tanikawa et al. ³¹	Reproducibility of landmark identification	0.66 to 1.23 mm**	NR
van Loon et al. ⁵²	Reliability of distance and volume measurements	-0.38 to 0.22 mm* 0.35 to 1.27 mm*, ***	0.77 to 0.96*
		-0.22 to 0.40 mm** 0.29 to 1.2 mm**, ****	0.70 to 0.97**
*Inter-rater reliability			
**Intra-rater reliability			
***Duplicate Measurement Error			
****VAS score			
Abbreviations: NR, Not Reported; VAS, Visual Analog Scale.			

Table 4. Precision and/or accuracy of the assessment modalities for the quantification of facial morphology, symmetry, and appearance in cleft lip and palate. (2/2)

DISCUSSION

This paper provides a comprehensive overview of the assessment modalities of non-ionizing three-dimensional surface images for the quantification of facial morphology, symmetry, and appearance in cleft lip and palate. It revealed a general preference for digital stereophotogrammetry as image acquisition method (74% of the included studies), which may reflect clinical practice and interest. All studies using digital 3D stereophotogrammetry as image acquisition method, with the exception of two, were published in the current decade. The reviewed imaging systems are capable to capture images of the complete head, but emphasis can be placed on anatomical regions particularly affected in cleft lip and palate, such as the nose, lips, and mid face. Mainly, the 3D images were analyzed using elementary measurements of distances, areas, and volumes; comprehensive statistical methods for superimposition, shape description and structuring; and subjective ratings using a Likert-type scale or a Visual Analog Scale.

The majority of the studies reported precision of their method as reproducibility of landmark identification on the 3D images. The observed values were in line with those of previous studies executed on stereophotogrammetric images of non-affected patients ($<1\text{mm}^{60,61}$). However, several other parameters can affect the internal validity of an imaging system. According to Richtsmeier et al., a measurement error in the collection of landmark coordinate data can be attributed to three sources: 1) precision, 2) error due to the imaging system (ability of the device to produce a good quality image), and error due to digitization (ability of the observer to correctly use specific hardware, software, and interface tools)^{62,63}. Several imaging systems have been successfully validated, such as the Genex 3D camera system⁶⁴, 3dMDface⁶², and Vectra H1⁶⁵.

The assessment of facial appearance on 3D images tries to mimic a lifelike situation. In contrast to 2D assessment, manipulation of the 3D image allows rating in all viewpoints. In this way, confounding elements such as camera angle and head tilt are eliminated^{51,66}. In addition, 3D images should be more informative when aspects of face perception are measured view-specific, because it enhances the abilities of the raters^{25,66}. However, Mosmuller and co-workers concluded that 2D and 3D assessment methods for the appearance of the nasolabial area are not correlated at all and it also remains unclear whether 2D or 3D images are more informative for these purposes³³.

This paper is the first systematic review in this research field emphatically reporting about 3D non-ionizing surface imaging and the associated (statistical) methodology. The literature search was performed in four comprehensively used databases in health and life sciences. All eligible studies

were published between 2000 and 2016, despite the lack of a time period restriction. Language bias could not be ruled out as our systematic search was based on English-language-dominated sources; yet no eligible articles in other languages were identified through the search. A slightly adapted version of the MINORS checklist was used as quality assessment tool. This checklist has been validated and the scientific use has been generally accepted²¹. Certain studies showed a suboptimal methodology after quality assessment for the following reasons: the data collection was not performed prospectively, or this aspect was not adequately reported; patients were not consecutively included; the study size was not calculated prospectively; or the study endpoint was assessed in a biased manner. The latter is an inherent feature of the included studies with objective assessment methods because blinding of the 3D images while placing the landmarks is impossible. In this way, the operator is always aware whether a cleft patient or control patient is processed.

Previous reviews addressing facial outcome assessment in cleft and palate also included non-ionizing 3D surface imaging methods. However, the focus in these reviews was mainly on the comparison of 2D and 3D images, and less on the methodological and statistical processing of the 3D images. Al-Omari et al. (2005) and Mosmuller et al. (2013) concluded that outcome assessment preferentially should be performed on 3D images rather than on 2D images^{67,68}. However, scoring on 2D images would be easier to perform and more applicable in daily practice because all cleft patients are photographed through the course of their treatment⁶⁸. According to Kuijpers et al. (2014) 3D imaging can be used for documentations of CLP patients, but there is a lack of evidence that 3D assessment methods are more informative than 2D assessment methods⁶⁹.

Cleft centers collect a wide spectrum of diagnostic data such as panoramic and lateral skull radiographs, dental impressions or intraoral dental scans, and facial and intraoral clinical photographs. These data can be collected for different purposes such as treatment planning, monitoring of treatment progress and treatment evaluation, but also cross-sectional and longitudinal research⁷⁰. This paper supports that non-ionizing 3D surface imaging can be of great added value in the routinely data collection of these institutions as it can be addressed for both quantitative and qualitative evaluation of the face and there is no need of physical storage. For these purposes, stereophotogrammetry also offers several advantages over laser-based and structured light-based surface scanning. The acquisition speed is significantly higher (up to 1.5 milliseconds) and it has a high surface coverage (up to 360° of the head) in a single shot. This makes it easier for practitioners to scan infants and young children, considering possible body movements during the course of scanning^{18,19,44,71}. Notwithstanding the attractive characteristics in morphological analysis and facial

appearance assessment, a 3D setup is still expensive to purchase and analysis of the images requires profound statistical analysis^{38,72}. In this regard, the routinely use of 3D methods is mainly reserved for high-income settings. As 2D assessment methods have proven to be reliable and informative both in subjective and objective outcome assessment^{10,73}, they appear to be more applicable in a low-income setting.

Three-dimensional methods are of added value for the objective assessment of morphology and symmetry if the images are also analyzed in a valid, three-dimensional manner. Analysis of shape and form variation, rather than elementary measurements of distances, areas, and volumes, yields interesting insights in the cleft related phenotypes. Several concepts of shape analysis have been proposed to detect asymmetry and abnormal morphology⁷⁴⁻⁷⁶. More recently, Claes and co-workers developed a theoretical concept to quantify and visualize morphological abnormalities, such as facial asymmetries. It applies the paradigm of detecting form differences as outliers compared to an appropriate form⁷⁷. This means in concrete terms that such 3D facial asymmetry assessment is accomplished by reference to the typical variation found in the general population rather than to the ideal of perfect symmetry⁷⁸. To accomplish this, an anthropometric mask is non-rigidly mapped onto the images resulting in homologous spatially dense (~10 000) quasi-landmark configurations⁷⁹. It can be concluded that non-ionizing 3D surface images are widely used in cleft research and that assessment of morphology, symmetry, and appearance can be performed in a reliable manner. Nevertheless, 3D analysis of these images is often methodologically sub-optimal. Researchers must fully utilize the content of 3D images to quantify morphology in a way that minimizes operator bias. It might be suggested that unbiased, three-dimensional shape analysis with an automated mapping strategy has potential in this research field.

REFERENCES

1. Hennekam R. C. M., Allanson J. E., Krantz I. D. *Gorlin's Syndromes of the Head and Neck*. Oxford University Press, New York: **2010**.
2. Mossey P. A., Little J., Munger R. G., Dixon M. J., Shaw W. C. Cleft lip and palate. *Lancet* **2009**;374:1773-85.
3. Meyer-Marcotty P., Gerdes A. B., Reuther T., Stellzig-Eisenhauer A., Alpers G. W. Persons with cleft lip and palate are looked at differently. *J Dent Res* **2010**;89:400-4.

4. Baudouin J. Y., Tiberghien G. Symmetry, averageness, and feature size in the facial attractiveness of women. *Acta Psychol (Amst)* **2004**;117:313-32.
5. Hatch C. D., Wehby G. L., Nidey N. L., Moreno Uribe L. M. Effects of Objective 3-Dimensional Measures of Facial Shape and Symmetry on Perceptions of Facial Attractiveness. *J Oral Maxillofac Surg* **2017**;
6. Farkas L. G., Hajnis K., Posnick J. C. Anthropometric and anthroposcopic findings of the nasal and facial region in cleft patients before and after primary lip and palate repair. *Cleft Palate Craniofac J* **1993**;30:1-12.
7. Assuncao A. G. The V.L.S. classification for secondary deformities in the unilateral cleft lip: clinical application. *Br J Plast Surg* **1992**;45:293-6.
8. Bongaarts C. A., Prah-Andersen B., Bronkhorst E. M., Prah C., Ongkosuwito E. M., Borstlap W. A., et al. Infant orthopedics and facial growth in complete unilateral cleft lip and palate until six years of age (Dutchcleft). *Cleft Palate Craniofac J* **2009**;46:654-63.
9. Daskalogiannakis J., Dijkman G. E., Kuijpers-Jagtman A. M., Ross R. B. Comparison of facial morphology in two populations with complete unilateral cleft lip and palate from two different centers. *Cleft Palate Craniofac J* **2006**;43:471-6.
10. Asher-McDade C., Roberts C., Shaw W. C., Gallagher C. Development of a method for rating nasolabial appearance in patients with clefts of the lip and palate. *Cleft Palate Craniofac J* **1991**;28:385-90; discussion 90-1.
11. Kuijpers-Jagtman A. M., Nollet P. J., Semb G., Bronkhorst E. M., Shaw W. C., Katsaros C. Reference photographs for nasolabial appearance rating in unilateral cleft lip and palate. *J Craniofac Surg* **2009**;20 Suppl 2:1683-6.
12. Okkerse J. M., Beemer F. A., Cordia-de Haan M., Heineman-de Boer J. A., Mellenbergh G. J., Wolters W. H. Facial attractiveness and facial impairment ratings in children with craniofacial malformations. *Cleft Palate Craniofac J* **2001**;38:386-92.
13. Morranti D. G., Shaw W. C. Use of standardized video recordings to assess cleft surgery outcome. *Cleft Palate Craniofac J* **1996**;33:134-42.
14. Trotman C. A., Faraway J. J., Essick G. K. Three-dimensional nasolabial displacement during movement in repaired cleft lip and palate patients. *Plast Reconstr Surg* **2000**;105:1273-83.
15. Ayoub A. F., Garrahy A., Hood C., White J., Bock M., Siebert J. P., et al. Validation of a vision-based, three-dimensional facial imaging system. *Cleft Palate-Craniofacial Journal* **2003**;40:523-9.

16. Djordjevic J, Lewis B. M., Donaghy C. E., Zhurov A. I., Knox J., Hunter L., et al. Facial shape and asymmetry in 5-year-old children with repaired unilateral cleft lip and/or palate: an exploratory study using laser scanning. *Eur J Orthod* **2014**;36:497-505.
17. Devlin M. F., Ray A., Raine P., Bowman A., Ayoub A. F. Facial symmetry in unilateral cleft lip and palate following alar base augmentation with bone graft: a three-dimensional assessment. *Cleft Palate Craniofac J* **2007**;44:391-5.
18. Lane C., Harrell W., Jr. Completing the 3-dimensional picture. *Am J Orthod Dentofacial Orthop* **2008**;133:612-20.
19. Heike C. L., Upson K., Stuhaug E., Weinberg S. M. 3D digital stereophotogrammetry: a practical guide to facial image acquisition. *Head Face Med* **2010**;6:18.
20. Liberati A., Altman D. G., Tetzlaff J., Mulrow C., Gotzsche P. C., Ioannidis J. P., et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* **2009**;151:W65-94.
21. Slim K., Nini E., Forestier D., Kwiatkowski F., Panis Y., Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* **2003**;73:712-6.
22. Ayoub A., Bell A., Simmons D., Bowman A., Brown D., Lo T. W., et al. 3D assessment of lip scarring and residual dysmorphology following surgical repair of cleft lip and palate: a preliminary study. *Cleft Palate Craniofac J* **2011**;48:379-87.
23. Bell A., Lo T. W., Brown D., Bowman A. W., Siebert J. P., Simmons D. R., et al. Three-dimensional assessment of facial appearance following surgical repair of unilateral cleft lip and palate. *Cleft Palate Craniofac J* **2014**;51:462-71.
24. Dadakova M., Caganova V., Dupej J., Hoffmannova E., Borsky J., Veleminska J. Three-dimensional evaluation of facial morphology in pre-school cleft patients following neonatal cheiloplasty. *J Craniomaxillofac Surg* **2016**;44:1109-16.
25. Desmedt D. J., Maal T. J., Kuijpers M. A., Bronkhorst E. M., Kuijpers-Jagtman A. M., Fudalej P. S. Nasolabial symmetry and esthetics in cleft lip and palate: analysis of 3D facial images. *Clin Oral Investig* **2015**;19:1833-42.
26. Hood C. A., Hosey M. T., Bock M., White J., Ray A., Ayoub A. F. Facial characterization of infants with cleft lip and palate using a three-dimensional capture technique. *Cleft Palate Craniofac J* **2004**;41:27-35.

27. Kuijpers M. A., Desmedt D. J., Nada R. M., Berge S. J., Fudalej P. S., Maal T. J. Regional facial asymmetries in unilateral orofacial clefts. *Eur J Orthod* **2015**;37:636-42.
28. Manyama M., Larson J. R., Liberton D. K., Rolian C., Smith F. J., Kimwaga E., et al. Facial morphometrics of children with non-syndromic orofacial clefts in Tanzania. *BMC Oral Health* **2014**;14:93.
29. Meyer-Marcotty P., Stellzig-Eisenhauer A. Dentofacial self-perception and social perception of adults with unilateral cleft lip and palate. *J Orofac Orthop* **2009**;70:224-36.
30. Oh T. S., Choi J. W., Koh K. S. Upper lip asymmetry perception using three-dimensional anthropometry in patients with unilateral cleft lip deformity. *J Craniofac Surg* **2011**;22:2080-3.
31. Tanikawa C., Takada K., van Aalst J., Trotman C. A. Objective three-dimensional assessment of lip form in patients with repaired cleft lip. *Cleft Palate Craniofac J* **2010**;47:611-22.
32. Russell A. J., Patel K. B., Skolnick G. B., Woo A. S. The Use of an Inferior Pennant Flap during Unilateral Cleft Lip Repair Improves Lip Height Symmetry. *Plast Reconstr Surg* **2015**;136:1046-53.
33. Mosmuller D. G. M., Maal T. J., Prah C., Tan R. A., Mulder F. J., Schwirtz R. M. F., et al. Comparison of two- and three-dimensional assessment methods of nasolabial appearance in cleft lip and palate patients: Do the assessment methods measure the same outcome? *J Craniomaxillofac Surg* **2017**;45:1220-6.
34. Weinberg S. M., Leslie E. J., Hecht J. T., Wehby G. L., Deleyiannis F. W. B., Moreno L. M., et al. Hypertelorism and Orofacial Clefing Revisited: An Anthropometric Investigation. *Cleft Palate-Craniofacial Journal* **2017**;54:631-8.
35. Duffy S., Noar J. H., Evans R. D., Sanders F. Three-dimensional analysis of the child cleft face. *Cleft Palate-Craniofacial Journal* **2000**;37:137-44.
36. Bugaighis I., Mattick C. R., Tiddeman B., Hobson R. 3D asymmetry of operated children with oral clefts. *Orthod Craniofac Res* **2014**;17:27-37.
37. Bugaighis I., Mattick C. R., Tiddeman B., Hobson R. 3D facial morphometry in children with oral clefts. *Cleft Palate Craniofac J* **2014**;51:452-61.
38. Bugaighis I., O'Higgins P., Tiddeman B., Mattick C., Ben Ali O., Hobson R. Three-dimensional geometric morphometrics applied to the study of children with cleft lip and/or palate from the North East of England. *Eur J Orthod* **2010**;32:514-21.
39. Bugaighis I., Tiddeman B., Mattick C. R., Hobson R. 3D comparison of average faces in subjects with oral clefts. *Eur J Orthod* **2014**;36:365-72.

40. Ayoub A, Garrahy A, Millett D, Bowman A, Siebert J. P., Miller J., et al. Three-dimensional assessment of early surgical outcome in repaired unilateral cleft lip and palate: Part 1. Nasal changes. *Cleft Palate Craniofac J* **2011**;48:571-7.
41. Ayoub A, Garrahy A, Millett D, Bowman A, Siebert J. P., Miller J., et al. Three-dimensional assessment of early surgical outcome in repaired unilateral cleft lip and palate: Part 2. Lip changes. *Cleft Palate Craniofac J* **2011**;48:578-83.
42. Bilwatsch S, Kramer M, Haeusler G, Schuster M, Wurm J, Vairaktaris E, et al. Nasolabial symmetry following Tennison-Randall lip repair: a three-dimensional approach in 10-year-old patients with unilateral clefts of lip, alveolus and palate. *J Craniomaxillofac Surg* **2006**;34:253-62.
43. Kishi N, Tanaka S, Iida S, Kogo M. The morphological features and developmental changes of the philtral dimple: a guide to surgical intervention in cases of cleft lip. *J Craniomaxillofac Surg* **2012**;40:215-22.
44. Krimmel M, Kluba S, Bacher M, Dietz K, Reinert S. Digital surface photogrammetry for anthropometric analysis of the cleft infant face. *Cleft Palate Craniofac J* **2006**;43:350-5.
45. Linden O. E., Taylor H. O., Vasudavan S., Byrne M. E., Deutsch C. K., Mulliken J. B., et al. Three-Dimensional Analysis of Nasal Symmetry Following Primary Correction of Unilateral Cleft Lip Nasal Deformity. *Cleft Palate Craniofac J* **2016**;
46. Meyer-Marcotty P., Alpers G. W., Gerdes A. B., Stellzig-Eisenhauer A. Impact of facial asymmetry in visual perception: a 3-dimensional data analysis. *Am J Orthod Dentofacial Orthop* **2010**;137:168.e1-8; discussion -9.
47. Meyer-Marcotty P., Kochel J., Boehm H., Linz C., Klammert U., Stellzig-Eisenhauer A. Face perception in patients with unilateral cleft lip and palate and patients with severe Class III malocclusion compared to controls. *J Craniomaxillofac Surg* **2011**;39:158-63.
48. Othman S. A., Ahmad R., Asi S. M., Ismail N. H., Rahman Z. A. Three-dimensional quantitative evaluation of facial morphology in adults with unilateral cleft lip and palate, and patients without clefts. *Br J Oral Maxillofac Surg* **2014**;52:208-13.
49. Othman S. A., Koay N. A. A. Three-dimensional facial analysis of Chinese children with repaired unilateral cleft lip and palate. *Scientific Reports* **2016**;6:
50. Stauber I., Vairaktaris E., Holst A., Schuster M., Hirschfelder U., Neukam F. W., et al. Three-dimensional analysis of facial symmetry in cleft lip and palate patients using optical surface data. *J Orofac Orthop* **2008**;69:268-82.

51. Stebel A., Desmedt D., Bronkhorst E., Kuijpers M. A., Fudalej P. S. Rating nasolabial appearance on three-dimensional images in cleft lip and palate: a comparison with standard photographs. *Eur J Orthod* **2016**;38:197-201.
52. van Loon B., Reddy S. G., van Heerbeek N., Ingels K., Maal T. J. J., Borstlap W. A., et al. 3D stereophotogrammetric analysis of lip and nasal symmetry after primary cheiloseptoplasty in complete unilateral cleft lip repair. *Rhinology* **2011**;49:546-53.
53. Bennett K. G., Thurston T. E., Vercler C. J., Kasten S. J., Buchman S. R. Harvesting the Buccal Fat Pad Does Not Result in Aesthetic Deformity in Cleft Patients: A Retrospective Analysis. *Plast Reconstr Surg* **2017**;140:362-8.
54. Da Silveira A. C., Daw J. L., Jr., Kusnoto B., Evans C., Cohen M. Craniofacial applications of three-dimensional laser surface scanning. *J Craniofac Surg* **2003**;14:449-56.
55. Bookstein F. L. A statistical method for biological shape comparisons. *J Theor Biol* **1984**;107:475-520.
56. Ercan I., Sigirli D., Ozkaya G. Examining the variations in the results of the Hotelling T2 test in case of changing baseline landmarks in the Bookstein coordinates. *Interdiscip Sci* **2015**;
57. Watson P. F., Petrie A. Method agreement analysis: a review of correct methodology. *Theriogenology* **2010**;73:1167-79.
58. Duffy S., Noar J. H., Evans R. D., Sanders R. Three-dimensional analysis of the child cleft face. *Cleft Palate Craniofac J* **2000**;37:137-44.
59. Bartlett J. W., Frost C. Reliability, repeatability and reproducibility: analysis of measurement errors in continuous variables. *Ultrasound Obstet Gynecol* **2008**;31:466-75.
60. Baysal A., Sahan A. O., Ozturk M. A., Uysal T. Reproducibility and reliability of three-dimensional soft tissue landmark identification using three-dimensional stereophotogrammetry. *Angle Orthod* **2016**;86:1004-9.
61. Othman S. A., Ahmad R., Mericant A. F., Jamaludin M. Reproducibility of facial soft tissue landmarks on facial images captured on a 3D camera. *Aust Orthod J* **2013**;29:58-65.
62. Aldridge K., Boyadjiev S. A., Capone G. T., DeLeon V. B., Richtsmeier J. T. Precision and error of three-dimensional phenotypic measures acquired from 3dMD photogrammetric images. *Am J Med Genet A* **2005**;138A:247-53.
63. Richtsmeier J. T., Paik C. H., Elfert P. C., Cole T. M., 3rd, Dahlman H. R. Precision, repeatability, and validation of the localization of cranial landmarks using computed tomography scans. *Cleft Palate Craniofac J* **1995**;32:217-27.

64. Weinberg S. M., Scott N. M., Neiswanger K., Brandon C. A., Marazita M. L. Digital three-dimensional photogrammetry: evaluation of anthropometric precision and accuracy using a Genex 3D camera system. *Cleft Palate Craniofac J* **2004**;41:507-18.
65. Camison L., Bykowski M., Lee W. W., Carlson J. C., Roosenboom J., Goldstein J. A., et al. Validation of the Vectra H1 portable three-dimensional photogrammetry system for facial imaging. *Int J Oral Maxillofac Surg* **2017**;
66. Tigue C. C., Pisanski K., O'Connor J. J., Fraccaro P. J., Feinberg D. R. Men's judgments of women's facial attractiveness from two- and three-dimensional images are similar. *J Vis* **2012**;12:
67. Al-Omari I., Millett D. T., Ayoub A. F. Methods of assessment of cleft-related facial deformity: a review. *Cleft Palate Craniofac J* **2005**;42:145-56.
68. Mosmuller D. G., Griot J. P., Bijnen C. L., Niessen F. B. Scoring systems of cleft-related facial deformities: a review of literature. *Cleft Palate Craniofac J* **2013**;50:286-96.
69. Kuijpers M. A. R., Chiu Y. T., Nada R. M., Carels C. E. L., Fudalej P. S. Three-dimensional imaging methods for quantitative analysis of facial soft tissues and skeletal morphology in patients with orofacial clefts: A systematic review. *PLoS ONE* **2014**;9:
70. WHO. Global strategies to reduce the health care burden of craniofacial anomalies: report of WHO meetings on international collaborative research on craniofacial anomalies. **2002**:
71. Da Silveira A. C., Daw J. L., Kusnoto B., Evans C., Cohen M. Craniofacial applications of three-dimensional laser surface scanning. *Journal of Craniofacial Surgery* **2003**;14:449-56.
72. Tzou C. H., Artner N. M., Pona I., Hold A., Placheta E., Kropatsch W. G., et al. Comparison of three-dimensional surface-imaging systems. *J Plast Reconstr Aesthet Surg* **2014**;67:489-97.
73. Nagy K., Mommaerts M. Y. Analysis of the cleft-lip nose in submental-vertical view, Part I--reliability of a new measurement instrument. *J Craniomaxillofac Surg* **2007**;35:265-77.
74. Klingenberg C. P., Barluenga M., Meyer A. Shape analysis of symmetric structures: quantifying variation among individuals and asymmetry. *Evolution* **2002**;56:1909-20.
75. Ferrario V. F., Sforza C., Poggio C. E., Tartaglia G. Distance from symmetry: a three-dimensional evaluation of facial asymmetry. *J Oral Maxillofac Surg* **1994**;52:1126-32.
76. Benz M., Laboureaux X., Maier T. The symmetry of faces. IOS Press, Amsterdam: G. Greiner, H. Niemann and T. Ertl, **2002**.
77. Claes P., Daniels K., Walters M., Clement J., Vandermeulen D., Suetens P. Dysmorphometrics: the modelling of morphological abnormalities. *Theor Biol Med Model* **2012**;9:5.

