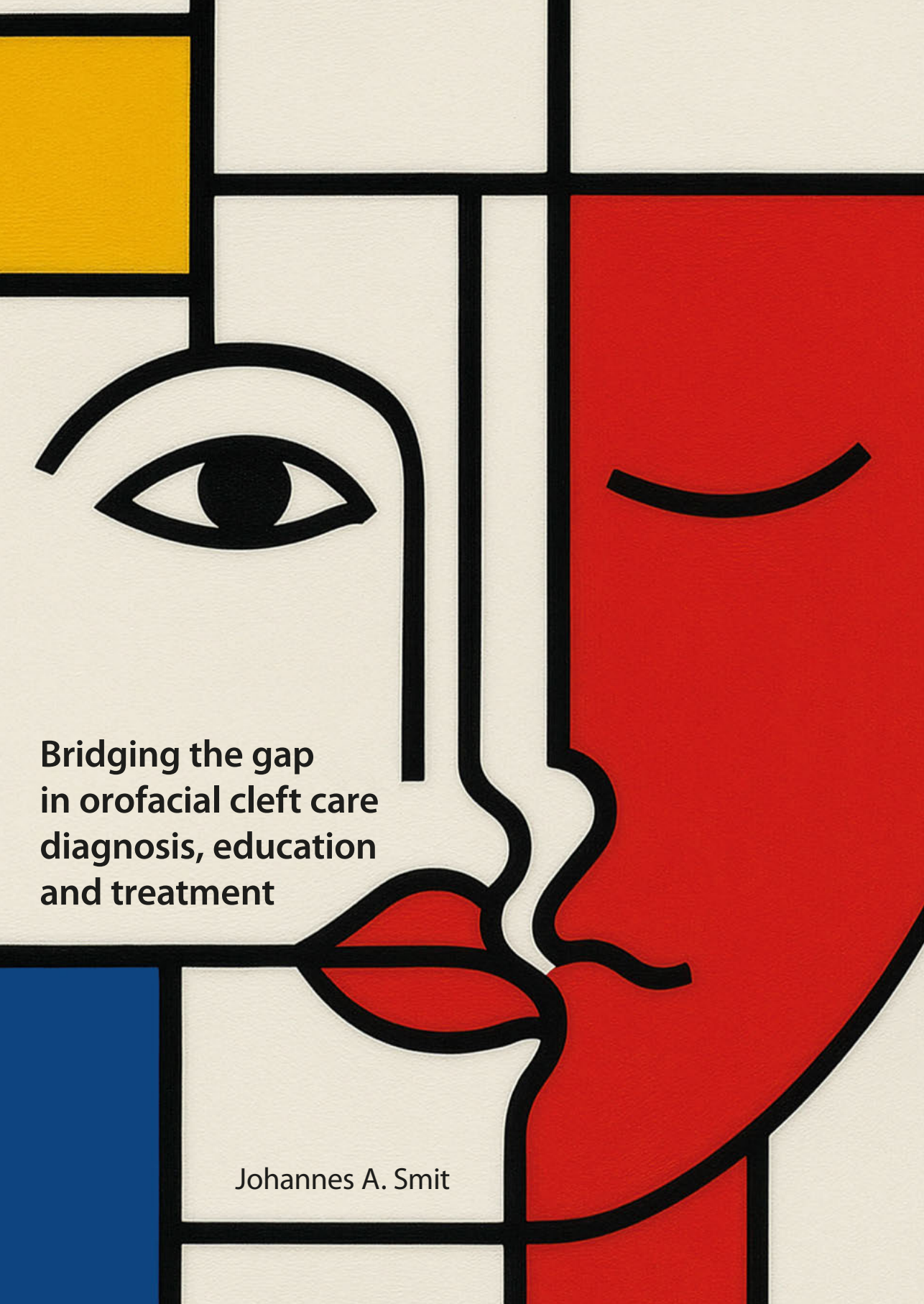

Bridging the gap in orofacial cleft care diagnosis, education and treatment

Johannes A. Smit

Bridging the gap in orofacial cleft care diagnosis, education and treatment

Johannes A. Smit

For my wife, family and friends

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Bridging the gap in orofacial cleft care diagnosis, education and treatment

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door
het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
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geboren te Amersfoort

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CHAPTER 1

INTRODUCTION AND AIMS OF THIS THESIS

Ruben P. Houkes, Johannes A. Smit, Peter A. Mossey, Peter J.W. Don Griot, Martin Persson, Amanda J. Neville, Edwin M. Ongkosuwito, Thomas J. Sitzman, Corstiaan C. Breugem

Cleft Palate Craniofacial Journal, 2023

1.1 GENERAL INTRODUCTION

Orofacial clefts (OFCs) are among the most common birth anomalies.[1] The prevalence of cleft lip and palate varies significantly globally, ranging from 3.4 per 10,000 up to 22.9 per 10,000 births.[2-5] Non-syndromic orofacial clefts can present in various forms (i.e. isolated cleft lip [CL], cleft lip alveolus [CLA], cleft lip [alveolus] and palate [CLAP] and isolated cleft palate [CP] varying in severity and laterality (unilateral or bilateral).[6] A cleft lip is characterized by a discontinuity in the upper lip due to incomplete fusion of the maxillary and medial nasal processes, whereas a cleft lip alveolus extends beyond the lip to involve the alveolar ridge, disrupting both the soft tissue and underlying bony structure, often leading to dental malocclusion and functional impairments. Causes of OFCs remain largely unknown, but a combination of genetic and environmental factors has an important share in the development.[7-8] These congenital anomalies can have an effect on appearance, speech and hearing development, cognition, mental health and ultimately on social integration. Affected children are more at risk for morbidity and mortality than their unaffected counterparts.[9-10] Many affected children experience psychological challenges related to orofacial clefts (e.g. bullying, 'not fitting in', discrimination).[11] Managing orofacial clefts is a multidisciplinary effort requiring involvement of various specialists (such as plastic surgery, speech and language pathology, maxillofacial surgery, pediatrics, dentistry, otolaryngology, audiology, psychology). While rehabilitation and treatment for cleft lip and palate are possible, they pose a significant burden to the affected individual, their family and society in both health and economic services.

1.2 DESCRIPTIVE EPIDEMIOLOGY

Data on incidence and prevalence of orofacial clefts remain unknown for some parts of the world. In other parts of the world where data are accessible, heterogeneity in sample sources (general population versus hospitals), inclusion criteria and methods of ascertainment exists, which makes comparability of data difficult.[12] Overall, findings indicate that OFCs occur in 1 in 700 live births globally. International data have shown that the prevalence of children with cleft lip (alveolus) with or without cleft palate varies between 3.4 and 22.9 per 10,000 live-borns.[13] This variation in prevalence is even more noticeable in isolated cleft palate; 1.3 up to 25.3 per 10,000 live-borns.[14] These

differences could partly be explained by the fact that isolated cleft palate is not visible externally, leading to underreporting. Highest rates of cleft lip, cleft alveolus and palate were found in China, Japan, and Latin America, while South Africa, Southern Europe, and Israel have demonstrated the lowest rates.[14-16] Sex ratios differ depending on the type of cleft. Cleft lip with or without cleft palate is more common in males, with a ratio of 2:1 (male to female). Isolated cleft palate is more common in females, with a ratio of 2:1 (female to male).[11] Cleft lip alveolus with or without cleft palate and isolated cleft palate are frequently associated with other congenital anomalies.

1.3 CLASSIFICATION OF CLEFT LIP AND PALATE

Classification is an important aspect in the study of epidemiology of OFCs. Orofacial clefts have different causes. Proper classification is a prerequisite for improving our understanding of embryology in cleft development and for comparing outcomes.[17] Detailed classification systems enable improved subgrouping of clefts, which can facilitate identification of (genetic) causes and biological mechanisms in etiology. The value of classification is perhaps best illustrated by wide ranges of prevalence and different recurrence risks for all subcategories of orofacial clefts, an important aspect for proper genetic counseling.[18-19]

Innovative classification systems were often designed to overcome limitations of previous systems. For instance, Victor Veau (1871 – 1949), a French surgeon active in Paris, created four subtypes of cleft palate based on embryological defects. Veau's classification responded to the complexity and impracticality of Truman W. Brophy's system (1848–1928).[20] Also designed from an embryological point of view was the classification system from Poul Fogh-Andersen.[20-21] Fogh-Andersen criticized other systems which used the alveolar process as a marking point as too arbitrary and suggested using the incisive foramen instead. In 1989, the LAHSHAL registration system was developed to categorize or describe cleft lip and/or palate. Through this system, a distinction could be made between uni- and bilateral clefts and the extension of the cleft.[22] LAHSHAL is an acronym for right lip, right alveolus, hard palate, soft palate, hard palate, left alveolus, left lip. The initial letter of each anatomical part can be written in uppercase (completely affected) or lowercase (partially affected), while a minimal cleft is indicated by an asterisk (*); a dot (•) is used to indicate that the anatomical part is normally

developed. Through the LAHSHAL system, over 12,000 combinations can be made to describe clefts in terms of anatomy and severity. More recently, the International Statistical Classification of Diseases and Related Health Problems (ICD) system has been promoted for both epidemiology and reimbursement.[23] The ICD system is used in the WHO Global Burden of Disease (GBD) project, which has made reporting by ICD codes required for most governmental health registries.[24-25] Healthcare insurance companies in both Europe and North America have also mandated use of the ICD system for reimbursements. These two forces have led to the broad implementation of the ICD system, despite concerns about its specificity, exclusivity, and comprehensiveness for classifying OFCs.

Although each of these classification systems has provided value, none of them achieved universal acceptance among care givers. Consequently, a great variety of classification systems is currently being used both nationally and internationally. This hampers mutual understanding, communication and treatment outcome comparison among specialists and prevents the development of a standardized classification or prevalence-tracking system.

1.4 EMBRYOLOGY OF CLEFT LIP AND PALATE

Cleft lip and/or palate is associated with over 400 syndromic disorders, including common syndromes such as Stickler syndrome and 22q11 deletion syndrome (Velocardiofacial syndrome).[26] Genes often associated with non-syndromic causes are MSX1, PVRL1, and FGFR2.[27] In 50% of cleft palate cases and 70% of cleft lip and palate cases, the cause is nonsyndromic.[28] In these cases, etiology is complex and not yet completely understood. Much of the embryological knowledge currently used by clinicians is derived from studies conducted by pioneering embryologists over 100 years ago, though verifying these studies using modern techniques remains challenging.[29-33] In the fourth week of embryogenesis, the five facial prominences appear and surround the stomodeum.[30] These prominences derive from the pharyngeal arches and are composed of mesenchyme that originates from the neural crest. Rostral to the forebrain, the frontonasal prominence appears.[29] The mandibular and maxillary prominences, which originate from the first branchial arch, bound the stomodeum laterally (via maxillary processes) and caudally (via mandibular processes).[30-32] The maxillary prominences expand

and form the cheeks together with the mandibular processes. This process brings the medial nasal prominences into contact, leading to their fusion during the sixth week of embryogenesis. The maxillary processes fuse with the medial nasal processes to form the upper lip.[34]

The development of the palate begins in the fifth week of gestation, following the formation of primary facial structures. At this stage, the palate consists of two parts: the primary and secondary palate (Figure 1). The intermaxillary segment gives rise to the primary palate, which contains the four incisors, the philtrum, and a small segment of the hard palate (anterior to the incisive foramen) (Figure 1; picture 1-3).[30,35] Two palatal shelves originating from the oral side of the maxillary processes precede the development of the secondary palate. The secondary palate encompasses the hard and the soft palate (posterior to the incisive foramen). The separated shelves grow caudally until the eighth week of gestation.[36-37] At this moment, the palatal shelves elevate to a horizontal position above the tongue and merge at the midline (Figure 1; picture 4-6). Historically, it was believed that a retracted tongue (as in Pierre Robin sequence) physically obstructed palatal shelf elevation, leading to cleft palate. However, recent studies suggest this condition is

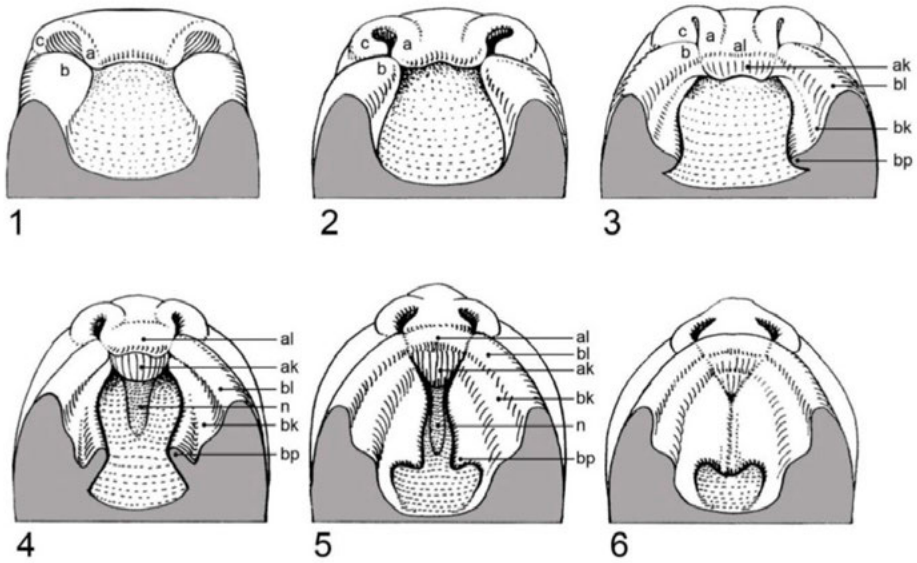

Figure 1. adapted from Vermeij-Keers et al, *Klinische Anatomie en Embryologie, 4e druk*, 2014, with permission.

caused by a developmental defect affecting tongue movement.[38] Fusion of the palate occurs from anterior to posterior, concluding with uvular fusion and including integration with the nasal septum.[39] Moreover, these shelves fuse with the primary palate anteriorly, and with the nasal septum cranially. These fusion processes, critical for the formation of a functional palate, are completed by the twelfth week of gestation.[40]

Clefts of the primary and secondary palate have different origins. A cleft in the primary palate occurs most frequently between the primary and secondary palate. A complete cleft lip can present in three subtypes: 1. Involvement of the lip only. 2. Involvement of the lip, nose, and alveolar ridge. 3. Extension to the foramen incisivum. This part of the palate is called the primary palate. Clefts of the primary palate are caused by increased apoptosis, increased bone resorption or a decreased volume of the premaxilla.[41-42] A cleft in the secondary palate can be due to failure of the shelves to adhere, elevate or fuse. Growth, rotation, and fusion of the prominences is hindered by genetic, mechanical, or teratogenic factors.[41-42]

1.5 ULTRASONOGRAPHY

Globally, transabdominal ultrasound (US) screening during the second trimester of pregnancy is frequently performed to evaluate the fetal face. It was initially introduced to detect neural tube defects. However, other anatomical structures, such as the fetal upper lip, are also readily visible on ultrasonography.[43] Moreover, it is important to note that accessibility to US screening varies widely across different regions and healthcare systems. Countries with access to ultrasound screening often follow different protocols, which vary in terms of frequency and extent of facial investigation.[44]

US evaluation of the philtrum and upper lip for possible cleft lip (with or without cleft palate) demonstrates a sensitivity of 88%, indicating its effectiveness in detecting these conditions.[45] For the complete group of patients with OFCs, this prenatal sensitivity is lower because of the extremely low detection rate of cleft palate only (0 – 1.4%).[45] This low detection rate is largely attributed to a lack of sonographic indicators, making it difficult to investigate the palate. Moreover, assessing the human palate is challenging, since the visibility is often obstructed by the tongue. Evaluation of the palate

is mandatory in cases of other anomalies, such as cardiac anomalies or micrognathia. Subtle forms of cleft lip, in which a small indentation in the vermillion border (the junction between the lip and skin) is seen (commonly referred to as a 'forme fruste'), are likely to be missed on ultrasound. In case of a cleft lip, the position of the alar base (nostrils) can guide ultrasonographers in determining whether the alveolar ridge of the palate is affected as well. Isolated incomplete cleft lip appears as a linear defect from the lip towards the nasal floor. In complete cleft lip, the lip defect can be easily visualized, although the nose distortion is likely to be minimal. Embryological fusion of the secondary palate begins at the incisive foramen, which serves as the central landmark, and progresses dorsally toward the uvula. This fusion process serves as a guide for ultrasonography. If the velum appears normally fused, the palate is expected to be intact, as the fusion of the palate progresses, in a zipper-like manner, from the incisive foramen dorsally. If a bifid or absent uvula is observed, it is often indicative of a defect in the palate. A "physiological" or intact uvula strongly resembles an 'equals sign', and this feature can be used as a diagnostic indicator.[46]

AIMS OF THIS THESIS

The thesis was initiated to better understand the anatomy and embryology of cleft lip and/or palate. By better understanding palatogenesis and development of craniofacial muscles, treatment of cleft lip and/or palate could be optimized and velopharyngeal insufficiency (VPI) and revision surgery could be reduced. Ultimately, this could result in improved patient and parent satisfaction, increased participation in social life and work, and less burden on the healthcare system, leading to an optimal quality of life. Moreover, a better understanding of the anatomy and embryology could enhance medical education and counseling future parents faced with a child with cleft lip or palate.

To compare treatment results among craniofacial specialists, but also to improve our understanding of the pathogenesis of craniofacial malformations, it is prudent to classify craniofacial clefts in a uniform way. In **Chapter 2,** a summary is provided of the most commonly used classification systems globally. Special focus is given to the ten most commonly used classifications and potential pitfalls of each system.

Although fistulae after primary palatoplasty are not uncommon, individual caregivers are confronted with difficulties in classification and optimal treatment, as fistulae cause multiple issues for patients, including nasal regurgitation, speech difficulties, and challenges in maintaining proper oral hygiene). In **Chapter 3** we discuss the opinions of craniofacial surgeons from 74 countries that participated in an International Cleft Palate Fistulae webinar. Our goal was to gain better insight into the classification systems being used and their limitations. In **Chapter 4**, a continuation of the previously mentioned chapter, a critical appraisal is performed in terms of surgical approaches of palatal fistulae.

In **Chapter 5**, a large national cohort of submucous cleft palate (SMCP) patients is investigated in terms of patient characteristics and the delay in diagnosis. In **Chapter 6**, the focus is on another subgroup of cleft palate patients, patients with Robin Sequence. These patients show a triad of symptoms, i.e. cleft palate, retrognathia and macroglossia or ankyloglossia. In this European study, we will focus on differences between countries with lower- and higher gross domestic product (GDP) per capita in terms of the diagnosis and treatment of Robin Sequence.

Another important aspect of prenatal diagnosis of cleft lip and palate is parental counseling. In the Netherlands, parents are allowed to opt for termination of pregnancy without any prerequisite to specify their reasons for choosing abortion. In 2007, all pregnant women in the Netherlands were offered a structural anomaly scan at the 20th gestational week. In **Chapter 7,** the influence of the 20-week anomaly scan on the prevalence of cleft lip, cleft lip and palate, and cleft palate patients in the Netherlands before and after nationwide introduction is assessed. Moreover, a comparison of termination rates of pregnancies is compared in the literature with other studies from Israel, UK, South Korea, USA and Denmark to provide international perspective.

Chapter 8 investigates the prioritization of craniofacial cleft care as a result of the COVID-19 pandemic. Major groups of patients with craniofacial anomalies are included, e.g. Robin sequence, primary cleft lip and/or palate surgery, craniosynostosis with and without increased intracranial pressure are taken into account.

COVID-19 restrictions affected collaborative on-site missions between Europe and Africa. The purpose of **Chapter 9** is to assess the effect of digital patient discussion in terms of peer consultation and training of residents and medical interns. These outcomes are compared to traditional on-site training between the Netherlands and Uganda. In addition to peer consultation through patient discussion, a more innovative way of medical education is investigated in **Chapter 10**. By using smart surgical glasses, colleagues from all over the world are able to participate in live-streamed surgeries while working at different locations and restricted by pandemic regulations.

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PART 1

EPIDEMIOLOGY, IMAGING AND TREATMENT OF OROFACIAL CLEFTS

CHAPTER 2

CLASSIFICATION SYSTEMS OF CLEFT LIP, ALVEOLUS AND PALATE: RESULTS OF AN INTERNATIONAL SURVEY

Ruben P. Houkes, Johannes A. Smit, Peter A. Mossey, Peter J.W. Don Griot, Martin Persson, Amanda J. Neville, Edwin M. Ongkosuwito, Thomas J. Sitzman, Corstiaan C. Breugem

Cleft Palate Craniofacial Journal, 2023

ABSTRACT

Objective
This study aimed to identify commonly used classification systems by cleft providers around the world, including the perceived indications and limitations of each system.

Design
A cross-sectional survey.

Participants
A total of 197 registrants from three international cleft/craniofacial meetings.

Intervention
Participants were sent a web-based questionnaire concerning cleft classification systems.

Main Outcome Measures
Frequency of commonly used classification systems, their perceived indications and limitations.

Results
A total of 197 respondents from 166 different centers completed the questionnaire. Healthcare professionals from all disciplines responded, with the most frequent respondents being plastic surgeons (38.1%), maxillofacial surgeons (28.4%) and orthodontists (23.9%). Eighteen different classification systems were in use. The most frequently used systems were the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (35.5%), LAHSHAL (34.0%), and Veau (32.5%) classification systems. Most respondents (32.5%) indicated that anatomical and morphological characteristics are essential components of a classification system. However, respondents indicated that their current classification systems lacked sufficient description of cleft extension and severity.

Conclusion
Great variety in the use of classification systems exists among craniofacial specialists internationally. The results recommend the usage of the LAHSHAL classification of OFCs, due to its comprehensiveness, relatively

high implementation rate globally, convenience of usage and complementarity with the ICD-10 system. Moreover, it can overcome deficiencies inextricably linked to ICD-10, such as incapacity to describe laterality and clefts of the alveolus. More international exposure to the merits of using the LAHSHAL classification system would be highly recommended.

Keywords
Classification system; cleft lip; cleft palate; orofacial cleft; survey.

INTRODUCTION

Orofacial clefts (OFCs) are the most common type of craniofacial anomaly, occurring in approximately 1:700 live births (Calzolari et al., 2007; Mossey et al., 2012; Mai et al., 2019; World Health Organization, 2021a). OFCs can have a profound impact on a person's quality of life, which can lead to problems with feeding, speech (e.g. velopharyngeal insufficiency), hearing (e.g. recurring otitis media), dentition (e.g. tooth decay), neurodevelopmental disorders, psychological aspects and socialization (Gomes et al., 2009; Wehby et al., 2010; Smallridge et al., 2015; Waylen et al., 2015; Tillman et al., 2018). The physiological severity of these problems is not correlated with the severity and location of the cleft. However, accurate cleft classification is essential for predicting treatment need, planning clinical interventions and evaluating treatment outcomes. Consequently, classifying clefts in a clear, easy to understand and concise manner is a key element of cleft care.

Cleft classification also plays an important role in studying the epidemiology of OFCs. OFCs are etiologically heterogeneous, and untangling the interactions of environmental and genetic risk factors leading to OFCs requires accurate classification of cleft type (Dixon et al., 2011). More specific classification systems enable greater subgrouping of clefts, which can facilitate identification of the causes and biologic mechanisms for OFCs. The value of cleft classification to epidemiology is perhaps best illustrated by the different recurrence risks for cleft lip, cleft lip and palate and cleft palate, which is a key difference used in genetic counseling (Sivertsen et al., 2008; Grosen et al., 2010). A standardized, accurate phenotypic classification of clefts is thus crucial to understand the epidemiology of OFCs.