78. Claes P., Walters M., Vandermeulen D., Clement J. G. Spatially-dense 3D facial asymmetry assessment in both typical and disordered growth. *J Anat* **2011**;219:444-55.
79. Claes P., Walters M., Clement J. Improved facial outcome assessment using a 3D anthropometric mask. *Int J Oral Maxillofac Surg* **2012**;41:324-30.

5.

QUANTIFYING SOFT TISSUE CHANGES IN CLEFT LIP AND PALATE USING NON-IONIZING THREE-DIMENSIONAL SURFACE IMAGING: A SYSTEMATIC REVIEW.

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N. *J Oral Maxillofac Surg* **2018** Oct;76(10):2210.e1-2210.e1

ABSTRACT

Purpose: The use of non-ionizing three-dimensional surface imaging in cleft lip and palate research is well-established, but general guidelines concerning the assessment of these images are lacking. The aim of this study was to review the methods for quantification of soft tissue changes on 3D surface images acquired prior to and after an orthopedic or surgical intervention in cleft lip and palate patients.

Methods: A systematic literature search was performed using databases MEDLINE (via PubMed), CENTRAL, Web of Science, and EMBASE. The literature search and eligibility assessment were performed by two independent reviewers in a non-blinded standardized manner. Only longitudinal studies reporting the assessment of pre- and postoperative 3D surface images and at least 10 cleft lip and/or palate patients were considered eligible.

Results: Fifteen unique studies (published between 1996 and 2017) were identified after eligibility assessment. The assessment of the 3D images was performed with landmark-dependent analyses, mostly supported with superimposition of the pre- and postoperative images. A wide spectrum of superimposition techniques is reported. The reliability of these assessment methods was often not or insufficiently reported.

Conclusion: Soft tissue changes subsequent to a surgical or orthopedic intervention can be quantified on 3D surface images using assessment methods that are primarily based on landmark identification, whether or not followed by superimposition. Operator bias is inherently enclosed in landmark-dependent analyses. The reliability of these methods is insufficiently reported.

INTRODUCTION

Clefts of lip and palate (CLP) represent a heterogeneous group of disorders affecting facial bony structures and soft tissues during gestation and arise in about 1 in 700 livebirths¹. These malformations are located in the midfacial area and the lips, nose, alveolar process, and palate are primarily affected². Clinical management includes surgical and non-surgical corrections to improve masticatory function, speech, breathing, hearing, and appearance of facial soft tissues^{1,3}. Surgical repair of lip, palate, and alveolus has been addressed to have a detrimental effect on maxillofacial

growth. This might result in a hypoplastic maxilla, nasolabial deformities and asymmetries, a concave midface, and a deformed dental arch^{3,4}. In this respect, longitudinal assessment of these patients can provide informative data to monitor the maxillofacial growth pattern and to quantify therapeutic effects. A wide variety of diagnostic tools has been utilized to quantify craniofacial dimensions in CLP: clinical anthropometry⁵, dental casts⁶, facial casts⁶⁻⁸, cephalometric X-rays⁹⁻¹¹, clinical facial photographs¹²⁻¹⁴, Computed Tomography^{15,16}, and Cone Beam Computed Tomography^{17,18}.

Three-dimensional (3D) surface imaging gained remarkable interest in the CLP research field in the last two decades. These image acquisition methods are fast, acquire 3D surface data in a reliable manner, and work without ionizing radiation¹⁹⁻²¹. Due to these characteristics, it appears to be an appropriate diagnostic tool for longitudinal assessment of maxillofacial characteristics of cleft patients.

Three-dimensional surface imaging was discussed next to other 2D and 3D imaging methods in the extensive papers of Brons et al.²² and Kuijpers et al.²³. It was concluded that stereophotogrammetry is a well-established image acquisition method for longitudinal assessment of facial dimensions²², but a paper reviewing the methods for the assessment of soft tissue changes using these 3D images has not been published up to now. Therefore, the aim of this study was to review the methods for quantification of soft tissue changes on 3D surface images acquired prior to and after an orthopedic or surgical intervention in cleft lip and palate patients.

MATERIALS AND METHODS

This paper is written in accordance to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines²⁴. The literature search aimed to identify all original articles reporting clinical trials with a quantitative outcome.

Data sources and search methods

Studies were identified using the electronic databases: MEDLINE (provided by PubMed, 1966-present), Web of Science (1955-present), EMBASE (1980-present), and CENTRAL (Cochrane Central Register of Controlled Trials) (1988-present). Search terms were combined to create an appropriate search string: cleft lip, cleft palate, three-dimensional imaging, anthropometry, (stereo)photogrammetry, surface scanning, and morphometry. The electronic search strings in the selected databases are shown in

Table 1. Backwards and forwards citation tracking (snowballing) was also performed, using reference lists and the Science Citation Index of all the articles eligible for inclusion in this paper. The time period was not restricted and only articles written in English, containing original data concerning humans were included. Only longitudinal studies with prospective data collection were considered eligible. Abstracts, expert opinions, conference summaries, reviews, case reports and series describing less than 10 cases per study group were excluded. Reports without a quantitative outcome and method development studies were also not considered eligible.

Electronic database	Search string
MEDLINE	(cleft lip[MeSH Terms] OR cleft lip[Tiab] OR cleft palate[MeSH Terms] OR cleft palate[Tiab]) AND (morphometr*[Tiab] OR photogrammetry[Mesh] OR photogrammetr*[Tiab] OR stereophotogrammetr*[Tiab] OR anthropometr*[Tiab] OR Imaging, Three-Dimensional[Mesh] OR 3D[Tiab] OR three-dimensional[Tiab])
Web of Science	(TS=("cleft lip") OR TS=("cleft palate") OR TS=("cleft lip and palate")) AND (TS=(morphometr*) OR TS=(stereophotogrammetr*) OR TS=(photogrammetr*) OR TS=("three dimensional imag*") OR TS=(anthropometr*))
EMBASE	"cleft lip/exp OR 'cleft lip':ab OR 'cleft palate'/exp OR 'cleft palate':ab OR 'cleft lip palate'/exp OR 'cleft lip palate':ab AND ('morphometry'/exp OR 'morphometry':ab OR 'stereophotogrammetry'/exp OR 'stereophotogrammetry':ab OR 'photogrammetry'/exp OR 'photogrammetry':ab OR 'three dimensional imaging'/exp OR 'three dimensional imaging':ab OR 'anthropometry'/exp OR 'anthropometry':ab) AND [embase]/lim
Cochrane Central Register of Controlled Trials (CENTRAL)	("cleft lip" OR "cleft palate" OR "cleft lip and palate") AND (morphometr* OR stereophotogrammetr* OR photogrammetr* OR three dimensional imag* OR anthropometr*)

Table 1. Electronic search strategies in the selected databases

Prior to reading the retrieved titles, abstracts, and articles, consensus was reached on the following inclusion criteria: digital 3D stereophotogrammetry, 3D laser-based surface imaging, or 3D structured light-based surface imaging as imaging acquisition method; clear description of the assessment methodology of the three-dimensional images; patients with cleft lip and/or palate without

syndromes and without age restriction; reporting assessment of soft tissue changes of any facial region subsequent to orthopedic or surgical interventions.

Study selection, data extraction and quality assessment

The search strategy was established a priori by all authors, and eligibility assessment was performed by two independent reviewers (LT & NDR) in a non-blinded standardized manner. The titles and abstracts of retrieved studies were independently reviewed, and subsequently full-text articles corresponding to the selected titles and abstracts were retrieved. The methodological quality of the included studies was analyzed according to MINORS. This is valid instrument designed to assess the methodological quality of non-randomized surgical studies, whether comparative or non-comparative^{25,26}. Disagreements concerning article selection or the quality assessment between the two reviewers were resolved by consensus after rereading and discussion with the other authors.

The following data were collected: (1) basic study characteristics: author(s), year of publication, and country; (2) population characteristics: sample size, age at enrollment, follow-up period; type of (surgical) intervention, cleft type, and studied facial region; (3) characteristics of the imaging and assessment method: image acquisition method, (anthropometric) landmarks used, superimposition technique of the pre- and postoperative images, outcome assessment, the reliability of the method, and use of a control group. Due to the retrospective nature of this study, it was granted an exemption in writing by the Ghent University institutional review board (IRB).

RESULTS

General description of the included studies

The search in the electronic databases was finalized on September 1, 2017. The schematic diagram of the literature search and screening process is shown in Figure 1. Overall, 1767 unique studies were identified after removal of duplicates, of which 15 met the inclusion criteria²⁷⁻⁴¹.

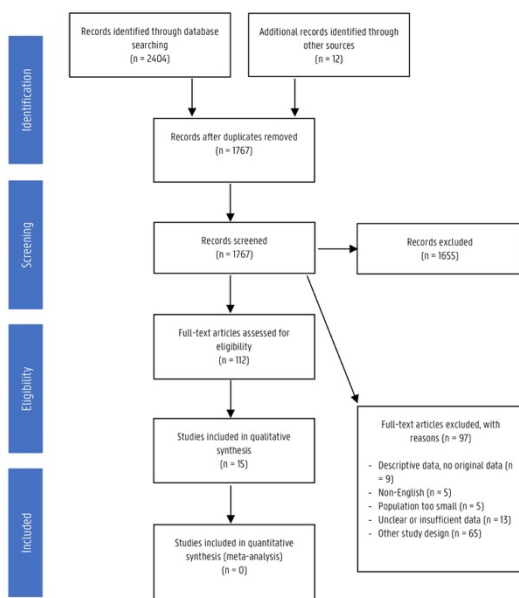


Figure 1. Schematic diagram of the literature search and screening process conform the PRISMA guidelines

The study characteristics are presented in Table 2. With the exception of two^{32,33}, all papers were published in the last two decades. Images were acquired in patients starting from an average age of 15 days. The observed patients had unilateral cleft lip (UCL; four studies^{27,38,42,43}), unilateral cleft lip and alveolus (UCLA; four studies^{27,35,37,43}), unilateral cleft lip and palate (UCLP; 17 studies^{27-35,37-41,43-45}), isolated cleft palate (CP; three studies^{32,33,41}), bilateral cleft lip and alveolus (BCLA; two studies^{35,36}), or bilateral cleft lip and palate (BCLP; seven studies^{31-36,45}). The studied anatomical regions were the nose, lips, mid face, and full face. Treatment outcome assessment was performed prior to and after following interventions: primary lip repair, (presurgical) nasoalveolar molding ((P)NAM), rapid maxillary expansion and Delaire facemask, secondary alveolar bone grafting, Le Fort I advancement, and secondary lip and/or nose repair. The included studies showed substantial methodological and clinical heterogeneity, so data of these studies could not be pooled by means of a meta-analysis.

Author	Year of publication	Country	Number of patients	Age at enrollment	Follow-up period	Anatomical region assessed	Cleft type(s)
Primary lip repair							
Schwenzer-Zimmerer et al. ²⁷	2008	Cambodia	11	13.8 (2 to 41) years (mean)	NR	Lips and nose	UCL, UCLA, UCLP
Singh et al. ²⁸	2007	Puerto Rico	15	37 weeks (mean)	4 weeks	Full face	UCLP
Secondary alveolar bone grafting							
Devlin et al. ²⁹	2007	United Kingdom	17	14.8 (11.0 to 27.0) years (mean)	6 months	Lips and nose	UCLP
Kau et al. ³⁰	2011	United States of America	10	7 to 21 years (range)	6 weeks	Nose	UCLP
Kimmel et al. ³¹	2011	Germany	22	13.0 (9 to 20) years (mean)	6 weeks	Lips and nose	UCLP, BCLP
Le Fort I advancement							
McCance et al. ³²	1997	United Kingdom	24	18-25 years (range)	12 months	Full face	UCLP, BCLP, CP
Stewart et al. ³³	1996	United Kingdom	24	NR	12 months	Full face	UCLP, BCLP, CP
Susaita et al. ³⁴	2015	United States of America	11	17.9 (±1.4) years (mean)	154.3 (±88.4) days (mean)	Lips and midface	UCLP, BCLP
Secondary lip and/or nose repair							
Nakamura et al. ³⁵	2016	Japan	22	17.8 (16 to 30) years (mean)	12 to 36 months	Nose	UCLA, UCLP, BCLA, BCLP
Nakamura et al. ³⁶	2011	Japan	10	17.1 (16 to 21) years (mean)	12 to 48 months	Lips and nose	BCLA, BCLP
Okawachi et al. ³⁷	2011	Japan	13	17.5 (16 to 22) years (mean)	12 to 36 months	Nose	UCLA, UCLP
van Loon et al. ³⁸	2010	The Netherlands	12	13 to 40 years (range)	3 months	Nose	UCL, UCLP
Nasoskeletal molding							
Chou et al. ³⁹	2017	United States of America	20	15.6 days (mean)	98 days (mean)	Lips and nose	UCLP
Singh et al. ⁴⁰	2005	Puerto Rico	10	28 (±2.0) days (mean)	112 (±2) days (mean)	Nose	UCLP
Rapid maxillary expansion and Delaire facemask							
Hoefert et al. ⁴¹	2010	Germany	14	5.6 (±0.82, UCLP) and 4.9 (±0.47, CP) years (mean)	14.3 months (UCLP) and 16.5 months (CP) (mean)	Full face	UCLP, CP
Abbreviations: NR, Not Reported; UCL, unilateral cleft lip; UCLA, unilateral cleft lip and alveolus; UCLP, unilateral cleft lip and palate; CP, isolated cleft palate; BCLA, bilateral cleft lip and alveolus; BCLP, bilateral cleft lip and palate.							

Table 2. Characteristics of the included studies

Quality assessment of the included studies

The results of the quality assessment are visualized with a bar chart in Figure 2. Generally, the items of the MINORS checklist 'inclusion of consecutive patients', 'prospective collection of data', 'unbiased assessment of the study endpoint', 'loss to follow-up less than 5%', and 'prospective calculation of the study size' achieved score 0 (not reported) or score 1 (not adequately reported), despite the prospective characteristics of the included studies. The items evaluating the study aim, the study endpoints, prospective collection of data, the follow-up period, and the statistical analyses varied between score 1 (reported, but not adequate) or score 2 (reported and adequate).

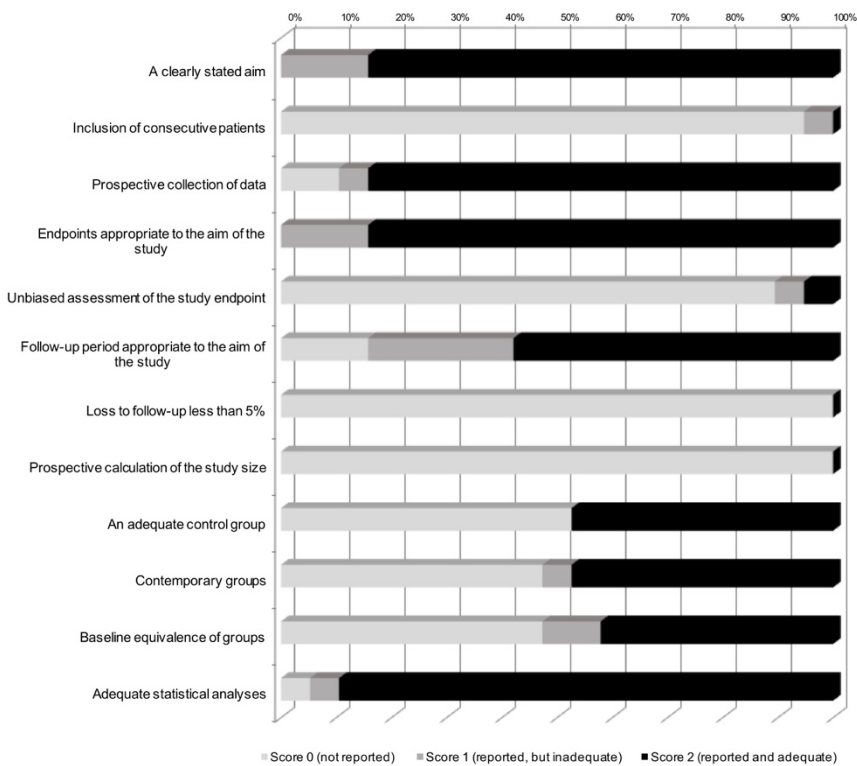


Figure 2: Quality assessment

Image acquisition methods

Table 3 shows the characteristics of the image acquisition methods. Stereophotogrammetry was used in the majority of the included studies (nine studies^{28-31,34,38-41}). This method is based on the reproduction of surface geometry and mapping of realistic color and texture data by taking two or more photographs of the same subject from different positions. A software tool merges these photographs and generates a composite 3D model^{19,20}.

Laser-based surface imaging was used in the remaining six studies^{27,32,33,35-37}. In this image acquisition method, the surface area of the target subject is scanned with a laser beam. Subsequently, this beam is scattered by the subject and registered by a camera at a known distance and the 3D coordinates of a surface point are calculated by using trigonometry^{20,46}.

Quantification of soft tissue changes

The methods for quantitative assessment of soft tissue changes are shown in Table 3. All studies performed a landmark-dependent analysis using homologous, pseudo-, and/or semi-landmarks. Superimposition of pre- and postoperative 3D images was performed in 11 studies. Following methods were applied: landmark-based superimposition of the eyes and forehead region using the least squares method (five studies^{30,33,35,37,41}); surface-based superimposition using the iterative closest point algorithm (two studies^{31,38}); landmark-based superimposition based on a balance point of a triangular plane defined by 3 landmarks representing the center of the skull base (one study²⁷); and Generalized Procrustes superimposition (one study²⁸). Two studies did not report the superimposition technique used^{32,34}. The remaining studies did not superimpose pre- and postoperative images. Soft tissue changes were quantified using linear, curvilinear, and angular measurements (three studies^{36,39,40}), calculation of Euclidean distances between pairs of homologous landmarks of original and mirrored images (one study²⁹), and Finite-element Scaling Analysis (one study⁴⁰).

Author	Year of Publication	Image acquisition method	Landmarks	Superimposition technique of pre- and postoperative images	Outcome assessment	Control group
Primary lip repair						
Schwenzer-Zimmerer et al. ²⁷	2008	Laser surface scanning	16 homologous and pseudo-landmarks modified according to Farkas (cheilion right and left, alar wing lat cleft and non-cleft, alar wing med cleft and non-cleft, columella anterior cleft and non-cleft, columella posterior cleft and non-cleft, philtrum lat cleft, cleft superior lat, cleft superior medial, philtrum lat cleft lat, philtrum lat cleft med, and labiale superior)	A triangular plane defined by the superior tragus points of both ears and the center point between the medial canthus of both eyes. The balance point was calculated as being the center of the skull base.	Linear measurements; distance mapping	25 non-cleft persons
Singh et al. ²⁸	2007	Stereophotogrammetry	5 homologous landmarks (pronasale, right and left alar curvature, and right and left medial canthus)	Generalized Procrustes superimposition	Principal Component Analysis and finite-element Scaling Analysis	10 matched non-cleft persons
Secondary alveolar bone grafting						
Devlin et al. ²⁹	2007	Stereophotogrammetry	21 homologous and pseudo-landmarks (exocanthion right and left, endocanthion right and left, glabella, soft tissue nasion, superior nostril right and left, alar crest right and left, alar base right and left, subnasion, superior columella right and left, pronasion, base of Cupid's bow, Peak of Cupid's bow right and left, cheilion right and left)	No superimposition	Square Euclidean distances between pairs of homologous landmarks of original and mirrored images	/
Kau et al. ³⁰	2011	Stereophotogrammetry	6 homologous landmarks (paranasale, subnasale, right and left alar curvature, alar right and left)	Superimposition of the facial structures not affected by surgery using the least squares method	Linear and angular measurements; asymmetry scores	/

Table 3. Image acquisition methods and procedures for quantitative assessment of soft tissue changes (1/4)

Krimmel et al. ³¹	2011	Stereophotogrammetry	7 homologous landmarks (nasion, pronasale, subnasale, subalar, cheilion, labiale superius, and alare curvature/ alare laterale)	Superimposition using the iterative closest point algorithm of a circular area with a diameter of 5cm and nasion as center point	Linear measurements	/
Le Fort I advancement						
McCance et al. ³²	1997	Laser surface scanning	NR	NR	Distance mapping	60 non-cleft persons
Stewart et al. ³³	1996	Laser surface scanning	18 homologous and pseudo-landmarks (nasion, sellion, pronasale, nasal dorsal point, subnasale, labiale superius, top point of the columella right and left, subalar right and left, alar curvature point right and left, alare right and left, lateral canthus right and left, and medial canthus right and left)	Superimposition by matching 10 landmarks across the eyes and forehead using the least squares method	Linear and angular measurements	/
Susarla et al. ³⁴	2015	Stereophotogrammetry	11 homologous landmarks (subnasale, labium superius, stomium, ear-to-ear junction right and left, medial canthus right and left, infraorbitalis right and left, and cheilion right and left)	NR	Linear and volumetric measurements	/
Secondary lip and/or nose repair						
Nakamura et al. ³⁵	2016	Laser surface scanning	5 homologous and semi-landmarks (center of right and left endocanthion, pronasale, the columellar base point, the point of tangency with the nasal dorsum and the tangent line occluding the center of the bilateral medial ocular angles, and the point of tangency with the columella and the tangent line including the columellar base)	Superimposition across the eyes and forehead using the least squares method (3D-Rugle V software)	Angular measurements; determination of 3D coordinates	20 matched non-cleft persons

Table 3. Image acquisition methods and procedures for quantitative assessment of soft tissue changes (2/4)

Nakamura et al. ³⁶	2011	Laser surface scanning	7 homologous, pseudo-, and semi-landmarks (center of right and left endocanthion, pronasale, the columellar base point, the widest point of the nasal ala right and left, the alar base point cleft and non-cleft, the point of tangency with the nasal dorsum and the tangent line occluding the center of the bilateral medial ocular angles, and the point of tangency with the columella and the tangent line including the columellar base)	No superimposition	Linear and angular measurements	10 matched non-cleft persons
Okawachi et al. ³⁷	2011	Laser surface scanning	11 homologous, pseudo-, and semi-landmarks (center of right and left endocanthion, pronasale, the columellar base point, the widest point of the nasal ala right and left, the alar base point cleft and non-cleft, the point of tangency with the nasal dorsum and the tangent line occluding the center of the bilateral medial ocular angles, and the point of tangency with the columella and the tangent line including the columellar base, and the vertically highest point of the nasal alar groove cleft and non-cleft)	Superimposition across the eyes and forehead using the least squares method (3D-Rugle V software)	Linear and angular measurements	20 matched non-cleft persons
van Loon et al. ³⁸	2011	Stereophotogrammetry	NR	A 5-step superimposition process using the iterative closest point algorithm	Volumetric measurements	/
Nasolabioalveolar molding						
Chou et al. ³⁹	2017	Stereophotogrammetry	4 homologous landmarks (labiale superius cleft side, crista philtri non-cleft, subnasale non-cleft, and subalare cleft)	No superimposition	Linear and area measurements	/

Table 3. Image acquisition methods and procedures for quantitative assessment of soft tissue changes (3/4)

Singh et al. ⁽⁴⁰⁾	2005	Stereophotogrammetry	28 homologous and semi-landmarks (soft tissue nasion, pronasale, right and left alar curvature, right and left posterior alar curvature, right and left superior alar curvature, midpoint between soft tissue nasion and pronasale, right and left alar, midpoint between right and left alar, right and left alar (deep), midpoint between right alar and right alar (deep), midpoint between right alar (deep) and pronasale, midpoint between left alar (deep) and pronasale, midpoint between left alar and left alar (deep), right and left subalare, right and left nostril (lateral), right and left columella, middle right and left columella, insertion of the columella base on the right and left side of the nose, and subnasale)	No superimposition	Linear, curvilinear, and angular measurements; Finite-element Scaling Analysis	/
Rapid maxillary expansion and Delaire facemask						
Hoefert et al. ⁽⁴¹⁾	2010	Stereophotogrammetry	7 homologous and semi-landmarks for superimposition (exocanthion right and left, endocanthion right and left, middle of eye axis, intersection of forehead axis with the inside eye circle, and intersection of forehead axis with the outside eye circle), 6 semi-landmarks for analysis of the midface (right and left midpoint of the distance between alare and cheilion, subnasale, right and left midpoint of the distance between exocanthion and cheilion, and midpoint of the distance between right and left midpoint of the distance between alare and cheilion), and 4 homologous and semi-landmarks for analysis of the lower face (midpoint of the distance between right and left midpoint of the distance between cheilion and menton, right and left midpoint of the distance between gonion and menton, and menton)	Superimposition using 7 landmarks across the eyes and forehead	Linear measurements	/
Abbreviations: MR, Not Reported						

Table 3. Image acquisition methods and procedures for quantitative assessment of soft tissue changes (4/4)

The reliability of the assessment methods is shown in Table 4 and was reported as the reproducibility of landmark identification [four studies^{27,29,33,39}] or the repeatability and reproducibility of volumetric measurements [one study³⁸]. Five studies did report anything concerning reliability of their assessment methods^{30-32,34,41}, two studies did not report evidence about their reproducibility of landmark identification^{28,40}, and three studies only reported the error of the image acquisition system³⁵⁻³⁷.

Author	Year of publication	Error of the method	Measurement error	Reliability coefficient
Schwenzer-Zimmerer et al. ²⁷	2008	Reproducibility of landmark identification	0.08 to 1.12 mm (mean 0.58 mm)* 0.01 to 0.98 mm (mean 0.43 mm)**	NR
Singh et al. ²⁸	2007	Reproducibility of landmark identification	NR	NR
Devlin et al. ²⁹	2007	Reproducibility of landmark identification	>2 mm in 2.43%** >1 mm in 16.51%**	NR
Kau et al. ³⁰	2011	NR	NR	NR
Krimmel et al. ³¹	2011	NR	NR	NR
McCance et al. ³²	1997	NR	NR	NR
Stewart et al. ³³	1996	Reproducibility of landmark identification	NR	0.95- 0.99**
Susarla et al. ³⁴	2015	NR	NR	NR
Nakamura et al. ³⁵	2016	Error of the image acquisition system	0.2 to 0.4 mm (mean 0.3 mm)	NR
Nakamura et al. ³⁶	2011	Error of the image acquisition system	0.2 to 0.4 mm (mean 0.3 mm)	NR
Okawachi et al. ³⁷	2011	Error of the image acquisition system	0.2 to 0.4 mm (mean 0.3 mm)	NR
van Loon et al. ³⁸	2010	Reliability of volumetric measurements	56.32 to 147.40 mm ³ 55.68 to 129.86 mm ³	0.96-1.00* 0.97-1.00**
Chou et al. ³⁹	2017	Reproducibility of landmark identification	NR	0.99**
Singh et al. ⁴⁰	2005	Reproducibility of landmark identification	NR	NR
Hoefert et al. ⁴¹	2010	NR	NR	NR
*Inter-rater reliability **Intra-rater reliability Abbreviations: NR, Not Reported.				

Table 4. Reliability of the assessment methods

DISCUSSION

This review has comprehensively discussed the assessment methods for quantification of soft tissue changes subsequent to a surgical or orthopedic intervention on 3D facial surface images of cleft patients. Images were mainly acquired with 3D digital stereophotogrammetry, and to a lesser extent with laser surface scanning. There is a general interest for quantification of soft tissue changes of the lips, the nose, and the midface. The assessment of the 3D images is performed with landmark-dependent analyses, mostly supported with superimposition of the pre- and postoperative images. The reliability of these assessment methods is often not or insufficiently reported.

The literature search was performed using structured search strings in four main databases of health and life sciences and the study selection was performed by two reviewers experienced in the drafting of systematic reviews. The time period of the search was not restricted. Nevertheless, only papers published during the last 20 years appeared to be eligible. This time span corresponds quite accurately with the period that laser surface scanning and stereophotogrammetry have been used in cleft lip and palate research. The systematic search was based on English-language-dominated sources so language bias could not be ruled out. However, no eligible articles in other languages were identified through the search.

By writing this review, several methodological weaknesses of the included papers were inherently encountered. The quality assessment revealed inadequate or missing reporting of the following items: inclusion of consecutive patients, the loss to follow-up, sample size calculation, and unbiased assessment of the study endpoint. The inadequate reporting of the first three items might be explained by the rather limited incidence of CLP. The difficulties encountered in collecting an appropriate patient sample might have encouraged researchers to apply less stringent methodological criteria. Unbiased assessment of the study endpoint could not be achieved. Observers were aware if they were assessing pre- or postoperative images, so could not be blinded.

Relying on the reported image acquisition systems in this review, 3D digital stereophotogrammetry has gained popularity when compared to other technologies. It has proven to be an easy to use technology in cleft research^{19,20}, but it remains expensive to utilize in a low-income setting. Nevertheless, the introduction of compact, handheld systems is likely to further popularize stereophotogrammetry in the near future⁴⁷.

Despite the fact that the quality of the images has evolved enormously and that the use has become more accessible, no clear consensus on the quantification methods of soft tissue changes can be proposed on the basis of this systematic review. Soft tissue changes were quantified using linear, curvilinear, area, or volumetric measurements, whether or not following superimposition of pre- and postoperative images, and by using a wide variety of homologous, pseudo-, and semi-landmarks (Table 3). All the included studies used landmark-dependent analyses and introduce in this way subjectivity by the obligation to manually select these landmarks⁴⁸.

Operator biases caused by landmark identification could be ruled out by using a 3D anthropometric mask followed by robust superimposition⁴⁸⁻⁵⁰. This anthropometric mask is a surface template covering the facial area of interest and consists of about 10,000 uniformly sampled points (quasi-landmarks). The robust superimposition aligns the surface images and facilitates measurement of spatial differences between corresponding quasi-landmarks⁴⁹. This method has already been applied in a longitudinal research project to detect 3D growth trajectories in a non-cleft population⁵¹, so future use of this landmark-independent analysis in a cleft population could also facilitate the assessment of soft tissue changes. Nevertheless, this assessment strategy is labor-intensive and requires highly trained experts to process the 3D images⁵².

In the middle of these difficulties lies an opportunity in the development of a publicly available, user-friendly software application for 3D assessment. In this way, retrospective multicenter studies with the same assessment methodology (with low risk of bias) to evaluate therapeutic effects or to monitor growth can be set up. At their turn, these studies can be the blueprint of future research projects. The ultimate goal is the worldwide cross-comparison of therapeutic effects to design evidence-based guidelines for surgical and non-surgical interventions in CLP treatment as suggested in the Eurocleft and Americleft studies^{53,54}.

Availability of cleft patient data for research purposes could be improved by the implementation of an international database. In 2000, the WHO Human Genetics Programme suggested to establish a publicly accessible research database on the Internet. Next to epidemiological, speech/tympanometric, audiometric, and radiographic data, it would be essential to also promote the collection of 3D dental casts and 3D facial surfaces.

It can be concluded that soft tissue changes subsequent to a surgical or orthopedic intervention can be quantified on 3D surface images. Assessment methods are primarily based on landmark identification, whether or not followed by superimposition. Operator bias are inherently enclosed in landmark-dependent analyses. The reliability of these methods is insufficiently reported.

ACKNOWLEDGEMENTS

None

REFERENCES

1. Mossey P. A., Little J., Munger R. G., Dixon M. J., Shaw W. C. Cleft lip and palate. *Lancet* **2009**;374:1773-85.
2. Hennekam R. C. M., Allanson J. E., Krantz I. D. *Gorlin's Syndromes of the Head and Neck*. Oxford University Press, New York: **2010**.
3. Shi B., Losee J. E. The impact of cleft lip and palate repair on maxillofacial growth. *Int J Oral Sci* **2015**;7:14-7.
4. Li Y., Shi B., Song Q. G., Zuo H., Zheng Q. Effects of lip repair on maxillary growth and facial soft tissue development in patients with a complete unilateral cleft of lip, alveolus and palate. *J Craniomaxillofac Surg* **2006**;34:355-61.
5. Vander Woude D. L., Mulliken J. B. Effect of lip adhesion on labial height in two-stage repair of unilateral complete cleft lip. *Plast Reconstr Surg* **1997**;100:567-72; discussion 73-4.
6. Ezzat C. F., Chavarria C., Teichgraeber J. F., Chen J. W., Stratmann R. G., Gateno J., et al. Presurgical nasosilveolar molding therapy for the treatment of unilateral cleft lip and palate: a preliminary study. *Cleft Palate Craniofac J* **2007**;44:8-12.
7. Maull D. J., Grayson B. H., Cutting C. B., Brecht L. L., Bookstein F. L., Khorrambadi D., et al. Long-term effects of nasosilveolar molding on three-dimensional nasal shape in unilateral clefts. *Cleft Palate Craniofac J* **1999**;36:391-7.
8. Bennun R. D., Perandones C., Sepiarsky V. A., Chantiri S. N., Aguirre M. I., Dogliotti P. L. Nonsurgical correction of nasal deformity in unilateral complete cleft lip: a 6-year follow-up. *Plast Reconstr Surg* **1999**;104:616-30.

9. Gnoinski W. M., Rutz G. A longitudinal cephalometric study from age 5 to 18 years on individuals with complete bilateral cleft lip and palate. *J Craniofac Surg* **2009**;20 Suppl 2:1672-82.
10. Lisson J. A., Heib N., von Moeller S., Spitzer W. J., Ludwig B. Treatment results at 10, 15, and 18 years of age in patients with complete bilateral cleft lip and palate: an intercenter comparison. *Cleft Palate Craniofac J* **2013**;50:19-24.
11. Heidbuchel K. L., Kuijpers-Jagtman A. M., Freihofer H. P. Facial growth in patients with bilateral cleft lip and palate: a cephalometric study. *Cleft Palate Craniofac J* **1994**;31:210-6.
12. Kohout M. P., Aljaro L. M., Farkas L. G., Mulliken J. B. Photogrammetric comparison of two methods for synchronous repair of bilateral cleft lip and nasal deformity. *Plast Reconstr Surg* **1998**;102:1339-49.
13. Liou E. J., Subramanian M., Chen P. K. Progressive changes of columella length and nasal growth after nasoalveolar molding in bilateral cleft patients: a 3-year follow-up study. *Plast Reconstr Surg* **2007**;119:642-8.
14. Pai B. C., Ko E. W., Huang C. S., Liou E. J. Symmetry of the nose after presurgical nasoalveolar molding in infants with unilateral cleft lip and palate: a preliminary study. *Cleft Palate Craniofac J* **2005**;42:658-63.
15. Suri S., Utreja A., Khandelwal N., Mago S. K. Craniofacial computerized tomography analysis of the midface of patients with repaired complete unilateral cleft lip and palate. *Am J Orthod Dentofacial Orthop* **2008**;134:418-29.
16. Alonso N., Tanikawa D. Y., Freitas Rda S., Canan L., Jr., Ozawa T. O., Rocha D. L. Evaluation of maxillary alveolar reconstruction using a resorbable collagen sponge with recombinant human bone morphogenetic protein-2 in cleft lip and palate patients. *Tissue Eng Part C Methods* **2010**;16:1183-9.
17. Dickinson B. P., Ashley R. K., Wasson K. L., O'Hara C., Gabbay J., Heller J. B., et al. Reduced morbidity and improved healing with bone morphogenetic protein-2 in older patients with alveolar cleft defects. *Plast Reconstr Surg* **2008**;121:209-17.
18. Shirota T., Kurabayashi H., Ogura H., Seki K., Maki K., Shintani S. Analysis of bone volume using computer simulation system for secondary bone graft in alveolar cleft. *Int J Oral Maxillofac Surg* **2010**;39:904-8.
19. Heike C. L., Upson K., Stuhaug E., Weinberg S. M. 3D digital stereophotogrammetry: a practical guide to facial image acquisition. *Head Face Med* **2010**;6:18.
20. Lane C., Harrell W., Jr. Completing the 3-dimensional picture. *Am J Orthod Dentofacial Orthop* **2008**;133:612-20.

21. Ayoub A, Garrahy A, Hood C., White J., Bock M., Siebert J. P., et al. Validation of a vision-based, three-dimensional facial imaging system. *Cleft Palate Craniofac J* **2003**;40:523-9.
22. Brons S, van Beusichem M. E., Bronkhorst E. M., Draaisma J., Berge S. J., Maal T. J., et al. Methods to Quantify Soft-Tissue Based Facial Growth and Treatment Outcomes in Children: A Systematic Review. *Plos One* **2012**;7:
23. Kuijpers M. A., Chiu Y. T., Nada R. M., Carels C. E., Fudalej P. S. Three-dimensional imaging methods for quantitative analysis of facial soft tissues and skeletal morphology in patients with orofacial clefts: a systematic review. *PLoS One* **2014**;9:e93442.
24. Liberati A, Altman D. G., Tetzlaff J., Mulrow C., Gotzsche P. C., Ioannidis J. P., et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* **2009**;151:W65-94.
25. Slim K, Nini E., Forestier D., Kwiatkowski F., Panis Y., Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg* **2003**;73:712-6.
26. Zeng X, Zhang Y., Kwong J. S., Zhang C., Li S., Sun F., et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med* **2015**;8:2-10.
27. Schwenzer-Zimmerer K., Chaitidis D., Berg-Boerner I., Krol Z., Kovacs L., Schwenzer N. F., et al. Quantitative 3D soft tissue analysis of symmetry prior to and after unilateral cleft lip repair compared with non-cleft persons (performed in Cambodia). *J Craniomaxillofac Surg* **2008**;36:431-8.
28. Singh G. D., Levy-Bercowski D., Yanez M. A., Santiago P. E. Three-dimensional facial morphology following surgical repair of unilateral cleft lip and palate in patients after nasoalveolar molding. *Orthod Craniofac Res* **2007**;10:161-6.
29. Devlin M. F., Ray A., Raine P., Bowman A., Ayoub A. F. Facial symmetry in unilateral cleft lip and palate following alar base augmentation with bone graft: a three-dimensional assessment. *Cleft Palate Craniofac J* **2007**;44:391-5.
30. Kau C. H., Medina L., English J. D., Xia J., Gateno J., Teichgraber J. A comparison between landmark and surface shape measurements in a sample of cleft lip and palate patients after secondary alveolar bone grafting. *Orthodontics (Chic.)* **2011**;12:188-95.
31. Krimmel M., Schuck N., Bacher M., Reinert S. Facial surface changes after cleft alveolar bone grafting. *J Oral Maxillofac Surg* **2011**;69:80-3.

32. McCance A. M., Moss J. P., Fright W. R., Linney A. D., James D. R. Three-dimensional analysis techniques--Part 1: Three-dimensional soft-tissue analysis of 24 adult cleft palate patients following Le Fort I maxillary advancement: a preliminary report. *Cleft Palate Craniofac J* **1997**;34:36-45.
33. Stewart A., McCance A. M., James D. R., Moss J. P. Three-dimensional nasal changes following maxillary advancement in cleft patients. *Int J Oral Maxillofac Surg* **1996**;25:171-7.
34. Susarla S. M., Berli J. U., Kumar A. Midfacial volumetric and upper lip soft tissue changes after Le Fort I advancement of the cleft maxilla. *J Oral Maxillofac Surg* **2015**;73:708-18.
35. Nakamura N., Okawachi T., Matsumoto K., Kimura N., Kibe T., Fuchigami T. Clinical and 3-Dimensional Analyses of Nasal Forms After Secondary Correction of Cleft Lip-Nose Deformities Using Extended Spreader Cartilage Graft With a Cross-Lap Joint Technique. *J Oral Maxillofac Surg* **2016**;74:1465.e1-.e21.
36. Nakamura N., Okawachi T., Nozoe E., Nishihara K., Matsunaga K. Three-dimensional analyses of nasal forms after secondary treatment of bilateral cleft lip-nose deformity in comparison to those of healthy young adults. *J Oral Maxillofac Surg* **2011**;69:e469-81.
37. Okawachi T., Nozoe E., Nishihara K., Nakamura N. 3-dimensional analyses of outcomes following secondary treatment of unilateral cleft lip nose deformity. *J Oral Maxillofac Surg* **2011**;69:322-32.
38. van Loon B., Maal T. J., Plooi J. M., Ingels K. J., Borstlap W. A., Kuijpers-Jagtman A. M., et al. 3D Stereophotogrammetric assessment of pre- and postoperative volumetric changes in the cleft lip and palate nose. *Int J Oral Maxillofac Surg* **2010**;39:534-40.
39. Chou P. Y., Hallac R. R., Ajiwe T., Xie X. J., Liao Y. F., Kane A. A., et al. The role of Nasoalveolar molding: A 3D Prospective analysis. *Sci Rep* **2017**;7:9901.
40. Singh G. D., Levy-Bercowski D., Santiago P. E. Three-dimensional nasal changes following nasoalveolar molding in patients with unilateral cleft lip and palate: geometric morphometrics. *Cleft Palate Craniofac J* **2005**;42:403-9.
41. Sade Hoefert C., Bacher M., Herberts T., Krimmel M., Reinert S., Goz G. 3D soft tissue changes in facial morphology in patients with cleft lip and palate and class III mal occlusion under therapy with rapid maxillary expansion and delaire facemask. *J Orofac Orthop* **2010**;71:136-51.
42. Liang S., Shapiro L., Tse R. Measuring Symmetry in Children With Cleft Lip. Part 3: Quantifying Nasal Symmetry and Nasal Normalcy Before and After Unilateral Cleft Lip Repair. *Cleft Palate Craniofac J* **2016**;
43. Wu J., Liang S., Shapiro L., Tse R. Measuring Symmetry in Children With Cleft Lip. Part 2: Quantification of Nasolabial Symmetry Before and After Cleft Lip Repair. *Cleft Palate Craniofac J* **2016**;53:705-13.

44. Alazzawi O, Morioka D, Miyabe M, Tosa Y, Ohkubo F, Yoshimoto S. Nasolabial Growth in Individuals With Unilateral Cleft Lip and Palate: A Preliminary Study of Longitudinal Observation Using Three-Dimensional Stereophotogrammetry. *J Craniofac Surg* **2017**;28:e449-e51.
45. Davidson E, Kumar A. R. A Preliminary Three-Dimensional Analysis of Nasal Aesthetics Following Le Fort I Advancement in Patients With Cleft Lip and Palate. *J Craniofac Surg* **2015**;26:e629-33.
46. Da Silveira A. C., Daw J. L., Jr., Kusnoto B, Evans C, Cohen M. Craniofacial applications of three-dimensional laser surface scanning. *J Craniofac Surg* **2003**;14:449-56.
47. Knoops P. G., Beaumont C. A., Borghi A, Rodriguez-Florez N, Breakey R. W., Rodgers W., et al. Comparison of three-dimensional scanner systems for craniomaxillofacial imaging. *J Plast Reconstr Aesthet Surg* **2017**;70:441-9.
48. Claes P, Walters M, Vandermeulen D, Clement J. G. Spatially-dense 3D facial asymmetry assessment in both typical and disordered growth. *J Anat* **2011**;219:444-55.
49. Claes P, Walters M, Clement J. Improved facial outcome assessment using a 3D anthropometric mask. *Int J Oral Maxillofac Surg* **2012**;41:324-30.
50. Claes P, Daniels K, Walters M, Clement J, Vandermeulen D, Suetens P. Dymorphometrics: the modelling of morphological abnormalities. *Theor Biol Med Model* **2012**;9:5.
51. Matthews H. S., Penington A. J., Hardiman R, Fan Y, Clement J. G., Kilpatrick N. M., et al. Modelling 3D craniofacial growth trajectories for population comparison and classification illustrated using sex-differences. *Sci Rep* **2018**;8:4771.
52. Fan Y, Matthews H, Kilpatrick N, Claes P, Clement J, Penington A. Facial morphology and growth following surgery for congenital midline cervical cleft patients. *Int J Oral Maxillofac Surg* **2018**;47:437-41.
53. Russell K, Long R. E., Jr., Hathaway R, Daskalogiannakis J, Mercado A, Cohen M, et al. The Americleft study: an inter-center study of treatment outcomes for patients with unilateral cleft lip and palate part 5. General discussion and conclusions. *Cleft Palate Craniofac J* **2011**;48:265-70.
54. Shaw W. C., Brattstrom V, Molsted K, Prahll-Andersen B, Roberts C. T., Semb G. The Eurocleft study: intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 5: discussion and conclusions. *Cleft Palate Craniofac J* **2005**;42:93-8.

6.

THE EFFECT OF AUTOLOGOUS ALVEOLAR BONE GRAFTING ON NASOLABIAL ASYMMETRY IN UNILATERAL CLEFT LIP AND PALATE

Thierens LAM, Kerckhof E, De Roo NMC, Temmerman L, Nadjmi N, Swennen G, Ortega-Castrillon A, Claes P, and De Pauw GAM. *J Craniofac Surg* **2020**;31:1687-91.

ABSTRACT

The objective of this study was to examine whether an autologous alveolar bone graft has an effect on the nasolabial asymmetry in unilateral cleft lip, alveolus, and palate. Fifteen children (mean age 7.5 ± 2.4 years) with non-syndromic unilateral cleft lip and palate (CLP) were included. Non-ionizing three-dimensional surface images were acquired prior to and three months after the alveolar bone grafting procedure. A 2D and a landmark-independent 3D asymmetry assessment were used to detect changes of asymmetry in the nasolabial area. For the 2D assessment, a cleft and non-cleft side ratio for 4 linear nasal and 2 linear labial distances was expressed as a Coefficient of Asymmetry (CA). The 3D asymmetry assessment comprised a robust superimposition of the face with its mirror image, expressed as a root-mean-square-error (RMSE) in mm. A significant decrease in the CA for the labial distance from the facial midline to the labial commissure was observed ($P=0.036$). Also, the CA for the labial distance from the facial midline to the highest point of Cupid's bow increased significantly ($P=0.028$). Non-significant changes were observed for the CA for the 2 nasal distances and the 2 other labial distances. No significant changes in 3D nasal asymmetry were detected ($P=0.820$). Alveolar bone grafting completes the alveolar ridge but has only little to no clinical effect on the asymmetry of the secondary cleft lip nasal deformity.

Keywords: facial asymmetry, unilateral cleft lip and palate, alveolar bone grafting, non-ionizing three-dimensional surface imaging, superimposition

INTRODUCTION

Facial attractiveness plays a major role in the social life and in the interaction among individuals¹. Attractive people experience benefits within today's society, are more popular, and are regarded as having more positive qualities and abilities than their less attractive counterparts². Despite the speed of decision-making about attractiveness, the process of judging facial appearance is complex³. It is advocated that facial attractiveness is only weakly correlated with the golden proportions of different parts of facial morphology or other facial ratios and angles^{4,5}. Moreover, it is claimed that facial attractiveness is profoundly influenced by two main characteristics. Next to symmetry there is averageness, referring to how closely a face resembles the majority of other faces within a population; non-average faces have more extreme characteristics than the average of a population^{6,7}.