During the history of cleft care, many classification systems have been developed and implemented. New classification systems have often been developed to classify clefts more accurately or to overcome limitations of existing systems. For example, the Veau classification system was developed as a response to the Brophy classification system, since Brophy was considered too complex and impractical (Allori et al., 2017). Another classification system is that of Fogh-Andersen, which was designed from an embryological point of view (Allori et al., 2017; Fogh-Andersen, 1971). Fogh-Andersen found that

the alveolar process as a marking point was too arbitrary and suggested to use the incisive foramen instead. In 1989, the LAHSHAL recording system or registration system was designed for paraphrasing cleft lip and palate in which a distinction could be made between unilateral and bilateral clefts and to describe the extent of clefting (i.e. total versus subtotal clefts) (Kriens, 1989). While each of these classification systems provided value, none achieved universal acceptance among providers.

More recently, the International Statistical Classification of Diseases and Related Health Problems (ICD) system has been promoted for both epidemiology and reimbursement (World Health Organization, 2021b). The ICD system is used in the WHO Global Burden of Disease (GBD) project, which has made reporting by ICD codes required for most governmental health registries (Truelsen et al., 2015; World Health Organization, 2021c). Healthcare payers in both Europe and North America have also mandated use of the ICD system for reimbursements. These two forces have led to broad implementation of the ICD system, despite concerns with its lack of specificity and comprehensiveness for classifying OFCs.

It is prudent to make a difference between registration and classification of clefts. For example, the ICD-10 classification, although described as a "classification", is actually a registration process for coding and categorization of disease as opposed to being designed for the primary purpose of classification *per se*. This article makes no particular distinction between registration and classification systems.

As a result of great variety in possible classification systems, craniofacial specialists often use different classification systems. This hampers mutual understanding, communication and treatment outcome comparison among specialists and prevents the development of a standardizing system. The aim of this article is to describe which classification systems are used globally, including their perceived indications and limitations. Furthermore, it aims to make a recommendation on which system is most suitable for global implementation so development of a global prevalence system and improvement of scientific data comparison is achievable.

METHODS

This study was a cross-sectional survey. A questionnaire was sent to 2,140 registrants of the 2015 Cleft Craniofacial meeting in Gothenburg, Sweden, the 2017 13th International Cleft Meeting in Chennai, India, and the 2019 European Cleft Palate Craniofacial Association (ECPCA) meeting in Utrecht, the Netherlands. The questionnaire was also sent to American Cleft Palate-Craniofacial Association (ACPA) members through the ACPA member portal and to members of the European Cooperation in Science and Technology (COST) Action and members of the European Cleft and Craniofacial Initiative for Equality in Care (ECCE).

The questionnaire comprised a combination of 20 multiple choice and open-ended questions investigating the use of cleft classification systems and specific reasons why craniofacial specialists opt for these classification systems (Supplementary data file 1). The respondents were asked to specify the limitations of their preferred system and to identify the elements they believed were essential in the ideal cleft classification system. The questionnaire was designed and distributed using SurveyMonkey, an online survey application. Responses were gathered anonymously. A reminder was sent 14 days after the initial invitation.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was adhered to while preparing this manuscript. Numbers and percentages are obtained from SurveyMonkey and bar charts were designed using SPSS (Statistical Program for Social Sciences, version 26; SPSS Inc., Chicago, IL, USA) statistical software. Approval of the Institutional Review Board was received.

RESULTS

A total of 197 respondents from 166 cleft centers and 61 countries completed the questionnaire between September 1, 2020 and October 31, 2020. Most respondents originated from Europe (50.0%), Asia (21.8%) and North America (13.2%) (Supplementary data file 2). Respondents included providers from a range of functions with the most frequent being plastic surgeons (38.1%), maxillofacial surgeons (28.4%), and orthodontists (23.9%) (Figure 1).

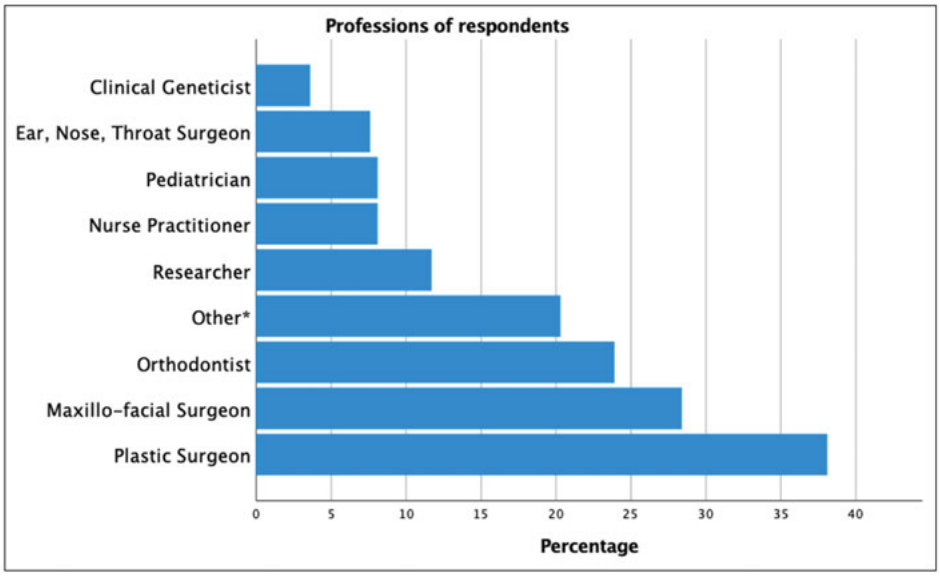

Figure 1. Distribution of professions among respondents.

† Note that the sum of the number of professions is greater than 197 and subsequently exceeds 100%. The reason for this is that quite often respondents answered the survey on behalf of their entire cleft care team and filled in multiple professions.

The majority of respondents noted that the registration/classification was done multiple times during cleft management. Seventy-nine percent of the respondents classified clefts at the first visit, 41.6% during the pre-operative work-up, and 26.4% re-evaluated the classification during primary surgery (Figure 2). Fifty-four percent of the respondents noted that the classification is mainly performed by a specific specialist, primarily by plastic surgeons, maxillofacial surgeons or cleft surgeons. Furthermore, according to 81.2% of respondents, classification was done for both clinical and research purposes. Forty-two percent of the respondents stated that they also classify clefts for a national registration and 25.4% classified for reimbursement purposes.

The most frequently employed classification systems were ICD-10 (35.5%), followed by LAHSHAL (34%), Veau (32.5%), Kernahan's striped-Y (22.8%) and the ACPA classification (Harkins et al., 1962) (21.3%) (Figure 3). A great variety existed in which classification systems were preferred both nationally and internationally, as shown in Table 1. Respondents from the United Kingdom were most homogenous in classifying clefts: 93.3% (14/15) respondents from the UK stated that they used LAHSHAL, since this was required for their

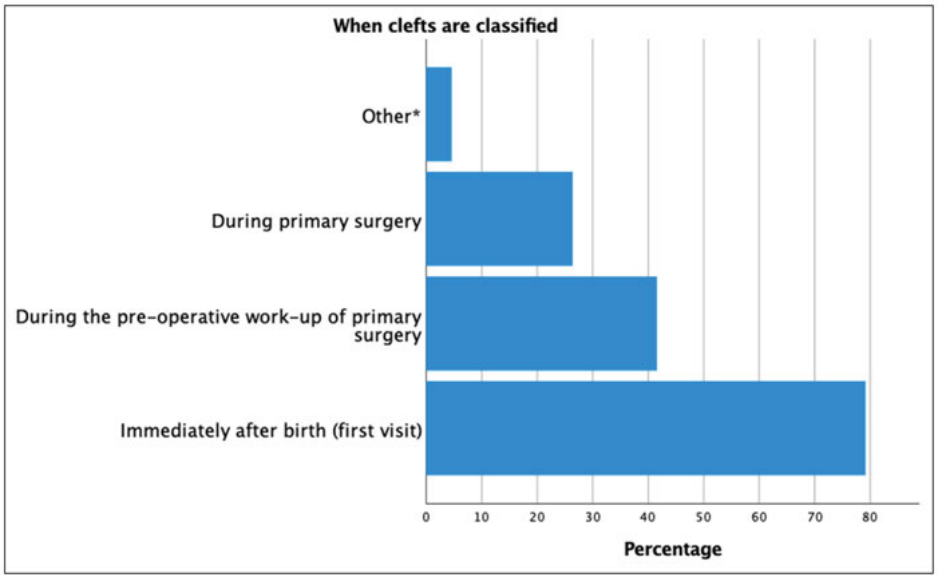

Figure 2. Timing of classifying clefts among respondents.
Abbreviations: SABG; secondary alveolar bone grafting.

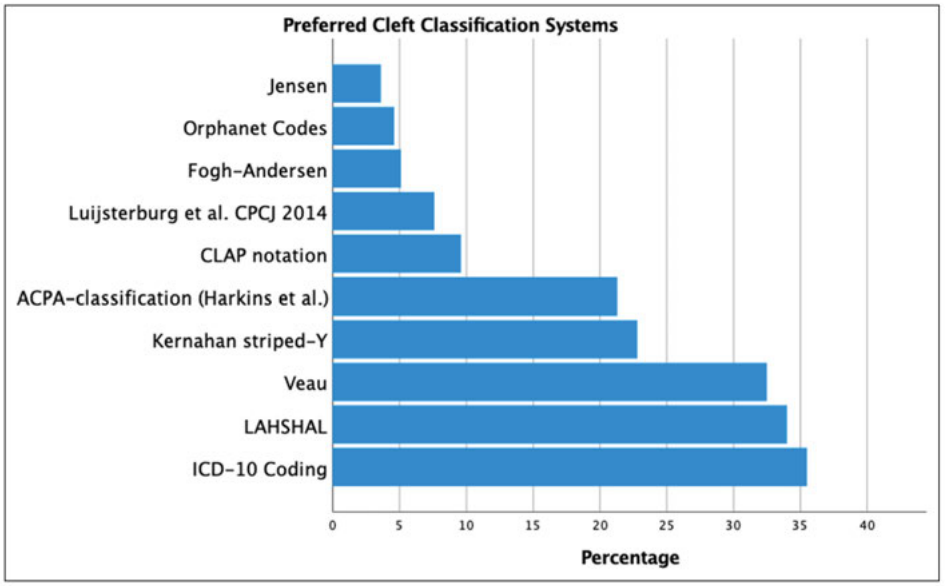

Figure 3. Preferred classification systems among respondents. It was possible for the participants to choose multiple systems.
Abbreviations: ACPA; American Cleft Palate-Craniofacial Association; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision.

Table 1. Systems used in countries with five or more respondents. Expressed in number of respondents.[a]

	LAHSHAL	Veau	Fogh-Andersen	Kernahan's striped-Y	ACPA (Harkins et al.)	CLAP notation	ICD-10	Orphanet codes	Jensen	Luijsterburg et al. CPCJ 2014
India (n = 24)	3	5	1	8	10	2	1	.	1	2
USA (n = 19)	3	13	.	1	8	5	13	.	1	.
UK (n = 15)	14	1	.	.	1	1	1	.	.	1
Germany (n = 10)	8	.	1	.	.	.	6	1	.	.
Netherlands (n = 10)	1	4	.	1	1	1	5	.	.	7
Sweden (n = 9)	.	3	1	2	.	.	6	1	.	.
Indonesia (n = 8)	3	2	.	1	.	2	4	.	.	1
Switzerland (n = 6)	6	.	1	.	1	.	.	1	.	.
Egypt (n = 5)	1	.	.	4	1	.	.	.	.	.
France (n = 5)	.	3	.	.	.	.	2	3	.	1

Abbreviations: ACPA: American Cleft Palate-Craniofacial Association; CLAP: cleft lip, alveolus and palate; CPCJ: Cleft Palate-Craniofacial Journal; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision; LAHSHAL: lip, alveolus, hard palate, soft palate, hard palate, alveolus, lip.

[a] Note that several participants responded to this question with multiple classification systems. Therefore the total of each column exceeds the participants per country.

national registry (CRANE, 2021). Multiple respondents reported that ICD-10 was required for reimbursement and registration purposes. Besides the ten classification systems proposed in our survey, respondents also indicated that another eight classification systems were used (Supplementary data file 3).

When asked which information was most essential when using a preferred cleft classification, 32.5% of the respondents indicated that anatomical and morphological characteristics were essential in the classification process (Table 2). Furthermore, almost 20% of the respondents stated that the extension and severity of the cleft were decisive for their preferred system. These variables were essential since they influence both the timing and choice of treatment, according to 26% of the respondents. The differentiation of incomplete versus complete clefts, submucous clefts and whether the alveolus was affected, were also of importance for planning suitable treatment. Other applications for classification were research, clear documentation and registration, and the evaluation of treatment results.

Table 2. Essential data and manners in which way this data is essential according to respondents

Essential data	N
- Anatomical and morphological characteristics	64
- Severity/extension of cleft	39
- The data influences timing and choice of treatment and surgery	52
- The data is important for research purposes	23
- The data is essential for documentation/registration	14
- The data is essential for evaluating treatment results	9

When asked to identify limitations of their current cleft classification system, a frequent limitation of the previously mentioned classification systems was the imprecise description of the anatomical and morphological cleft characteristics (i.e. the severity and extension of the cleft) (Table 3).

Furthermore, commonly used systems often did not include submucous clefts, Simonart's bands and nasal deformities. Another limitation cited was the fact that some clefts also failed to fit precisely into one of the categories of the used system. Due to these previously mentioned limitations, 8.6% (n = 17) of respondents would not recommend their used classification system to other cleft caregivers.

Table 3. Recurring limitations per classification system. The numbers represent the number of respondents addressing a limitation to a particular system.

	Anatomical description is too imprecise	SMCP not included	Lack of graphic information	Cleft does not fall neatly in categories	Too elaborate
LAHSHAL	21	7	1	1	.
Veau	24	3	2	1	.
Fogh-Andersen	2	.	.	.	.
Kernahan's striped-Y	12	2	.	.	.
ACPA	13	.	1	1	1
CLAP	5	.	1	.	.
Jensen	1	.	.	1	.
ICD-10	21	.	1	.	.
Orphanet Codes	2	.	.	1	.
Luijsterburg	1	.	.	1	1

Abbreviations: ACPA: American Cleft Palate-Craniofacial Association; CLAP: cleft lip, alveolus and palate; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision; LAHSHAL: lip, alveolus, hard palate, soft palate, hard palate, alveolus, lip.

An ideal classification should have a more precise description of the severity and extension of the cleft, according to 71 respondents (36.2%). Another important feature of an ideal classification is that the classification system is easy to use, which was mentioned by 43 respondents (21.8%). Twenty-one (34.4%) countries of a total of 61 countries within our respondents have a national registry for OFCs (Supplementary data file 4). In the United States of America, registry is state-dependent. Furthermore, 19.3% did not use a local or hospital registry.

DISCUSSION

The present study demonstrates great heterogeneity among clinicians involved in cleft care when they classify OFCs. A total of 197 clinicians from 166 centers around the globe completed the questionnaire. Respondents used eighteen different cleft registration or classification systems. Frequently cited limitations of existing systems were imprecise description of cleft extension and severity, failure to include submucous cleft palate, and difficulty in precisely classifying all clefts within the provided categories of a system.

As is mentioned in the introduction of this article, it is important to make a difference between registration and classification of clefts. Since systems that only register or register and classify are both commonly used for seemingly the same purposes, we did not distinguish between the two systems since we were only interested in the way OFC diagnoses were collected.

As respondents note, the anatomical description and the description of the extension or severity of the cleft are both the main components and greatest limitations at the same time for the majority of systems. For example, the Veau classification differentiates between the soft and hard palate but does not take into account cleft lip/alveolus and the morphological severity of palatal clefts (Veau, 1931). The ICD-10 system has been greatly improved compared to the ICD-9 system concerning the extensiveness of the anatomical varieties of clefts, but it does not allow for the documentation of morphological severity (i.e. completeness), laterality, the presence of asymmetry in the case of bilateral cleft lip/alveolus, microforms, or for clefts of the alveolus (Wang et al., 2014; Allori et al., 2016; McBride et al., 2016). A system which solves at least one of these problems, the laterality problem, is the Kernahan striped-Y classification system (Kernahan, 1971). Though, it cannot be used for verbal communication or description in the text format nor can it be used for computer archiving (Kernahan, 1973). It was commonly used in the era of paper-based medical records, but its usage seems to have has diminished considerably with the advent of electronic health records (EHRs).

Kriens made some valuable suggestions about an ideal classification system. He stated that the following were pre-requisites in an ideal recording system or index for CLP: it should be: 1. Simple, so as to be accepted. 2. Concise, for accurate recording. 3. Flexible, to account for even rare presentations. 4. Exact, to facilitate research and statistics. 5. Morphological, to be able to visually assess. 6. Graphic, for clarity and to avoid ambiguity (Kriens, 1989). In an attempt to reach this ideal classification system, Kriens developed the LAHSHAL system.

LAHSHAL is a palindrome which is based upon the anatomy of the patient and proceeds from the right side towards the left side, designed to facilitate the recording during clinical examination. Each column of the acronym is filled as follows to confirm whether that part of the anatomy is involved. A capital letter is noted when an anatomic structure is completely clefted while

a lowercase letter is noted when the cleft is only incomplete. Furthermore, some symbols can be used to describe other deviations. Namely, an asterisk (*) is noted when minimal clefting (e.g., lesser-form cleft lip, notched alveolus, submucous cleft palate) occurs, and a dot (•/.) means that the anatomic feature is unaffected. A plus sign can be noted in the L column when a skin band (i.e. a Simonart's band) is present. Note in table 3 that a number of participants indicated that the LAHSHAL lacks anatomic specificity. However, not all clinicians are fully aware of the potential of this extremely elaborate classification system. Due to its extensiveness, over 12,000 combinations can be made when using the LAHSHAL system for OFCs. As such, it is extremely detailed but as a result of this it has a steep learning curve to implement it in clinical practice. Finally, the LAHSHAL system lends it well to use in electronic health records.

McBride et al. have suggested that ideally, a coding system for OFCs should be precise, logical, reproducible, accurate, and sufficiently descriptive (McBride et al., 2016). They suggest that it must be precise enough to differentiate between subphenotypes; it should be user-friendly and accurate to be used globally between various health care professionals and epidemiologists with little need for training. It should also be sufficiently descriptive to differentiate laterality and completeness to facilitate the future of genetic and etiological research while being easily interpreted by users from different research and clinical backgrounds. In addition to these requirements, the coding system must remain relevant to the current globally recognized system of recording disease, the ICD-10 system. McBride et al. illustrated how LAHSHAL codes could be converted to ICD-10, and potentially be automated using an algorithm (McBride et al., 2016). Therefore, the LAHSHAL classification (or a variant) and the Luijsterburg et al. classification, as described in this manuscript, are potentially useful tools and could be a complement to the ICD-10 system.

Several limitations of this study have to be addressed. A total of 197 respondents among 2,140 invitations completed our survey. Some healthcare professionals received multiple invitations when they attended more than one congress. It was not clearly mentioned whether a respondent had to respond individually or on behalf of their entire cleft team. Consequently, the response rate is unknown. Furthermore, participation bias is inseparable with cross-sectional survey studies, which hinders making

global recommendations. This survey demonstrated that LAHSHAL and Luijsterburg *et al*., were most used. Since the usage of Luijsterburg *et al*. is limited to Europe, we recommend LAHSHAL as optimal classification system. Another limitation of the survey is that no distinction was made between state, regional registries and national registries. For example, in the USA, some states have state registries although a national registry does not exist. Therefore, we excluded the USA from this specific question. Moreover, this questionnaire involved only clinicians involved in the care of patients with OFCs. Policy makers, hospital staff members involved in the financial reimbursement and insurance companies were not involved in the survey despite their role in the cleft care process.

CONCLUSIONS

Great variety of classification systems currently used exists among clinicians when confronted with patients with OFCs. Because future advances in our understanding of the molecular pathogenesis of OFCs will require us to compare precisely phenotyped cohorts of patients with clefts, further research and involvement among geneticists and embryologists is needed to provide optimal comprehension of classifying clefts amongst all craniofacial specialists. Classifying clefts with a universally implemented classification system is essential for improved communication between craniofacial specialists and comparison of scientific data globally. According to the results of this study, LAHSHAL could be the most suited universal classification system, due to its extensiveness, relatively high implementation rate and convenient usage to complement the ICD-10 system. Potentially, this could make up for the deficiencies of the ICD-10 codes that do not indicate laterality, completeness, and clefts of the alveolus. For more international acceptance, standardization and better communication globally it is prudent to demonstrate to users the merits of the LAHSHAL classification system.

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CHAPTER 3

UNRAVELING A MAJOR BURDEN OF OROFACIAL CLEFTS ANALYSES: CLASSIFICATION OF CLEFT PALATE FISTULAS BY CLEFT SURGEONS

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ABSTRACT

Objective
The objective of this study was to investigate how cleft surgeons classify palatal fistulas. We focused on three different anatomical locations (ie, hard palate, soft palate, junction hard/soft palate) to analyze agreement/disagreement at various anatomical locations.

Design
Cross-sectional survey study.

Participants
Participants in an international webinar that focused on palatal fistula treatment were included.

Intervention
Participants were presented with a survey pre- and post-webinar.

Main outcomes
Frequency of used classification systems for classifying oronasal fistulas and the inter-rater reliability of the Pittsburgh classification system.

Results
A total of 141 participants completed the questionnaires prior to the webinar and 109 participants completed the survey after the webinar. In total, four classification systems were used (ie, Pittsburgh, Pakistan Comprehensive Fistula Classification [PCFC], anatomical and 'other'). The Pittsburgh classification was the most commonly used system in all cases. However, Pittsburgh inter-rater reliability was low ($\kappa = 0.136$ pre-webinar, and $\kappa = 0.174$ post-webinar). Surprisingly, a substantial shift was observed from the anatomical to Pittsburgh classification after the webinar, indicating increased awareness of the usability of the Pittsburgh classification system.

Conclusions
This study demonstrates a large heterogeneity with regards to the classification of cleft palate fistulas. Interestingly, a shift was observed from the anatomical to Pittsburgh classification after the webinar. However, the inter-rater reliability for using the Pittsburgh classification was low. Classifying palatal fistulas in a homogenous fashion could enhance comparison of primary palate repair and could improve treatment of palatal fistulas.

Keywords
hard palate; soft palate; surgical complications.

INTRODUCTION

Cleft palate fistulas could be a complication of cleft palate repair. Three recent reviews indicate an incidence of 4.9-10.1% of the patients after primary palatoplasty, while a higher incidence seems to be correlated to the width of the cleft at the time of primary closure.[1-3] Fistulas can have substantial impact on patient quality of life as they may negatively affect speech (e.g. nasal air loss on high-pressure consonants, perpetuation of the use of compensatory articulation, cause discomfort when liquids pass through the fistula from the oral to the nasal cavity, and lead to dental and oral hygiene problems, including halitosis.[4-7] Another problem is the high recurrence risk after secondary surgery.[1]

Palatal fistulas can occur in multiple locations of the palate and in different degrees of severity. They can be located in the anterior section of the palate (i.e. located labial-alveolar and in the ventral part of the hard palate), in the mid-palate (i.e. dorsal part of the hard palate), at the junction of the hard and soft palate and in the soft palate. Sizes of postoperative fistulas vary widely, from 1-2 millimeters up to multiple centimeters (the equivalent of an unrepaired cleft).

In 2007, a review was conducted by Smith *et al*. to assess different classification systems for palatal fistulas.[8] They found numerous articles classifying fistulas in different manners and these classification systems were often incomplete or inaccurate. As a result, the authors conceived their own fistula classification system, known as the Pittsburgh classification. It classifies fistulas based on their anatomical location, dividing the palate, alveolus and lip into seven distinct regions. The regions order from zone 1, indicating a bifid uvula to zone 7, indicating a fistula in the labial-alveolar region.

In addition to variations in location of palatal fistulas, each location possibly has numerous surgical approaches and options and specific impacts on speech. In order to compare the different surgical techniques and subsequent outcomes, it is necessary to classify fistulas uniformly. Until consensus is reached, comparison of treatment and communication between cleft surgeons and speech pathologists is hard to achieve, and therefore hinders progress in examining, investigating and possibly decreasing the disease burden of palatal fistulas.

The aim of this study was to assess the variety of classification systems used to characterize palatal fistulas. Our second aim was to measure the inter-rater variability of the used classification system. Consequently, we also investigated whether there was a change in the choice of classification system used before and after the special webinar about palatal fistulas.

MATERIAL AND METHODS

This cross-sectional study included two surveys that were sent to 242 participants from 74 countries who attended the "Palatal Fistulas: Prevention, Classification & Treatment" webinar hosted in Amsterdam, the Netherlands on July 1 and 2, 2021. The pre- and post-webinar questionnaire consisted of nine patient cases with different fistulas (Supplemental Data Content 1). Participants were asked how they would classify and treat each patient from the presented images. The participants were asked fourteen days prior to the webinar to fill out the first questionnaire. A reminder was sent seven days prior to the webinar and the first survey was closed at the start of the webinar.

After the webinar, participants were again asked to complete a survey with the same questions and images regarding the same nine fistula cases. Reminders were sent after seven and fourteen days respectively. We examined agreement/disagreement of classification between participants pre- and post-webinar. Surveys were included if a participant answered all the questions. Surveys were created and sent through Castor EDC. Inter-rater reliability was calculated with Fleiss Multirater Kappa scores by using SPSS (Statistical Program for Social Sciences, version 28; SPSS Inc., Chicago, IL, USA). Ethical approval for this study was waived by the local Ethical Committee (W22_158) and participants gave consent for processing all data anonymously for scientific purposes. The reporting was in adherence with the STROBE checklist.

RESULTS

A total of 141 participants (response rate 58.3%) completed the questionnaire prior to the webinar, and 114 (response rate 47.1%) responded after the webinar. Pre-webinar, most participants were plastic surgeons (n=73; 51.8%), followed by maxillofacial surgeons (n=47; 33.3%) and ENT surgeons (n=7; 5.0%), pediatric surgeons (n=5; 3.5%) and other specialties (n=9;6.4%). Both the Pittsburgh classification system and an anatomical description, i.e. a literal description of what the participant saw in the photograph, were used most often prior to the webinar (Figure 1). On average, 45.4% of the participants classified palatal fistulas according to the Pittsburgh classification system, while 44.8% of participants used an anatomical description to classify palatal fistulas. An average of 1.4% of the participants used the Pakistan Comprehensive Fistula Classification system and 8.4% classified fistulas in another way than previously mentioned prior to the webinar. After the webinar, an average of 71.4% of the participants used the Pittsburgh classification system and an average of 20.4% used anatomical descriptions to classify fistulas. For the Pakistan Comprehensive Fistula Classification system, an average of 2.7% of the participants indicated that they used this to classify fistulas after the webinar. Another 5.5% of the participants used other methods to classify fistulas. A trend could be identified in which participants classified palatal fistulas more according to the Pittsburgh classification system after the webinar (45.4% versus 71.4%) and tended to use anatomical descriptions and other methods less (respectively 44.8% versus 20.4% and 8.4% versus 5.5%).

Although for each case, a substantial percentage of participants agreed on one Pittsburgh classification, inter-rater reliability was very low ($\kappa = 0.136$; 95% confidence interval 0.131 – 0.142 pre-webinar versus $\kappa = 0.174$; 95% confidence interval 0.170 – 0.179 post-webinar). A more detailed evaluation of the Pittsburgh classification on case level shows great heterogeneity in answers of participants (Supplemental Data Content 2). A similar phenomenon was observed within the anatomical descriptions. Although tendencies by participants towards a certain description (or group within a classification system) were observed, there still exists a large variety among participants regarding the classification of palatal fistulas.

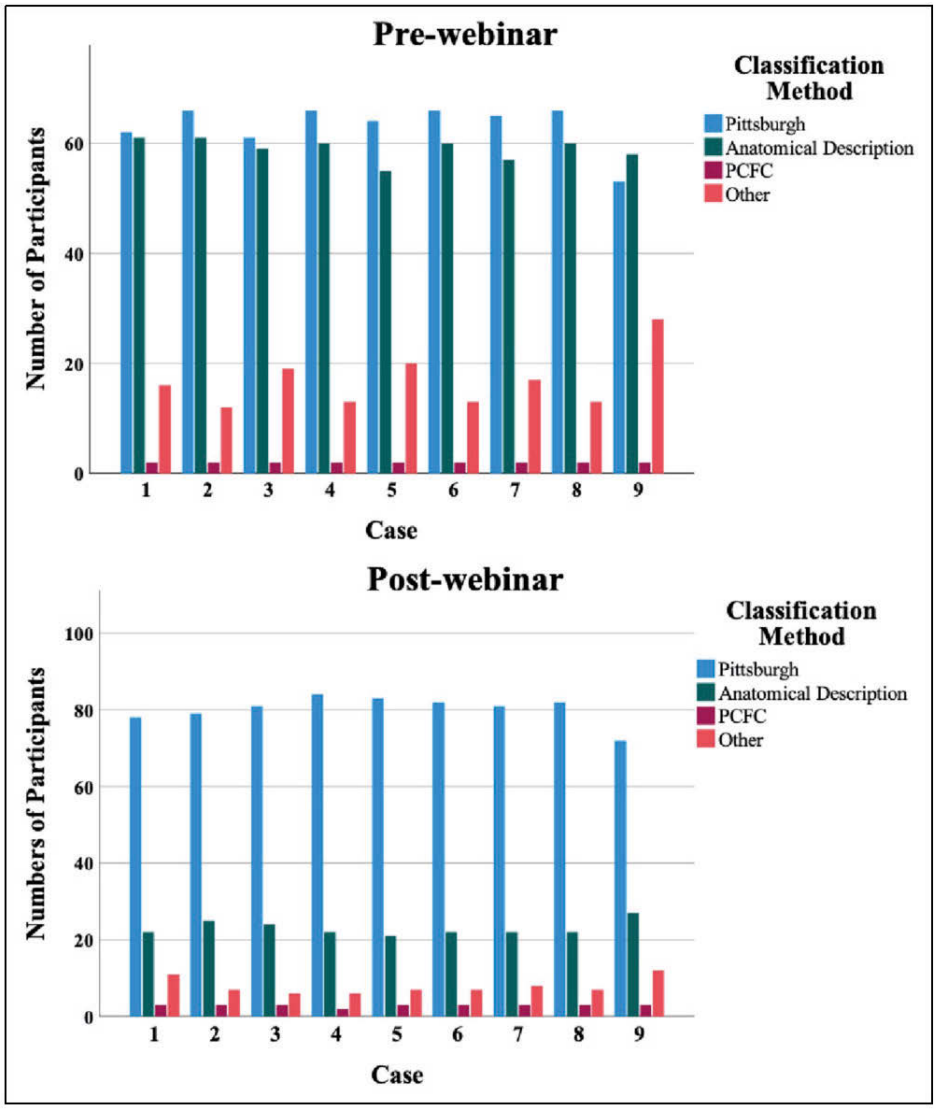

Figure 1. Pre- and post-webinar differences between classification methods used for classifying of fistulas by participants.

DISCUSSION

There is great variety in the size and location of palatal fistulas and no standardization in classifying them, even with existing classification systems. Furthermore, due to the relatively low absolute numbers of fistulas per hospital after palatoplasty, it remains a challenge for clinicians to build up experience regarding classifying and treating fistulas. This challenge emphasizes the importance of assessing what classification systems for fistulas are currently being used by clinicians, and determining the inter-rater agreement of these systems.

The participants of this survey most frequently used the Pittsburgh classification system or anatomical descriptions to classify fistulas. A few respondents used the Pakistan Comprehensive classification system [9]. Compared to the literature, the Pittsburgh classification system is often the primary system used by clinicians. [1,10-11] Still, anatomical descriptions are also frequently used in scientific literature.[12-13] The Pakistan Comprehensive Classification System however has not been cited yet to our knowledge in scientific literature besides the manuscript of the original author.[9]

Sitzman *et al*. published a study in 2018 that showed very limited inter-rater agreement for eight surgeons using the Pittsburgh classification system.[14] This is in line with our findings, where we found $\kappa = 0.136$ pre-webinar versus $\kappa = 0.174$ post-webinar. Consequently, confusion may occur in communication between different specialists when using the Pittsburgh classification, possibly referring to different types of fistulas, and thereby hampering treatment evaluation.

The impact of fistulas on patient burden is often not discussed and may be undervalued. For example, the Global Burden of Disease project measures, based on global data, the burden of disease of a variety of diseases, including that for clefts.[15] The burden of clefts is measured through weighing certain aspects of patient disability, namely: 1. "Disfigurement level 1 due to orofacial cleft. Has a slight, visible physical deformity that others notice, which causes some worry and discomfort" (0.011; 95% uncertainty interval, 0.005-0.021). 2. "Disfigurement level 2 due to orofacial cleft. Has a visible physical deformity that causes others to stare and comment. As a result, the person suffering from a cleft is worried and has trouble sleeping and concentrating" (0.067; 95% uncertainty interval, 0.044-0.096). 3. "Disfigurement level 2

and speech problems due to orofacial clefts. (combined disability weights) (0.115; 95% uncertainty interval, 0.076-0.164)."[16] Although speech problems, which can be caused by fistulas, are taken into the equation, it is noticeable that most emphasis is placed on the physical appearance of clefts. This is understandable, the physical appearance of patients with clefts can have an impact on the patient's mental well-being.[17] Still, as others have described, the impact of fistulas on patients with clefts can be profound.[4-5] By not integrating fistulas in the weighing of disability of clefts, measuring the burden of disease will be less accurate.

Some of the limitations of the current study are as follows: First, participants had to classify the patients based on a single photograph. In everyday clinical practice, a better inspection of the fistula from different angles and palpation of the palate is performed for better examination of its location. Due to this limited information, participants were impaired in assessing the location of the fistula. As a result, the degree of consensus between different participants could be lower than in physical outpatient consultation visits, subsequently underestimating the inter-rater reliability of classification systems. Second, although the country of origin from all participants in the webinar were known, we did not include a specific question devoted to the country of origin of respondents. Therefore, we do not know if our respondents' group is a reliable reflection of the global craniofacial community. Furthermore, the vast majority of respondents were either maxillofacial surgeons or plastic surgeons. No speech therapists did participate in the webinar, and the effect of the size and location of a fistula on speech was not taken into account in this survey. Due to the great impact of fistulas on speech, this was a major limitation of this study. To further increase external validity, all craniofacial team members should be included from countries all over the world.

Although this study primarily focusses on a classification system used for fistulas, we feel that a classification should be created where, after the birth of a child, a cleft classification is created, that could be extended with the possibility to include whether the patient did or did not develop a fistula after primary palatoplasty. In doing so, the impact of a fistula could consider the initial severity of presentation so that we can better understand the burdens of disease and treatment. However, this system should be developed based on a large international consensus, to achieve a higher international implementation rate.

CONCLUSION

There is large variation among clinicians concerning the classification of oronasal fistulas, even among those using the classification system. Consequently, craniofacial specialists do not speak the same language when classifying palatal fistulas or worse, they think they speak the same language but interpret it in different ways. As of yet, no wide implemented classification system for oronasal fistulas with a decent inter-rater reliability exists. To achieve the formation of larger datasets for evaluating the treatment outcomes and assessing the prevalence of different manifestations of fistulas, a more accurate system could be designed, or more training should be provided to physicians involved classifying these palatal fistulas.

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CHAPTER 4

DIFFERENT SURGICAL APPROACHES TO THE TREATMENT OF CLEFT PALATE FISTULAE AS PERCEIVED BY CLEFT SURGEONS

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ABSTRACT

Objective

Palatal fistulas after palatoplasty could pose difficulties for both patients and surgeons. Numerous surgical approaches are available to treat palatal fistulas. In this manuscript, we investigate surgical treatment options for palatal fistula repair looking at the different anatomical locations, and we create a summary of surgical approaches to facilitate the decision-making process for palatal fistulae repair.

Design

In this cross-sectional survey, nine anonymized patient cases with palatal fistulae that differed in severity and anatomical location were presented to participants from the International Cleft Master Course in Amsterdam about "Palatal Fistulas". Participants were invited to participate in this survey. A total of 141 participants reported their preferred surgical treatment options for fistula repair at different anatomical locations.

Results

We created different options for fistula treatment, catalogued by fistula location. This overview gives the surgeon possible approaches for each location. If the soft palate is involved, this overview underscores the importance of including velopharyngeal insufficiency management into the fistula repair. For hard palate involvement, our overview lists techniques available for nasal lining repair and for oral lining repair in each region.

Conclusions

We provide a comprehensive overview of potential surgical approaches to repair palatal fistulae. This inventory of techniques is grouped per location to support surgeons in their decision-making process when confronted with a palatal fistula.

Keywords

Acellular dermal matrix; cleft palate; fistulae; palatal fistulae; surgical techniques; survey.

INTRODUCTION

Cleft lip and palate is a common congenital malformation, with an incidence of approximately 1 in 700 live births.[1] After surgical repair, the development of palatal fistulae shows a wide range of incidence rates, varying from 4.9% to 31.3%.[2-3] Additionally, surgical treatment of fistulas is complicated by a high recurrence rate of up to 33%.[4] Factors contributing to fistula formation are multifactorial and often difficult to determine but may include the width of the cleft, the ratio of cleft width to available surrounding palatal tissues for reconstruction and the surgeon's level of skills, scarring from previous surgery, surgical factors (e.g. excessive tension on the suture line, injudicious use of electrocautery on the medial edges, too tight knots) and patient factors (finger sucking postoperatively, nutritional deficiency postoperatively, compliance).[5-6]

Patients suffering from palatal fistulae can either be asymptomatic or they experience speech problems, nasal regurgitation of fluids, and difficulty in maintaining oral hygiene.[7-8] Fistulae can be classified based on anatomical description, using the Pittsburgh classification or the Pakistan Comprehensive fistula classification.[9] The most prevalent anatomical location for fistulae is at the junction of the hard and soft palate, followed by fistulae located in the hard palate (2) and fistulae in the soft palate (3).[2] Various surgical approaches are described which enable the repair of palatal fistulae, e.g. oral mucoperiosteal flap, buccal flap, facial artery musculomucosal (FAMM) flap, Furlow palatoplasty.[10] The debate continues on whether oronasal fistulae occur more frequently after a two-stage palate repair compared to the single-stage repair.[11-12] This comparison remains challenging due to the substantial impact of confounders such as surgeon experience, cleft phenotype and patient characteristics. To determine the most appropriate surgical approach, it is essential to consider multiple factors, including size, shape and location of the fistula, as well as whether it is a primary or a recurrent fistula.[13] It is important to note that there is a lack of consensus and limited literature that focuses on managing fistulas following primary surgery.[14-15] While categorization and the relationship of fistulas associated with primary repair requires further study, the focus of this study is on how to address a fistula once it is present.

The aim of this cross-sectional study is to summarize the clinical surgical strategies of cleft surgeons from around the world on palatal fistula repair per anatomical location. A secondary objective is to investigate the influence of a digital webinar on the preferred choice for closing palatal fistulas.

MATERIAL AND METHODS

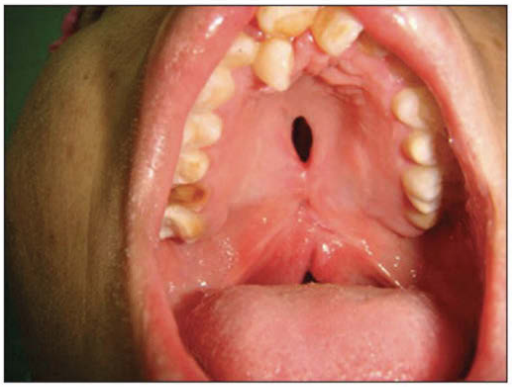
In this cross-sectional survey study, two questionnaires were sent to 242 participants from 74 different countries who attended the "Palatal Fistulas: Prevention, Classification & Treatment" Master Course hosted in Amsterdam, the Netherlands in June 2021. The complete scientific program can be found in Supplemental Data Content 1. All participants attended the webinar digitally, it was not possible to attend this master course physically. Most of the participants were either plastic, maxillofacial, ENT or pediatric surgeons. Speech language pathologists and residents in training for the previously mentioned specialties were also included. Speech language pathologists, (PhD) students and residents not in training were excluded from this questionnaire since they do not perform palatal surgery. These questionnaires were sent before and after the webinar. Nine patient cases were presented with different oronasal fistulae, each case was accompanied with a digital image, some of which were adapted from the Surgical Atlas of Cleft Palate and Palatal Fistulae by Prof. Ghulam Qadir Fayyaz (Figure 1, Supplemental Data Content 2).16 The nine patient cases were selected from a large database by ten of the course organizers. Criteria for selection were the following: both females and males included, all three anatomical locations covered (i.e. soft palate, hard palate and junction soft/hard palate), several degrees (i.e. 1 – 5 mm fistula, 5 – 20 mm fistula and >20 mm fistula). These patient cases were presented in a random fashion in terms of severity and anatomical location. For readability, we rearranged the order and brought together patient cases categorized in three anatomical locations (i.e. soft palate, hard palate and junction soft/hard palate). The questions in the survey were designed to ascertain the participants' preferred surgical approach in each individual case. If the nasal lining closure negate the possibility of doing a marked out oral closure, participants were not able to fill in an answer for oral closure with that patient case. Participants received an invitation to complete the survey fourteen days prior to the webinar. A reminder was sent seven days before the event. The survey was closed at the start of the webinar.

The second questionnaire, which mirrored the cases and images from the first questionnaire, was sent immediately after the conclusion of the webinar. A reminder to complete the webinar was sent seven and fourteen days after the event respectively. Only fully completed questionnaires were included in the analysis. The questionnaires were created and distributed through Castor Electronic Data Capturing (EDC). The data were subsequently analyzed using Statistical Program for Social Sciences (SPSS, version 29; SPSS Inc., Chicago, IL, USA). The Pearson Chi-Square test was used to compare the distribution of answers between the two groups. The Fisher-Freeman-Halton Exact Test was used to compare the distribution of answers between groups. A p value of < 0.05 was considered a significant result. Ethical approval for this study was waived by the local Ethical Committee (W22_158 #22.205) and participants provided consent for the anonymous processing of their data for scientific purposes. Reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist guidelines.

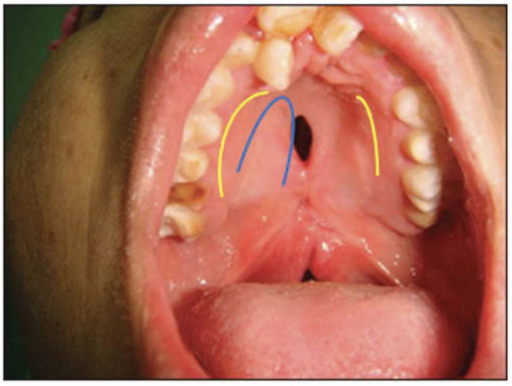
RESULTS

A total of 141 participants, representing a response rate of 58.3%, completed the questionnaires before the webinar. After the webinar, 109 participants (response rate of 45.0%) completed the survey. In the pre-webinar group, the largest group of participants consisted of plastic surgeons (n = 73; 51.8%), followed by maxillofacial surgeons (n = 47; 33.3%), Ear, Nose, and Throat (ENT) surgeons (n = 7; 5.0%), pediatric surgeons (n = 5; 3.5%). Nine participants were active in other disciplines (6.4%). Eleven participants (7.8%) did not have any experience with primary cleft palate surgeries, 18 participants (12.8%) did less than 10 primary surgeries annually. An additional thirty-one (22.0%) did between ten and twenty-five primary cleft palates per year, thirty-six (25.5%) did between twenty-five and fifty primary cleft palate surgeries per year and lastly forty-five surgeons (31.9%) treated over fifty patients with primary cleft palates per year. Respondents were categorized into two groups. The first group consisted of respondents who performed less than 25 primary palatoplasties per year (infrequent palatoplasty group; n = 49; 37.7%). The second group consisted of respondents who performed 25 or more primary palatoplasties per year (frequent palatoplasty group; n = 81; 62.3%). In general, most participants advocated a two-layer closure (n = 124; 88.0%). Some even suggested a third layer (n = 7; 5.0%). Acellular dermal matrices (ADMs) were

13-year-old boy with palatal fistula (10 mm) in hard palate and severe VPI
This patient would also receive a simultaneous operation to improve soft palate function?
- Yes
- No



How would you classify this fistula?
……
How would you close the nasal mucosa:
1. Vomer flap (green line)
2. Oral mucosal flap (Red incision)
3. FAMM flap
4. Buccal myomucosal flap
5. Other…… [please specify]



For oral mucosa closure:
1. Oral mucoperiosteal flap (yellow incision)
2. Oral mucoperiosteal flap (blue incision)
3. Buccal buccinator mucosal flap
4. FAMM flap ventrally based (left side patient)
5. FAMM flap ventrally based right side patient
6. FAMM flap dorsally based
7. Buccal fat flap
8. Tongue flap
9. Other…… [please specify]

For the VPI surgery I would perform (on oral endoscopy the space is 10 mm between soft palate and nasopharynx)
- IVVP
- Pharyngeal flap
- Furlow plasty
- Z plasty including unilateral buccal flap
- Bilateral buccal flap

Figure 1. An example of a patient case from the digital survey.

only used by 24 respondents (17.0%). Figures 2 and 3 present a comprehensive summary of all the respondents' mentioned surgical approaches for the presented cases.

Soft palate

Case 1 presented a patient suffering from a fistula located at the soft palate and junction hard/soft palate three weeks post-surgery. The majority of respondents indicated, prior to the webinar, to wait 6 months before deciding on any surgical intervention (n = 110; 84.6%). After the course, this treatment strategy remained the most popular (n = 96; 84.2%), while a minority would prefer to close the fistula after 4 weeks (n = 16; 14.0%) and only 2 respondents (1.8%) would perform immediate surgery.

In case 2, a patient was shown with a combination of a large hard palate and small soft palate fistula requiring nasal mucosa closure. Before the webinar, the most frequently suggested option for treatment was performing a mucoperiosteal flap (n = 59; 45.4%), which was comparable after the congress (n = 44; 38.6%). Interestingly, for the closure of the oral mucosal layer, a shift was observed from performing oral mucoperiosteal flaps to the Furlow palatoplasty (n = 50; 38.5% and n = 49; 43.0% respectively).