Individuals with cleft lip and palate (CLP) often express dissatisfaction with their facial appearance and show emotional distress as they were frequently confronted with negative comments during childhood and adolescence^{8,9}. Persons with CLP are looked at differently, as proven by eye tracking¹⁰. Symmetry in the nasolabial area of individuals with CLP is distorted and several surgical and non-surgical interventions have been considered to improve this asymmetry. In this respect, beneficial effects have been attributed to alveolar bone grafting regarding nasolabial symmetry¹¹⁻¹⁴, upper lip length¹⁵, and the position of the nostril at the cleft side¹⁴⁻¹⁶, or might have no effect at all¹⁷. Although the numerous research projects about this topic, conclusions were not unanimous.

Two-dimensional assessment on clinical photographs allows the quantification of nasolabial morphology and asymmetry¹⁴⁻¹⁶. This approach only requires a (digital) single-lens reflex (SLR) camera in a standardized set-up. However, considerable significant data is lost when 3D anomalies are quantified using 2D assessment method. Non-ionizing 3D surface images such as laser surface scanning or stereophotogrammetry can address these shortcomings and can allow for the analysis of the full three-dimensional content.

The objective of this study was to examine whether an autologous alveolar bone graft has an influence on the nasolabial asymmetry in unilateral cleft lip, alveolus, and palate using a two-dimensional and a three-dimensional assessment method.

MATERIALS AND METHODS

The study was approved by the respective Ethics Committees (Belgian reference number: B670201629060) and is in accordance with the Declaration of Helsinki. The participants of this study provided written informed consent.

Subjects and intervention

Caucasian children with unilateral cleft lip, alveolus, and palate requiring a bone graft to complete the alveolar ridge were included in this study. Patients with syndromes or systemic disorders were not included. Collapsed alveolar ridges were restored prior to the autologous alveolar bone grafting with a bonded or removable expander. The bone grafting procedure was performed under general

anesthesia. The iliac crest of the contralateral side was used as donor site. The graft was a combination of cancellous and cortical bone and was placed up to the piriform rim so that its surface was elevating the nasal floor mucosa.

Imaging

Nasolabial asymmetry was evaluated on digital 2D and 3D images. Imaging was performed with a surface laser scanner or a stereophotogrammetric camera. The laser surface scanner (Planmeca Proface®, Planmeca Oy, Helsinki, Finland) consists of 2-high resolution cameras and an eye-safe Class I laser with a scanning time of 10 seconds. The data were reconstructed by Planmeca Romexis® 3.0.1 software. The stereophotogrammetric camera (Vectra®M3 Canfield, Parsippany, USA) has six cameras capturing images in 3.5 milliseconds. The six images were reconstructed into one 3D image in Vectra® Capture Module (Canfield, Parsippany, USA). Before imaging, glasses were removed, and hair was tightened up. Patients were positioned in the natural head position and were instructed to avoid any movement during scanning. They were also instructed to show a neutral facial expression and to avoid conscious tension of the facial musculature. Frontal clinical photographs were hard to standardize over the different centers, so 2D images were extracted from the 3D images in both the cleft and control group. Imaging was performed prior to (T0) and three months after (T1) the alveolar bone grafting.

Assessment of nasolabial asymmetry

The **two-dimensional nasolabial asymmetry assessment** was performed as described by Fudalej and coworkers¹⁸. It was previously applied to a comparable study group and showed good intra-observer reliability. A framework with three reference lines was created. The intercanthal line was used as a horizontal reference line (H1). A horizontal line H2, parallel to H1 and through point subnasale, and a vertical line V, perpendicular to H1 and H2 and intersecting H1 and H2 at the midpoint between inner canthi. Figure 1 shows the framework and the measured distances a, b, c, d, e, and f. Each measurement was made on both cleft and non-cleft sides. The Coefficient of Asymmetry (CA) for each variable was noted as 'A' for distance 'a', 'B' for distance 'b'... and was calculated according to the following formula:

$$\text{Coefficient of asymmetry (\%)} = [(\text{non-cleft side}) - (\text{cleft side}) / \text{non-cleft side}] \times 100$$

Asymmetry is therefore expressed as a proportion of the difference in measurements between sides relative to a measurement on the non-cleft side.

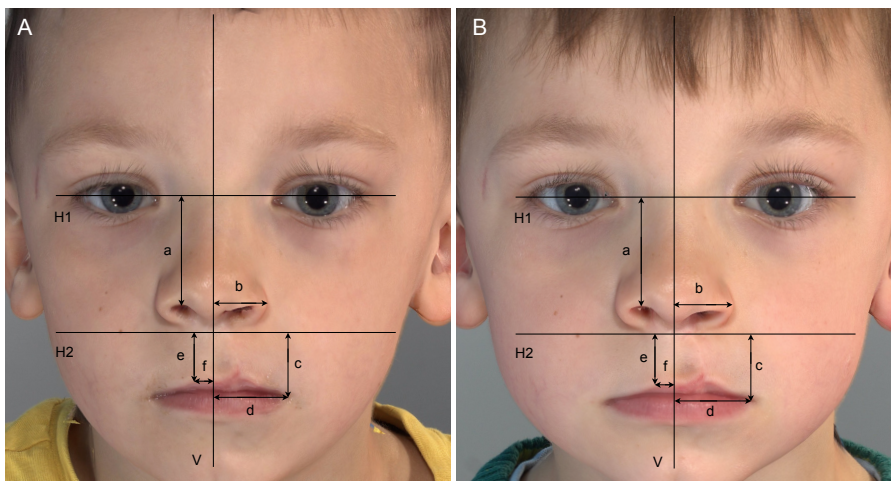


Figure 1. Anthropometric measurements made on a frontal photograph, before (A) and after (B) alveolar bone grafting; H1 = horizontal reference line passing through Inner canthi (Intercanthal line); H2 = reference line parallel to H1 passing through soft tissue point subnasale; V = reference line perpendicular to H1 and H2; intersecting H1 and H2 at the midpoint between Inner canthi; a = distance from H1 to the highest point on the contour of the nares between the nasal tip and ala; b = distance from V to the furthest from midline point on the ala; c = distance from H2 to labial commissure; d = distance from V to labial commissure; e = distance from H2 to the highest point of Cupid's bow (crista philtri); and f = distance from V to the highest point of Cupid's bow (crista philtri).

The **three-dimensional nasal asymmetry assessment** was performed using an established superimposition protocol for comparison of a face with its mirror image. This technique allows accurate and comprehensive quantification of biological phenotypes using an accurate and reliable superimposition technique¹⁹. Spatially-dense localization of asymmetries was achieved using an anthropometric mask consisting of uniformly sampled quasi-landmarks that were automatically indicated on 3D facial images¹⁹. After robust, least-squares superimposition of the face with its mirror image, the magnitude of spatial discrepancies between corresponding quasi-landmarks was calculated²⁰⁻²². The degree of asymmetry was expressed using a root-mean-squared-error (RMSE) (mm). A color map of superimposed pre- and postoperative images was generated for the

visualization of the soft tissue changes (Figure 2). Signed color maps were analyzed by direct observations and by using data provided by accompanying histograms with a color range from -2.5 mm (blue) to +2.5 mm (yellow).

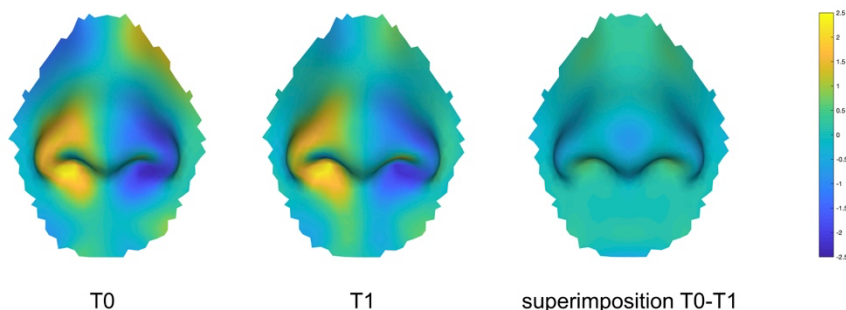


Figure 2. Color maps of the preoperative (T0) and postoperative (T1) nasal region. The image at the right side represents the superimposition of T0 and T1 and therefore the actual soft tissue changes. The colours range from -2.5 mm (blue) to +2.5 mm (yellow).

Statistical analysis was performed with SPSS 25 (IBM, Armonk, New York, USA). Intraclass Correlation Coefficients (ICC's) were calculated to determine the intra-examiner agreement by reassessing ten randomly selected images with an interval of four weeks. The pre- and postsurgical CA of the anthropometric measurements on 2D images and the pre- and postsurgical RMSE value (mm) measured on the 3D images were not normally distributed. Therefore, these data were analyzed with a non-parametric Wilcoxon signed ranked test.

RESULTS

A sample of 15 children with unilateral cleft lip, alveolus, and palate was included in this study. The mean age was 7.5 (± 2.4) years. The proportion of boys to girls was 9:6. The majority of the clefts were left-oriented (10/15).

The intra-examiner agreement for the six measurements of the 2D assessment is shown in Table 1. The ICC's ranged from 0.735 (0.442-0.886) up to 0.932 (0.838-0.972), indicating a good to very good agreement²³.

	ICC	95% CI (Lower-upper bound)	p
CA A	0.825	0.612 – 0.027	< 0.001
CA B	0.909	0.786 – 0.963	< 0.001
CA C	0.841	0.642 – 0.934	< 0.001
CA D	0.932	0.838 – 0.972	< 0.001
CA E	0.735	0.442 – 0.886	< 0.001
CA F	0.895	0.754 – 0.957	< 0.001
ICC, Intraclass Correlation Coefficient; CI, Confidence Interval; lower-upper bound, lower and upper confidence interval limits; p, level of significance; CA, Coefficient of Asymmetry			

Table 1. Intra-examiner agreement of the 2D assessment

Table 2 shows the medians, 25th and 75th percentiles of the **2D assessment**. Children showed no significant change in the CA for distance a, b, c, and e after the alveolar bone grafting. The CA for distance d decreased significantly after the intervention (P= 0.036). In contrast, the CA for distance f increased significantly (P=0.028).

		T0			T1				
		Percentiles			Percentiles				
		25 th	50 th (median)	75 th	25 th	50 th (median)	75 th		
2D	CA A	-6.06	-2.63	0.00	-6.25	-2.78	-1.28	-0.114	0.910
	CA B	-4.55	9.80	18.52	-2.17	6.98	16.33	-0.170	0.865
	CA C	-1.79	1.52	5.08	-1.92	0.00	4.65	-0.245	0.807
	CA D	-12.96	-6.25	3.45	-4.41	-1.72	9.68	-2.101	0.036
	CA E	0.00	4.76	16.00	2.63	6.25	18.18	-1.503	0.133
	CA F	-25.00	-12.50	25.00	-40.00	-13.33	18.75	-2.203	0.028
3D	RMSE (mm)	0.99	1.29	1.54	1.03	1.28	1.45	-0.227	0.820
T0, preoperative; T1, postoperative; Z, Z-value; p, level of significance; CA, Coefficient of Asymmetry; RMSE, Root Mean Square Error; mm, millimetre.									

Table 2. Comparative statistics of the 2D and 3D asymmetry assessment

The relationships between the pre- and postoperative measurements for all six parameters of the 2D assessment are visualized by means of scatterplots in Figure 3.

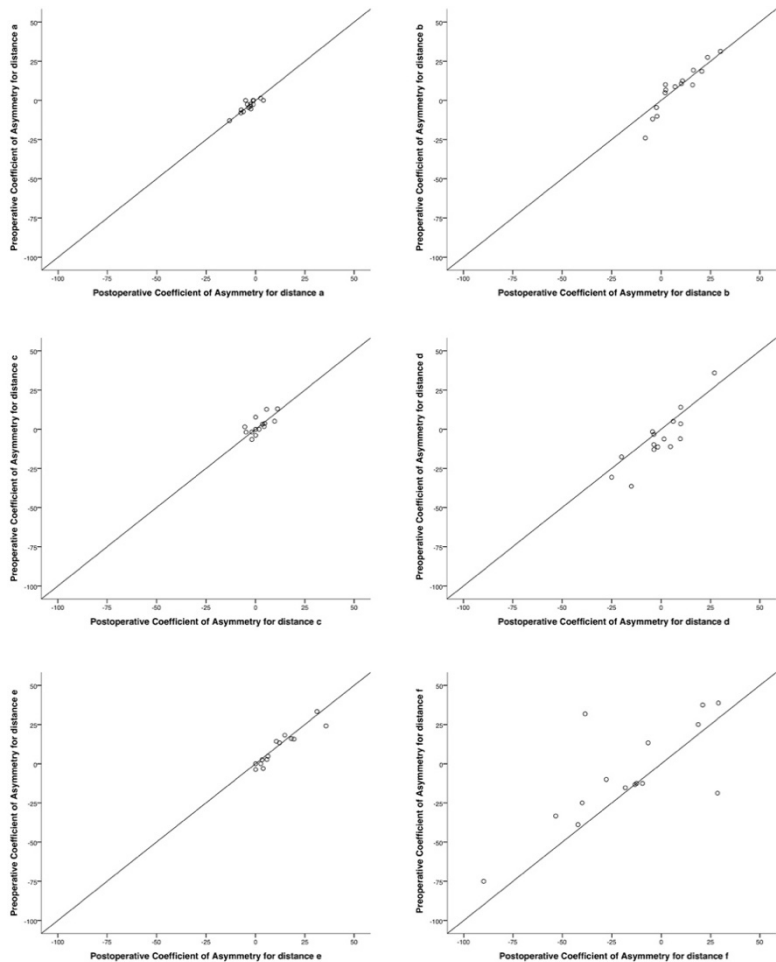


Figure 3. Scatterplots representing the relationship of the pre- (T0) and postoperative (T1) measurements of the 6 parameters (CA for distance a-f) of the 2D assessment. Improvement of the CA for distance d and deterioration of the CA for distance e could be observed.

The **3D assessment** detected no significant changes in nasal asymmetry ($P= 0.820$) (Table 2). The median RMSE (25th-75th percentile) of T0 was 1.29 mm (0.99 mm - 1.54 mm). The median RMSE after the alveolar bone grafting was 1.28 mm (1.03 mm - 1.45 mm), so it remained quasi unchanged. This is visualized by means of a scatterplot in Figure 4.

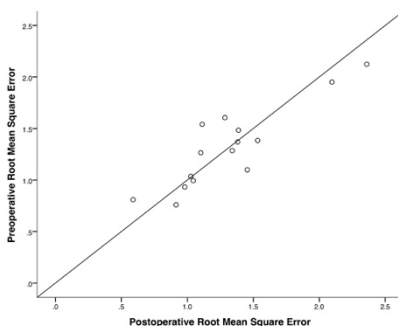


Figure 4. Scatterplot representing the relationship of the pre- and postoperative measurements of the 3D assessment. No significant changes could be observed.

DISCUSSION

The nasolabial area is the part of the cleft face that is rated as the least attractive by affected adolescents^{24,25}. This secondary cleft lip nasal deformity is defined as those distortions that persist despite primary operative maneuvers. It is a result of failure to correct, undercorrection, or relapse²⁶. Unilateral deformities are characterized by a short hemicolumella, a flattened nostril, a wide alar base, and an inferiorly/posteriorly displaced alar root on the cleft side. Also, an asymmetric nasal tip with relatively more projection and definition on the non-cleft side can be observed²⁶. Claims have been made that alveolar bone grafting, besides completion of the alveolar ridge, also improves one or more characteristics of the secondary cleft lip nasal deformity¹¹⁻¹⁶. Therefore, this study investigated the effect of alveolar bone grafting on the asymmetry of the secondary cleft lip nasal deformity.

The assessment of the pre- and postoperative data did not show significant improvement of the nasal asymmetry. The 2D assessment showed no significant changes for CA for distance a ($P=0.910$) and b ($P=0.865$). Similarly, the 3D assessment was unable to detect significant differences measured on the soft tissues ($P=0.820$). On the other hand, labial asymmetry demonstrated significant improvement for the distance between V and the labial commissure and significant worsening for the distance between V and the crista philtrum.

However, these labial changes in the horizontal plane should be interpreted with caution. Minor differences in facial expression such as a little laugh or muscle tension might have affected the position of the anthropometric landmarks. Darby et al. investigated the effect of smiling on facial asymmetry in non-cleft adults and concluded that overall facial asymmetry increased in magnitude from rest to natural and to maximum smile²⁷. Similarly, Al-Rudainy et al. investigated the effect of facial expression on facial asymmetry in a sample of 4-year-old children with a repaired UCLP. They concluded, similarly to Darby et al., that the residual facial asymmetry was accentuated at maximum smile^{27,28}. Therefore, it is of the utmost importance to minimize the effect of facial expression and to standardize image acquisition. Children should be provided with clear and detailed instructions about their facial expression. Also, multiple images (repeated measures) with the same facial expression should be acquired. Subsequently, these images can be used to create an averaged composite image. This should enhance the reproducibility of the method.

Generally, previous research concerning this topic concluded that nasal and/or labial asymmetry improved after an alveolar bone graft^{11-13,15}. In contrast, Sander et al. did not observe any significant improvement of the nasal asymmetry¹⁷. The findings of the latter study are in accordance with our findings. The mean preoperative (T0) and postoperative (T1) RSME in the study of Sander et al. were 1.18 ± 0.33 mm and 1.09 ± 0.40 mm respectively, indicating a slight, but non-significant improvement. The median (25th-75th percentile) preoperative (T0) and postoperative (T1) RSME in the current study were 1.29 mm (0.99 mm - 1.54 mm) and 1.28 mm (1.03 mm - 1.45 mm) respectively, indicating a slight and non-significant deterioration. The conclusions of all aforementioned studies were based on landmark-dependent analyses performed on conventional photographs¹⁵ or 3D surfaces images^{11-13,17}. These landmark-dependent analyses are more prone to bias than 3D shape analysis with an automated mapping strategy²⁹. The robust superimposition (modification of Procrustes superimposition) as used in the current study achieves a more accurate result than the best-fit

method²². However, manual landmark selection and subsequent construction of reference structures such as in the 2D assessment of the current study also inherently incorporates operator bias. Minimal deviations of the facial midline or 2 horizontal reference lines might have affected the coefficients of asymmetry.

The timing of the postoperative image acquisition has a dual explanation. First, the optimal follow-up period is determined by the intersection of minimal facial growth and maximal resolution of postoperative edema. In this way, the net effect of the procedure on the asymmetry of the nose and lips can be extracted. However, the complete resolution of facial edema after alveolar bone grafting over time has not been thoroughly investigated. Pavri et al. investigated this aspect following rhinoplasty and observed only a two-third decrease at 1 month and 95 percent decrease at six months³⁰. Taking into account that the current study investigated growing individuals, the follow-up period of three months in the current study should represent this adequate intersection. Secondly, the appointment three months postoperatively is standard after an alveolar bone grafting, so it was not necessary to burden the parents with extra appointments. The follow-up period of 3 months is in contrast with previous research reporting postoperative image acquisition at 6 weeks, 6 months, or 12 months^{11-13,15,17}.

The three-dimensional images acquired for this study enable a static asymmetry assessment. However, the lips and nose are dynamic anatomic regions during social interactions. Asymmetry of motion initiation and form might add supplementary understanding to the perception of facial asymmetry³¹. Three-dimensional motion capture systems (often referred to as 4D imaging or dynamic facial imaging) acquire up to 60 frames per second and allows quantification of changes in facial movement over time³². Hallac et al. quantified the asymmetry of facial movements in (pre)adolescents with cleft lip and/or palate. It was observed that individuals with a cleft lip have an increased facial asymmetry during voluntary smile and during a lip pucker with maximal orbicularis oris contraction. Despite the surgical lip repair, the motion path shape during the expressions was more asymmetric in comparison to non-affected individuals³¹.

The pre-operative (and also the post-operative) asymmetry of the nose and lips of this study sample was in the range of a similar study using the same 2D methodology¹⁸. Therefore, taking into account the limited effect of the alveolar bone graft on the asymmetry of the secondary cleft lip nasal deformity, surgical revision can be recommended after further craniofacial growth. Cleft patients and

their parents should be aware of this. Generally, it is recommended that a secondary correction of the cleft lip nasal deformity, if required, is performed during young adulthood and after any orthognathic correction. Major deformities in children with functional or psychological problems might form an exemption to this²⁶.

CONCLUSIONS

Overall, alveolar bone grafting did not significantly improve the asymmetry of the secondary cleft nose deformity. Only 2 horizontal parameters detecting labial asymmetry showed discrete significant changes. However, the clinical relevance of the latter is considered limited.

ACKNOWLEDGEMENTS

The authors would like to thank Ms. Lies Pottel and Ms. Elke Van de Castelee for their support with the data collection and analysis; Dr. Stefanie De Buyser for the statistical analyses; and in extent, all children and parents participating in this study.

REFERENCES

1. Jacobson A. Psychological aspects of dentofacial esthetics and orthognathic surgery. *Angle Orthod* **1984**;54:18-35.
2. Urbanova W., Brudnicki A., Strydom H., Bronkhorst E. M., Katsaros C., Fudalej P. S. Nasolabial aesthetics correlates poorly with skeletal symmetry in unilateral cleft lip and palate. *J Plast Reconstr Aesthet Surg* **2013**;66:e1-7.
3. Meyer-Marcotty P., Alpers G. W., Gerdes A. B., Stellzig-Eisenhauer A. Impact of facial asymmetry in visual perception: a 3-dimensional data analysis. *Am J Orthod Dentofacial Orthop* **2010**;137:168 e1-8; discussion -9.
4. Kiekens R. M., Kuijpers-Jagtman A. M., van 't Hof M. A., van 't Hof B. E., Maltha J. C. Putative golden proportions as predictors of facial esthetics in adolescents. *Am J Orthod Dentofacial Orthop* **2008**;134:480-3.

5. Kiekens R. M., Kuijpers-Jagtman A. M., van 't Hof M. A., van 't Hof B. E., Straatman H., Maltha J. C. Facial esthetics in adolescents and its relationship to "ideal" ratios and angles. *Am J Orthod Dentofacial Orthop* **2008**;133:188 e1-8.
6. Thornhill R., Gangestad S. W. Human facial beauty : Averageness, symmetry, and parasite resistance. *Hum Nat* **1993**;4:237-69.
7. Rhodes G., Yoshikawa S., Clark A., Lee K., McKay R., Akamatsu S. Attractiveness of facial averageness and symmetry in non-western cultures: in search of biologically based standards of beauty. *Perception* **2001**;30:611-25.
8. Thomas P. T., Turner S. R., Rumsey N., Dowell T., Sandy J. R. Satisfaction with facial appearance among subjects affected by a cleft. *Cleft Palate Craniofac J* **1997**;34:226-31.
9. Turner S. R., Thomas P. W., Dowell T., Rumsey N., Sandy J. R. Psychological outcomes amongst cleft patients and their families. *Br J Plast Surg* **1997**;50:1-9.
10. Meyer-Marcotty P., Gerdes A. B., Reuther T., Stellzig-Eisenhauer A., Alpers G. W. Persons with cleft lip and palate are looked at differently. *J Dent Res* **2010**;89:400-4.
11. Devlin M. F., Ray A., Raine P., Bowman A., Ayoub A. F. Facial symmetry in unilateral cleft lip and palate following alar base augmentation with bone graft: a three-dimensional assessment. *Cleft Palate Craniofac J* **2007**;44:391-5.
12. Kau C. H., Medina L., English J. D., Xia J., Gateno J., Teichgraber J. A comparison between landmark and surface shape measurements in a sample of cleft lip and palate patients after secondary alveolar bone grafting. *Orthodontics (Chic.)* **2011**;12:188-95.
13. Krimmel M., Schuck N., Bacher M., Reinert S. Facial surface changes after cleft alveolar bone grafting. *J Oral Maxillofac Surg* **2011**;69:80-3.
14. Lee W., Park H. J., Choi H. G., Shin D. H., Uhm K. I. Nostril base augmentation effect of alveolar bone graft. *Arch Plast Surg* **2013**;40:542-5.
15. Kim S. W., Park S. O., Choi T. H., Hai do T. Change in upper lip height and nostril sill after alveolar bone grafting in unilateral cleft lip alveolus patients. *J Plast Reconstr Aesthet Surg* **2012**;65:558-63.
16. Wu Y., Wang G., Yang Y., Zhang Y. Influence of alveolar-bone grafting on the nasal profile: unilateral cleft lips, alveoli, and palates. *J Craniofac Surg* **2010**;21:1904-7.
17. Sander M., Daskalogiannakis J., Tompson B., Forrest C. Effect of alveolar bone grafting on nasal morphology, symmetry, and nostril shape of patients with unilateral cleft lip and palate. *Cleft Palate Craniofac J* **2011**;48:20-7.