Hard palate

In case 3 involving a patient with a hard palate fistula, the preferred choice of treatment, prior to the meeting, was to perform orthodontic alignment before surgical closure (n = 70; 53.8%), which relatively increased after the webinar (n = 71; 62.3%). Concerning the nasal closure, prior to webinar, the overall preferred choice was the Vomer flap (green incision) (n = 51; 39.2%) whereas the oral mucosal flap (yellow incision) was more preferred post-webinar (n = 44; 38.6%). The experienced palatoplasty group preferred the Vomer flap (green incision) (n = 36; 44.4%) vs the oral mucosal flap (yellow incision) (n = 22; 44.9%) in the less experienced group. This significant difference also existed in the oral closure strategy. The frequent palatoplasty group most often opted for the oral mucoperiosteal flap (yellow incision, A) (n = 33; 40.7%) and the infrequent group most often for the oral mucoperiosteal flap (blue incision, A) (n = 12; 24.5%).

Case 4 presented a patient suffering from a hard palatal fistula with the need for nasal mucosa closure. Most participants opted for a vomer flap as

treatment plan (n = 53; 40.8%). However, after the meeting, the majority of the respondents chose oral mucosal flaps (n = 48; 42.1%). Between the groups of frequent palatoplasty surgeons and infrequent palatoplasty surgeons, a significant difference (p = 0.045) was found where surgeons who perform palatoplasty more frequently preferred a Vomer flap (green line) (n = 35; 43.2%) and participants from the infrequent palatoplasty group, the oral mucosal flap was chosen (blue incision) (n = 24; 49.0%). For closure of the oral mucosal layer in this case, the oral mucoperiosteal flap (red incision [A]) remained the suggested treatment option of choice (n = 36; 27.7%) prior to the meeting versus after the webinar (n = 37; 32.5%) [Supplemental Data Content 2]).

The patient in case 5 was suffering from a hard palatal fistula. For nasal mucosal layer closure, most attendees chose to perform mucoperiosteal flaps (yellow incision) as the treatment strategy before attending the meeting (n = 89; 68.5%) as well as after the congress (n = 83; 72.8%). In contrast, the oral mucoperiosteal flaps (red incision [A]) were selected most for oral mucosal closure after the webinar (n = 75; 65.8%).

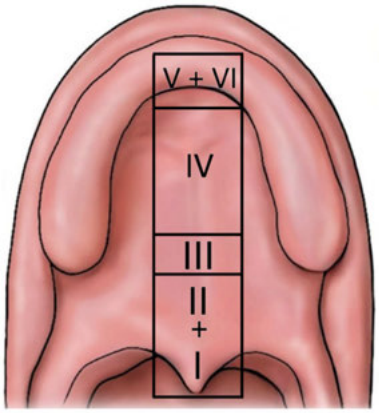
Case 6 involved a patient having a fistula located at the hard palate with severe velopharyngeal insufficiency (VPI). The most popular treatment option for nasal mucosal layer closure amongst the respondents pre-webinar was the vomer flap (n = 62; 47.7%) as well as post-webinar (n = 56; 49.1%). The oral mucoperiosteal flap (yellow incision) was the preferred method for closing the oral mucosal layer after the meeting (n = 66; 57.9%).

Junction hard/soft palate

In case 7, a patient with a large fistula located at the junction of the anterior and posterior halves of the hard palate and extends to the junction of the hard and soft palate was presented. Participants indicated that they preferred to close the nasal mucosa with oral mucoperiosteal flap (n = 54; 41.5% before the meeting), as did the participants after the meeting (n = 49; 43.0%). Interestingly, for closing the oral mucosal layer, the buccal buccinator mucosal flap was preferred after the webinar (n = 43; 37.7%).

In case 8, in which a six-year-old girl with a large palatal fistula (18 mm in length) in the ventral half of the hard palate was show. The oral mucoperiosteal

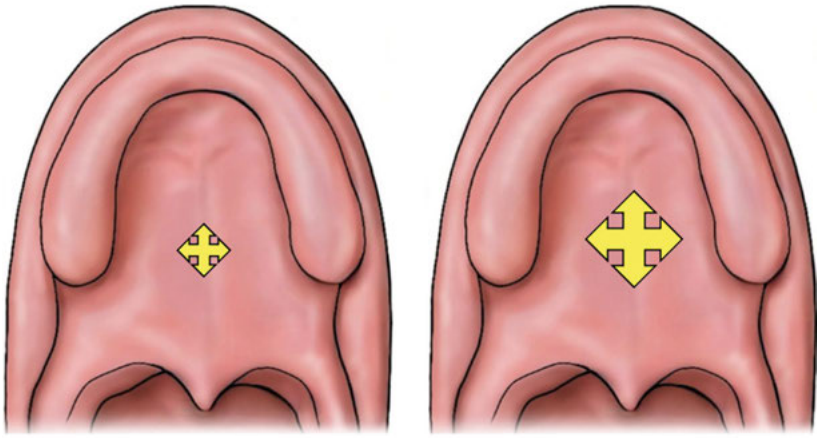
flap (yellow incision) was initially chosen for nasal mucosal closure (n = 81; 62.3%), while after the webinar the selection of this treatment option was more or less the same (n = 75; 65.8%). In addition, for closing the oral mucosal layer, the preference was an oral mucoperiosteal flap (green incision) both pre- and post-webinar (n = 42; 32.3% vs n = 34; 29.8%). The frequent palatoplasty group most often chose either the oral mucoperiosteal flap (green incision) or the bilateral mucoperiosteal flap (for both n = 24; 29.6%) whereas the infrequent group most often opted for the oral mucoperiosteal flap (green incision) (n = 18; 36.7%).



	Medium defect (i.e. size 1 – 5 mm)	Large defect (i.e. size > 5 mm)
Soft palate:	revision palatoplasty through double-opposing Z-plasty (i.e. Furlow) revision palatoplasty through straight-line mucosal incision with IVVP	
Hard palate:	Nasal lining: - Vomer flap - Nasal floor and sidewall - Buccal myomucosal flap - FAMM flap - Buccal fat flap - Inferior turbinate flap	Oral lining: - Oral mucoperiosteal flap - Buccal myomucosal flap - FAMM flap - Buccal fat flap - Tongue flap

Abbreviations: FAMM: facial artery musculomucosal; IVVP: intravelar veloplasty; VPI: velopharyngeal insufficiency.

Figure 2. An overview of all surgical options per anatomical region.



Anatomical	Pittsburgh	Nasal lining	Oral lining
Lingual/labial alveolar	V + VI	Vomer flap Nasal sidewall Inferior turbinate flap	Oral mucoperiosteal flap BMFF FAMM flap
Hard palate	IV	Vomer flap Oral mucoperiosteal turnover flap Buccal myomucosal flap Nasal sidewall Free radial flap (very large defect)	Buccal flap FAMM flap Furlow plasty Oral mucoperiosteal flap Tongue flap Free radial flap (very large defect)
Junction	III *	See figure 3	See figure 3
Soft palate	II	Furlow plasty Revision palatoplasty	Furlow plasty Revision palatoplasty
		In case of VPI: Furlow plasty IVVP / revision palatoplasty Bilateral BMMF Pharyngeal flap Z-plasty including unilateral buccal flap	
Uvula	I	Uvuloplasty	

Abbreviations: BMMF: buccal myomucosal flap; FAMM: facial artery musculomucosal; IVVP: intravelar veloplasty; VPI: velopharyngeal insufficiency.
* Dependent on size, please see figure 3

Figure 3. Surgical options per anatomical region dependent of size of the fistula.

In case 9, a twelve-year-old girl was presented with a large cleft palate (covering almost the complete hard and soft palate). The use of a free flap was the preferred choice for oral closure prior to the webinar (n = 38; 29.2%). After the webinar, this surgical approach remained the most chosen option (n = 38; 33.3%). For nasal closure, the oral mucoperiosteal flap (red incision) was the most popular surgical approach both before (n = 35; 26.9%) and after the webinar (n = 48; 42.1%). A total of 25.4% (n = 33) would perform simultaneous surgery to improve soft palate function if VPI was present.

Figures 2 and 3 show an overview of all surgical options per anatomical region.

DISCUSSION

Although prevention of palatal fistulae development is an important goal in primary cleft palate surgery, palatal fistulae are well known complications of palate repair. This study introduces an inventory of techniques, subsequently grouped by location to support surgeons in their decision-making process when confronted with a palatal fistula.

Palatal fistulae can be a great burden to patients, due to nasal regurgitation and speech impairment.[17-18] Correlations between VPI and quality of life have been demonstrated multiple times.[19-20] Adequate planning and proper treatment of fistulae is very important since surgical treatment of fistulae may have a high recurrence rate of up to 33%.[4] Adequate intervention is paramount for both patients and cleft surgeons. There appears to be no gold standard regarding regional approaches to the surgical treatment of fistulae. In this large cross-sectional survey, surgeons from all over the world proposed different approaches for each patient case and high levels of consensus were reached at the end of the meeting. Carefully identification of the problem is of paramount importance, together with clear knowledge and expertise of all possible surgical approaches as per anatomical location in the form of a schematic toolbox that makes it easier to finalize and choose the best suitable technique. Results of this study could serve as a guide for colleagues that are confronted with difficult fistula cases in the future. In the literature,

only a few studies have been conducted on palatal fistulae in which surgeons were asked their opinion on surgical options, often with limited participants involved.[13,21-24] Although numerous surgical techniques are available, none of them have been proved to be superior. In the absence of international guidelines, surgeons are most likely to choose surgical techniques based on anatomical location, width and size of the fistula, age of the patient and surgical experience with specific techniques.[13-14] In this current study, most respondents indicated that they would prefer local tissue advancement in order to close both nasal and oral mucosal layers. This is in concordance with previous research, in which surgeons suggested mucosal turn-over flaps.[13-14] Although Rothermel *et al*. only included 17 craniofacial specialists in their cross-sectional survey, results remain consistent in our study with 141 participants (agreement up to 67%), underlining the substantial preference for mucoperiosteal flaps.

It is important to emphasize that in concordance with Rothermel et al. this study emphasizes the assessment of the function of the palate that is very important when fistulae are treated.[13] Moreover, in soft palate involvement, relocation of the levator sling is an important part of the procedure in addition to closure of the fistula. As demonstrated in the overview (Figure 2), several options including the Furlow palatoplasty, bilateral buccal flap or the unilateral buccal flap can facilitate levator muscle reconstruction.[25-27]

This study indicates that most respondents (88.0%; $n = 124$) advocate a two-layer closure. However, some (5.0%; $n = 7$) even suggest a third layer. ADMs can be introduced in palatal fistula repair, offering a scaffold for tensionless closure and tissue regeneration. These matrices could enhance neovascularation and epithelialization, reducing the risk of fistula recurrence.[28-29] There is still no consensus on superiority of closure with ADM compared to closure without use of ADM. In the current study, nearly 80% of the respondents indicated not to use ADM, while 17% indicated that they would sometimes introduce dermal matrices in fistula repair. This is different with the survey study carried out by Rothermel *et al*. reporting 64% of participant occasionally using ADMs and 36% never using ADMs.[13] This noticeable difference could partly be explained by differences in sample size (eighteen versus 141), but also because the Rothermel *et al.* study was performed under surgeons working in the US, where ADMs are freely available, while the current study has representatives from all over the world. Simpson *et al*. performed a similar survey amongst members of the American Cleft Palate Craniofacial Association (ACPA), reporting 22% of

which used ADMs on all patients, 45% introduced ADMs only if excessive tension was noted during surgery and 33% of participants which responded to never used ADMs.[23] Since participants in the current study originate from 74 countries, versus participants from the ACPA all working in the United States of America a national tendency to introduce ADMs could account for this difference. According to earlier research, up to 11 – 12% of recurrence rates were found when ADMs were introduced between nasal and oral mucosa.[28-29] Higher fistula rates (17%) were found when mucosal defects were covered with ADM.[30] In addition to the cost of ADM, another reason to avoid ADM is that it is a non-vascularized graft that could also potentially act as a foreign body nidus for infection in an environment with a high bacterial load.

Several limitations of the current study should be addressed. Responses of our participants were based purely on digital pictures. In a normal outpatient consultation clinic, doctors are able to both look and palpate the palatal fistula, which might change surgical treatment approaches and therefore could skew results of this study. Moreover, surgeons may also change what they actually do on the day of surgery when they can better examine the patient under general anesthetic. Additionally, the country of origin of all our respondents was not specifically asked in the survey for privacy reasons. However, we did know the country of origin for all participants of the webinar (242 participants from 74 unique countries) resulting in a large representative group of cleft specialists globally. A substantial strength of this study is the large size of surgeons included in this cross-sectional survey. Moreover, the group of specialists is expected to be a proper representation of all specialists globally due to a high response rate, large sample size, multiple countries involved and different levels of expertise amongst participants.

CONCLUSION

In this study, an inventory is presented with frequently mentioned treatment options for surgical repair of palatal fistulae at different anatomical locations. Most craniofacial cleft specialists would close hard palate fistulae with oral mucoperiosteal flaps (both oral and nasal mucosa), while Furlow palatoplasty was mostly mentioned in soft palate fistulae. The majority of participants did not use ADMs or third layers in fistula repair.

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CHAPTER 5

INCIDENCE OF SYMPTOMATIC SUBMUCOUS CLEFT PALATE IN THE NETHERLANDS: A RETROSPECTIVE COHORT STUDY OVER A PERIOD OF 22 YEARS

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ABSTRACT

Objective
To analyze the incidence of submucous cleft palate (SMCP) in a large national database and raise awareness among referring providers: pediatricians, speech pathologists, and dentists to minimize delay in diagnosis.

Design
Retrospective cohort study.

Setting
Tertiary setting.

Patients
Patients were extracted from the "Dutch Association for Cleft and Craniofacial Anomalies" database. A total of 6916 patients were included from 1997 until 2018 and divided into 2 groups (ie, SMCP versus cleft palate [CP]). Patients born before 1997 and adopted patients were excluded.

Interventions
Clefts were classified as either hard of soft palatal involvement based on anatomical landmarks at first consultation.

Main Outcome Measures
Primary outcomes were the patient characteristics in both groups (ie, gender, birth weight, gestational age, and additional anomalies). Secondary outcome was the time of diagnosis among subgroups.

Results
In total, 532 patients were diagnosed with SMCP (7.7%). Birth weight, gestational age, and additional anomalies did not differ between subgroups, but there were more males in the SMCP group ($P < .001$). The median age of diagnosis of the SMCP group was significantly higher than of the CP group (987 vs 27 days; $P < .001$). Over the course of 22 years, the time of diagnosis for SMCP did not decrease.

Conclusion
Submucous cleft palate represents <10% of the Dutch cleft population and 19.4% of all CP. Time of diagnosis for SMCP is significantly longer when compared with time of diagnosis of CP, and this has not changed over the study period of 22 years.

Keywords
Bifid uvula; cleft palate; orofacial clefts; submucosal; submucosal cleft palate.

INTRODUCTION

Submucous cleft palate (SMCP) is a rare subtype of cleft palate (CP). Although numerous authors describe the incidence of CP, only a few small studies have been conducted on SMCP. Submucous cleft palate was first described in 1825 by Roux (1825). All subtypes are characterized by muscular diastasis of the soft palate with an intact oral and nasal mucosal lining and various different combinations of anatomical abnormalities (Bluestone et al., 2014). Calnan identified a triad of clinical criteria enabling clinicians to diagnose SMCP: a bifid uvula, a notch in the posterior end of the hard palate and a zona pellucida in the midline of the soft palate (Calnan, 1954). Patients who have velopharyngeal insufficiency in the absence of Calnans' triad are classified as occult SMCP (Kaplan, 1975).

Cleft palate with cleft lip (CLP) is almost always diagnosed before the first year of life. However, Hanny et al. demonstrated that 25% of all patients with CP are diagnosed after 12 months of age (Hanny et al., 2016). Because SMCP is more difficult to diagnose, it could be missed during the initial after birth screening and is therefore often diagnosed late, even later than the mucous CP mentioned by Hanny et al. (Rozendaal et al., 2012). Ten Dam et al. found a median age of 3.7 years at time of diagnosis for SMCP (Ten Dam et al., 2013). Moreover, a recent study demonstrated that 79% of patients with SMCP required surgery (Ha et al., 2013). It is therefore crucial to diagnose these children early in life, offer them speech therapy, and if needed perform surgery to minimize adversary effects later in life. Moreover, because a delay in diagnosis could eventually result in hearing impairment and delay in speech development (Ten Dam et al., 2013).

The main objective of this current study is to accurately describe the incidence, patient demographics, and time of diagnosis of patients with SMCP registered in a national database. This information could increase awareness among craniofacial specialists and accommodate early diagnosis at the time when adversary effects are still preventable (eg, delay in speech development).

METHODS

This study is a retrospective cohort study that includes all cleft patients registered in a national database (Dutch Society of Orofacial Cleft and Craniofacial Malformations, NVSCA database) between January 1997 and December 2018 (Vermeij-Keers, 2009). Since January 1997, all craniofacial specialists from tertiary cleft surgery hospitals in the Netherlands (n = 14, 8 academic centers, 6 nonacademic hospitals) register patients with clefts via a digital form. The form comprises of 3 sections (ie, general registration, craniofacial abnormalities, and additional anomalies). The goal of the standardized registration is to provide insight in the distribution of patient demographics (of subtypes) of cleft patients in the Netherlands. Registration is performed by a member of the cleft team during the first outpatient consultation visit.

Characteristics, including gender, ethnicity of patients (adopted vs autochthonous), type of clefts (lip, hard/soft palate, nose; mucosal vs submucosal clefts), birth weight, gestational age, and additional anomalies (eg, atrial/ventricular septal defects, apneas, and hypospadias) were collected. Due to a significant percentage of missing data (ie, >50%), adopted patients, and patients born before January 1997 had to be excluded. Furthermore, patients with cleft lip (CL) and CLP were excluded from further analysis due to heterogeneity of study population. In the current study, only symptomatic SMCP patients are included.

A subdivision was made between patients with SMCP versus patients with CP to investigate the incidence of SMCP and patient demographics. A further analysis was done for patients with or without additional anomalies. The time of diagnosis was investigated for the SMCP cohort and compared to the time of diagnosis of CP patients. The definition of time of diagnosis is the total amount of days between the date of birth and date of registration. Statistical analyses were performed using SPSS (Statistical Program for Social Sciences, version 25; SPSS Inc). For continuous data, normal distributions were evaluated by the Shapiro-Wilk test and Kolmogorov-Smirnov test. If a continuous variable was normally distributed, an independent t test was used. If a continuous variable was not normally distributed, a Mann-Whitney U test was executed to test for differences between groups. A Pearson $\chi 2$ test was carried out to investigate the association between 2 categorical variables

(eg, gender). A Pearson r was applied to investigate correlations between 2 variables. A threshold of $P < .05$ was used to determine statistical significance. The STROBE-checklist (Strengthening the Reporting of Observational Studies in Epidemiology) was adhered to in the preparation of this article.

RESULTS

In total, 6916 patients with clefts were registered in the Nederlandse Vereniging voor Schisis en Craniofaciale Afwijkingen (NVSCA) database. Of these patients, 532 patients were diagnosed with SMCP; 2208 patients with all other CP (combined to a total of 2740 patients with CP); 2322 patients with CLP and 1854 patients with CL (Figure 1). Of those patients with SMCP, 192 patients were diagnosed with a combination of submucosal cleft of the hard and soft palate (36.1%) and 340 (63.9%) patients were diagnosed with isolated submucosal soft palate cleft (Figure 2). According to the NVSCA database,

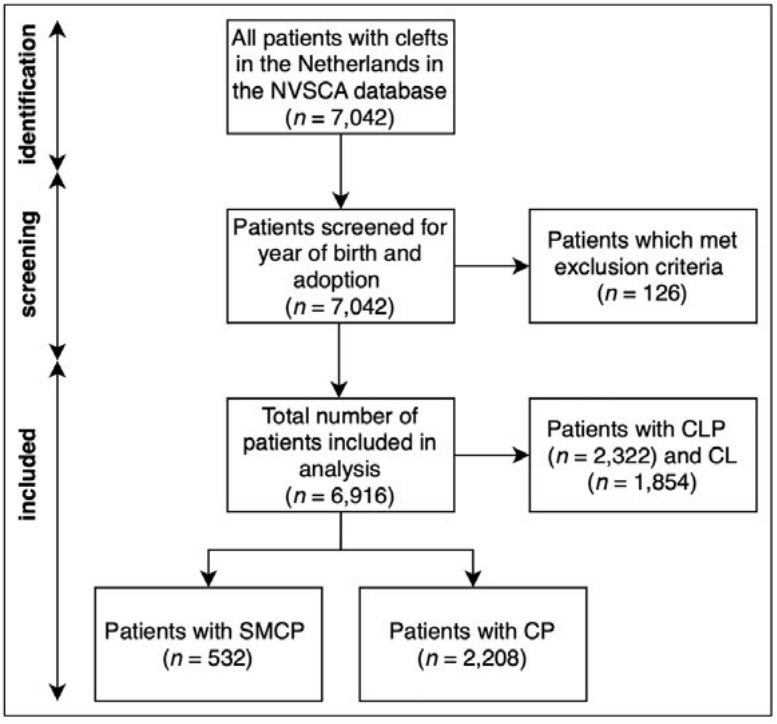

Figure 1. Patient identification and screening.

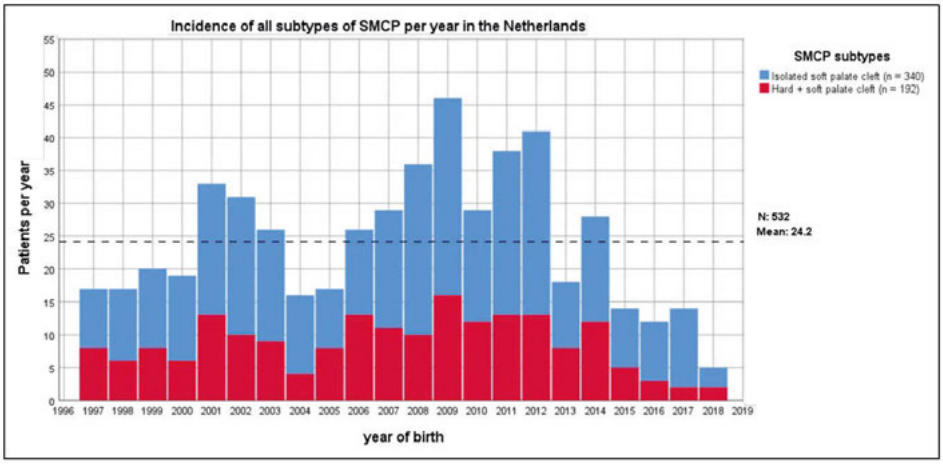

Figure 2. Incidence of subtypes of submucous cleft palate (SMCP) per year in the Netherlands according to the NVSCA database.

314.4 patients per year are born with clefts in the Netherlands. Of these, 24.2 (7.7%) patients are diagnosed with SMCP per year.

Patient characteristics (ie, birth weight, gestational age, gender, and the occurrence of additional anomalies) were analyzed for the SMCP and CP groups (Table 1). The median birth weight of patients with SMCP was 3255 g (≈7 pounds and 2.8 ounces) versus 3314 g (≈7 pounds and 4.9 ounces) for all other CP (P = .693). The median gestational age was 39.0 weeks for both the SMCP and CP groups (P = .373). Additional anomalies were seen in 132 (24.8%) patients in the SMCP subgroup versus 562 (25.5%) patients in the CP group (P = .760). In the SMCP subgroup, 58.3% (n = 310) was male and 41.5% (n = 221) was female (the total of patients does not add up to 100% due to missing data, n = 1). In the CP subgroup, 45.0% (n = 994) was male and 54.8% (n = 1210) was female (missing data in 4 patients). Thus, no differences were found between the SMCP group and CP group concerning birth weight, gestational age, and additional anomalies, but there were significantly more men in the SMCP subgroup versus the CP group (ratio M/F 1.40 vs 0.82; $P <$ .001).

Table 1. Patient Characteristics.

Characteristics	SMCP (*n* = 532)	All other CP[a] (*n* = 2208)	*P*
Gender[b] M/F ratio Male Female	1.40 310 (58.3%) 221 (41.5%)	0.82 994 (45.0%) 1210 (54.8%)	*< 0.001*
Birth weight (g.) Lbs. + oz. (± oz.)	3255 (± 876) 7 + 2.8 (± 30.9)	3314 (± 812) 7 + 4.9 (± 28.6)	*0.693*
Gestational age (weeks)	39.0 (± 2.0)	39.0 (± 2.0)	*0.373*
Other structural anomalies	132 (24.8%)	562 (25.5%)	*0.760*

Abbreviations: CP: cleft palate; SMCP: submucosal cleft palate.
[a] Total CP = SMCP + all other CP
[b] Note that the total of patients for gender in subgroups does not add up to 100% due to missing data (n = 5).

Additional anomalies were seen in 24.8% in the SMCP subgroup and in 25.5% of the CP group (*P* = .760). To investigate the presence of additional anomalies within different tracts more accurately, SMCP was compared to all other patients with CP specified on all 10 tracts. A list of anomalies with frequencies among patients with SMCP and all other CP is provided (Table 2). Common anomalies seen in patients with SMCP were atrial/ventricular septal defects (n = 23; 4.3%), hypospadias (n = 6; 1.1%) and apneas (n = 4; 0.8%).

Table 2. Other structural anomalies in SMCP versus all other patients with CP

Affected tract	SMCP (*n* = 532)	All other CP (*n* = 2208)
None	400 (75.2%)	1646 (80.4%)
Circulatory tract	45 (8.5%)	134 (6.1%)
Respiratory tract	21 (3.9%)	208 (9.4%)
Central nervous system	21 (3.9%)	44 (2.0%)
Urogenital tract	12 (2.3%)	30 (1.4%)
Upper extremity	11 (2.1%)	33 (1.5%)
Digestive tract	11 (2.1%)	42 (1.9%)
Lower extremity	3 (0.6%)	26 (1.2%)
Thorax	3 (0.6%)	19 (0.9%)
Vertebral column	3 (0.6%)	13 (0.6%)
Skin	2 (0.4%)	13 (0.6%)

Abbreviations: CP: cleft palate; SMCP: submucosal cleft palate.

Finally, the time of diagnosis was analyzed per registration year. This time was defined as the total number of days between the date of birth and the date of registration. The median time of diagnosis for all patients with CP was 27 days (ie, slightly less than a month), with an interquartile range (IQR) of 75 days. The median time of diagnosis of SMCP was significantly longer: 987 days (ie, 2 years, 8 months, and 13 days), with an IQR of 1587 days. The time of diagnosis is significantly longer for the SMCP compared to the CP group ($P <$ .001) and did not decrease over time ($R^2 = 0.010$; Figure 3). To minimize bias, we excluded the last 4 years (ie, median + ¼ IQR) of registration to prevent an underestimation in the last years of our study.

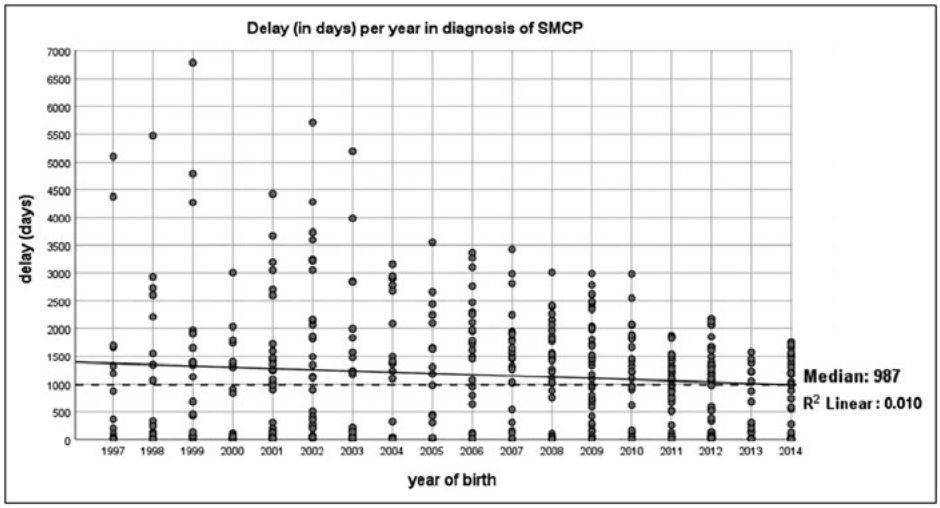

Figure 3. Time of diagnosis of submucous cleft palate (SMCP; in days) per year.

DISCUSSION

This study demonstrates that SMCP is a relatively common subtype of CP in the Netherlands. In this study, 19.4% (532/2740) of all patients with CP were diagnosed with SMCP. Furthermore, the current study confirms that the time of diagnosis for SMCP remains long, at the age of approximately 3 years.

Several discrete discrepancies were found with recent literature. Discrepancies between incidence and subtypes of SMCP can partly be explained by the fact that it is difficult to accurately classify the anatomy based on a clinic examination during outpatient consultation visits. We found that 7.7% of all patients with clefts were diagnosed with SMCP, while Ten Dam et al. reported that 3.5% of all cleft patients were patients with SMCP (Ten Dam et al., 2013). Although both studies focused on a Dutch population, the difference could be attributed to a smaller study sample: 28 SMCP of 800 total cleft patients in the Ten Dam study versus 524 SMCP of 6916 cleft patients in the current study. Other studies conducted earlier focused on school children for the calculation of the incidence of SMCP (Stewart et al., 1971; Bagatin, 1985). Stewart et al. focused on >10 000 school children and found a total of 9 patients with SMCP, which resulted in an incidence of 1:1200 (Stewart et al., 1971). Bagatin conducted similar research on 9720 Zagrebian school children and found 5 patients with SMCP, which resulted in an incidence of 1:1944 (Bagatin, 1985). Differences in reported incidences could partly be explained by variances in genes accountable for clefting among different study populations (Reiter et al., 2012). Moreover, Stewart et al. and Bagatin investigated asymptomatic children, where in the current study symptomatic children were examined (ie, solely cleft patients were registered). Compared to all live births in the Netherlands from 1997 to 2018 (ie, 185 913 on average per year), the national prevalence of SMCP is 1:7688 (Centraal Bureau voor Statistiek, 2013). A general overview of incidences of SMCP among different studies is provided (Table 3).

Table 3. Incidence of SMCP in literature.

Study	Total of SMCP	Study population	SMCP as percentage of all clefts studied	Incidence of SMCP in total population
Current study	532	6916 patients (SMCP + CLP + CP + CL)	7.6%	1:7688[a]
Ten Dam et al. (2013)	28	800 patients (SMCP + CLP + CP + CL)	3.5%	-
Velasco et al. (1988)	1	6000 school children	-	1:6000
Bagatin (1985)	5	9720 school children	-	1:1944
Shprintzen et al. (1985)	19	25 patients with bifid uvulae	-	-
Kono et al. (1981)	33	478 patients (CP)	6.9%[b]	-
Weatherley-White et al. (1972)	61	10 836 school children	-	1:1200
Stewart et al. (1971)	9	> 10 000 school children	-	1:1200

Abbreviations: CL: cleft lip; CLP: cleft lip and palate; CP: cleft palate; SMCP: submucous cleft palate.
[a] Based on the average live births per year according to the Centraal Bureau voor Statistiek (2013) "Central Office of Statistics of the Netherlands."
[b] Kono et al did not study patients with CL and CLP.

Differences between studies are mainly dependent on study population and study size. Gender distribution among patients with SMCP was similar to other studies (Park et al., 2002; Ten Dam et al., 2013). In the current study, 58.3% of patients with SMCP was male and 41.5% was female. In the cohort studied by Ten Dam et al., 61% and 39% of the 28 patients with SMCP were male and female, respectively (Ten Dam et al., 2013). In another study, 54.3% and 45.7% of the 46 patients with SMCP were male and female, respectively (Park et al., 2002). No previous studies among patients with SMCP were conducted on both birth weight and gestational age. Compared to the average birth weight from 2001 to 2013, as reported by Statistics Netherlands, patients with SMCP in this study weighed less than the national average (3255 g ≃ 7 pounds and 2.8 ounces for patients with SMCP compared to 3433 g ≃ 7 pounds and 9.1 ounces for all newborns in the Netherlands) (Centraal Bureau voor Statistiek, 2013). Unfortunately, no average gestational age of Dutch newborns is available. A previous study by Wyszynski et al. also found that patients with orofacial clefts are more at risk to have a lower birth weight but did not see increased risk of premature birth (Wyszynski et al., 2003). Further research needs to be conducted to compare our findings to other study populations with regard to birth weight and gestational age.

The median age of diagnosis for SMCP was found to be at 987 days (ie, 2 years, 8 months, and 13 days). This is earlier than previously reported (3.9-4.9 years) (Reiter et al., 2011; Ten Dam et al., 2013), which could be explained by a small sample size (ie, 28 patients with SMCP) (Ten Dam et al., 2013) and the use of a more dated cohort (start cohort in 1981 versus 1997) (Reiter et al., 2011). The long time of diagnosis means that patients with SMCP remain undiagnosed for a long time, which could impair speech development and cause other adversary effects later on (Ten Dam et al., 2013). In addition, in a recent study by Ha et al., 79% of SMCP patients required surgery (eg, for speech improvement) (Ha et al., 2013). It is therefore crucial to diagnose these children early in life, offer them speech therapy and perform surgery, if necessary, to minimize adversary effects later on. Parents of patients seek medical help in advanced stages of SMCP, often when speech therapists cannot further improve speech (Ten Dam et al., 2013). This study did not investigate

why patients with a SMCP were send to the physicians, but a recent study by Hanny et al. has demonstrated that these patients often have feeding problems as babies and subsequently speech problems needing speech therapy later in life. Although midwives/pediatricians should investigate the mouth/palate after birth, pediatricians should be aware that children with feeding problems and possible nasal regurgitation could have a submucous cleft. Moreover, if patients need speech therapy because of nasal speech, speech pathologists should also be aware of a possible SMCP. Unfortunately, we found that the time of diagnosis did not decrease throughout the years of registration. In the United Kingdom, it has been advocated that midwives, pediatricians, and gynecologists should not only look at the palate but also perform digital examinations to diagnose SMCP more accurately and earlier (Royal College of Paediatrics and Child Health, 2018). In the Netherlands, midwives are only obliged to look and not feel for a possible submucous cleft.

A large sample size of patients with SMCP was analyzed from multiple hospitals, and only 3 exclusion criteria (ie, adopted patients with clefts, patients born before 1997 and patients with CL and CLP) were applied. Consequently, this study has a high external validation. A possible drawback of the study is the classification used in the Netherlands that focused solely on the hard and soft palate, compared to the more elaborate classifications used by Khan et al. (hard palate anterior of the incisive foramen affected; palatine muscles of the maxillary bone affected; palatine muscles of the palatine bone affected; soft palate affected) (Khan et al., 2013), or the even more elaborate scoring system used by Sommerlad et al., who created a scoring system from 1 to 9, taking in account the hard palate, the uvula, and muscles of the palate (Sommerlad et al., 2004). Another possible disadvantage is the way in which additional anomalies were registered. The registration of additional anomalies is a snapshot at the first outpatient consultation. Thus, additional anomalies that developed later in life were not reported (eg, undiagnosed heart/digestive tract anomalies). Due to the retrospective design of this study, we were not able to investigate which percentage of patients with SMCP needed speech surgery. More research is needed to address this specific question.

CONCLUSION

This study demonstrates that SMCP is a rare subtype of cleft in the Netherlands. Submucous cleft palate represents 7% of all clefts seen in the Netherlands and 19.4% of all CP in the Netherlands, with an incidence of 1:7688 live births over the studied period of 22 years. Time of diagnosis is evident and remains long over the years compared to time of diagnosis of other CP. Moreover, the results of this study underline the fact that the SMCP subpopulation does not differ from other subtypes of clefts with regard to birth weight, gestational age, and additional anomalies, which make an elaborated physical examination (look and palpate the oral cavity) even more essential in early diagnosis. Improvement in knowledge on SMCP among pediatricians, midwives, and speech pathologists could raise awareness, which expedites diagnosis and could prevent potential adversary effects later in life.

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CHAPTER 6

DIFFERENCES IN ANALYSIS AND TREATMENT OF UPPER AIRWAY OBSTRUCTION IN ROBIN SEQUENCE ACROSS DIFFERENT COUNTRIES IN EUROPE

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ABSTRACT

The goal of this study was to explore the availability of diagnostic and treatment options for managing upper airway obstruction (UAO) in infants with Robin Sequence (RS) in Europe. Countries were divided in lower- (LHECs, i.e., PPP per capita < $4000) and higher-health expenditure countries (HHECs, i.e., PPP per capita ≥ $4000). An online survey was sent to European healthcare professionals who treat RS. The survey was designed to determine the availability of diagnostic tools such as arterial blood gas analysis (ABG), pulse oximetry, CO_2 analysis, polysomnography (PSG), and sleep questionnaires, as well as to identify the used treatment options in a specific center. Responses were received from professionals of 85 centers, originating from 31 different countries. It was equally challenging to provide care for infants with RS in both LHECs and HHECs (3.67/10 versus 2.65/10, $p = 0.45$). Furthermore, in the LHECs, there was less access to ABG (85% versus 98%, $p = 0.03$), CO_2 analysis (45% versus 70%, $p = 0.03$), and PSG (54% versus 93%, $p < 0.01$). There were no significant differences in the accessibility concerning pulse oximetry, sleep questionnaires, home saturation monitoring, nasopharyngeal tubes, Tuebingen plates, and mandibular distraction. This study demonstrates a large difference in available care for infants with RS throughout Europe. LHECs have less access to diagnostic tools in RS when compared to HHECs. There is, however, no difference in the availability of treatment modalities between LHECs and HHECs.

Keywords
Cross-sectional survey; Europe; Health expenditure per capita; Robin sequence; Upper airway obstruction.

INTRODUCTION

Robin sequence (RS) was first described in 1923 by the French stomatologist Dr. Robin [1]. Since the first publication, many discussions have arisen about the definition, the diagnosis, and the treatment of RS. In 2016, during a consensus meeting, agreement was reached on the original triad of symptoms described by Robin; micrognathia, glossoptosis, and a varying degree of upper airway obstruction (UAO) [2]. Although a U-shaped cleft palate is a common finding in RS, it is not required for the diagnosis [2]. RS is a rare congenital anomaly, with incidences ranging from 1 in 8,500 to 1 in 30,000 live born infants according to the definition used [3, 4]. It is a highly heterogeneous condition with breathing difficulties ranging from very mild to life-threatening. Severe breathing difficulties range from 1,7–65% [5, 6]. Mortality in Robin sequence is not directly related to respiratory obstruction. Associations were found between mortality and other anomalies (e.g., cardiac and central nervous system anomalies) [5, 6]. During sleep, infants with RS may suffer from oxygen desaturations, obstructive sleep apnea (OSA) and insomnia, which might cause neurocognitive impairment in the long-term development [7]. Accurate diagnosis of UAO is crucial, since it is associated with comorbidity (e.g., growth failure, pulmonary hypertension, impaired psychomotor development) [7, 8]. In most cases, conservative management (e.g., prone positioning) of UAO in RS is sufficient. Patients with UAO that persist despite conservative management ultimately need surgical intervention. To determine which (surgical) intervention is best suitable for the individual RS patient, the level of UAO needs to be determined through diagnostic testing. A recent systematic review showed a large variety in the use of diagnostics for both UAO treatment indications and evaluations, where polysomnography (PSG) was considered the gold standard for assessing UAO and pulse oximetry being second best [8]. This review also included other diagnostic tools to assess UAO: arterial blood-gas analysis (ABG) and CO_2 analysis as a separate modality than ABG or PSG. Furthermore, Logjes et al. suggest to investigate the use of sleep questionnaires as a tool to assess UAO, while normative PSG data in neonates/infants are awaited in RS [8]. If a conservative management of UAO remains insufficient, several (non-)surgical interventions are available. Non-surgical interventions such as prone/lateral positioning, insertion of a nasopharyngeal tube (NPT), and a Tuebingen palatal plate (TPP) all have proven to relieve UAO in infants with RS. If UAO still remains present, surgical interventions such as mandibular distraction

osteogenesis (MDO) or mandible traction with K-wires could be considered [9, 10]. There is a substantial variation among institutions across Europe for both diagnostics and treatment options in UAO [11]. A standardized, internationally accepted protocol for the assessment and management of UAO in RS could guide healthcare professionals in the timing of assessmentand indications to prevent escalation of UAO. Creating such a protocol might be a challenge, as there are large (financial) differences between countries in Europe (e.g., health expenditure per capita in purchasing power parity in international dollars (PPP) ranges from $600 to over $8500) [12]. The purpose of the study was to investigate the availability of diagnostic tools that could help with the assessment of UAO in infants with RS and to obtain anoverview of currently used and available treatment optionsthat could resolve UAO in infants with RS. Our hypothesisis that countries with a lower PPP will have less accessibility in diagnostic and treatment tools when confronted with UAO in RS.

MATERIAL AND METHODS

In this cross-sectional study, a questionnaire was sent to healthcare professionals diagnosing and treating RS throughout Europe who attended the European Cleft Palate Craniofacial Association meeting in Utrecht, the Netherlands (2019), the European Cleft and Craniofacial Initiative for Equality in Care meeting in Tallinn, Estonia (2021), and/or the International Palatal Fistulas Master Course in Amsterdam, the Netherlands (2021). We created this survey, together with multiple cleft care professionals in Europe. Initial invitations for the questionnaire were sent out on August 1, 2021. Seven days after the initial invitation, a reminder was sent to the participants that did not completethe survey yet. If craniofacial specialists from specific European countries were missing, we reached out to them personally to represent all European countries to the best extent. Data collection was finished in January 2022. The questionnaire consisted of both open and multiple-choice questions in order to assess which diagnostics (i.e., ABG, CO_2 analysis, pulse oximetry, PSG, sleep questionnaires and home saturation monitors) and treatment modalities (i.e., nasopharyngeal tubes, TPP, MDO) were accessible in the European countries (Supplementary Data File 1: Questionnaire). For the classification of PSG, the American Academy of Sleep criteria by

Ferber et al. were used [13]. Diagnostic and treatment options that are most commonly used in Robin sequence care were included in oursurvey. A survey study by Van Lieshout et al. was used for the consideration to include or exclude diagnostic and treatment modalities [10]. For example, tongue-lip adhesion (TLA), mandible traction with K-wires, and tracheostomy were not included in our questionnaire, due to the relatively limited use across Europe [10, 14]. Responses were excluded from our analysis when < 50% of the questionnaire was completed. European countries included in our analysis were based on the definition used in the Statute of the Council of Europe [15]. Additionally, we have scored the participating countries according to the members of the European Union [16]. To compare countries with higher- and lower-health expenditure within Europe, we used the World Development Indicators Database by the World Bank. We created an overview of the health expenditure per capita in purchasing powerparity in international dollars (PPP) of all the respondents' countries [12]. We used this overview to divide the corre-spondents into two groups: "lower-health expenditure percapita countries" (LHECs) (i.e., PPP < $4000 per capita) versus "higher-health expenditure per capita countries" (HHECs) (i.e., PPP≥ $4000 per capita) (Fig. 1). The health expenditure per country was based on most recent available data (2019). The cut-off value for PPP of $4.000 was based on the unweighted average of health expenditure of all 31 respondents' countries in our study ($4026.88). The questionnaire was created and sent with Castor Electronic Data Capture (EDC). Figures were created using GraphPad Prism version 9.3.1 for Windows, GraphPad Software, San Diego, California, USA, www.graphpad.com. To compare the availability in diagnostics and treatment options for higher- versus lower-health expenditure countries, the Pearson X2 test and Fisher's exact test were performed forbinary data using SPSS (Statistical Program for Social Sciences, version 28; SPSS Inc., Chicago, IL, USA). For ordinal data, the results are presented as means with its ranges, and differences were tested with the Pearson X2 trend test. P-values lower than 0.05 were considered to be statistically significant. Ethical approval for the study was not required and was waived by the Human Research Ethics committee of the University of Amsterdam (W21 _170 # 21.185). All participants explicitly consented that their responses could be processed for publication purposes. We applied the STROBE-checklist (Strengthening the Reporting of Observational Studies in Epidemiology) in the preparation of this manuscript.

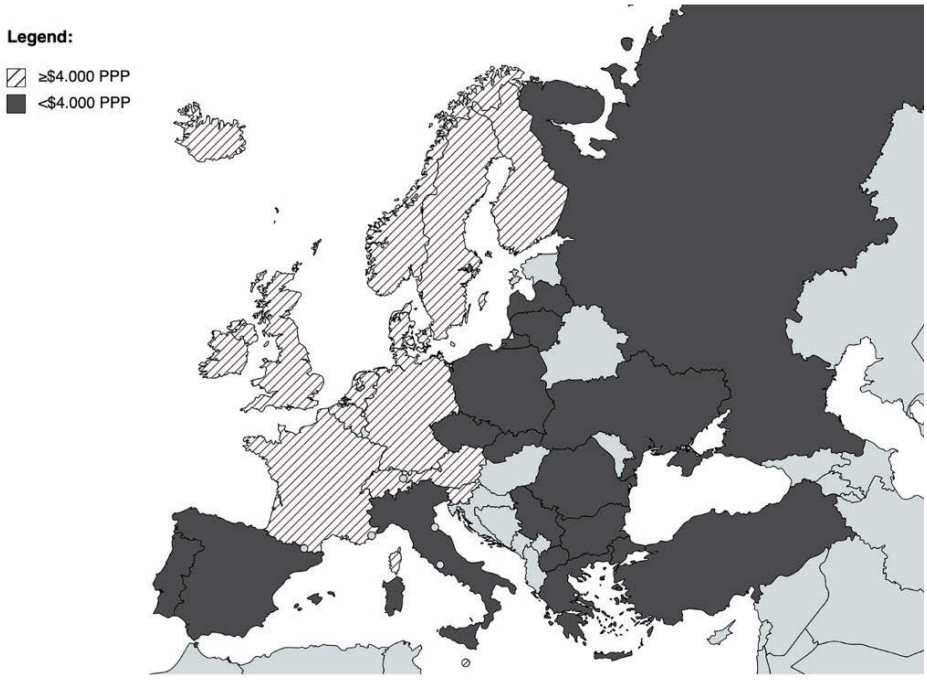

Figure 1. Map of Europe that shows the countries that were represented in the survey divided in European countries with lower-health expenditure per capita (i.e., PPP < $4000) versus higher-health expenditure per capita (i.e., PPP ≥ $4000)

RESULTS

Demographics

A total of 85 healthcare providers from 31 European countries (66.0% of 47 European countries) completed the survey. More specifically, 22 of the 27 countries of the European Union (81.5%) were represented in this questionnaire [16]. Figure 2 shows the profession of the participants. Most respondents were plastic surgeons (n = 27; 31.8%), maxillo-facial surgeons (n= 18; 21.2%), orthodontists (n= 9; 10.6%), and pediatric surgeons (n = 9; 10.6%). Fifty-two healthcare providers (61.2%) originated from HHECs and the other 33 healthcare professionals (38.8%) came from LHECs. Respondents from both groups indicated that it was equally challenging to diagnose and treat UAO in RS, on a scale from one (no challenge) to ten (very challenging) (3.67/10in LHECs versus 2.65/10 in HHECs; p = 0.45).