18. Fudalej P., Katsaros C., Hozyasz K., Borstlap W. A., Kuijpers-Jagtman A. M. Nasolabial symmetry and aesthetics in children with complete unilateral cleft lip and palate. *Br J Oral Maxillofac Surg* **2012**;50:621-5.
19. White J. D., Ortega-Castrillon A., Matthews H., Zaidi A. A., Ekrami O., Snyders J., et al. MeshMonk: Open-source large-scale intensive 3D phenotyping. *Sci Rep* **2019**;9:6085.
20. Claes P., Daniels K., Walters M., Clement J., Vandermeulen D., Suetens P. Dymorphometrics: the modelling of morphological abnormalities. *Theor Biol Med Model* **2012**;9:5.
21. Claes P., Walters M., Clement J. Improved facial outcome assessment using a 3D anthropometric mask. *Int J Oral Maxillofac Surg* **2012**;41:324-30.
22. Claes P., Walters M., Vandermeulen D., Clement J. G. Spatially-dense 3D facial asymmetry assessment in both typical and disordered growth. *J Anat* **2011**;219:444-55.
23. Altman D. G. *Practical Statistics for Medical Research*. Chapman and Hall, London: **1991**.
24. Semb G., Brattstrom V., Molsted K., Prah-Andersen B., Zuurbier P., Rumsey N., et al. The Eurocleft study: intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 4: relationship among treatment outcome, patient/parent satisfaction, and the burden of care. *Cleft Palate Craniofac J* **2005**;42:83-92.
25. Shaw W. C., Brattstrom V., Molsted K., Prah-Andersen B., Roberts C. T., Semb G. The Eurocleft study: intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 5: discussion and conclusions. *Cleft Palate Craniofac J* **2005**;42:93-8.
26. Allori A. C., Mulliken J. B. Evidence-Based Medicine: Secondary Correction of Cleft Lip Nasal Deformity. *Plast Reconstr Surg* **2017**;140:166e-76e.
27. Darby L. J., Millett D. T., Kelly N., McIntyre G. T., Cronin M. S. The effect of smiling on facial asymmetry in adults: a 3D evaluation. *Aust Orthod J* **2015**;31:132-7.
28. Al Rudainy D., Ju X., Mehendale F., Ayoub A. The effect of facial expression on facial symmetry in surgically managed unilateral cleft lip and palate patients (UCLP). *J Plast Reconstr Aesthet Surg* **2019**;72:273-80.
29. Thierens L. A. M., De Roo N. M. C., De Pauw G. A. M., Brusselaers N. Assessment modalities of non-ionizing three-dimensional images for the quantification of facial morphology, symmetry, and appearance in cleft lip and palate: a systematic review. *Int J Oral Maxillofac Surg* **2018**;47:1095-105.
30. Pavri S., Zhu V. Z., Steinbacher D. M. Postoperative Edema Resolution following Rhinoplasty: A Three-Dimensional Morphometric Assessment. *Plast Reconstr Surg* **2016**;138:973e-9e.

31. Hallac R. R., Feng J., Kane A. A., Seaward J. R. Dynamic facial asymmetry in patients with repaired cleft lip using 4D imaging (video stereophotogrammetry). *Journal of Cranio-Maxillofacial Surgery* **2017**;45:8-12.
32. Popat H., Richmond S., Benedikt L., Marshall D., Rosin P. L. Quantitative analysis of facial movement-
-a review of three-dimensional imaging techniques. *Comput Med Imaging Graph* **2009**;33:377-83.

A RETROSPECTIVE RADIOGRAPHIC
ASSESSMENT OF SKELETAL
MATURATION DURING
PREADOLESCENCE IN PATIENTS WITH A
CLEFT LIP AND/OR PALATE.

Thierens LAM, Manalili L, De Roo NMC, Verdonck A, Cadenas de Llano-Pérula M, and De Pauw GAM. *(submitted to Clin Oral Investig)*

7.

ABSTRACT

Objectives: Aberrant growth of the maxillomandibular complex in patients with cleft lip and/or palate (CL/P) can be managed with dentofacial orthopaedics. However, no consensus has been reached regarding timing and evolution of the maturational stages. Therefore, the aim of this study is to determine if patients with CL/P have an increased risk for delayed craniofacial maturation.

Materials and Methods: A sample of 246 cleft patients and 210 non-affected individuals was retrospectively compiled. Cephalometric radiographs taken between the ages of 10 and 14 years (girls) and 12 and 16 years (boys) were collected and assessed with the Cervical Vertebral Maturation (CVM) method.

Results: In boys, no significant association between the presence of CL/P and a CVM score of CS3 or higher was observed in any age subsample. This was similar for a CVM score of CS5 or higher. Girls in the CL/P group had a significant lower predicted probability of having a CVM score of at least CS3 in the subsample with age 11 to 12 ($P = 0.001$) and a borderline non-significant lower predicted probability of having a CVM score of at least CS5 in the subsample with age 12 to 13 ($P = 0.055$).

Conclusions: The current study demonstrated a discrete delay in skeletal maturation before the pubertal growth spurt of (pre)adolescents with CL/P, especially girls. This delay was less apparent at the end of the pubertal growth spurt.

Clinical relevance: It is of utmost importance to identify each patient's individual maturational status in order to determine the optimal timing for treatment with dentofacial orthopaedics.

Keywords: cleft lip and/or palate, CVM, skeletal maturation, dentofacial orthopaedics

INTRODUCTION

Orofacial clefts (OFC's) arise in about 1.7 per 1000 live born babies¹. These birth defects entail an undeniable impact on the children's Quality of Life². Despite the substantial therapeutic advances during the last decades, orofacial clefts are still associated with difficulties concerning speech, hearing, dental function and esthetics, and facial appearance¹.

The growth of the maxilla in adolescents with cleft lip and/or palate (CL/P) can be restricted in three dimensions. This can be attributed to the severity of the cleft but also to iatrogenic effects of previous

surgeries such as closure of the lip and/or palate. It has been demonstrated that the magnitude of these iatrogenic effects correlates with the experience and case load of the surgeon³⁻⁵. However, basal skeletal characteristics⁵, missing lateral incisors as a sign of inherent tissue hypoplasia⁵, and altered embryonic development of the pituitary gland resulting in growth hormone deficiency^{6,7} are also considered as relevant contributing factors.

Abnormal or disturbed growth of the maxillomandibular complex can be approached in two different ways, depending on the maturational status of the patient and the extent of the anomaly. Orthognathic surgery, in combination with pre- and post-orthodontic treatment, allows three-dimensional jaw rehabilitation in a mature patient by one or two-step procedures. On the other hand, facial growth and development during childhood or early adolescence can be guided by dentofacial orthopaedic treatment. Transverse, anteroposterior, and to a lesser extent also vertical discrepancies can be treated using appliances as maxillary expanders, headgear, functional appliances, face mask, or bone-anchored maxillary protraction with intermaxillary elastics⁸. The latter is a more recent treatment modality for skeletal class III that has demonstrated satisfying results in CL/P patients^{9,10}.

Success in dentofacial orthopaedics is highly dependent on the patient's maturational stage. Therefore, it is important to determine the period of accelerated growth of the relevant skeletal structure to achieve the most favorable response with the least potential morbidity¹¹. The individual skeletal maturity can be assessed using biological indicators such as increase in body height¹², skeletal maturation of the hand and wrist¹³, and the Cervical Vertebral Maturation^{11,14}. The Cervical Vertebral Maturation (CVM) method was introduced by Lamparski and further refined by Baccetti and coworkers^{11,15,16}. It is a validated method that allows estimation of the skeletal maturation using a cephalometric radiograph. This imaging method is also routinely used for orthodontic purposes, so the radiation dose can be minimized^{17,18}.

The aim of this study is to determine if patients with cleft lip and/or palate have an increased risk for delayed skeletal maturation by assessing their cervical vertebral maturation and comparing it with that of a matched, non-affected control group.

MATERIALS AND METHODS

The study was approved by the Ethical Committees of Ghent University Hospital (2019/1064) and University Hospitals Leuven (S63027) and has been performed in accordance with the Declaration of Helsinki.

The study had a retrospective design and comprised patients with an orofacial cleft treated by the Leuven Cleft Lip and Palate Team and the Centre of Congenital Facial Anomalies of the Ghent University Hospital. The following inclusion criteria were used: uni- or bilateral cleft lip, alveolus, and/or palate, isolated cleft palate, no syndromes, and an age between 10 and 14 (girls) and 12 and 16 (boys). Only subjects with a clearly readable cephalometric radiograph were considered eligible. The age limits were based on the average timing of the peak height velocity, which is at 13.5 years old for boys and 11.5 years old for girls¹⁹. Syndromic patients were excluded in order to isolate the effect of cleft lip and/or palate on growth. The non-affected control group was compiled at the Department of Orthodontics at the Ghent University Hospital and comprised patients with a clearly readable cephalometric radiograph as part of the diagnostic data prior to an orthodontic treatment. The same age limits as in the study sample were applied for boys and girls in the control group.

The selected cephalometric radiographs were cropped using Preview (Apple, Cupertino, CA, USA) to an image with only the cervical spine visible. This was performed by the first author in order to avoid observer bias such as age estimation based on tooth development or diagnosis of an OFC (Figure 1).



Figure 1. A cropped cephalometric radiograph with only the cervical vertebrae C2, C3, and C4 visible

The set of radiographs was randomized and numerically coded to ensure blinding. Skeletal maturational status was determined with the Cervical Vertebral Maturation (CVM) method¹¹. The CVM method allows classification into six cervical stages (CS1-6) based on a visual appraisal of two morphological characteristics of the cervical vertebrae C2, C3, and C4 (Figure 2). First, it considers the presence or absence of a concavity at the lower border of the body of C2, C3, and C4. Secondly, the shape of the body of C3 and C4 is assessed. Four basic shapes are considered: trapezoid (the superior border is tapered from posterior to anterior), rectangular horizontal (the heights of the posterior and anterior borders are equal; the superior and inferior borders are longer than the anterior and posterior borders), squared (the posterior, superior, anterior, and inferior borders are equal), and rectangular vertical (the posterior and anterior borders are longer than the superior and inferior borders)¹¹. Cervical Stage (CS) 1 and 2 are the optimal stages for transverse and anteroposterior orthopaedic interventions in the maxilla. CS 3 and 4 are optimal stages for an anteroposterior orthopaedic intervention in mandible^{11,20}.

The complete set of cephalometric radiographs was assessed by one observer (LM). One hundred and seventeen randomly selected radiographs were re-assessed by the same observer on a second occasion, and also by a second observer (LT) in order to determine intra- and interobserver agreement. This specific number was determined to be the minimal amount of radiographs needed to show with 80% certainty that the lower limit of the 95% confidence interval for an ICC of 0.80 was not less than 0.70 when having two observers²¹.

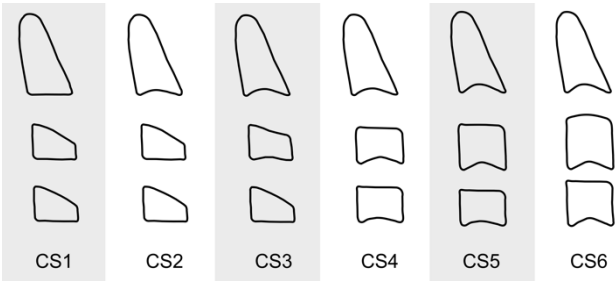


Figure 2. Stages CS1 to CS6 of the CVM method (based on Baccetti et al.⁷⁾

Analyses were performed in SPSS version 25 (IBM, Armonk, New York, USA). Intra- and interobserver agreement were determined by means of the Intraclass Correlation Coefficient (ICC). The ICC was expressed as a weighted kappa value. All analyses were performed separately for boys and girls. Chi square tests were used to test if there is an association between presence of a cleft and having a CVM score of CS3 or higher / of CS5 or higher. Mann-Whitney U tests were used to test if the mean ranking of the CVM score is different between the cleft group and control group. This test was also used per age category. Logistic regression analysis with age (categorical), presence of a cleft, and their two-way interaction as fixed factors in the model, was used to test if there was an association between the presence of a cleft and having a CVM score of CS3 or higher / CS5 or higher according to age category.

RESULTS

The application of the in- and exclusion criteria resulted in a study group of 246 patients. The sample characteristics with the distribution according to the age, sex, and cleft type are shown in Table 1. A control group of 210 patients was compiled. A table containing the detailed distribution of CVM stages in each age group for both genders was added as an Addendum 1.

	Girls					Boys					
	Age (years)				SUBTOTAL (n)	Age (years)				SUBTOTAL (n)	TOTAL (n)
	10-11	11-12	12-13	13-14		12-13	13-14	14-15	15-16		
Control (n)	25	28	29	34	116	29	23	22	20	94	210
Cleft (n)	21	23	26	22	92	38	43	43	30	154	246
Cleft type					Cleft type						
CL 9 (9.8%)					CL 20 (13.0%)						
UCLA 9 (9.8%)					UCLA 11 (7.1%)						
UCLP 39 (42.4%)					UCLP 68 (44.2%)						
BCLP 11 (12.0%)					BCLP 38 (24.7%)						
CP 24 (26.1%)					CP 17 (11.0%)						
Abbreviations: n, number; CL, cleft lip; UCLA, unilateral cleft lip and alveolus; UCLP, unilateral cleft lip and palate; BCLP, bilateral cleft lip and palate, and CP, cleft palate.											

Table 1. Sample characteristics

The ICC between the two observers was 0.907 with a 95% confidence interval of 0.850-0.940, while the ICC within one observer was 0.891 with a 95% confidence interval of 0.840-0.925. Both indicate excellent agreement²².

For both boys and girls in this sample, there was a significant association between the presence of a cleft and a CVM score of CS3 or higher (P from Chi square test = 0.033 and 0.031 respectively), with control patients being more likely to have a CVM score of CS3 or higher compared to cleft patients (risk ratio = 76.6/63.6 = 1.20 and 69.0/54.3 = 1.27 respectively). No association between the presence of a cleft and having a CVM score of CS5 or higher was found in any of the two genders (P value from Chi square test = 0.849 and 0.069 respectively).

Boys showed no significant difference in mean ranking on the CVM score between control and cleft children (P value from Mann-Whitney U test = 0.231). This non-significant association was also detected in each age subsample. In girls, a significant difference in mean ranking on the CVM score between control and cleft children was detected (P value from Mann-Whitney U test = 0.010), with

control patients having a higher mean rank than cleft patients. However, this association was only significant for the age subsample 11 to 12 years (P value from Mann-Whitney U test < 0.001).

Logistic regression analysing the association between the presence of a cleft and having a CVM score of CS3 or higher/CS5 or higher according to age category was performed for each sex. In boys, no association between the presence of a cleft and CVM score of CS3 or higher or a score of CS5 or higher was detected in any age subsample (Figures 3 and 4).

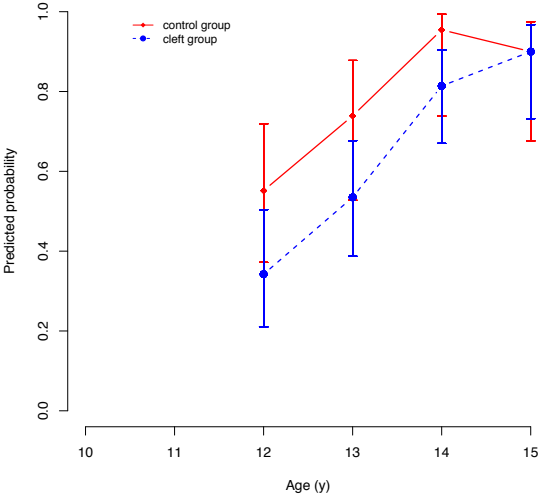


Figure 3. Predicted probability of having a CVM score of at least CS3 in cleft and control boys for each age subsample

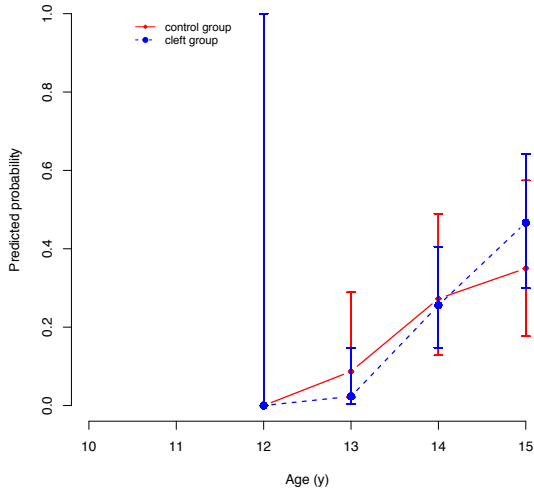


Figure 4. Predicted probability of having a CVM score of at least CS5 in cleft and control boys for each age subsample

For girls, the subsample with age 11 to 12 showed a significant association between the presence of a cleft and CVM score of CS3 or higher, with the cleft group having 90.0% lower estimated odds of CS3 or higher compared to the control group [95% CI goes from 62.0% to 97.4% lower odds, p-value = 0.001] (Figure 5). Similarly, the subsample with age 12 to 13 showed a borderline non-significant association between the presence of a cleft and CVM score of CS5 or higher, with the cleft group having 75.20% lower estimated odds of CS5 or higher compared to the control group [95% CI goes from 94.0% lower odds to 3.2% higher odds, p-value = 0.055] (Figure 6).

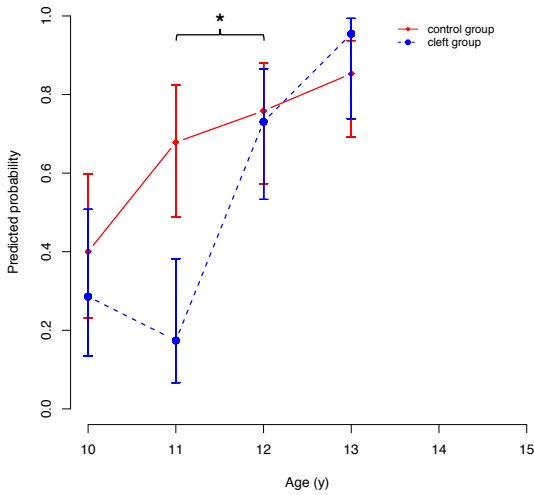


Figure 5. Predicted probability of having a CVM score of at least CS3 in cleft and control girls for each age subsample. The significant association for the subsample with age 11 to 12 is indicated with an asterisk (*)

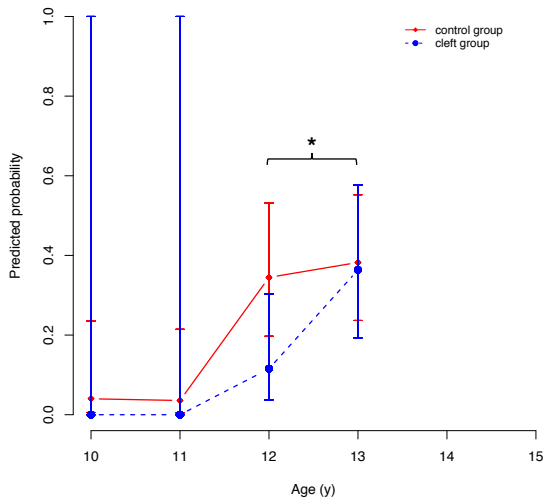


Figure 6. Predicted probability of having a CVM score of at least CS5 in cleft and control girls for each age subsample. The borderline non-significant association for the subsample with age 12 to 13 is indicated with an asterisk (*)

DISCUSSION

In the sample of the current study, boys and girls with a cleft lip and/or palate were less likely to have a CVM score of CS3 or higher (risk ratio = 0.83 (boys) and 0.79 (girls)) than non-affected individuals. In contrast, there was no significant association between the presence of a cleft and having a CVM score of CS5 or higher. These observations could substantiate the assumption that the growth spurt in cleft patients starts at a later chronological age, is of a shorter duration and therefore might proceed at a higher velocity. Regrettably, due to the cross-sectional nature of the data, no robust statistical model as a time-to-event analysis could be applied to confirm this hypothesis. However, a logistic regression model could detect that cleft girls have a significantly lower predicted probability of having a CVM score of at least CS3 in the subsample with age 11 to 12 ($P = 0.001$). Although strictly non-significant ($P = 0.055$), we also could say that girls showed a (borderline) lower predicted probability of having a CVM score of at least CS5 in the subsample with age 12 to 13.

Clefts associated with a syndrome were excluded during patient sampling to isolate the effect of the cleft on growth. Nevertheless, inter-subject variability cannot be excluded completely in the study sample. Patients with a cleft lip, cleft lip and alveolus, or cleft lip and palate have a distinct different genotype than patients with an isolated cleft palate. However, it is unknown if the expression of these different genotypes results in differences regarding start, length, and intensity of the pubertal growth spurt.

CVM staging of cleft patients and subsequent comparison with a non-affected control group in a cross-sectional design has been performed previously. Sun and Li calculated odds ratios to test whether cleft patients were more likely not to reach CVM stage 3 or higher. They concluded that Han Chinese cleft boys and girls are at higher risk for a delayed skeletal maturation^{23,24}. Ravi and Ravikala concluded that there is a delay in skeletal maturation at a younger age (10-13 years) but not at an older age (13-15 years) in children with unilateral cleft lip and palate (UCLP)²⁵. Although this conclusion has common grounds with the discrete trend observed in the current study, the smaller study sample (60 children with UCLP and 60 non-affected controls) of Ravi and Ravikala might have affected the statistical power. Flieger et al. concluded that cleft patients achieve various CVM scores at later chronological age compared to non-affected patients. However, the absent distinction between boys and girls in both the study and control groups subverts the validity of the results²⁶.

Cesur et al. also observed a delayed skeletal maturation for boys and girls under the age of 11 in a sample of 85 children with UCLP²⁷.

Newborn cleft children present impaired craniofacial development before any surgical intervention. Therefore, growth impairment could be classified to some extent as an intrinsic characteristic of the cleft condition. These children present an aberrant genotype, although associated with a highly variable phenotype. It has been observed that sella tursica morphology is deviant in newborn cleft children. This might explain why a subset of this population has occult midline, neural and learning deficiencies, and hypophyseal/endocrine and somatic growth problems²⁸. Growth hormone deficiency has also been observed 40 times more often in cleft children than in their non-affected peers⁷. It also suggested that the nutritional status during early life (feeding problems due to the presence of the cleft) could also be associated with delayed skeletal maturity. Nevertheless, no causal relationship could be demonstrated²⁹. A cleft palate can prevent a newborn cleft child from creating sufficient negative pressure necessary to feed, and can limit the normal use of the tongue to compress the nipple³⁰. This results in significantly lower weight gain per week in newborns with a cleft³¹.