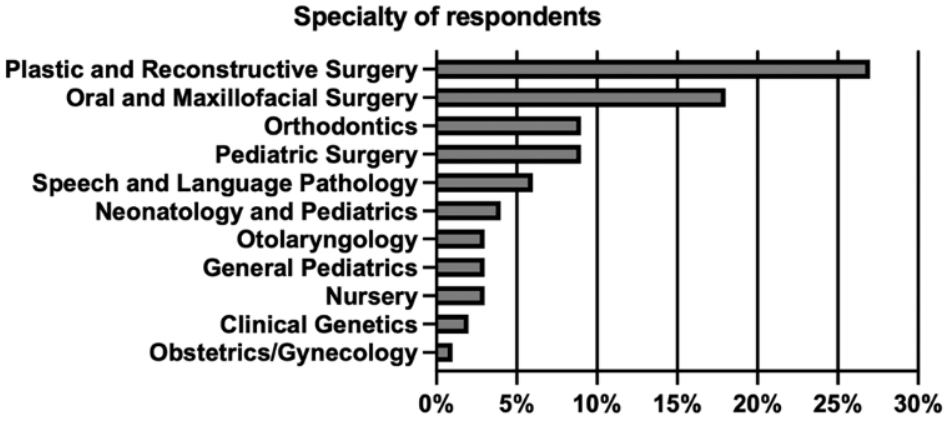

Figure 2 Distribution of the medical specialties of respondents

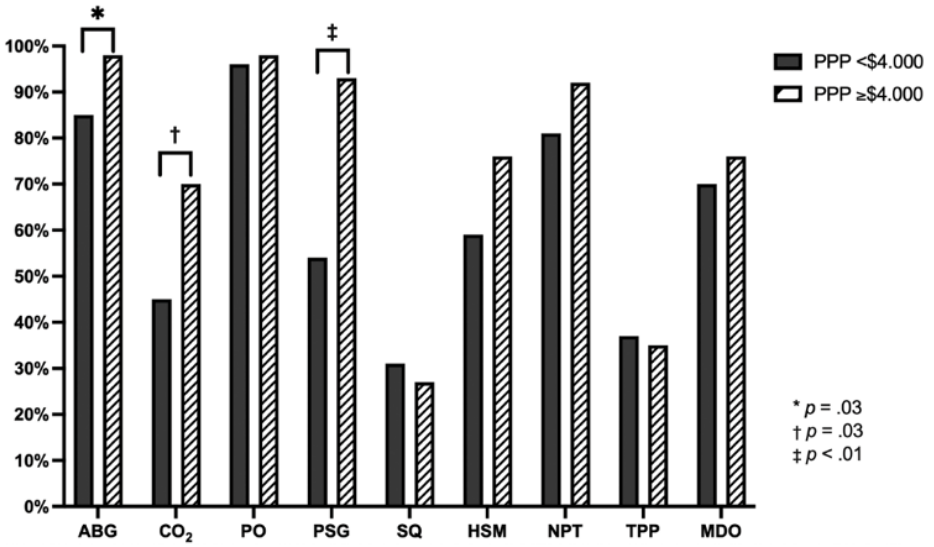

Figure 3. The availability of diagnostics and treatment modalities of upper airway obstruction in European countries with higher-health expenditure versus lower-health expenditure. The results are shown as a percentage of the total within subgroups. Statistical differences are indicated.

ABG, arterial blood gas analysis; CO_2, CO_2 analysis; HSM, home saturation monitoring; MDO, mandibular distraction osteotomy; NPT, nasopharyngeal tube; PO, pulse oximetry; PPP, health expenditure per capita in purchasing power parity in international $; PSG, polysomnography; SQ, sleep questionnaire; TPP, Tuebingen palatal plate

Baseline characteristics of both groups were similar (Supplemental Data File 2). Figure 3 presents an overview of the differences in available diagnostic tools and treatment options for upperairway obstruction in RS. When comparing countries withlower- and higher-health expenditure, there were significant differences concerning the availability of ABG (85%versus 98%, p = 0.03), CO_2 analysis (45% versus 70%, p = 0.03), and PSG (54% versus 93%, p < 0.01). No significant differences were found in accessibility of pulse oxi-metry (p = 1.00), the use of sleep questionnaires (p = 0.78), and home saturation monitoring (p = 0.18). An overview of possible diagnostic instruments per country is provided in Supplementary Data File 3 and for treatment options in Supplementary Data File 4; results with an asterisk demonstrate differences in diagnostic and treatment tools among hospitals in the same country.

Arterial blood gas analysis

A total of 98% of respondents (n = 51) from HHECs reported to use ABG versus 85% (n = 28) in LHECs (p = 0.03) (Fig. 3). However, no significant difference was found in the qualitative comparison of ABG between HHECs and LHECs (p = 0.15) (Fig. 4). Costs were indicated as a limiting factor to perform ABG in 8% (n= 4) of the respondents from HHECs versus 11% (n= 3) in LHECs (p = 0.69).

CO_2 analysis

A total of 70% (n = 33) of the respondents from HHEC sindicated to use CO_2 analysis versus 45% (n = 13) in the LHECs (p= 0.03) (Fig. 3). The availability

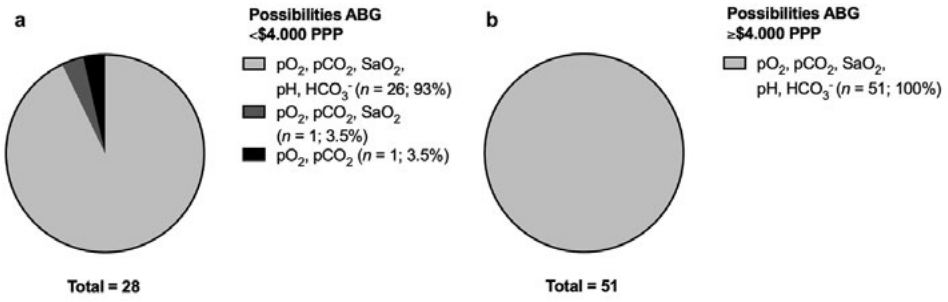

Figure 4. The availability of different types of arterial blood gas analysis measurements in a lower-health expenditure European countries and b higher-health expenditure European countries.

HCO_3, hydrogen carbonate; pCO_2, partial pressure of carbon dioxide; pH, potential hydrogen; pO_2, partial pressure of oxygen; PPP, health expenditure per capita in purchasing power parity in international $; SaO_2, oxygen saturation

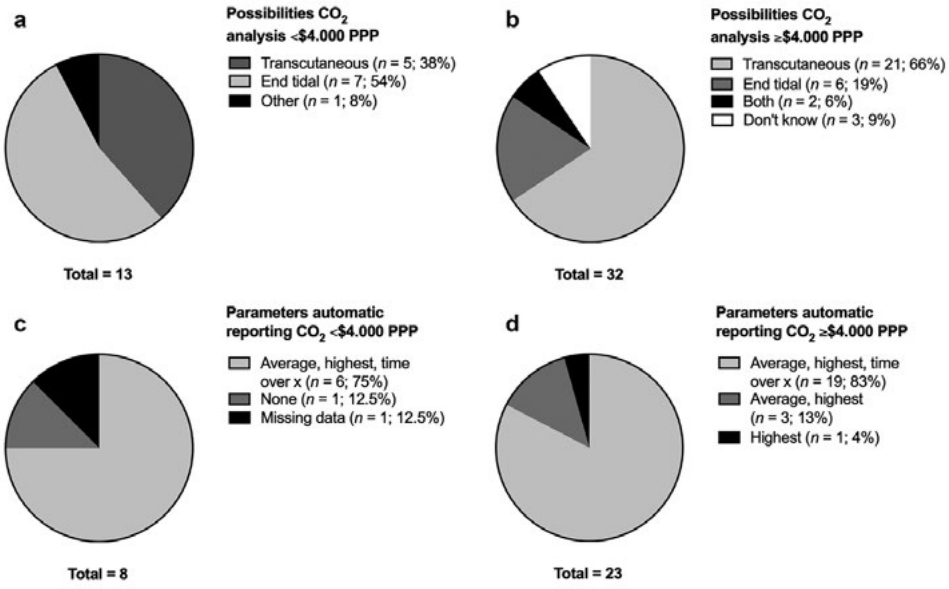

Figure 5. Options for qualitative CO_2 analysis in a lower-health expenditure European countries and b higher-health expenditure European countries. Availability of automatic reporting of CO_2-measurements is shown in c for lower- and in d for higher-health expenditure countries respectively.

of different types of CO_2 analysis (i.e., transcutaneous, end-tidal or other) differed significantly between high and low health expenditure countries (p = 0.05) (Fig. 5a, b). Figure 5c, d present the parameters for CO_2 analysis (i.e., average CO_2, highest CO_2 and time over x). Costs of CO_2 analysis were considered of importance for selecting this modality in 8% (n = 1) of cases in LHECs versus 0% in HHECs (p = 0.27).

Pulse oximetry

Ninety-eight percent (n = 41) of the respondents from HHECs responded to have pulse oximetry testing available versus 96% (n = 27) in the LHECs (p = 1.00) (Fig. 3). In HHECs, 76% (n = 31) of the participants that had access to pulse oximetry also had access to continuous automatic reporting of average saturation, lowest saturation and oxygen desaturation index. Two percent (n = 1) had access to lowest saturation and oxygen desaturation index and another 5% (n = 2) had access to lowest saturation and the oxygen saturation index. Seventeen percent (n = 7) had no access to automatic reporting of saturation. In LHECs, 44% (n = 12) of the participants were able to obtain automatic

reporting of average saturation, lowest saturationand oxygen desaturation index, 7% (n = 2) had access to average and lowest saturation, 11% (n = 3) were only able to measure saturation, and 37% (n = 10) had no access to automatic reporting of saturation. Quality differed significantly between high and low health expenditure subgroups (p = 0.01). Costs of pulse oximetry were of importance in 5% (n = 2) in HHECs versus 19% (n = 5) in LHECs (p = 0.16).

Polysomnography

A total of 93% (n = 37) of the respondents from HHECs reported to use PSG versus 54% (n = 15) in the LHECs (p < 0.01) (Fig. 3). There was a significant difference in quality of PSG between high and low health expenditure subgroups (p = 0.05) (Fig. 6). Costs of PSG were considered equally important in HHECs compared to LHECs (6% [n = 2] versus 7% [n = 1] p = 1.00).

Sleep questionnaire

The sleep questionnaires were used in 27% of respondents from HHECs (n= 10) and in 31% of partakers from LHECs (n = 8) (p = 0.78). In HHECs, 40% (n = 4) used the 22-item Pediatric Sleep Questionnaire, 10% (n = 1) the I'M SLEEPY questionnaire, 20% (n = 2) the Sleep Clinical Record, and 30% (n = 3) used their own sleep questionnaire. In LHECs, 63.5% (n = 5) used the 22-item Pediatric Sleep Question-naire, and 37.5% (n = 3) used their own questionnaire.

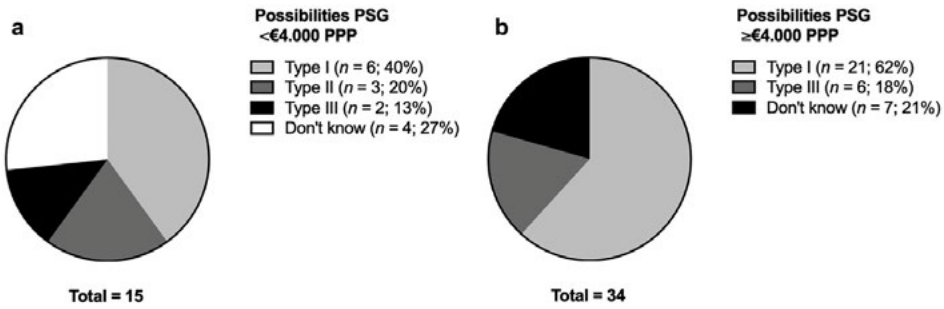

Figure 6. Types of polysomnography tools available and being used in a lower- versus b higher-health expenditure European countries. The Ferber et al. classification for polysomnography was used [13]

Treatment modalities

Nasopharyngeal tubes were indicated to be available in 92% (n = 34) of correspondents from HHECs, compared to 81% (n = 22) in LHECs (p = 0.27). Tuebingen palatal plates were accessible in 35% (n= 13) of correspondents from HHECs, versus 37% (n = 10) in LHECs (p = 1.00). Mandibular distraction osteotomy was available in 76% (n = 28) of correspondents from HHECs, compared to 70% (n = 19) in the other group (p = 0.78) (Fig. 3).

DISCUSSION

The present study was designed to explore the availability of diagnostic and treatment options for managing upper airway obstruction (UAO) in infants with Robin sequence (RS) in Europe. We have demonstrated that there is a substantial variation in the availability of objective diagnostic tools between European countries. ABG, CO_2, and PSG are not equally accessible for LHECs compared to HHECs. These differences are not only limited to availability; there is also a difference in quality of these diagnostic tools. LHECs have less access to tools that can objectively analyze UAO ininfants with RS compared to HHECs. Accessibility to these diagnostic tools could play a crucial role in the management of UAO in these infants. Due to the lack of an internationally accepted, evidence-based, standardized protocol for diagnosing and managing UAO in RS, substantial variation exists among healthcare providers when confronted treating RS [8, 17]. PSG is often mentioned in the literature for demonstrating the severity of RS. Types of PSG, the best timing to perform PSG, and other PSG-associated variables for assessing UAO in infants with RS vary widely in the literature [8, 18, 19].

In the HHECs, PSG was most frequently used to measure UAO. This is in concordance with other studies [8, 18]. Type I PSG is recommended in several national guidelines, and 62% of the respondents in the HHECs used this method to measure UAO [20, 21]. However, in practice, accessibility to PSG is often limited or it is not available at all [22]. Consequently, only 54% (n = 15) of the respondents from LHECs used PSG for the measurements of UAO. Of those 15 respondents, only 6 used type I PSG. Type II PSG was used in 20% and type III was performed in 13%. Lack of use in type I PSG may lead to an underestimation of the obstructive pathology. Healthcare professionals from LHECs relied mostly on pulse oximetry and ABG. Hypoxemia and hypercapnia can easily be detected by pulse oximetry and

ABG. Since these are relatively simple methods, they are easy accessible [23, 24]. We hypothesize that the lower availability of ABG and CO_2 analysis in LHECs may be due to the baseline characteristics of this subgroup. Although not significantly different, there are relatively more non-doctors in LHECs than in HHECs. Our results show that 27% of HHECs use questionnaires to assess UAO in RS versus 31% in LHECs. This small difference demonstrates the general accessibility of this diagnostic tool. Although only validated for children above the age of two, the 22-Item Pediatric Sleep Questionnaire was most frequently used in both subgroups. Questionnaire that are validated for testing infant OSA, such as the Infant Sleep Questionnaire, were not reported by our respondents [25]. This might be as the 22-Item Pediatric Sleep Questionnaire is considered the best screening questionnaire for pediatric OSA and is extensively studied [26]. I'M SLEEPY and the Sleep Clinical Record questionnaire have not yet been tested and validated in RS patients. Both questionnaires have been described to testpediatric OSA in non-RS populations [27, 28]. A substantial group (30% in HHECs and 37.5% in LHECs) used their own created questionnaire. This variation in questionnaires that are being used hampers proper comparison of treatment outcomes in RS. We have hypothesized that a financial barrier in LHECs would explain differences in accessibility for diagnostic tools and treatment options in RS. However, the costs of the available diagnostics were not indicated as a limiting factor for performing them in LHECs compared to HHECs. Another possible explanation for the differences between higher- and lower-health expenditure countries could be a scarcity of expertise or knowledge, an absence ofother resources, or a combination of these options.

There are several treatment options available for RS. The nasopharyngeal tube (NPT) is indicated as a useful treatmentmodality in treating infants with RS [29, 30]. It is associated with few complications [22, 29, 31]. NPA is available in more than 80% of the hospitals in higher- and lower-health expenditure countries, making it a helpful accessible tool throughout Europe. The Tuebingen palatal plate (TPP) is a non-invasive alternative to surgical interventions such as MDO or tongue-lip adhesion, while still reducing the mixed-obstructive apnea index to near-normal values [32]. However, 35% of HHECs and 37% of LHECs currently have access to TPP. These results are higher than we had expected, as it is almost double of what previous literature suggested [10]. TPP has shown positive results regarding airway- and feeding-related outcomes, as well as having beneficial impact on cognitive

and psychosocial development in infants with RS [32–35]. We hypothesize that these results have caused clinicians from outside of Tuebingen, Germany, to visit this center, learn about the orthodontic device, and to then apply it in the hospitals in their own countries. This is substantiated by other articles published over the past few years, from research groups outside of Germany, regarding TPP or similar orthodontic airway devices [36–40]. Distraction osteogenesis of the mandible was first described in 1992 [41]. The distraction corrects the micrognathia associated with RS. MDO is reported to be of value in ensuring a proper airway [42–44]. It is also associated with improved nutritional outcomes [45–47]. MDO is a valuable asset in managing infants with RS [48]. However, it is only available for 70% and for 76% of the respondents from LHECs and HHECs respectively. We feel that this value is higher than the national average, as we have so many respondents from tertiary centers. The national heterogeneity of possibilities for diagnosis and treatment of RS suggests centralization of health care, showing that specialized care is only available in tertiary centers. This is in line with the common practice of the past decennia where healthcare has been centralized to decrease costs and increase quality [49, 50].

Several limitations of this study have to be addressed. Although we aimed to include responses from all European countries, we did not manage to receive responses from healthcare professionals of all countries. Furthermore, there are twelve countries from which we only have a single contributor, possibly hampering the results, as one center might not be representative for the possibilities in the whole country. Furthermore, we have several results that suggest a difference between LHECs and HHECs; however, due to the small sample sizes, these results are not significant. Another limitation to highlight is that most of the correspondents in our study work in tertiary centers, and therefore, our results might be affectedby selection bias. Strengths of this cross-sectional survey study are that it is the first questionnaire that compares diagnostics and treatment options for higher- versus lower-health expenditure countries throughout Europe. Overall, 66% of the European countries are represented in this study. Since participants were allocated to either higher- or lower- health expenditure European countries after completing the survey, self-selection bias was averted. Infants with RS are a challenging group for craniofacial specialists due to the high morbidity and even mortality in these infants. As a consequence of the relatively low incidence of this congenital anomaly, it is important that treatment of RS

is focused in specialized tertiary hospitals. By centralization of care for RS infants, diagnostics and treatment can be optimized in the best possible way to create a uniform European protocol and ultimately equal care across Europe. The current study showed that even within Europe, large differences are noticeable in RS care. This study could serve as an important indicator for other rare diseases and anomalies (e.g., Beckwith-Wiedemann Syndrome or hemifacial microsomia). It is expected that for other rare diseases and anomalies, significant differences can be identified in level of care for patients across countries as well. Centralization of care for rare diseases and creating European guidelines could result in optimal care for patients that is accessible for every patient suffering from a rare craniofacial congenital disease. We believe that the results we have presented are important for clinical monitoring and intervention. Learning what is necessary for adequate monitoring could lead to better allocation of resources, which is especially important in a low-resource setting.

CONCLUSIONS

The aim of the present cross-sectional survey was to explore the availability of diagnostic and treatment options for managing upper airway obstruction in infants with RS in Europe. This study has identified considerable differences in accessibility of diagnostic tools available for RS infants. These inequalities are noticed between European countries but also within European countries itself. Quality of the diagnostic tools also vary between higher- versus lower-health expenditure European countries. The findings of this European inventory for diagnostic tools and treatment possibilities provide insights for the possible start of creating national and international guidelines that are suitable for both higher-and lower-health expenditure countries. Together with consensus on minimal diagnostic criteria of UAO in RS, the overall quality of diagnostics and treatment in Europe can be improved aiming to substantially reduce comorbidities and mortality.

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CHAPTER 7

DECREASE IN PREVALENCE OF CLEFT LIP, ALVEOLUS AND PALATE AFTER NATIONWIDE INTRODUCTION OF THE SECOND-TRIMESTER ANOMALY SVAN IN THE NETHERLANDS

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ABSTRACT

Objective
Some studies have suggested that introducing a second-trimester anomaly scan (SAS) leads to increased rates of termination of pregnancy (TOP) in fetuses with orofacial clefts (OFCs). The aim of this study was to evaluate the impact of a nationwide introduction of SAS on the prevalence of live births with OFCs in the Netherlands.

Design
Retrospective cohort study.

Setting
Tertiary setting.

Population
Included in the study were all patients diagnosed with OFCs as recorded in the "Dutch Association for Cleft Palate Anomalies" database between 1997 and 2019.

Interventions
Patients were divided into three categories: cleft lip with or without alveolus (CL/A), cleft lip, alveolus and palate (CLAP) and cleft palate (CP) based on anatomical landmarks at the first consultation.

Main outcome measures
Prevalence rates of OFCs before and after the nationwide introduction of the SAS on January 1, 2007 were compared.

Results
Overall, 1899 patients were diagnosed with CL/A, 2586 with CLAP and 2927 with CP. The prevalence of clefts before and after introduction of the SAS did not differ ($P = 0.85$). The prevalence of CL/A decreased ($P = 0.04$), and that of CLAP decreased ($P = 0.01$) and that of CP increased ($P = 0.02$).

Conclusions
This study demonstrates a significant decrease in the prevalence of CL/A and CLAP after introduction of the SAS. However, due to an increase in CP, the prevalence of all patients born with OFCs has not changed in the Netherlands between 1997 and 2019.

Keywords
Epidemiology; ethics/Health policies; folic acid; prenatal development; registry; ultrasound.

INTRODUCTION

Orofacial clefts (OFCs) are one of the most common birth anomalies.[1] The prevalence of OFCs varies significantly in Europe, ranging from 1.0 per 1000 in the UK, to 1.66 per 1000 in the Netherlands, up to 2.62 per 1000 live births in Finland.[2–4] For the purpose of this study, OFCs will be divided into three categories: cleft lip with or without alveolus (CL/A), cleft lip, alveolus and palate (CLAP) and cleft palate (CP).[5]

In 2007, the second-trimester anomaly scan (SAS) was introduced nationwide in the Netherlands and performed in almost all pregnancies at approximately 20 gestational weeks.[6] The SAS is a transabdominal two-dimensional (2D) ultrasound screening test. It was initially introduced for the detection of neural tube defects, however other anatomical structures are evaluated as well, including the fetal upper lip.[6] Once an anomaly is suspected on the SAS, the pregnant woman is referred to a center of prenatal diagnosis, where an advanced anomaly scan (AAS) is performed. Due to the wide-spread availability of SAS, it is rare in the Netherlands for a baby to be born with an OFC with lip involvement that was not prenatally diagnosed.[7] In a systematic review by Maarse et al., prenatal detection rates of 2D ultrasounds ranged from 9–100% for CL/P and 0–22% for CP in low-risk women.[7]
Two studies with low sample sizes have demonstrated that in certain countries, prenatally diagnosed isolated OFCs resulted in high rates of termination of pregnancy (TOP) (ie, South Korea 27.3% and Israel 93.3%).[8,9] Moreover, a small Dutch study showed a decrease in prevalence in OFC patients since 2003, even prior to the introduction of the SAS in the Netherlands in 2007.[2] Two possible explanations were provided by the authors: an increase in 2D ultrasounds resulting in greater prenatal detection of OFCs, leading to more terminations of affected pregnancies, and an increased use of folic acid.[2] Globally, however, the nationwide impact the SAS had on the prevalence of OFCs has never been examined.

The main objective of this study is to investigate the prevalence rates and demographics of OFCs and their three categories in the Dutch population over a period of 23 years. In addition, the potential relationship between the nationwide introduction of SAS and the rate of TOP in fetuses with OFCs in the Netherlands is examined. The hypothesis was that implementation of such a diagnostic test could lead to an increase in TOP with respect to OFCs.

METHODS

In this retrospective cohort study, we included all patients with OFCs registered in the NVSCA database of the Dutch Association for Cleft Palate and Craniofacial Anomalies, between January 1, 1997 and December 31, 2019. Specialists from all Dutch cleft palate teams have registered patients with OFCs via a digital form during the first postnatal outpatient consultation since January 1, 1997.[5] Note that the three parts (ie, general patient characteristics, oral clefts features, and associated anomalies of the head/neck and other organ systems) of the NVSCA registration form have been validated.[10–12] The purpose of this registration is, among other things, to provide an overview of the Dutch OFC population. The health insurance companies use the numbers of registrations annually to determine whether the teams are treating enough patients to recognize them as "cleft palate centers". The accuracy of the database is therefore of paramount importance to all cleft teams.

In low-risk women, the SAS is performed in primary healthcare centers by midwives and sonographers. If an increased risk of OFCs exists, such as a previous pregnancy with OFC or a family history of OFC, parents are referred to secondary healthcare centers. When structural anomalies are found, parents are referred to one of the tertiary healthcare centers for prenatal diagnostics (university medical centers and specialized peripheral centers). An AAS is performed and the pregnant woman is then referred to a multidisciplinary cleft palate team for counseling and genetic testing, if desired.

The following data was used from the NVSCA database: date of birth, gender, anatomical (laterality of the lip and pre-maxilla/maxilla, ie, alveolus, hard and soft palate including uvula) and morphological (complete, incomplete, submucous or hypoplasia) description of clefts, adoption/refugee status, birth weight, gestational age, associated congenital anomalies of the head/neck area and those of other organ systems were collected.[2,5] These anomalies were diagnosed and registered once after birth in consultation with members of the cleft palate team. Note that any OFC patient may have one or more congenital anomalies of the head/neck and/or other organ systems. Congenital anomalies that were not visible on the SAS (eg, glossoptosis, tracheomalacia, microtia, macrostomia, pectus excavatum, dermatological anomalies) were also registered in this study. A pediatrician was involved

in examination of these children, and if necessary, a clinical geneticist was consulted.

Adopted/refugee patients (n = 642) were excluded from the study to minimize bias in Dutch prevalence estimates. Subsequently OFCs were subdivided into three categories: cleft lip with or without alveolus (CL/A), CLAP and cleft palate (CP). Live born OFC children that died in the neonatal period before visiting a cleft palate team (estimated at n = 20 per year) were probably also registered in the NVSCA database.[5] The frequencies of patients with OFCs per year were compared to the number of live births per year according to the "Centraal Bureau voor Statistiek" (Central Office of Statistics of the Netherlands).[13]

Patients born with OFCs before and after the national introduction of the SAS in January 1, 2007 were compared. To allow for some time for adoption to this introduction, three groups were compared (ie, pre-nationwide introduction of the SAS [January 1997 – December 2005] versus the transition phase [January 2006 – December 2008] versus post-nationwide introduction of the SAS [January 2009 – December 2019]). Additionally, data stratification was made for each OFC category concerning patients with associated congenital anomalies of head/neck area and/or other organ systems. The number of patients with additional congenital anomalies per category was also calculated.

Statistical analyses were performed using SPSS (Statistical Program for Social Sciences, version 26; SPSS Inc., Chicago, IL, USA). For continuous data, normal distributions were evaluated by the Shapiro-Wilk test and Kolmogorov-Smirnov test. If a continuous variable was normally distributed, an independent t-test was used. If a continuous variable was not normally distributed, a Mann-Whitney U test was executed to test for differences between groups. For more than two groups, a Chi-square test was used to compare binary/ordinal data and a Kruskal-Wallis test was performed to test differences for continuous data that was not normally distributed. A threshold of $P < 0.05$ was used to determine statistical significance. The STROBE-checklist (Strengthening the Reporting of Observational Studies in Epidemiology) was adhered to in the preparation of this manuscript. Guidelines of the World Medical Association's Declaration of Helsinki were followed and IRB approval was given for this study (local institutional review board of the Amsterdam University Medical Center W20_237 # 20.273).

RESULTS

A total of 7402 patients with OFCs were included in this study: 1889 patients were diagnosed with CL/A (25.5%), 2586 patients (34.9%) with CLAP, and 2927 patients (39.5%) with CP (Supplemental 1). Consequently, clefts occur in 1/575 live births in the Netherlands (1/2255 CL/A; 1/1647 CLAP and 1/1455 CP). CL/A occurs in 4,43, CLAP in 6,07 and CP in 6,87 per 10,000 live births. After subdividing the total cohort into two groups (I: born before January 1, 2006 and II: born after January 1, 2009), the prevalence between these groups did not differ (1/578 versus 1/587, P = 0.85) (Figure 1).

Patient characteristics were compared between CL/A, CLAP and CP categories as shown in Table 1. More females were affected in CP compared to CL/A and CLAP (P < 0.001). In addition, birth weight was significantly lower in patients with CP compared to the other two categories (3423 gram ≈ 7 pounds and 8.7 ounces; 3350 gram ≈ 7 pounds and 6.2 ounces and 3298 gram ≈ 7 pounds and 4.3 ounces for CL/A, CLAP and CP, respectively). Gestational age was significantly higher in CL/A (P < 0.001). Patients with associated congenital anomalies were most often seen in CP compared to the other categories (P < 0.001).

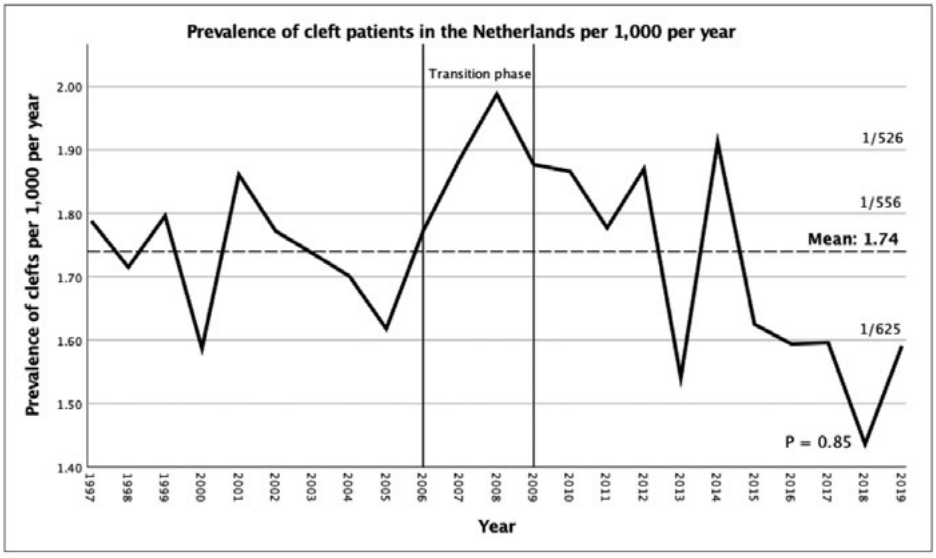

Figure 1. Prevalence of cleft patients in the Netherlands per 1000 per year.

Table 1. Patient characteristics.

	CL/A (*n* = 1889)	CLAP (*n* = 2586)	CP (*n* = 2927)	P
Gender [a] M/F ratio	1.83	2.14	0.91	
Male (*n*)	1222 (64.7%)	1762 (68.1%)	1393 (47.6%)	*< 0.001* [b]
Female (*n*)	666 (35.3%)	824 (31.9%)	1527 (52.2%)	
Birth weight (g.)	3423 (764)	3350 (775)	3298 (840)	*< 0.001* [c]
Lbs. + oz (± oz)	7 + 8.7 (26.9)	7 + 6.2 (27.3)	7 + 4.3 (29.6)	
Gestational age (weeks)	40.0 (2.0)	39.0 (2.0)	39.0 (2.0)	*< 0.001* [c]
Associated congenital anomalies	510 (27.0%)	462 (17.9%)	997 (34.1%)	*< 0.001* [b]

Abbreviations: CL/A: cleft lip with or without alveolus; CLAP: cleft lip, alveolus and palate; CP: cleft palate.

[a] *Note that the total number of patients for gender in CL/A and CP does not reach 100% due to missing data (n = 1 for CL/A and n = 7 for CP).*

[b] *Chi-square test*

[c] *Kruskal-Wallis test*

Finally, prevalence of OFC categories was investigated in the years 1997 to 2019 (Table 2). Additionally, for each category a subanalysis was performed for patients with associated congenital anomalies. Prevalence of CL/A decreased after the introduction of SAS (Figure 2; P = 0.04). CL/A combined with associated congenital anomalies remained stable over time (Supplemental 2; P = 0.91). CLAP decreased over the years (Figure 3; P = 0.01), whilst CLAP combined with associated anomalies remained stable (Supplemental 3; P = 0.73). Prevalence of CP increased after 2007 (Figure 4; P = 0.02) and CP with anomalies also increased (Supplemental 4; P = 0.04).

Table 2. Prevalence of subcategories of OFCs in the Netherlands.

	Pre-nationwide introduction (January 1997 – December 2005)			Transition phase (January 2006 – December 2008)			Post-nationwide introduction (January 2009 – December 2019)				
Type of OFC [a]	**Total births**	**Births affected**	**Prevalence (per 10,000)**	**Total births**	**Births affected**	**Prevalence (per 10,000)**	**Total births**	**Births affected**	**Prevalence (per 10,000)**	**PR (pre- vs post)**	**P-value (pre vs. post)**
All OFCs	1,785,815	3091	17.31	551,027	1037	18.82	1,922,924	3274	17.03	0.98	NS
CL/A	1,785,815	843	4.72	551,027	260	4.72	1,922,924	786	4.09	0.87	0.04
- CL/A -	1,785,815	624	3.49	551,027	61	1.11	1,922,924	556	2.89	0.83	<0.01
- CL/A +	1,785,815	219	1.23	551,027	199	3.61	1,922,924	230	1.20	0.98	NS
CLAP	1,785,815	1166	6.53	551,027	338	6.13	1,922,924	1082	5.63	0.86	0.01
- CLAP-	1,785,815	970	5.43	551,027	274	4.97	1,922,924	880	4.58	0.84	<0.01
- CLAP +	1,785,815	196	1.10	551,027	64	1.16	1,922,924	202	1.05	0.95	NS
CP	1,785,815	1082	6.06	551,027	439	7.97	1,922,924	1406	7.31	1.21	0.02
- CP -	1,785,815	720	4.03	551,027	277	5.03	1,922,924	933	4.85	1.20	0.03
- CP +	1,785,815	362	2.03	551,027	162	2.94	1,922,924	473	2.46	1.21	0.04

Abbreviations: CL/A: cleft lip, alveolus; CLAP: cleft lip, alveolus and palate; CP: cleft palate; NS: not significant; OFC: orofacial cleft; PR: prevalence ratio.

[a] In case of associated congenital anomalies, the '+' sign is present. If there are no associated congenital anomalies, this is displayed with a '–' sign.

[b] Mann–Whitney U test

Figure 2. Prevalence of CL/A in the Netherlands over time.

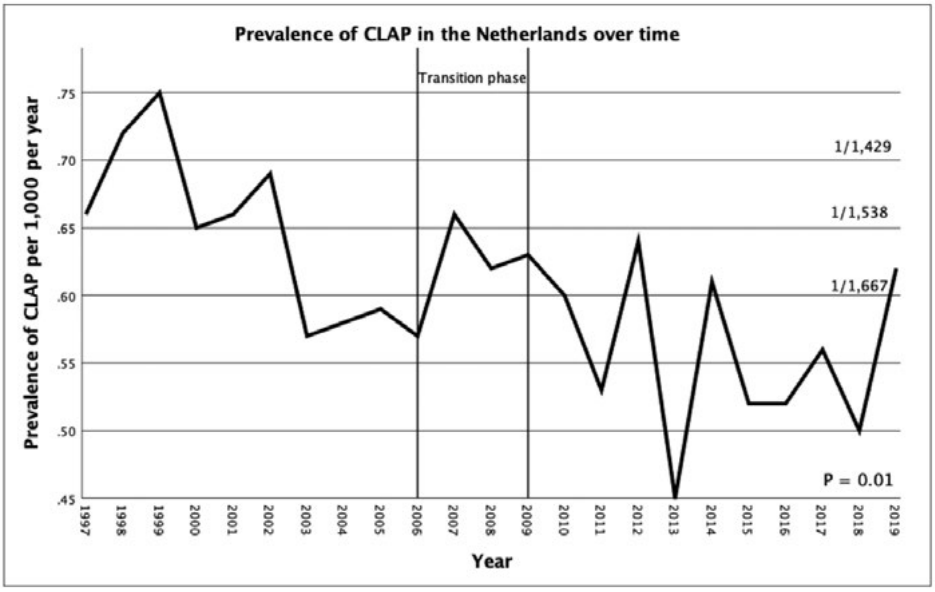

Figure 3. Prevalence of CLAP in the Netherlands over time.

Figure 4. Prevalence of CP in the Netherlands over time.

DISCUSSION

This study demonstrates a significant decline in CL/A and CLAP prevalence in live-born OFC children after the national introduction of the SAS in the Netherlands on January 1, 2007. However, the overall prevalence of OFCs did not change due to an increase in patients with CP. To our knowledge, no publication describing the effect of the introduction of the SAS on a nationwide prevalence of OFCs is currently available.

The overall prevalence of OFCs (1.74 per 1000 live births) in this study is slightly higher compared to the prevalence of a previous small Dutch study and other literature from European countries and one American study.[2,3,14] Gender distribution in OFC categories was consistent with other studies.[15,16] Our data next shows that patients with CP had a significant lower birth weight and gestational age than patients with CL/A and CLAP ($P < 0.001$). Kaye et al. reported in 97 patients with OFCs that birth weight, however, did not differ between the three categories ($P = 0.12$).[17] This difference could be attributed to the huge difference in sample sizes (7402 versus 97). Additionally, patients with CP are more likely to have associated congenital anomalies, which may or may not be part of a syndrome and a higher incidence for a low birth weight.[18]

Table 3. TOP rate in literature.

Study	Country	Investigated birth years	Total terminations (*n*)	Study population OFC patients (*n*)	TOP rate of prenatal diagnosis	TOP rate total OFC population
Bronshtein *et al.*[8]	Israel	1986-1996	14	15 [a]	93.3%	NR
Ensing *et al.*[6]	The Netherlands	2001-2010	39	123 [b]	32.5%	NR
Han et al.[9]	Korea	2009-2013	3	11 [a]	27.3%	NR
Jones *et al.*[22]	United States of America	1992-1999	2	28 [a]	25%	7.1%
Davalbhakta *et al.*[23]	United Kingdom	1995-2000	3	90 [a]	10%	3.3%
Shaikh *et al.*[24]	United Kingdom	1991-1998	2	270 [a]	8.7%	0.7%
Fleurke-Rozema *et al.*[25]	The Netherlands	2008-2012	19	333 [c]	5.7%	NR
Paaske *et al.*[26]	Denmark	1980-2014	18	398 [b]	NR	4.5%

Abbreviations: NR: not reported; OFC: orofacial cleft; TOP: termination of pregnancy
[a] monocenter study; [b] single-state study; [c] two-center study.

Compared to the mean Dutch national birth weight from 2001 to 2013 (3433 grams), patients with OFCs weighed slightly less than the national average (3423 grams for CL/A, 3350 for CLAP and 3298 for CP, not adjusted for gestational age).[19] With regard to gestational age, Wyszynski et al. found similar mean gestational ages for CL/P and CP (39.1 weeks and 39.4 weeks, respectively).[20]

The prevalence of CL/A (with or without associated congenital anomalies) decreased and the prevalence of CL/A with associated congenital anomalies remained the same before and after nationwide introduction of the SAS. The prevalence increased for CP and CP with associated congenital anomalies after nationwide introduction of the SAS. Using a similar study design, however, Malic et al. found a decrease in prevalence for all patients with OFCs over a 23-year period and a significant decrease between the periods 1994 to 2003 vs 2004 to 2017, especially for CP.[21] These differences are most likely due to demographic differences between the Netherlands and Ontario, Canada. Malic et al.[21] explain the overall decrease as follows: as CL and CLP can be diagnosed antenatally with ultrasonographic screening, higher screenings rates may have resulted in TOP. This latter finding is in line with Rozendaal et al., who found a significant decrease in OFC prevalence due to

CL/P in the Netherlands in the period 1997–2006.[2] The first use of prenatal ultrasound to detect congenital anomalies was performed in the early 1990s and before 2007 more than 90% of pregnant women in the Netherlands had already undergone one or more ultrasounds.[2] Since January 1, 2007, however, the quality of screening has improved with the nationwide introduction of SAS, performed by specialized sonographers.

In our cohort, there is an association between the national introduction of the SAS and the decrease in prevalence in patients with CLAP, but the overall prevalence of OFCs remained stable due to a significant increase in patients with CP. In a previously conducted monocenter study in Amsterdam, however, Ensing et al. found that the SAS did not lead to an increase in TOP (number of patients with OFCs 123 versus 7402 in the current study).[6] These authors used a completely different study population, i.e., prenatally diagnosed patients with OFCs and total live births in one Dutch province versus postnatal diagnosed patients with OFCs and total live births in the Netherlands. Internationally, the rate of TOP after prenatal OFC diagnosis ranges between 8.7–93.3% (Table 3).[6,8,9,22–26]

A weakness of our study, as with Malic et al.[21] and Rozendaal et al.,[2] is that we have no direct evidence that the significant decrease in the prevalence of patients with CL/A and CLAP is caused by TOP. It is well known that non-syndromic OFCs have a multifactorial cause, including smoking, alcohol, folic acid deficiency, maternal drug use (eg, anti-epileptic drugs) and lifestyle.[15,27] Although no specific data on alcohol consumption and smoking during pregnancy have been collected in the NVSCA database, there was a general decrease in alcohol and tobacco use among the Dutch population, during the course of this study.[28] In addition, several national projects have been launched since 2008 to improve information about adequate periconceptional use of folic acid (supplement of 400 μg per day) in order to reduce the risk of congenital anomalies. However, according to the Dutch Food Consumption Survey 2012–2016, the folic acid intake of about a quarter to a third of women of child-bearing age, especially those with a lower level of education, remains insufficient. Folic acid fortification of flour is not allowed in the Netherlands.[29] Furthermore, there is no consensus in the literature about periconceptional folic acid supplementation and the reduction of OFCs.[21] A Cochrane review on periconceptional folic acid at normal doses described no evidence of any preventive effects on cleft lip and cleft palate.[30] The contribution of the SAS to the decline in prevalence

of patients with CL/A and CLAP is therefore more likely. Future studies should answer the question of why parents choose TOP. Other factors that might be involved in the trend over time (eg, maternal/paternal age at birth, plural birth, assisted reproductive technology, changing socio-demographics of the population) are not included in the NVSCA database or collected by the Central Office of Statistics in the Netherlands. Future research should focus on these confounders. Exact absolute or relative numbers on how many pregnant women chose to perform the SAS are not registered by the NVSCA database or the Central Office of Statistics of the Netherlands.

Another weakness, described in a national validation study, is the underreporting of associated congenital anomalies in the NVSCA database due to delayed diagnosis and deficient recording.[12] These anomalies were only assessed during the first (postnatal) outpatient consultation, but most become apparent in the early years of life.[31] However, there is currently no (digital) link between the prenatal diagnosis (mother's patient file) and the postnatal OFC diagnosis (the child's patient file), but it is expected that the associated structural anomalies found prenatally will be registered in the NVSCA database. Finally, this study has very limited covariates, which seem to preclude more in-depth statistical analysis to better understand the observed trends.

In our cohort, CLAP with associated anomalies did not change significantly. In contrast, CP and CP with anomalies increased, since anomalies are most commonly seen in the CP.[32] Therefore, future prospective cohort studies need to investigate the effect of prenatal OFC diagnoses with and without associated structural anomalies and the relation to TOP.

Our results do not explain the increased prevalence of patients with CP. A possible explanation could be the increased prevalence of obesity, since obesity could result in CP.[33] The percentage of obese patients in the Dutch population increased from 8.4% in 1997 to 14.2% in 2017.[34] Future prospective studies should focus on the correlation between CP and obesity, diabetes and maternal drug use that may lead to CP. It should be acknowledged that with respect to CP, prenatal detection rates of 2D ultrasound are quite poor (ranging from 0–22% in low-risk women).[7] Thus, we would not expect the implementation of SAS to have any impact on the numbers of this particular subset of OFC patients.

This study raises several ethical discussion points. Since the Dutch Abortion Act (1981), women have the legal right to terminate a pregnancy, with or without birth defects, before the 24th week, which is the viability threshold.[35] All hospitals and special clinics in the Netherlands that are authorized to perform TOPs are obliged to register TOPs annually, but indications for TOP are not included. These registries show a gradual increase in second trimester TOPs up to and including 2019, especially in gestational weeks 21–23 performed in hospitals after SAS.[36] This implies that there has been an increase in the number of TOPs with congenital anomalies. Since the specific indications for TOP are not included in the Netherlands, we must be careful with interpreting the decline in prevalence of OFCs. Legal regulations concerning TOP are different in other European countries. In the UK, the Abortion Act states that TOP is considered legal when two registered medical practitioners agree that there is a substantial risk of the fetus suffering from physical and/or mental abnormalities to the extent that the child would be severely handicapped.[37] However, there is no legal definition of what is considered a 'substantial' risk.[38] In Belgium, TOP is allowed up to 12 weeks, after which it is only allowed for proven severe and incurable diseases of the fetus.[39] Stock et al. conducted a study of parental attitudes towards prenatal testing and TOP after a CL/CP diagnosis.[40] The results clearly demonstrated that the way the diagnosis is communicated affects the decision-making of parents-to-be regarding further testing and TOP. Some respondents had felt pressure to make a quick decision, with a minority regretting having an amniocentesis, and/ or experiencing significant distress due to the need for unnecessary TOP. These findings should inform future techniques and strategies for counseling expectant parents.

CONCLUSIONS

This retrospective study of 7402 patients with OFCs, demonstrates a significant decrease in prevalence of children born with CL/A and CLAP after the nationwide introduction of the SAS in the Netherlands in 2007. However, the overall prevalence of OFCs did not change due to an increase of the number of patients born with a CP. Though national abortion registries showed a gradual increase in second trimester TOPs up to and including 2019, with an implied increase in the number of TOPs pertaining to fetuses with congenital anomalies, there was no direct evidence that the significant decrease in the prevalence of patients with CL/A and CLAP was caused by TOP.

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PART 2

NEW DEVELOPMENTS AND FUTURE PERSPECTIVES IN OROFACIAL CLEFT EDUCATION (DURING THE COVID PANDEMIC)

CHAPTER 8

PRIORITIZING CLEFT/CRANIOFACIAL SURGICAL CARE AFTER THE COVID-19 PANDEMIC

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ABSTRACT

Background

It is anticipated that in due course the burden of emergency care due to COVID-19 infected patients will reduce sufficiently to permit elective surgical procedures to recommence. Prioritizing cleft/craniofacial surgery in the already overloaded medical system will then become an issue. The European Cleft Palate Craniofacial Association, together with the European Cleft and Craniofacial Initiative for Equality in Care, performed a brief survey to capture a current snapshot during a rapidly evolving pandemic.