The CVM method is an established procedure to determine the proper timing of dentofacial orthopaedics. Despite its long track record, the method remains a topic for debate. Reliability, repeatability, accuracy, and reproducibility are reported to be highly variable, going from low, moderate, substantial, to high³²⁻³⁶. Perinetti et al. introduced a more extended and objective, morphometric CVM code staging system. They applied this novel method on a cohort of the Oregon Growth Study. It was observed that cases outside the reported norms were not frequent and most of the exceptions were seen in CVM stage 4. Generally, they concluded that the classic CVM method might require more comprehensive staging instructions and that inter-subject variability might be relevant in terms of duration of the single CVM stages³⁷.

The discrepancies in the number of included subjects between the sex specific age categories in cleft and control might have negatively affected the power the study. These discrepancies might also lead to unequal variances between the cleft and control group or a type I error.

Clinically, cleft patients present a wide spectrum of transverse and/or anteroposterior deformities of the maxilla and mandible. A substantial part of the malocclusions related to these deformities can be

approached in a non-surgical manner if the intervention is well timed. Generally, optimal timing for the transverse correction of the maxilla is during the CVM stages CS1 and CS2. The current study suggests that these stages might occur at an older chronological age, especially in girls. However, when the cleft is not only limited to the lip or the palate, the timing of maxillary transverse correction is rather dictated by the dental development than the skeletal age. In unilateral cleft lip and alveolus (UCLA), unilateral cleft lip and palate (UCLP), and bilateral cleft lip and palate (BCLP) the development of the cleft-adjacent canine(s) dictates the timing of the early secondary bone grafting and subsequently the timing of the preoperative orthopaedic expansion of the maxilla³⁸. After all, this expansion is often required to restore the alveolar morphology and to improve access to the receptor site during surgery. Solis et al. concluded that the development of the cleft-adjacent canine in complete UCLP was 1.39 years delayed in comparison to a non-affected population³⁹.

In a Class III relationship due to deficient maxillary growth, maxillary protraction can be performed by means of a face mask or with bone-anchored maxillary protraction (BAMP) and class III intermaxillary elastics. The latter approach has gained remarkable interest and has recently been subject of comprehensive research in UCLP. Three-dimensional assessment of the maxilla, mandible and the glenoid fossa showed similar effects in patients with and without clefts^{10,40}. The optimal timing of anteroposterior correction with effect on both the upper and lower jaw is during CVM stages CS1 and CS2. Again, the current study suggests that these stages might occur at an older chronological age, especially in girls.

The current study demonstrated, within its limitations, a discrete delay in skeletal maturation before the pubertal growth spurt of (pre)adolescents with CL/P, especially in girls. Further research must investigate the clinical significance of this delay and its effect on the timing of dentofacial orthopaedic treatment.

REFERENCES

1. Mossey P. A., Little J., Munger R. G., Dixon M. J., Shaw W. C. Cleft lip and palate. *Lancet* **2009**;374:1773-85.
2. de Oliveira R. L., de Santana Santos T., de Almeida Teixeira J. L., Martins-Filho P. R., da Silva L. C. Health-Related Quality of Life Patients With a Cleft Lip and/or Palate. *J Craniofac Surg* **2015**;26(8):2315-9.
3. Ross R. B. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. *Cleft Palate J* **1987**;24:5-77.
4. Kapucu M. R., Gursu K. G., Enacar A., Aras S. The effect of cleft lip repair on maxillary morphology in patients with unilateral complete cleft lip and palate. *Plast Reconstr Surg* **1996**;97:1371-5; discussion 6-8.
5. Meazzini M. C., Tortora C., Morabito A., Garattini G., Brusati R. Factors that affect variability in impairment of maxillary growth in patients with cleft lip and palate treated using the same surgical protocol. *J Plast Surg Hand Surg* **2011**;45:188-93.
6. Roitman A., Laron Z. Hypothalamo-pituitary hormone insufficiency associated with cleft lip and palate. *Arch Dis Child* **1978**;53:952-5.
7. Rudman D., Davis T., Priest J. H., Patterson J. H., Kutner M. H., Heymsfield S. B., et al. Prevalence of growth hormone deficiency in children with cleft lip or palate. *J Pediatr* **1978**;93:378-82.
8. De Clerck H. J., Proffit W. R. Growth modification of the face: A current perspective with emphasis on Class III treatment. *Am J Orthod Dentofacial Orthop* **2015**;148:37-46.
9. Garib D., Yatabe M., de Souza Faco R. A., Gregorio L., Cevidanes L., de Clerck H. Bone-anchored maxillary protraction in a patient with complete cleft lip and palate: A case report. *Am J Orthod Dentofacial Orthop* **2018**;153:290-7.
10. Yatabe M., Garib D. G., Faco R. A. S., de Clerck H., Janson G., Nguyen T., et al. Bone-anchored maxillary protraction therapy in patients with unilateral complete cleft lip and palate: 3-dimensional assessment of maxillary effects. *Am J Orthod Dentofacial Orthop* **2017**;152:327-35.
11. Baccetti T., Franchi L., McNamara J. J. The Cervical Vertebral Maturation (CVM) Method for the Assessment of Optimal Treatment Timing in Dentofacial Orthopedics. *Semin Orthod* **2005**;11:119-29.
12. Bjork A. Variations in the growth pattern of the human mandible: longitudinal radiographic study by the implant method. *J Dent Res* **1963**;42(1)Pt 2:400-11.
13. Bjork A., Helm S. Prediction of the age of maximum puberal growth in body height. *Angle Orthod* **1967**;37:134-43.

14. O'Reilly M. T., Yanniello G. J. Mandibular growth changes and maturation of cervical vertebrae--a longitudinal cephalometric study. *Angle Orthod* **1988**;58:179-84.
15. Baccetti T., Franchi L., McNamara J. A., Jr. An improved version of the cervical vertebral maturation (CVM) method for the assessment of mandibular growth. *Angle Orthod* **2002**;72:316-23.
16. Lamparski D. G. Skeletal age assessment utilizing cervical vertebrae. *Am J Orthod Dentofacial Orthop* **1972**;67:458-9.
17. Szemraj A., Wojtaszek-Slominska A., Racka-Pilszak B. Is the cervical vertebral maturation (CVM) method effective enough to replace the hand-wrist maturation (HWM) method in determining skeletal maturation?-A systematic review. *Eur J Radiol* **2018**;102:125-8.
18. Cericato G. O., Bittencourt M. A., Paranhos L. R. Validity of the assessment method of skeletal maturation by cervical vertebrae: a systematic review and meta-analysis. *Dentomaxillofac Radiol* **2015**;44:20140270.
19. Cooke D. W., Divall S. A., Radovick S. Chapter 24 - Normal and Aberrant Growth in Children. In: S. Melmed, K. S. Polonsky, P. R. Larsen and H. M. Kronenberg (eds) *Williams Textbook of Endocrinology* (Thirteenth Edition). **2016**; Philadelphia
20. Franchi L., Baccetti T., McNamara J. A., Jr. Mandibular growth as related to cervical vertebral maturation and body height. *Am J Orthod Dentofacial Orthop* **2000**;118:335-40.
21. Zou G. Y. Sample size formulas for estimating intraclass correlation coefficients with precision and assurance. *Stat Med* **2012**;31:3972-81.
22. Altman D. G. *Practical Statistics for Medical Research*. Chapman and Hall, London: **1991**.
23. Sun L., Li W. R. Cervical vertebral maturation of female children with orofacial clefts. *Cleft Palate Craniofac J* **2013**;50:535-41.
24. Sun L., Li W. R. Cervical vertebral maturation of children with orofacial clefts. *Cleft Palate Craniofac J* **2012**;49:683-8.
25. Ravi M., Ravikala S. Assessment of skeletal age in children with unilateral cleft lip and palate. *Int J Clin Pediatr Dent* **2013**;6:151-5.
26. Flieger R., Kopczynski P., Matthews-Brzozowska T. Analysis of skeletal maturity of children with cleft palate in terms of healthy children by the CVM method. *Adv Clin Exp Med* **2015**;24:99-102.
27. Cesur E., Altug A. T., Toygar-Memikoglu U., Gumru-Celikel D., Tagrikulu B., Erbay E. Assessment of sella turcica area and skeletal maturation patterns of children with unilateral cleft lip and palate. *Orthod Craniofac Res* **2018**;21:78-83.

28. Nielsen B. W., Molsted K., Kjaer I. Maxillary and sella turcica morphology in newborns with cleft lip and palate. *Cleft Palate Craniofac J* **2005**;42:610-7.
29. Jensen B. L., Dahl E., Kreiborg S. Longitudinal study of body height, radius length and skeletal maturity in Danish boys with cleft lip and palate. *Scand J Dent Res* **1983**;91:473-81.
30. Bessell A., Hooper L., Shaw W. C., Reilly S., Reid J., Glenny A. M. Feeding interventions for growth and development in infants with cleft lip, cleft palate or cleft lip and palate. *Cochrane Database Syst Rev* **2011**;CD003315.
31. Jones W. B. Weight gain and feeding in the neonate with cleft: a three-center study. *Cleft Palate J* **1988**;25:379-84.
32. Santiago R. C., de Miranda Costa L. F., Vitral R. W., Fraga M. R., Bolognese A. M., Maia L. C. Cervical vertebral maturation as a biologic indicator of skeletal maturity. *Angle Orthod* **2012**;82:1123-31.
33. Zhao X. G., Lin J., Jiang J. H., Wang Q., Ng S. H. Validity and reliability of a method for assessment of cervical vertebral maturation. *Angle Orthod* **2012**;82:229-34.
34. Gabriel D. B., Southard K. A., Qian F., Marshall S. D., Franciscus R. G., Southard T. E. Cervical vertebrae maturation method: poor reproducibility. *Am J Orthod Dentofacial Orthop* **2009**;136:478 e1-7; discussion -80.
35. Sohrabi A., Babay Ahari S., Moslemzadeh H., Rafighi A., Aghazadeh Z. The reliability of clinical decisions based on the cervical vertebrae maturation staging method. *Eur J Orthod* **2016**;38:8-12.
36. Cunha A. C., Cevidanes L. H., Sant'Anna E. F., Guedes F. R., Luiz R. R., McNamara J. A., et al. Staging hand-wrist and cervical vertebrae images: a comparison of reproducibility. *Dentomaxillofac Radiol* **2018**;47:20170301.
37. Perinetti G., Bianchet A., Franchi L., Contardo L. Cervical vertebral maturation: An objective and transparent code staging system applied to a 6-year longitudinal investigation. *Am J Orthod Dentofacial Orthop* **2017**;151:898-906.
38. Weissler E. H., Paine K. M., Ahmed M. K., Taub P. J. Alveolar Bone Grafting and Cleft Lip and Palate: A Review. *Plast Reconstr Surg* **2016**;138:1287-95.
39. Solis A., Figueroa A. A., Cohen M., Polley J. W., Evans C. A. Maxillary dental development in complete unilateral alveolar clefts. *Cleft Palate Craniofac J* **1998**;35:320-8.
40. Yatabe M., Garib D., Faco R., de Clerck H., Souki B., Janson G., et al. Mandibular and glenoid fossa changes after bone-anchored maxillary protraction therapy in patients with UCLP: A 3-D preliminary assessment. *Angle Orthod* **2017**;87:423-31.

GENERAL DISCUSSION AND FUTURE OUTLOOK

8.

The research papers of Chapter 3 to 7 provide evidence-based answers to the general hypotheses by applying the methodology and by accomplishing the aims that were postulated in Chapter 2. These hypotheses focused on (1) outcome assessment of the early surgical interventions of unilateral cleft patients in Flanders, (2) objective evaluation of facial surface data acquired with non-ionizing 3D surface imaging, and (3) the onset and/or velocity of skeletal maturation in cleft lip and/or palate patients.

EARLY SURGICAL OUTCOME IN UNILATERAL CLEFTS

Based on the results of **Chapter 3**, it can be concluded that there are no significant differences in dental arch relationship (representing the early surgical outcome) of 5- to 6-year-old unilateral cleft patients treated in two Flemish cleft centers. However, clinical equivalence could only be accepted for sagittal occlusion and was uncertain for other outcomes.

Generally, the results of our study are in line with other studies using the 5-Year-Olds' Index and Huddart/Bodenham scoring system as outcome measure. A collaboration of two European cleft centers and a center in the United States compared the dental arch relationship of 5-year-old patients and found means of 2.05 (± 0.95), 2.12 (± 0.86) and 2.42 (± 1.07)¹. Investigators of Radboud University (The Netherlands) compared the effect of infant orthopedics and obtained averages of 2.23 (± 0.84) in patients treated with infant orthopedics and 2.16 (± 0.85) in patients treated without infant orthopedics at the age of 6². The mean scores for the modified Huddart/Bodenham scoring system in our study were in line with results of studies performed in Bangladesh (-8.26 ± 7.12) and Japan (-6.43 ± 3.34 and -8.01 ± 4.29)^{3,4}. Despite these conclusions, substantive differences can be observed in the cleft management protocols of these university-based cleft centers. Their current protocols are designed based on the experiences of practitioners and their colleagues, and by using the literature available at that time. At the European level, these substantive different protocols are no exception. The Eurocleft project showed that 201 collaborating teams practiced 194 different protocols for one cleft subtype⁵. Although we failed to detect significant differences in outcomes between the two centers, the treatment protocols showed differences, especially in timing of the hard palate closure. Kuijpers-Jagtman and Long described the main advantage of delayed hard palate closure. The detrimental effect of scar tissue on the maxillary growth would be smaller if the closure is delayed. Disadvantages of this procedure are the possibility of worse speech performance and the need of

obturation of the palatal defect for several years before repair⁶. Nollet and co-workers concluded that protocols with closure of the hard palate at 18 months, 22 months and 9 years old showed the best dental arch relationships. Generally, case load and skill of the surgeon are more important factors for the quality of the results⁷.

OBJECTIVE EVALUATION OF FACIAL SURFACE DATA ACQUIRED WITH NON-IONIZING 3D SURFACE IMAGING TECHNOLOGIES

Chapter 4 and 5 reported the assessment modalities of 3D facial surface images acquired for longitudinal and cross-sectional research in cleft lip and palate. The last decade, the use of image-capturing systems based on stereophotogrammetry and laser surface imaging has become widespread due to reasonable pricing and ease of use. Both clinical and academic institutions are potential users of these technologies. In a clinical setting, 3D facial surface images are primarily used to *visualize* particular morphological traits. On the other hand, academics use these images to *quantify* shape and changes in shape over time. The latter formed the rationale behind the papers of chapter 4 and 5. Therefore, the current methods to objectively assess facial morphology, symmetry, and appearance, and to detect soft tissue changes subsequent to a surgical or orthopaedic intervention were investigated. Generally, both papers generated similar conclusions. Notwithstanding that all included papers used 3D images, the analysis was often methodologically suboptimal. The most common flaws were that 3D Images were spatially analyzed in only 2 dimensions or that the analysis was subject to operator bias. Landmark identification as basis for elementary measurements or image superimposition was identified as a major contributor to these operator bias. Claes and co-workers developed and refined a landmark-independent analysis of facial surface images^{8,9}. In this context, MeshMonk was recently presented. It is an openly available toolbox for accurate and comprehensive quantification of biological phenotypes¹⁰. This approach is also suitable for purposes as predicting a complete shape from DNA and synthetic growth and ageing of a face¹¹⁻¹³.

Chapter 6 is an application to cleft lip and palate of the automated quantification strategies described in the previous paragraph. The effect of an autologous alveolar bone graft on the nasolabial asymmetry in patients with unilateral cleft lip, alveolus, and palate was investigated. Available literature concerning this topic concluded that nasal and/or labial asymmetry improved after an

alveolar bone graft¹⁴⁻¹⁷. In contrast, Sander et al. did not observe any significant improvement of the nasal asymmetry¹⁸. The findings of the latter study are in accordance with our findings. The conclusions of all aforementioned studies were based on landmark-dependent analyses performed on conventional photographs¹⁶ or 3D surfaces images^{14,15,17,18}. As discussed in the previous paragraph, these landmark-dependent analyses are more prone to bias than 3D shape analysis with an automated mapping strategy¹⁹. The robust superimposition (modification of Procrustes superimposition) as used in the current study achieves a more accurate result than the best-fit method²⁰. Therefore, it was concluded that alveolar bone grafting did not significantly improve the asymmetry of the secondary cleft nose deformity. Only 2 horizontal parameters detecting labial asymmetry showed discrete significant changes. However, the clinical relevance of the latter is considered limited. This conclusion provides useful information for the counseling of children needing an alveolar bone grafting and their parents. It is recommended that a secondary correction of the cleft lip nasal deformity, if required, is performed during young adulthood and after any orthognathic correction. Major deformities in children with functional or psychological problems might form an exemption to this²¹.

THE ONSET AND/OR VELOCITY OF SKELETAL MATURATION IN CLEFT LIP AND/OR PALATE PATIENTS

Chapter 7 provides evidence-based information for orthodontists on the timing of dentofacial orthopedics in cleft children. The aim of this controlled study was to determine if patients with cleft lip and/or palate have an increased risk for delayed skeletal maturation. The results of the current study substantiate the assumption that the growth spurt in cleft patients starts at a later chronological age, is of a shorter duration and therefore might proceed at a higher velocity. A logistic regression model detected that cleft girls have a significantly lower predicted probability of having a CVM score of at least CS3 in the subsample with age 11 to 12 ($P = 0.001$). Although strictly non-significant ($P = 0.055$), we also could say that girls showed a (borderline) lower predicted probability of having a CVM score of at least CS5 in the subsample with age 12 to 13. CVM staging of cleft patients and subsequent comparison with a non-affected control group in a cross-sectional design has been performed previously. Sun and Li calculated odds ratios to test whether cleft patients were more likely not to reach CVM stage 3 or higher. They concluded that Han Chinese cleft boys and girls are at higher risk for a delayed skeletal maturation^{22,23}. Ravi and Ravikala concluded that there is a delay in skeletal maturation at a younger age (10-13 years) but not at an older age (13-15 years) in children with

unilateral cleft lip and palate (UCLP)²⁴. Flieger et al. concluded that cleft patients achieve various CVM scores at later chronological age compared to non-affected patients. Cesur et al. also observed a delayed skeletal maturation for boys and girls under the age of 11 in a sample of 85 children with UCLP²⁵. The conclusions of the current study suggest that orthopedic corrections of transverse and/or anteroposterior deformities of the maxilla and mandible during CVM stages CS1 and CS2 might occur at an older chronological age, especially in girls.

CRITICAL APPRAISAL OF THE STUDY METHODOLOGY

Generally, clinical research on cleft lip and palate as in papers 3, 6, and 7 was challenging for various practical reasons. First, there is the fragmented pattern of patient care. In Flanders, cleft teams are organized by the hospitals themselves. Each team has their own (surgical) protocol and composition, and the number of treated individuals also varies manifestly. Therefore, it takes a considerable amount of time to obtain a sufficiently large sample for an adequately powered study. Secondly, there are often ethical objections to examine the effect of an intervention on an evidence-based manner. The drafting and implementation of prospective, randomized clinical trials have, in this regard, many obstacles. Observational studies, often with a retrospective of prospective design, are necessary to evaluate interventions. Thirdly, due to the slow and subtle effects of various procedures on dentofacial growth and development, longitudinal follow up of patients is very time consuming, since it can take up to 10 years until the influence of a particular intervention reflects in craniofacial morphology¹. Finally, there is a great phenotypic variability of cleft lip and palate patients, which hampers the demonstration of causality and decision-making. The latter could be observed in chapter 3 as no distinction was made in the magnitude of the (palatal) cleft. This in turn could have had an effect on the results of the study because a larger cleft also might entail a less favorable skeletal result in the long run. The phenotypic variability could also have influenced the results of chapter 7. In this study, clefts associated with a syndrome were excluded during patient sampling to isolate the effect of the cleft on growth. Nevertheless, inter-subject variability could not be excluded completely in the study sample. Patients with a cleft lip, cleft lip and alveolus, or cleft lip and palate have a distinct different genotype than patients with an isolated cleft palate. However, it is unknown if the expression of these different genotypes results in differences regarding start, length, and intensity of the pubertal growth spurt. A subgroup analysis of the isolated cleft palates would have been underpowered (respectively

24 and 17 patients). Therefore, the analyses were repeated while excluding patients with isolated cleft palate and the same conclusions were obtained. These analyses were included as Addenda 2 and 3.

The three-dimensional images acquired for the study of chapter 6 enable a static asymmetry assessment. However, the lips and nose are dynamic anatomic regions during social interactions. Asymmetry of motion initiation and form might add supplementary understanding to the perception of facial asymmetry²⁶. Three-dimensional motion capture systems (often referred to as 4D imaging or dynamic facial imaging) acquire up to 60 frames per second and allows quantification of changes in facial movement over time²⁷. Hallac et al. quantified the asymmetry of facial movements in (pre)adolescents with cleft lip and/or palate. It was observed that individuals with a cleft lip have an increased facial asymmetry during voluntary smile and during a lip pucker with maximal orbicularis oris contraction. Despite the surgical lip repair, the motion path shape during the expressions was more asymmetric in comparison to non-affected individuals²⁶.

The timing of the postoperative image acquisition in chapter 7 has a dual explanation. First, the optimal follow-up period is determined by the intersection of minimal facial growth and maximal resolution of postoperative edema. In this way, the net effect of the procedure on the asymmetry of the nose and lips can be extracted. However, the complete resolution of facial edema after alveolar bone grafting over time has not been thoroughly investigated. Pavri et al. investigated this aspect following rhinoplasty and observed only a two-third decrease at 1 month and 95 percent decrease at six months²⁸. Taking into account that the current study investigated growing individuals, the follow-up period of three months in the current study should represent this adequate intersection. Secondly, the appointment three months postoperatively is standard after an alveolar bone grafting, so it was not necessary to burden the parents with extra appointments. The follow-up period of 3 months is in contrast with previous research reporting postoperative image acquisition at 6 weeks, 6 months, or 12 months¹⁴⁻¹⁸.

CLEFT CARE IN FLANDERS

Efficient multidisciplinary teamwork is a keystone in cleft care. Numerous research projects have emphasized the strong relationship between high quality outcomes at one hand, and the

centralization of cleft care and an adequate caseload of caregivers at the other hand. In the United Kingdom, the Clinical Standards Advisory Group (CSAG) performed a government-sponsored study two decades ago. They did undertake a critical appraisal of the organization of cleft centers and quantified the dentofacial outcomes, patient satisfaction, and speech outcome. In their conclusions, the CSAG reported an alarming fragmentation of cleft care and poor dentofacial outcomes. Based on these conclusions, recommendations for the UK Government were made. The main recommendations were that²⁹⁻³²:

- expertise should be concentrated in limited number of cleft centers (8-15 instead of 57),
- the range of expertise required in the team and the quality of standards required should be clearly indicated by purchasers of care,
- clinicians should agree on a common nationwide database for all cleft patients,
- information on all cleft patients should be made available for comparative studies,
- the Office of National Statistics should improve the recording of cleft births²⁹⁻³².

A follow-up survey from 2015 reported about the implementation of these recommendations. The number of cleft centers or managed clinical networks had been reduced in the UK from 57 to 11 (for a population of about 67 million and a surface 242 000km²), surgeons in each center operated on at least 35 cases every year, and outcomes had improved³³. The Netherlands also reorganized cleft care and has 11 cleft centers for a population of 17 million and a surface of 42 000km²³⁴.

The current situation in Flanders is clearly different from that of the UK and The Netherlands. Cleft care is not regulated on the regional (Flemish) level, and few data are available to assess treatment outcomes. To our knowledge, a minimum of eight hospitals across the region offer cleft care for a population of 6.5 million and a surface of about 14 000km². Only 2 of those cleft teams officially register cleft births following the standards of the Dutch Association of Cleft Palate and Craniofacial Anomalies. Nevertheless, the regional government is authorized for the recognition of healthcare providers and healthcare institutions, and quality assurance of healthcare institutions. The Flemish Agency for Care and Health has defined recognition standards for specific functions (intensive care unit, emergency unit, palliative care), specific medical and medical-technical services (radiotherapy services, burns center, transplant center), networks (stroke care, rare diseases), and reference centers. At this moment, cleft care is not registered in one of the aforementioned components. However, recognition can also be obtained at an international level. The European Reference Network for rare

and/or complex craniofacial anomalies and ear, nose and throat disorders (ERN CRANIO) is 1 of the 24 networks of expert healthcare providers from across Europe and is supported by the European Union. The goals of the ERN are the development of clinical skill/clinician access to expert advice; increased patient access to high-quality expert care/advice (accurate diagnosis & high-quality treatment); and increased diagnosis-specific information available to healthcare professionals, patients and their families. Membership of the ERN CRANIO is obtained following an extensive, peer reviewed assessment³⁵. The ERN CRANIO has adopted the existing clinical guidelines for cleft lip and palate of the Netherlands (Dutch guideline for 'Schisis') to ensure clinical recommendations are made available to clinicians based on research of the highest quality³⁴. In the near future, membership of the reference network might act as a foundation for recognition by the local authorities in Flanders.

The rationalization process in health care as discussed in previous paragraphs has gained ground internationally. Its main advantages are cost control and quality improvement. Notwithstanding these arguments, it is undeniable that health care policies also must consider patient values³⁶. Two American studies emphasized that patients have strong preferences for local care. In the first study, a scenario of potentially resectable pancreatic cancer was used. It was observed that nearly three quarters of patients indicated that they would prefer local surgery even when travel to a regional center would result in lower operative mortality risk³⁶. A second study of preferences in breast cancer treatment showed that most patients requiring radiation therapy are willing to delay treatment for several weeks rather than leave their city for more prompt treatment³⁷. In conclusion, regional authorities must also include patient preferences for location of care in their decision-making when quantifying the expected value of centralization of care.

Based on the observations of the current situation and the experiences in the UK and The Netherlands, a structured organization and legal framework for cleft care in Flanders is required. We might suggest a maximum of 4 to 5 officially recognized teams when considering the population, the surface of Flanders, and patient preferences for location of care. In addition, it is necessary to reevaluate the financial implications for the parents of children with a cleft requiring an orthodontic treatment. The refund system for orthodontics only considers certain age criteria. It does not provide distinct increased refunds (except 1 limited additional refund) for an extensive orthodontic treatment in several phases.

STRUCTURED DATA COLLECTION

Progress in clinical care requires a continuous critical evaluation of performed interventions. This outcome assessment is only possible when patient data are consecutively gathered in a structured manner. In the 2002 Report of the World Health Organization (WHO) meetings on International Collaborative Research on Craniofacial Anomalies, a set of minimum records and associated timing was proposed. Generally, these minimum records included dental casts, clinical photographs, panoramic and lateral skull radiographs at 5-6 years, 10 years and >18 years³⁸. Recent technological advances in three-dimensional imaging such as (low dose) cone beam computed tomography (CBCT) and stereophotogrammetry appeared to be a useful substitute of a component of or addition to this protocol³⁹. Table 1 shows the patient data that should be collected on a regular basis in case of a complete unilateral or bilateral cleft. The diagnostic data for the work up and postoperative assessment of an alveolar bone grafting procedure, an orthodontic treatment, or orthognathic surgery are not included in this table³⁹.

	Primary surgery	3 years	5 to 6 years	10 years	15 years	End of treatment
(Digital) Dental casts			✓	✓	✓	✓
Intraoral Clinical Photographs			✓	✓	✓	✓
Extraoral Clinical Photographs	✓	✓	✓	✓	✓	✓
Stereophotogrammetry			✓	✓	✓	✓
Orthopantomogram			✓			
Low dose CBCT				✓	✓	✓
Speech/Typanometry		✓	✓	✓		
Audiometry		✓	✓	✓		

Table 1. Standard data collection for complete unilateral or bilateral clefts.

The definition of treatment success in cleft care from the doctor's point of view does not always coincide with the patient's point of view. Therefore, the International Consortium for Health Outcomes Measurement (ICHOM) attempts to change how we evaluate and talk to patients about their health. A new paradigm focusing on health outcomes, i.e. the results that matter to patients, has been developed. An ICHOM Standard Set for Cleft Lip and Palate was composed for collection of data at

particular moments. These sets focus on the degree of health on the one hand, and burden of treatment and complications at the other hand. Standard sets of variables should be collected from patients, clinicians, and/or administrative sources at following time points: first doctor's visit, 3 months, 30 days following surgical intervention (lip and palatal closure), 5 years, 8 years, 12 years and 22 years⁴⁰.

CONCLUSIONS

The following **conclusions** can be formulated in response to the **specific aims** of Chapter 2:

AIM 1

To assess the dentoalveolar relationship of 5- to 6-year-old cleft patients in two university-based cleft centers in order to evaluate the early surgical treatment outcome and to compare these results with the international standards.

CONCLUSION

The dental arch relationship of 5- to 6-year-old unilateral cleft patients treated in two Belgian cleft centers are clinically equivalent based on sagittal occlusion, despite substantial differences in their treatment protocol. Clinical equivalence for other parameters was not confirmed. There is a strong correlation between the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system.

AIM 2

To explore the modalities of state-of-the-art non-invasive imaging technologies for longitudinal and cross-sectional evaluation of facial morphological characteristics in patients with orofacial clefts.

CONCLUSION

It can be concluded that non-ionizing 3D surface images are widely used in longitudinal and cross-sectional cleft research. The assessment methods used are primarily based on landmark identification, whether or not followed by superimposition. Operator bias is inherently enclosed in these landmark-dependent analyses. The reliability of these methods is insufficiently reported.

CHAPTER 3

CHAPTER 4 & 5

AIM 3

To assess the influence of an alveolar bone graft on the nasolabial asymmetry of unilateral cleft patients.

CONCLUSION

Overall, alveolar bone grafting did not significantly improve the asymmetry of the secondary cleft nose deformity. Only 2 horizontal parameters detecting labial asymmetry showed discrete significant changes. However, the clinical relevance of the latter is considered limited.

CHAPTER
6

AIM 4

To determine if patients with CL/P have an increased risk for a delayed skeletal maturation in order to optimize the timing of dentofacial orthopedics

CONCLUSION

A discrete delay in skeletal maturation before the pubertal growth spurt was observed in (pre)adolescents with CL/P, especially in girls. This delay was less apparent at the end of the pubertal growth spurt.

CHAPTER
7

RECOMMENDATIONS FOR RESEARCH

The content of this thesis has provided evidence-based knowledge in various domains to handle clinical and methodological issues. Targeted and specific data collection to assess the effect of (non-) surgical interventions remains a fundamental aspect of cleft research. This can take place in addition to the structured data collection for epidemiological goals and the assessment of treatment outcomes and complications as discussed in the previous section. The following clinical domains in cleft care require more evidence-based background:

- The long-term effects of Nasoalveolar Molding (NAM) in infants with uni- and bilateral complete clefts, the impact of the associated burden of care for this specific intervention, and its cost-effectiveness,
- The long-term skeletal, dentoalveolar, and facial effects of orthopedic interventions in growing cleft preadolescents such as bone-anchored maxillary protraction (BAMP)
- The effect of orthognathic surgery (LeFort I advancement) on the mid face soft tissues in cleft individuals with the methodology of Chapter 6
- The final treatment outcome (dentoalveolar and facial parameters, smile and dentogingival esthetics, and Oral Health-Related Quality of Life (OHRQoL)) of cleft patients with a finalized treatment process,
- The use of clear aligners for the orthodontic treatment of cleft patients (nasalveolar molding, maxillary expansion, and presurgical orthodontics) in terms of treatment efficacy, oral hygiene, and pain perception^{41,42}

The performance of clinical research in Flanders with high-quality methodology and inclusion of an adequate number of cleft patients requires a coordinated multicenter collaboration. Therefore, this thesis and the papers that compose it can be seen as an impulse to build up a sustainable collaboration that benefits science and our patients.

REFERENCES

1. Flinn W., Long R. E., Garattini G., Semb G. A multicenter outcomes assessment of five-year-old patients with unilateral cleft lip and palate. *Cleft Palate Craniofac J* **2006**;43:253-8.
2. Bongaarts C. A., Kuijpers-Jagtman A. M., van 't Hof M. A., Prah-Andersen B. The effect of infant orthopedics on the occlusion of the deciduous dentition in children with complete unilateral cleft lip and palate (Dutchcleft). *Cleft Palate Craniofac J* **2004**;41:633-41.
3. Haque S., Alam M. K., Khamis M. F. Treatment Outcome of Bangladeshi UCLP Patients Based on Both Phenotype and Postnatal Treatment Factors using Modified Huddart Bodenham (mHB) Index. *Cleft Palate Craniofac J* **2018**;55:966-73.
4. Mikoya T., Shibukawa T., Susami T., Sato Y., Tengan T., Katashima H., et al. Dental arch relationship outcomes in one- and two-stage palatoplasty for Japanese patients with complete unilateral cleft lip and palate. *Cleft Palate Craniofac J* **2015**;52:277-86.
5. Shaw W. C., Semb G., Nelson P., Brattstrom V., Molsted K., Prah-Andersen B., et al. The Eurocleft project 1996-2000: overview. *J Craniomaxillofac Surg* **2001**;29:131-40; discussion 41-2.
6. Kuijpers-Jagtman A. M., Long R. E. The Influence of Surgery and Orthopedic Treatment on Maxillofacial Growth and Maxillary Arch Development in Patients Treated for Orofacial Clefts. *Cleft Palate Craniofac J* **2000**;37:1-12.
7. Nollet P. J., Katsaros C., van 't Hof M. A., Semb G., Shaw W. C., Kuijpers-Jagtman A. M. Treatment outcome after two-stage palatal closure in unilateral cleft lip and palate: a comparison with Eurocleft. *Cleft Palate Craniofac J* **2005**;42:512-6.
8. Claes P., Walters M., Clement J. Improved facial outcome assessment using a 3D anthropometric mask. *Int J Oral Maxillofac Surg* **2012**;41:324-30.
9. Claes P., Daniels K., Walters M., Clement J., Vandermeulen D., Suetens P. Dysmorphometrics: the modelling of morphological abnormalities. *Theor Biol Med Model* **2012**;9:5.
10. White J. D., Ortega-Castrillon A., Matthews H., Zaidi A. A., Ekrami O., Snyders J., et al. MeshMonk: Open-source large-scale intensive 3D phenotyping. *Sci Rep* **2019**;9:6085.
11. Claes P., Hill H., Shriver M. D. Toward DNA-based facial composites: preliminary results and validation. *Forensic Sci Int Genet* **2014**;13:208-16.
12. Matthews H., Penington A., Clement J., Kilpatrick N., Fan Y., Claes P. Estimating age and synthesising growth in children and adolescents using 3D facial prototypes. *Forensic Sci Int* **2018**;286:61-9.

13. Imaizumi K, Taniguchi K, Ogawa Y, Matsuzaki K, Nagata T, Mochimaru M, et al. Three-dimensional analyses of aging-induced alterations in facial shape: a longitudinal study of 171 Japanese males. *Int J Legal Med* **2015**;129:385-93.
14. Kau C. H., Medina L, English J. D., Xia J., Gateno J., Teichgraber J. A comparison between landmark and surface shape measurements in a sample of cleft lip and palate patients after secondary alveolar bone grafting. *Orthodontics (Chic.)* **2011**;12:188-95.
15. Krimmel M., Schuck N., Bacher M., Reinert S. Facial surface changes after cleft alveolar bone grafting. *J Oral Maxillofac Surg* **2011**;69:80-3.
16. Kim S. W., Park S. O., Choi T. H., Hai do T. Change in upper lip height and nostril sill after alveolar bone grafting in unilateral cleft lip alveolus patients. *J Plast Reconstr Aesthet Surg* **2012**;65:558-63.
17. Devlin M. F., Ray A., Raine P., Bowman A., Ayoub A. F. Facial symmetry in unilateral cleft lip and palate following alar base augmentation with bone graft: a three-dimensional assessment. *Cleft Palate Craniofac J* **2007**;44:391-5.
18. Sander M., Daskalogiannakis J., Tompson B., Forrest C. Effect of alveolar bone grafting on nasal morphology, symmetry, and nostril shape of patients with unilateral cleft lip and palate. *Cleft Palate Craniofac J* **2011**;48:20-7.
19. Thierens L. A. M., De Roo N. M. C., De Pauw G. A. M., Brusselaers N. Assessment modalities of non-ionizing three-dimensional images for the quantification of facial morphology, symmetry, and appearance in cleft lip and palate: a systematic review. *Int J Oral Maxillofac Surg* **2018**;47:1095-105.
20. Claes P., Walters M., Vandermeulen D., Clement J. G. Spatially-dense 3D facial asymmetry assessment in both typical and disordered growth. *J Anat* **2011**;219:444-55.
21. Allori A. C., Mulliken J. B. Evidence-Based Medicine: Secondary Correction of Cleft Lip Nasal Deformity. *Plast Reconstr Surg* **2017**;140:166e-76e.
22. Sun L., Li W. R. Cervical vertebral maturation of female children with orofacial clefts. *Cleft Palate Craniofac J* **2013**;50:535-41.
23. Sun L., Li W. R. Cervical vertebral maturation of children with orofacial clefts. *Cleft Palate Craniofac J* **2012**;49:683-8.
24. Ravi M., Ravikala S. Assessment of skeletal age in children with unilateral cleft lip and palate. *Int J Clin Pediatr Dent* **2013**;6:151-5.
25. Cesur E., Altug A. T., Toygar-Memikoglu U., Gumru-Celikel D., Tagrikulu B., Erbay E. Assessment of sella turcica area and skeletal maturation patterns of children with unilateral cleft lip and palate. *Orthod Craniofac Res* **2018**;21:78-83.

26. Hallac R. R., Feng J., Kane A. A., Seaward J. R. Dynamic facial asymmetry in patients with repaired cleft lip using 4D imaging (video stereophotogrammetry). *Journal of Cranio-Maxillofacial Surgery* **2017**;45:8-12.
27. Popat H., Richmond S., Benedikt L., Marshall D., Rosin P. L. Quantitative analysis of facial movement--a review of three-dimensional imaging techniques. *Comput Med Imaging Graph* **2009**;33:377-83.
28. Pavri S., Zhu V. Z., Steinbacher D. M. Postoperative Edema Resolution following Rhinoplasty: A Three-Dimensional Morphometric Assessment. *Plast Reconstr Surg* **2016**;138:973e-9e.
29. Sandy J. R., Williams A. C., Bearn D., Mildinhal S., Murphy T., Sell D., et al. Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 1: background and methodology. *Cleft Palate Craniofac J* **2001**;38:20-3.
30. Williams A. C., Bearn D., Mildinhal S., Murphy T., Sell D., Shaw W. C., et al. Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 2: dentofacial outcomes and patient satisfaction. *Cleft Palate Craniofac J* **2001**;38:24-9.
31. Sell D., Grunwell P., Mildinhal S., Murphy T., Cornish T. A., Bearn D., et al. Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 3: speech outcomes. *Cleft Palate Craniofac J* **2001**;38:30-7.
32. Bearn D., Mildinhal S., Murphy T., Murray J. J., Sell D., Shaw W. C., et al. Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 4: outcome comparisons, training, and conclusions. *Cleft Palate Craniofac J* **2001**;38:38-43.
33. Ness A. R., Wills A. K., Waylen A., Al-Ghatam R., Jones T. E., Preston R., et al. Centralization of cleft care in the UK. Part 6: a tale of two studies. *Orthod Craniofac Res* **2015**;18 Suppl 2:56-62.
34. Federatie Medische Specialisten. "Behandeling van patiënten met een schisis." Retrieved 29 April 2020, from eling_van_patienten_met_een_schisis/organisatie_van_zorg_patienten_met_schisis.html.
35. Mathijssen I., de Ruiter R., Spivak O. "European Reference Network CRANIO." **2020**, from <https://ern-cranio.eu>.
36. Finlayson S. R., Birkmeyer J. D., Tosteson A. N., Nease R. F., Jr. Patient preferences for location of care: implications for regionalization. *Med Care* **1999**;37:204-9.
37. Palda V. A., Llewellyn-Thomas H. A., Mackenzie R. G., Pritchard K. I., Naylor C. D. Breast cancer patients' attitudes about rationing postlumpectomy radiation therapy: applicability of trade-off methods to policy-making. *J Clin Oncol* **1997**;15:3192-200.
38. WHO. Global strategies to reduce the health care burden of craniofacial anomalies: report of WHO meetings on international collaborative research on craniofacial anomalies. **2002**:

39. De Mulder D., Cadenas de Llano-Perula M., Willems G., Jacobs R., Dormaar J. T., Verdonck A. An optimized imaging protocol for orofacial cleft patients. *Clin Exp Dent Res* **2018**;4:152-7.
40. International Consortium of Health Outcomes Measurements (ICHOM). Cleft Lip & Palate Data Collection Reference Guide. **2018**:1-53.
41. Meazzini M. C., Tortora C., Mazzoleni F., Autelitano L. Comparison of Pain Perception in Patients Affected by Cleft and Cranio Facial Anomalies Treated With Traditional Fixed Appliances or Invisalign. *Cleft Palate Craniofac J* **2020**;57:35-42.
42. Batra P., Gribel B. F., Abhinav B. A., Arora A., Raghavan S. OrthoAligner "NAM": A Case Series of Presurgical Infant Orthopedics (PSIO) Using Clear Aligners. *Cleft Palate Craniofac J* **2019**;1055665619889807.

SUMMARY

The **first study** investigated the early surgical outcome of Flemish cleft lip and palate patients. Data collection was performed in Ghent University Hospital and University Hospitals Leuven. The dental arch relationship of seventy-three 5- to 6-year-old patients with complete UCLP was evaluated on plaster casts using the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system. The sagittal occlusion, overbite, and overjet were also recorded. Inter- and intra-examiner agreement were determined using Intraclass Correlation Coefficients. The Results revealed no significant mean difference in outcome based on the 5-Year-Olds' Index, the modified Huddart/Bodenham scoring system, overjet, and overbite. For mean difference in sagittal occlusion the hypothesis that both centers are clinically equivalent was confirmed. A good to very good inter- and intra-examiner agreement was found. It could be concluded that the dental arch relationship of 5- to 6-year-old unilateral cleft patients treated in two Flemish cleft centers are clinically equivalent based on sagittal occlusion, despite substantial differences in their treatment protocol. Clinical equivalence for other parameters was not confirmed. The scores for the 5-Year-Olds' Index and the modified Huddart/Bodenham scoring system were comparable with those of other international study results.

The **second and third study** focused on the use of non-ionizing three-dimensional surface imaging in cleft lip and palate research. The use of this technology is emerging in this research field, but methodologically properly designed assessment methods of the images are not well established. Therefore, the aim of these two systematic reviews was to explore the assessment modalities of these imaging technologies for longitudinal and cross-sectional evaluation of facial morphological characteristics in patients with clefts.

For both papers, a systematic literature search was performed using MEDLINE (via PubMed), CENTRAL, Web of Science, and EMBASE. The first review included only cross-sectional studies, the second review only longitudinal studies. Only papers with prospective or retrospective data collection using 3D non-ionizing surface imaging, with a subjective or objective outcome assessment, and at least 10 cleft lip and/or palate patients were considered eligible.

The first review identified 1767 unique studies and 33 met the inclusion criteria. The images were objectively assessed using elementary measurements and comprehensive statistical methods for superimposition, shape description, and structuring. Subjective assessment was performed using a Likert-type scale or a Visual Analog Scale. It could be concluded that non-ionizing 3D surface images

were widely used, but 3D analysis of the images is often lacking or methodologically sub-optimal. Researchers must fully utilize the content of the 3D images to quantify morphology in a way that minimizes operator bias. The second review identified 15 unique studies after eligibility assessment. The assessment of the 3D images was performed with landmark-dependent analyses, mostly supported with superimposition of the pre- and postoperative images. A wide spectrum of superimposition techniques is reported. The reliability of these assessment methods was often not or insufficiently reported. It could be concluded that soft tissue changes subsequent to a surgical or orthopedic intervention can be quantified on 3D surface images using assessment methods that are primarily based on landmark identification, whether or not followed by superimposition. Operator bias is inherently enclosed in landmark-dependent analyses. The reliability of these methods is insufficiently reported. It might be suggested that unbiased, three-dimensional shape analysis with an automated mapping strategy has potential in this research field.

Study 4 was an application of the acquired knowledge of study 2 and 3. The objective of this study was to examine whether an autologous alveolar bone graft has an effect on the nasolabial asymmetry in unilateral cleft lip, alveolus, and palate. Fifteen children (mean age 7.5 ± 2.4 years) with non-syndromic unilateral cleft lip and palate (CLP) were included. Non-ionizing three-dimensional surface images were acquired prior to and three months after the alveolar bone grafting procedure. A 2D and a landmark-independent 3D asymmetry assessment were used to detect changes of asymmetry in the nasolabial area. For the 2D assessment, a cleft and non-cleft side ratio for 4 linear nasal and 2 linear labial distances was expressed as a Coefficient of Asymmetry (CA). The 3D asymmetry assessment comprised a robust superimposition of the face with its mirror image, expressed as a root-mean-square-error (RMSE) in mm. The results showed a significant decrease in the CA for the labial distance from the facial midline to the labial commissure was observed ($P=0.036$). Also, the CA for the labial distance from the facial midline to the highest point of the Cupid's bow increased significantly ($P=0.028$). Non-significant changes were observed for the CA for the 2 nasal distances and the 2 other labial distances. No significant changes in 3D nasal asymmetry were detected ($P=0.820$). Overall, it was concluded that alveolar bone grafting did not significantly improve the asymmetry of the secondary cleft nose deformity. Only 2 horizontal parameters detecting labial asymmetry showed discrete significant changes. However, the clinical relevance of the latter is considered limited.

Finally, **study 5** focused on the timing and evolution of the craniofacial maturation of cleft patients. Dentofacial orthopaedics is a group of different therapies to correct aberrant growth of the maxillomandibular complex. These therapies must be applied in the most appropriate stage(s) of maturation. However, no consensus has been reached regarding timing and evolution of this craniofacial maturational stages in cleft patients. Therefore, the aim of this study was to determine if patients with CL/P have an increased risk for delayed craniofacial maturation. A sample of 246 cleft patients and 210 non-affected individuals was retrospectively compiled. Cephalometric radiographs taken between the ages of 10 and 14 years (girls) and 12 and 16 years (boys) were collected and assessed with the Cervical Vertebral Maturation (CVM) method. The results showed that in boys no significant association between the presence of CL/P and a CVM score of CS3 (about 1 year before the start of the pubertal growth spurt) or higher was observed in any age subsample. This was similar for a CVM score of CS5 (after the pubertal growth spurt) or higher. Girls in the CL/P group had a significant lower predicted probability of having a CVM score of at least CS3 in the subsample with age 11 to 12 ($P = 0.001$) and a borderline non-significant lower predicted probability of having a CVM score of at least CS5 in the subsample with age 12 to 13 ($P = 0.055$). In conclusion, a discrete delay in skeletal maturation before the pubertal growth spurt of (pre)adolescents with CL/P, especially in girls, was observed. This delay was less apparent at the end of the pubertal growth spurt.

SUMMARY (DUTCH)

Studie 1 onderzocht de vroege chirurgische uitkomst van patiënten met een unilaterale schisis van de lip, de kaakwal en het verhemelte in Vlaanderen. De gegevensverzameling werd uitgevoerd in het Universitair Ziekenhuis Gent en de Universitaire Ziekenhuizen Leuven. Er werd onderzocht of beide centra klinisch equivalente chirurgische resultaten hadden. De tandboogrelatie van drieënzeventig 5- tot 6-jarige patiënten met volledige unilaterale schisis werd geëvalueerd op gipsmodellen met behulp van de 5-Year-Olds' Index en het modified Huddart/Bodenham scoring systeem. De sagittale occlusie, de sagittale overbeet en verticale overbeet werden ook geregistreerd. De overeenkomst in scoring tussen de 2 examinatoren en binnen 1 examinator op verschillende tijdstippen werd bepaald met behulp van intraclass correlatiecoëfficiënten. De resultaten lieten geen significant gemiddeld verschil in uitkomst zien op basis van de 5-Year-Olds' Index, het modified Huddart/Bodenham scoring system, de sagittale overbeet en de verticale overbeet. Voor een gemiddeld verschil in sagittale occlusie werd de hypothese bevestigd dat beide centra klinisch equivalent zijn. Er werd een goede tot zeer goede inter- en intra-examinatorovereenkomst gevonden. Er kon geconcludeerd worden dat de tandboogrelatie van 5- tot 6-jarige patiënten met een complete unilaterale lip-, kaak- en verhemeltespleet behandeld in twee Vlaamse centra klinisch equivalent was op basis van sagittale occlusie, ondanks substantiële verschillen in hun behandelprotocol. Klinische equivalentie voor andere parameters werd niet bevestigd. De scores voor de 5-Year-Olds' Index en het modified Huddart/Bodenham scoring system waren vergelijkbaar met die van andere internationale studieresultaten.

In de **tweede en derde studie** werd het gebruik van niet-ioniserende driedimensionale beeldvorming bij orofaciale schisis onderzocht. Het gebruik van deze technologie is populair in dit onderzoeksgebied, maar het ontbreekt aan methodologisch goed ontworpen beoordelingsmethoden voor de verkregen driedimensionale beelden. In deze twee systematische reviews werden daarom de beoordelingsmodaliteiten van deze beeldvormingstechniek voor respectievelijk longitudinale en cross-sectionele evaluatie van morfologische kenmerken van schisispatiënten onderzocht. Voor beide studies werd een systematisch literatuuronderzoek uitgevoerd in de databases MEDLINE (via PubMed), CENTRAL, Web of Science en EMBASE. De eerste review omvatte studies met een cross-sectioneel design, de tweede review de studies met een longitudinaal design. Alleen papers met prospectieve of retrospectieve gegevensverzameling met niet-ioniserende driedimensionale beeldvorming, met een subjectieve of objectieve uitkomstbeoordeling, en ten minste 10 patiënten met een gespleten lip en/of verhemelte kwamen in aanmerking.

Bij de eerste review werden 1767 studies geïdentificeerd en 33 unieke studies voldeden aan de inclusiecriteria. De resultaten toonden dat de driedimensionale beelden objectief werden beoordeeld met behulp van elementaire metingen of uitgebreide statistische methoden voor superimpositie, vormbeschrijving en structurering. Subjectieve beoordeling werd uitgevoerd met behulp van een Likert-schaal of een visuele analoge schaal. Er werd geconcludeerd dat niet-ioniserende driedimensionale beelden veelvuldig gebruikt werden, maar dat de beeldanalyse vaak in slechts 2 dimensies of methodologisch suboptimaal werd uitgevoerd. Er werd dan ook geconcludeerd dat onderzoekers de driedimensionale inhoud van beelden ten volle moeten gebruiken om voor de kwantificatie van morfologie, symmetrie, en voorkomen op een manier die de kans op operator bias minimaliseert. De tweede review identificeerde 15 unieke studies die voldeden aan de inclusiecriteria. De beoordeling van de beelden in de longitudinale studies werd uitgevoerd met landmark-afhankelijke analyses, meestal ondersteund met superimpositie van de pre- en postoperatieve beelden. Er werd gebruikt gemaakt van een breed spectrum van superpositietechnieken. De betrouwbaarheid van deze beoordelingsmethoden werd vaak niet of onvoldoende gerapporteerd. Er kon worden geconcludeerd dat veranderingen in faciale weefsels na een chirurgische of orthopedische ingreep kunnen gekwantificeerd worden op niet-ioniserende driedimensionale beelden met behulp van beoordelingsmethoden die voornamelijk zijn gebaseerd op herkenning van landmarks, al dan niet gevolgd door superimpositie. Operatorbias zijn steeds een inherent gevolg van landmark-afhankelijke analyses. In het algemeen, gebaseerd op beide systematische reviews, kan ook worden gesuggereerd dat een geautomatiseerde, driedimensionale vormanalyse verschillende voordelen met zich meebrengt in het objectiveren van faciale morfologie, symmetrie, voorkomen en veranderingen van faciale weefsels na een interventie.

Studie 4 was een toepassing van de methodologie uit studie 2 en 3. Het doel van deze studie was te onderzoeken of een autoloog alveolair bottransplantaat een effect heeft op de nasolabiale asymmetrie bij patiënten met een unilateraal gespleten lip, kaak en gehemelte. Vijftien kinderen (gemiddelde leeftijd 7.5 ± 2.4 jaar) met niet-syndromale unilaterale gespleten lip, kaak en gehemelte werden geïncludeerd. Niet-ioniserende driedimensionale beelden van het aangezicht werden gemaakt vóór en drie maanden na het uitvoeren van het alveolair bottransplaat. Een tweedimensionale en een landmark-onafhankelijke driedimensionale beoordeling werden gebruikt om veranderingen van de asymmetrie in het nasolabiale gebied te detecteren. Voor de tweedimensionale beoordeling werden verhoudingen tussen de schisiszijde en de niet-schisiszijde

van 4 lineaire nasale en 2 lineaire labiale afstanden berekend en uitgedrukt als een coëfficiënt van asymmetrie (CA). De driedimensionale analyse omvatte een robuuste superimpositie van het gezicht en zijn spiegelbeeld, uitgedrukt als een root-mean-square-error (RMSE) in mm. De resultaten toonden een significante afname van de CA voor de labiale afstand van de faciale middenlijn tot de labiale commissuur ($P = 0.036$). Ook nam de CA voor de labiale afstand van de faciale middenlijn tot het hoogste punt van de Cupid's bow aanzienlijk toe ($P = 0.028$). Er werden niet-significante veranderingen waargenomen voor de CA voor de 2 nasale afstanden en de 2 andere labiale afstanden. De driedimensionale analyse van de nasale asymmetrie vertoonde geen significante verbeteringen ($P = 0.820$). Algemeen werd geconcludeerd dat een autologe alveolaire bottransplantatie de asymmetrie van het nasolabiale complex niet significant verbeterde. Slechts 2 horizontale parameters die labiale asymmetrie detecteren, vertoonden discrete significante veranderingen. De klinische relevantie van deze laatste bevinding moet echter als beperkt beschouwd worden.

Studie 5 richtte zich ten slotte op de timing en evolutie van de craniofaciale maturatie bij patiënte met een orofaciale schisis. Dentofaciale orthopedie is een groep van verschillende therapieën om afwijkende groei van het maxillomandibulaire complex te corrigeren. Elk therapie moeten worden toegepast in het meest geschikte stadium van de craniofaciale maturatie. Er is echter geen consensus over de timing en evolutie van deze craniofaciale maturatiestadia bij patiënten met een orofaciale schisis. Het doel van deze studie was om te bepalen of deze patiënten een verhoogd risico hebben op vertraagde craniofaciale maturatie. Een steekproef van 246 patiënten met een orofaciale schisis en 210 individuen zonder schisis werd retrospectief samengesteld. Cefalometrische röntgenfoto's tussen 10 en 14 jaar (meisjes) en 12 en 16 jaar (jongens) werden verzameld en beoordeeld met de Cervical Vertebral Maturation (CVM) methode. De resultaten toonden aan dat bij jongens geen significant verband tussen de aanwezigheid van orofaciale schisis en een CVM-score van CS3 (ongeveer 1 jaar voor het begin van de puberale groeispurt) of hoger werd geobserveerd in geen enkele subgroep voor leeftijd. Dit was vergelijkbaar voor een CVM-score van CS5 (na de puberale groeispurt) of hoger. Meisjes met een orofaciale schisis hadden een significant lagere kans op een CVM-score van ten minste CS3 in de subgroep voor leeftijd van 11 tot 12 jaar ($P = 0.001$) en een niet-significant lagere kans op een CVM-score van ten minste CS5 in de subgroep voor leeftijd van 12 tot 13 jaar ($P = 0.055$). Algemeen werd geconcludeerd dat er een discrete vertraging in craniofaciale maturatie was vóór de puberale groeispurt van (pre)adolescenten met orofaciale schisis, vooral bij meisjes. Deze vertraging was minder duidelijk aan het einde van de puberale groeispurt.

ACKNOWLEDGEMENTS

Bij de start van mijn specialisatiejaren orthodontie in 2011 was de wetenschappelijke lijn over schisis op onze afdeling nog onontgonnen gebied. De mogelijkheden die mij toen geboden werden om deze nieuwe onderzoekslijn op de rails te zetten, hebben na een lang en intensief proces geleid tot dit proefschrift. Het finaliseren van dit werk verplicht me en geeft me ook uitgebreid de mogelijkheid de mensen die mee aan de wieg stonden, inhoudelijk bijgedragen of mee gereflecteerd hebben, of onvoorwaardelijke steun gegeven hebben, uitvoerig te bedanken.

Prof. De Pauw, Guy, dit verhaal start in oktober 2011. De mogelijkheid die je me enkele maanden voordien bood om het prachtige beroep van orthodontist te studeren, zal ik altijd blijven erkennen en waarderen. Het onderzoeksproject dat een belangrijke pijler van deze specialisatie vormt, vindt voor mij plaats in het schisisteam. Je geeft me de kans om de inhoud van dit project (en de daaropvolgende studies) volledig vrij in te vullen. In je overvolle agenda als afdelingshoofd en diensthoofd vind je steeds de tijd om de methodologie te bespreken, een kritische blik te werken op een manuscript of de mogelijkheden tot een externe samenwerking te bespreken. Na mijn afstuderen in 2015 bied je mij ook de mogelijkheid om in combinatie met een halftijdse job als orthodontist in een privépraktijk een PhD op starten. Ik moet erkennen dat de vrijheid en het vertrouwen die je me de sindsdien gegeven hebt, niet als evidentie kan gezien worden. Je was ook steeds degene die op de meest spannende of drukke momenten het hoofd koel hield en altijd verzekerde dat alles in orde zou komen. En zo geschiedde.

Prof. Brusselaers, Nele, onze wegen kruisen in 2016. Het enthousiasme en de steun die je voordien aan de dag had gelegd bij de masterproef van Noëmi, waaien al snel over naar mij. Je drive werkt aanstekelijk en resulteert al snel in verschillende publicaties. Ik heb enorm veel opgestoken over wetenschappelijk schrijven en het publiceren van papers. Je was altijd enorm toegankelijk en pijlsnel in het beantwoorden van e-mails, maar tegelijk inhoudelijk kritisch wanneer de laatste hand aan een manuscript moest gelegd worden. Het was ook fijn om te horen dat je na je jaren aan het Karolinska Institutet een nieuwe professionele uitdaging in België gevonden hebt.

Prof. Cadenas, Maria, de grondslag van onze samenwerking wordt in 2016 op Europees congres in Stockholm gelegd. Een eerdere samenwerking met het schisisteam van UZ Leuven had dan al geresulteerd in een mooie paper en er bleken veel mogelijkheden om dit uit te breiden. Na een lange administratieve reis resulteerde dit dan in een joint PhD met de UGent en KU Leuven. Je bleek een heel betrokken en geëngageerde promotor en jouw bijdragen hebben dit werk naar een hoger niveau getild.

Prof. Verbeeck, Ronald, mijn eerste stappen in wetenschappelijk onderzoek werden in 2009 in uw labo gezet. In het kader van de masterproef tijdens mijn studie tandheelkunde maar ook de jaren nadien spendeerde ik talloze uren in blok B met het samenstellen en mengen van cementen en adhesieven en het evalueren van de mechanische eigenschappen. Uw enthousiaste manier van lesgeven en vertellen hebben mijn interesse in wetenschappelijk onderzoek destijds aangewakkerd. Na uw emeritaat bleef u tot mijn grote dank steeds beschikbaar om studies mee op starten of manuscripten te reviseren.

Een woord van dank richt ik ook graag tot de leden van de examencommissie: Prof. Luc Martens, dr. Liesbeth Temmerman, Prof. Rita Cauwels, Prof. Kristiane Van Lierde, Prof. Constantinus Politis, Prof. Greet Hens en Prof. Patrick Thevissen. Ik wil jullie bedanken om dit proefschrift aan een kritische analyse te onderwerpen. Jullie opmerkingen en suggesties waren bijzonder leerrijk en zijn de kwaliteit alleen maar ten goede gekomen.

Datacollectie en -analyse bij klinisch onderzoek is een intensief werk en ik kon hierbij rekenen op de hulp van vele mensen. Veronique Thienpont, jij hielp me bij het nemen van afdrukken bij de 5-jarige schisispatiëntjes. Prof. An Verdonck, jij was mijn eerste aanspreekpunt toen ik een samenwerking met de KU Leuven wou opzetten. Ik ben je heel dankbaar voor het ter beschikking stellen van onderzoeksdata en je bijdrage aan verschillende manuscripten. Arianne Lewyllie, jij hielp in Leuven en Gent bij de datacollectie en het scoren van de gipsmodellen. Prof. Peter Claes en dr. Alejandra Ortega-Castrillon, jullie hulp was onontbeerlijk bij de verwerking van de 3D beelden. Laura Manalili, jouw masterproef was de eerste die ik begeleidde. De data die je nauwgezet verzamelde en analyseerde, kon ik nadien nog verder uitbreiden en vormden de basis voor de laatste studie van dit proefschrift. Prof. Nasser Nadjmi en Prof. Gwen Swennen, bedankt om datacollectie in jullie respectievelijke centra mogelijk te maken. Jullie bijdragen maakten het mogelijk om een voldoende

grote steekproef te bekomen. Dr. Stefanie De Buyser, bedankt voor de uitgebreide statische analyses en rapporten.

Mama en papa, dit moment lijkt me ideaal om even terug te kijken op de afgelopen 15 jaar. Na mijn middelbaar school in Antwerpen kwam ik uiteindelijk in Gent terecht, de stad waar Céline studeerde en waar ook jullie gestudeerd hadden. Ik kreeg de vrijheid om de richting van mijn keuze te studeren, ging op kot, kreeg fantastische vrienden en beleefde er prachtige jaren als student. Bedankt hiervoor. Jullie hebben me van jongs af aan heel duidelijke en kostbare waarden en normen meegegeven die ik tot op de dag van vandaag gebruik. Jullie leerden me onder andere met weinig woorden dat een mooi resultaat het gevolg is van onvoorwaardelijke inzet. Hierin schuilt ook jullie bijdrage aan dit proefschrift. Wat had ik ook graag gehad dat opa dit moment kon meemaken.

Mijn 2 lieve zussen, Céline en Frédérique, bedankt om de afgelopen 30 jaar mijn drukke aanwezigheid te verdragen en me tegelijk te voorzien van jullie nuchtere analyses. Het doet me enorm veel plezier hoe jullie Aimée een warm hart toe dragen.

Liefste kleine Aimée, jij kwam ter wereld toen de laatste paragrafen van dit proefschrift net neergepend waren. Sindsdien brengt jouw aanwezigheid brengt ons intens geluk.

Liefste Noëmi, jij verdient het slotakkoord in dit dankwoord. Jouw analytisch denken heeft me geholpen bij elke stap van dit proefschrift en je nauwkeurigheid is nauwelijks te evenaren. Maar een nog grotere bijdrage was je steun de afgelopen 5 jaar. Je stond op elk moment pal achter me en geloofde als geen ander dat deze PhD een succes zou worden. Sinds de geboorte van Aimée schittert ons geluk nog wat extra. Het maakt met ontzettend trots te zien hoe je ons gezin omringt met liefde.

It seems the best is yet to come.

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Scientific Reviewing

Ad hoc reviewer for:

- European Journal of Orthodontics
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- Cleft Palate-Craniofacial Journal

LIST OF PUBLICATIONS

1. Thienpont V., **Thierens L. A. M.**, De Pauw G. A. M. Orthodontische handling bij schisispatiënten. Het Tandheelkundig Jaar 2015 **2015**;151-68.
2. **Thierens L. A. M.**, Brusselsaers N., De Roo N. M. C., De Pauw G. A. M. Effects of labial adhesion on maxillary arch dimensions and nasolabial esthetics in cleft lip and palate: a systematic review. Oral Dis **2017**;23:889-96.
3. **Thierens L. A. M.**, Verhoeven B., Temmerman L., De Pauw G. A. M. An esthetic evaluation of unilateral canine substitution for a missing maxillary lateral incisor. J Esthet Restor Dent **2017**;29:442-9.
4. De Roo N. M. C., **Thierens L. A. M.**, Temmerman L., Dekeyser E., Boelens J., De Pauw G. A. M. The evaluation of the transport medium for extracted premolars prior to cryopreservation: an in vitro study. Cell Tissue Bank **2018**;19:697-704.
5. De Roo N. M. C., **Thierens L. A. M.**, Temmerman L., De Pauw G. A. M. The evaluation of the transport medium for extracted premolars prior to cryopreservation: a systematic literature review. Cell Tissue Bank **2018**;19:259-67.
6. **Thierens L. A. M.**, De Roo N. M. C., De Pauw G. A. M., Brusselsaers N. Assessment modalities of non-ionizing three-dimensional images for the quantification of facial morphology, symmetry, and appearance in cleft lip and palate: a systematic review. Int J Oral Maxillofac Surg **2018**;47:1095-105.
7. **Thierens L. A. M.**, De Roo N. M. C., De Pauw G. A. M., Brusselsaers N. Quantifying Soft Tissue Changes in Cleft Lip and Palate Using Nonionizing Three-Dimensional Imaging: A Systematic Review. J Oral Maxillofac Surg **2018**;76:2210 e1- e13.
8. **Thierens L. A. M.**, Lewyllie A., Temmerman L., De Roo N. M. C., Verdonck A., Cadenas de Llano Perula M., et al. A retrospective intercenter comparison of two surgical protocols through the dental arch relationship of 5- to 6-year-old unilateral cleft patients. Clin Oral Investig **2019**;23:1777-84.
9. **Thierens L. A. M.**, Moerman S., Van Elst C., Vercruysse C., Maes P., Temmerman L., et al. The in vitro remineralizing effect of CPP-ACP and CPP-ACPF after 6 and 12 weeks on initial caries lesion. J Appl Oral Sci **2019**;27:e20180589.

10. **Thierens L. A. M.**, Van de Velde T., De Pauw G. A. M. Orthodontic Management of a Migrated Maxillary Central Incisor With a Secondary Occlusal Trauma. Clin Adv Periodontics **2020**;10:23-9.
11. **Thierens L. A. M.**, Kerckhof E., De Roo N. M. C., Temmerman L., Nadjmi N., Swennen G., et al. The Effect of Autologous Alveolar Bone Grafting on Nasolabial Asymmetry in Unilateral Cleft Lip and Palate. J Craniofac Surg **2020**;31:1687-91.
12. Van de Velde F. E. G., Ortega-Castrillon A., **Thierens L. A. M.**, Claes P., De Pauw G. A. M. The effect of manual lymphatic drainage on patient recovery after orthognathic surgery-A qualitative and 3-dimensional facial analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 2020; *Epub Ahead of Print*
13. De Roo N. M. C., Deboosere E., **Thierens L. A. M.**, Vercruysse C., Temmerman L., Verbeeck R. M. H., et al. The orthodontic bonding properties of human enamel after cryopreservation. Dent Mater J 2020; *Epub Ahead of Print*

ADDENDA

Addendum 1 - Distribution of CVM stages in each age group for both genders

			Cervical Vertebral Maturation Score					
			CS1	CS2	CS3	CS4	CS5	CS6
			Count	Count	Count	Count	Count	Count
Male	control group	≥12 - 13	8	5	6	10	0	0
		≥ 13 - 14	3	3	13	2	2	0
		≥14 - 15	0	1	6	9	4	2
		≥15 - 16	0	2	1	10	3	4
		Total	11	11	26	31	9	6
	cleft group	≥12 - 13	10	15	9	4	0	0
		≥ 13 - 14	10	10	12	10	0	1
		≥14 - 15	2	6	8	16	4	7
		≥15 - 16	2	1	3	10	8	6
		Total	24	32	32	40	12	14
Female	control group	≥ 10 - 11	9	6	5	4	0	1
		≥ 11 - 12	2	7	10	8	1	0
		≥12 - 13	1	6	2	10	7	3
		≥ 13 - 14	2	3	2	14	9	4
		Total	14	22	19	36	17	8
	cleft group	≥ 10 - 11	8	7	3	3	0	0
		≥ 11 - 12	8	11	3	1	0	0
		≥12 - 13	4	3	6	10	2	1
		≥ 13 - 14	1	0	3	10	5	3
		Total	21	21	15	24	7	4

Addendum 2 - Estimated probabilities of CS3 or higher after exclusion of CP

Estimates^a

Group	Age (y)	Mean	Std. Error	95% Wald Confidence Interval	
				Lower	Upper
cleft group	≥15 - 16	.89	.058	.72	.97
	≥14 - 15	.82	.063	.66	.91
	≥ 13 - 14	.55	.081	.39	.70
	≥12 - 13	.33	.082	.20	.51
control group	≥15 - 16	.90	.067	.68	.97
	≥14 - 15	.95	.044	.74	.99
	≥ 13 - 14	.74	.092	.53	.88
	≥12 - 13	.55	.092	.37	.72

a. Sex = Male

Estimates^a

Group	Age (y)	Mean	Std. Error	95% Wald Confidence Interval	
				Lower	Upper
cleft group	≥ 13 - 14	.92	.074	.61	.99
	≥12 - 13	.74	.101	.50	.89
	≥ 11 - 12	.20	.089	.08	.43
	≥ 10 - 11	.25	.108	.10	.51
control group	≥ 13 - 14	.85	.061	.69	.94
	≥12 - 13	.76	.079	.57	.88
	≥ 11 - 12	.68	.088	.49	.82
	≥ 10 - 11	.40	.098	.23	.60

a. Sex = Female

Addendum 3 - Estimated probabilities of CSS or higher after exclusion of CP

Estimates^a

Group	Age (y)	Mean	Std. Error	95% Wald Confidence Interval	
				Lower	Upper
cleft group	≥15 - 16	.46	.094	.29	.65
	≥14 - 15	.26	.071	.15	.42
	≥ 13 - 14	.03	.026	.00	.16
	≥12 - 13	.00	.000	.00	1.00
control group	≥15 - 16	.35	.107	.18	.57
	≥14 - 15	.27	.095	.13	.49
	≥ 13 - 14	.09	.059	.02	.29
	≥12 - 13	.00	.000	.00	1.00

a. Sex = Male

Estimates^a

Group	Age (y)	Mean	Std. Error	95% Wald Confidence Interval	
				Lower	Upper
cleft group	≥ 13 - 14	.31	.128	.12	.59
	≥12 - 13	.11	.070	.03	.34
	≥ 11 - 12	.00	.000	.00	1.00
	≥ 10 - 11	.00	.000	.00	1.00
control group	≥ 13 - 14	.38	.083	.24	.55
	≥12 - 13	.34	.088	.20	.53
	≥ 11 - 12	.04	.035	.01	.21
	≥ 10 - 11	.04	.039	.01	.24

a. Sex = Female