Methods

A questionnaire was sent to the 2242 participants who attended 1 of 3 recent international cleft/craniofacial meetings.

Results

The respondents indicated that children with Robin sequence who were not responding to nonsurgical options should be treated as emergency cases. Over 70% of the respondents indicated that palate repair should be performed before the age of 15 months, an additional 22% stating the same be performed by 18 months. Placement of middle ear tubes, primary cleft lip surgery, alveolar bone grafting, and velopharyngeal insufficiency surgery also need prioritization. Children with craniofacial conditions such as craniosynostosis and increased intracranial pressure need immediate care, whilst children with craniosynostosis and associated obstructive sleep apnea syndrome or proptosis need surgical care within 3 months of the typical timing. Craniosynostosis without signs of increased intracranial pressure needs correction before the age of 18 months.

Conclusions

This survey indicates several areas of cleft and craniofacial conditions that need prioritization, but also certain areas where intervention is less urgent. We acknowledge that there will be differences in the post COVID-19 response according to circumstances and policies in individual countries.

INTRODUCTION

On March 11, 2020, the World Health Organization declared COVID-19 to be a global pandemic, which classifies the outbreak as an international emergency.[1] Healthcare is one of the major COVID-impacted areas, where medical supplies and services in hospitals are being reprioritized, with only urgent oncology and emergency trauma surgeries are being performed, while elective surgical care is being postponed. As elective surgeries are being postponed, a significant excess of surgical patients is being created in addition to those patients who were already on waiting lists before the COVID-19 crisis. Depending on how long the COVID-19 outbreak will prevail, unequivocally, many elective nonacute surgeries will become urgent at some point in time. Moreover, once the coronavirus crisis decreases, many hospitals will have problems prioritizing nonacute surgery.

To ensure optimum care in these difficult circumstances and to minimize adverse consequences for patients, the European Cleft Palate Craniofacial Association together with the European Cleft and Craniofacial Initiative for Equality in Care would like to facilitate the dialogue and discussion with health authorities about prioritizing surgical interventions. Therefore, we developed a questionnaire aimed at defining acceptable timeframes or maximum ages when various types of cleft or craniofacial surgery should be performed after the COVID-19 crisis. We acknowledge that there will be differences in the post COVID-19 response according to circumstances and policies in individual countries.

METHODS

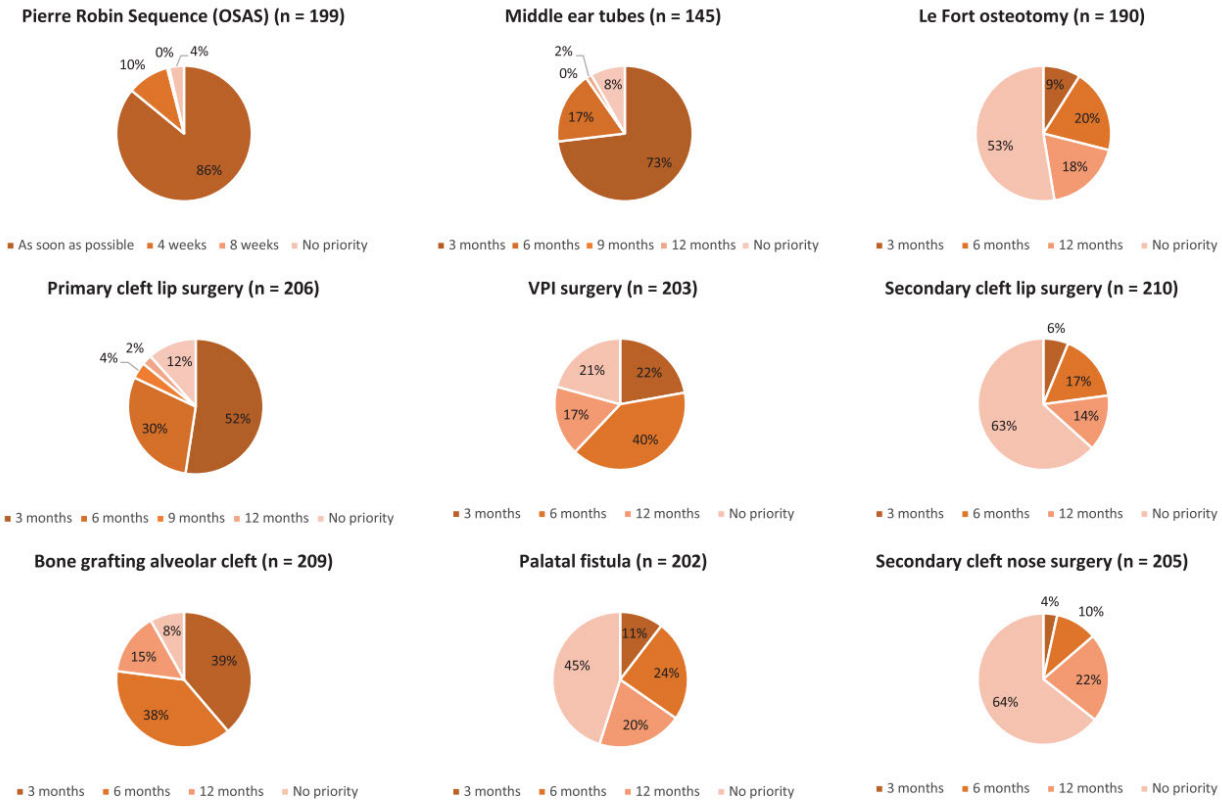
A questionnaire was sent to 2242 participants of the 2015 European Cleft Craniofacial meeting in Gothenburg, Sweden; the 2017 13th International Cleft Meeting in Chennai, India; and the 2019 European Cleft Palate Craniofacial Association meeting in Utrecht, the Netherlands. The questionnaire is added in Supplemental Digital Content 1 and includes 19 questions about acceptable waiting times with regard to cleft and craniofacial surgery. (See appendix, Supplemental Digital Content 1, which displays the questionnaire use for this study, http:// links.lww.com/PRSGO/B486.)

This survey aimed to capture a snapshot of current opinions at a narrow time window during the rapidly evolving COVID pandemic. Respondents were therefore given a window of 10 days to respond. A reminder was sent after 7 days.

RESULTS

We received 281 responses (response rate, 12.5%); however, specialists working in the same cleft/craniofacial center filled in only one form for the whole group. Most respondents originated from Europe (62.6%), which is followed by those from Asia (20.1%) and the United States (9.7%). The majority of respondent physicians were specialized in plastic surgery (33.3%), maxillofacial surgery (24.7%), and orthodontics (17.2%). The questionnaire revealed that the medical practice of respondents was severely restricted owing to the COVID-19 virus pandemic: on a scale of 0 to 100 (0, no restrictions at all; 100, extremely severe restrictions), the median reported number was 90.0 with an interquartile range of 36.5.

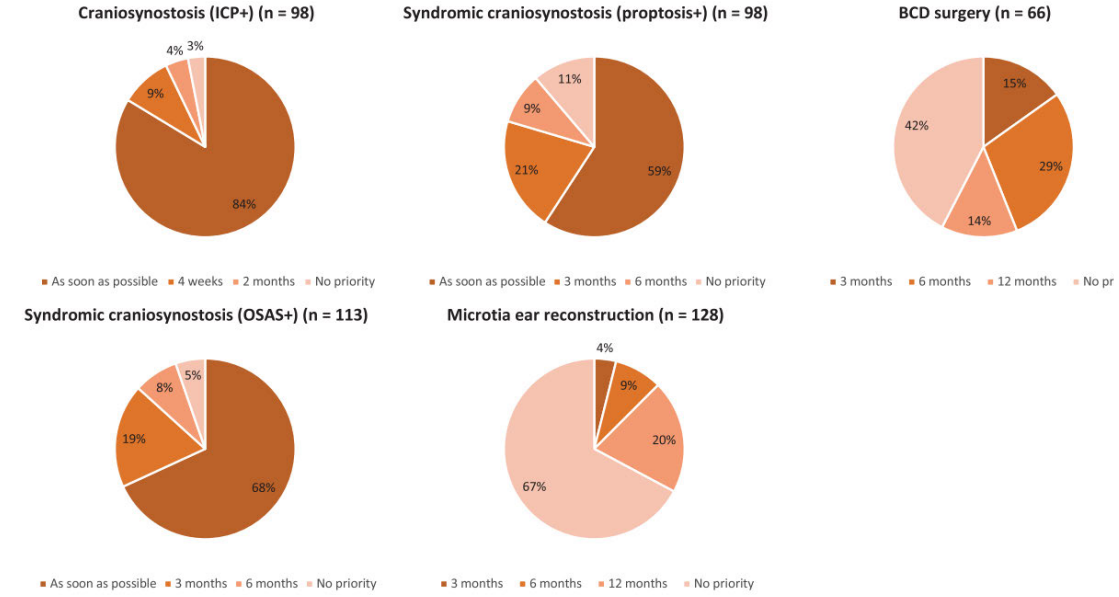
The survey revealed that there were several procedures with regard to cleft surgery that were considered high priority (Table 1). Of all respondents involved in cleft surgery (n = 206), 82% felt that primary lip surgery could be maximally delayed from the normal protocol by up to 6 months (Fig. 1). Of the 228 respondents performing palate surgery, 55% (n = 125) indicated that the (soft) palate should be closed before the age of 12 months, while >70% of the respondents indicated that palate repair should be performed before the age of 15 months, with an additional 22% stating by 18 months. At the comments section, many surgeons indicated that because of solving the "solidarity problem" with the coronavirus, many would accept these as "absolute maximum" and that most surgeons felt that delaying past the age of 12 months would normally be the age limit. The placement of middle ear tubes in children with problems related to cleft lip and palate could be postponed up to 6 months according to 90% of the 145 respondents, although the majority (73%) recommended a delay of 3 months. With regard to surgical intervention in children with Robin sequence who suffer from obstructive sleep apnea syndrome (OSAS) and do not respond to positional changes, 86% of the 199 respondents said it should be performed immediately and 96% of the respondents indicated that this should be done within 4 weeks.



OSAS: obstructive sleep apnea syndrome; VPI: velopharyngeal insufficiency.

Figure 1. Acceptable waiting times for cleft surgery.

With regard to secondary speech surgery, 62% of all 203 respondents (n = 126) even felt that a waiting time of 6 months is acceptable, while 79% of the 203 (n = 160) respondents felt that a wait of maximally 12 months was acceptable. Bone grafting in patients with an alveolar cleft should be performed within 6 months according to 77% of the 209 respondents. Finally, regarding palatal fistula closure, Le Fort I osteotomy with orthodontic pretreatment and secondary cleft lip and nose surgery, participants felt that these procedures should be less prioritized.



BCD: bone conducting device; ICP: intracranial pressure; OSAS: obstructive sleep apnea syndrome.

Figure 2. Acceptable waiting times for craniofacial conditions. BCD, Bone conducting device.

The survey revealed that there are several procedures with regard to craniofacial surgery that are considered high priority (Table 1; Figs. 2, 3). First, a craniosynostosis correction should be performed as soon as possible in patients with signs of intracranial pressure (ICP), according to 84% of the 98 respondents. Craniosynostosis without signs of ICP should be operated on before the age of 18 months according to 91% of 76 respondents (n = 69), and 66% of all 76 respondents (n = 50) even felt that this should be done before the age of 12 months. Furthermore, patients with syndromic craniosynostosis

and signs of obstructive breathing/OSAS or proptosis should undergo surgery as soon as possible, with a maximum acceptable delay of 3 months.

For patients without signs of ICP, surgery by using springs/endoscopic strip removal should be performed before the age of 6 months. A group of respondents (66% of 68 respondents) indicated to opt for an open procedure, which should ideally be done before the age of 12 months. Craniofacial surgeries that were considered not necessary to prioritize included the implantation of a bone conduction device and ear reconstruction in microtia patients.

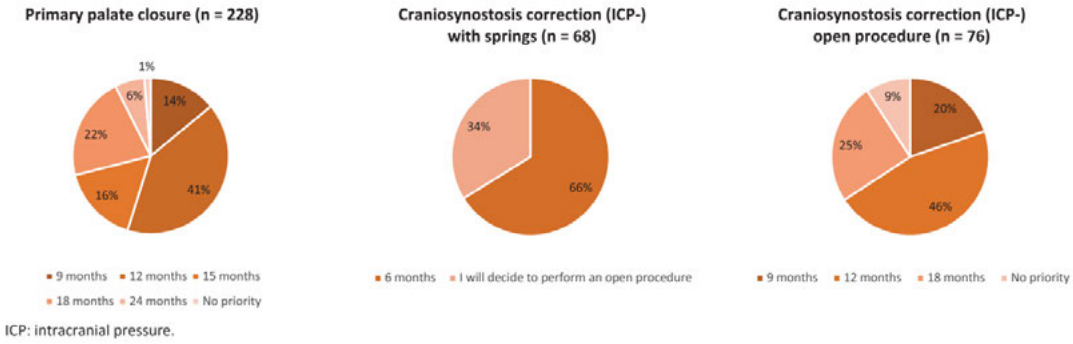


Figure 3. Ages (months) when surgery should be performed.

Table 1. Summary of acceptable times to wait for surgery

CLEFT SURGERY		CRANIOFACIAL SURGERY	
Delay acceptable (months)			
Immediate:	Robin sequence needing surgery (86%)	Immediate:	: Craniosynostosis with increased ICP (84%)
< 6 months:	Middle ear tubes (90%)	< 3 months:	Craniosynostosis with OSAS signs (87%)
	Primary lip surgery (82%)	< 3 months:	Craniosynostosis with proptosis signs (80%)
	Bone grafting (77%)		Microtia ear reconstruction (67%)
< 12 months:	VPI surgery (79%)		Bone conducting device surgery (42%)
Less priority:	Secondary cleft nose (64%)	Less priority	
	Secondary cleft lip (63%)	<6 months	Craniosynostosis with springs (66%)
	Le Fort I osteotomy (53%)	<18 months	Craniosynostosis correction without signs ICP (91%)
	Palatal fistula (45%)		
Surgery before specific age:			
< 18 months:	(Soft) palate surgery (93%)	< 6 months	Craniosynostosis with springs (66%)
		< 18 months	Craniosynostosis correction without signs ICP (91%)

DISCUSSION

Due to the COVID-19 pandemic, elective surgeries are being postponed and it is expected that many hospitals will have problems prioritizing nonacute surgery once the COVID-19 crisis decreases. To facilitate the dialogue and discussion with health authorities about prioritizing surgical interventions, a questionnaire was sent to specialists working in cleft and craniofacial care worldwide. This has
led to a snapshot of acceptable waiting times for cleft and craniofacial surgery. In relation to this, it is of paramount importance to take into account that the health expenditure per inhabitant varies significantly between countries,[2] and access to healthcare remains uneven across countries and social groups, according to socioeconomic status, place of residence, ethnic group, and

gender.[3] This contributes significantly to the available provision of care, and even more so in the aftermath of COVID-19 pandemic.

A higher response rate would have strengthened this study; however, due to the dire consequences of COVID-19, we chose for a response window of just 10 days. Moreover, many participants reported to have responded on behalf of their center after correspondence with their team members. As we used a mailing list with email addresses of attendees of three different international cleft/craniofacial conferences, some of our potential respondents could have been invited multiple times with different email addresses, or it could have included individuals who are not directly involved in patient care anymore. This might have also reduced the response rate. Therefore, the actual response rate of the current study is unknown.

With regard to cleft surgery, the specialists indicated that (1) surgical intervention in children with Robin sequence who suffer from OSAS not responding to conservative measures and subsequently needing surgery should not be delayed. (2) Primary cleft lip, bone grafting, placement of middle ear tubes, and velopharyngeal insufficiency (VPI) surgeries can be delayed by several months. (3) Closure of the (soft) palate can be delayed for several months, although most respondents do suggest closure before the age of 15 months. (4) Palatal fistula closure, Le Fort I osteotomy, and secondary cleft lip and nose surgeries do not need to be prioritized and can therefore safely be postponed. With regard to craniofacial surgery, the specialists indicated that (1) a craniosynostosis correction
should be performed as soon as possible in patients with signs of ICP and within 3 months when they have OSAS or proptosis, (2) craniosynostosis correction in patients without signs of ICP can be delayed by several months, and (3) the implantation of a bone conducting device and ear reconstructions have less priority and may therefore safely be postponed.

We are fully aware that this study did not include a comparison with the "normal" timing protocol for each center, for example, there are significant variations in the timing of cleft palate surgery between centers. However, we do feel that the information obtained does give some indications about prioritizing cleft/craniofacial surgery because government and state recommendations do not provide clear guidance on how plastic and reconstructive surgeons should approach elective surgeries.[4,5] Moreover, the

pediatric surgical population is unique for several reasons—most notably the time-sensitive nature of many pediatric interventions.[6] The overview presented here is intended as a complementary guide, and healthcare providers, local and national regulatory bodies will have to determine actual practice in each hospital or facility. Any additional restrictions that are applied by such bodies should supersede the timeframes mentioned here.

The American Cleft Palate-Craniofacial Association (ACPA) has released a statement providing guidance on cleft-lip– or cleft-palate–related surgeries during the COVID-19 pandemic.[7] This survey complements and supports much of their guidance. However, individual circumstances and the best interests of each patient will dictate what happens in practice. The ACPA advises that (1) primary cleft lip surgery can be delayed; (2) cleft palate repair may be delayed; (3) neonatal airway management associated with Robin sequence is essential, and local protocols should be followed on a case-by-case basis; (4) VPI surgery may be safely delayed for several months or even longer; (5) delaying secondary surgeries related to cleft lip and nose should be considered; and (6) orthognathic surgery may be suggested to manage occlusion, sleep apnea, or appearance, but orthognathic surgery in patients with cleft lip and palate can be delayed. When the ban on elective surgery is being lifted, this survey supports the notion also suggested by the ACPA to choose to prioritize palate repair surgery over VPI surgery, starting with the oldest children. However, the stage a child has reached in their language development may also be relevant in this decision. Because COVID-19 transmission is primarily through droplet spread, teams that perform procedures in the head and neck are at a high risk for infection. Therefore, where available and possible, preoperative COVID-19 testing should be done.

In addition to the advice provided by the ACPA, the American College of Surgeons, the American Society of Anesthesiologists, the Association of periOperative Registered Nurses, and the American Hospital Association have made a joint statement and released a list of 10 issues that should be addressed before a healthcare organization resumes elective surgeries that have been delayed.[8] Furthermore, the Royal College of Surgeons of England published recommendations that are structured under 9 themes to allow services to provide safe and efficient patient care, but also to ensure that when surgery resumes, it will be sustainable in the face of the recurrent pandemic in the future.[9]

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CHAPTER 9

IMPROVING PATIENT CARE BY VIRTUAL CASE DISCUSSION BETWEEN PLASTIC SURGEONS AND RESIDENTS OF UGANDA AND THE NETHERLANDS

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ABSTRACT

Introduction

Traditional on-site missions of plastic surgeons from "high-income countries" in "low- and middle-income countries" are often limited in time and lack proper follow-up. Regular digital collaboration could lead to a more impactful and durable exchange of knowledge for plastic surgeons and residents in both settings.

Aims

The aim of this study was to evaluate the satisfaction of the first twelve months of weekly digital meetings, explore advantages/disadvantages, and to provide tools for similar initiatives.

Methods

Weekly meetings started from August 2021. An encrypted digital connection allowed residents and plastic surgeons from Uganda and the Netherlands to discuss cases for educational purposes, where treatment options were considered. After twelve months, a survey was sent to participants from both countries to indicate the meetings' strengths, weaknesses, and possible improvements.

Results

A total of 18 participants responded to the questionnaire (ten plastic surgeons, six residents, and two researchers). The strengths of the meetings were the accessibility of the meetings, knowledge exchange and practice for residents' final exams. Possible improvements included having a clear format for patient discussion, a session moderator and better internet connectivity. Moreover, a database to assess the impact of the given intervention on the patient cases by evaluating postoperatively (e.g. three months), could further improve clinical care.

Conclusions
Virtual patient discussions subjectively contributed to medical education at both locations. Improved digital infrastructure and a collaborative database could further maximize learning capacity. Furthermore, digital proctoring is a promising way to establish sustainable collaborations between high- and low-resource countries.

Keywords
Education, Medical; Global health; Healthcare disparities; Program evaluation; Remote consultation

INTRODUCTION

Access to surgical care is not equally distributed worldwide. Over 4.8 billion people currently do not have access to safeand affordable surgical care.[1] With limited qualified physicians and surgeons, combined with restricted time and resources, it is hard to properly train new surgeons.[2] Until now, surgical care and education from abroad were often provided by traditional collaborative on-site missions between low- and middle-income countries (LMICs) and high-income countries. However, they are often limited to two to three weeks' time, raising barriers for all physicians involved to contact their international colleagues. To improve learning experiences for residents andthereby improve surgical care, other ways of education should be explored. The aim of this study was to describe the first twelve months of experience with virtual grand rounds, to share the results of the questionnaire, and to provide tools for future similar medical initiatives.

MATERIALS AND METHODS

Plastic surgeons and residents from Kampala, Uganda and Rotterdam, Beverwijk and Amsterdam in the Netherlands participate in weekly digital meetings. These meetings were initiated in August 2021 by Interplast Holland and the head of the department of plastic surgery in Kampala. An encrypted digital connection (Zoom for Healthcare, version 5.7.4) allowed the participants to discuss patients in a pseudonymized manner (i.e. recognizable patient characteristics [e.g. tattoos] and eyes were blurred, no date-of-birth or names were disclosed) with multi-layer security encryption and compliant with HIPAA regulations. Patients gave oral consent to be discussed for educational/consulting purposes.

A cross-sectional survey study was performed aiming to evaluate the success of these meetings. Twelve months after the start of the meetings, a questionnaire was sent to all participants (n = 22) asking them for both strengths and weaknesses of these meetings as well as to propose improvements. Castor Electronic Data Capture (Castor EDC, version 2022.5.0, Castor, Amsterdam, the Netherlands) was used to build and send the questionnaires (Supplemental Data 1). The initial survey was sent through e-mail on September 1, 2022, and a reminder was sent fourteen days

afterward. The study was performed in accordance with the Declaration of Helsinki.

RESULTS

A total of 47/52 meetings (90%) were pursued. All 80 patientcases that were discussed are displayed in Figure 1 and Supplemental Data File 2. The participants in this project, 22 participants in total, consisted of twelve plastic surgeons (55%), eight (plastic) surgery residents (36%) and two researchers (9%). Eighteen participants completed the questionnaire (response rate: 82%; Supplemental Data File 3).

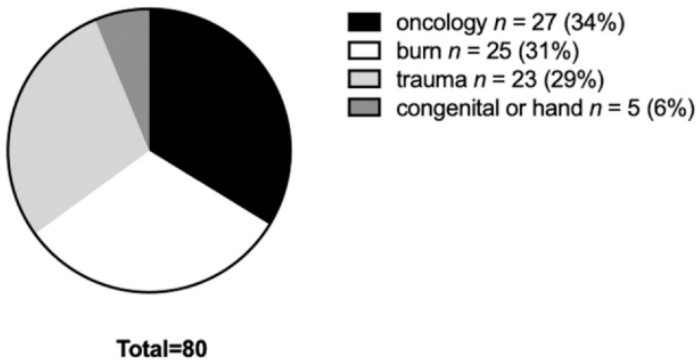

Figure 1. Case-load discussed in the first 12 months, divided in trauma-related reconstructions, oncological-related reconstructions, reconstructions related to burns, and hand surgery.

The accessible discussion of patient cases was a frequently mentioned strength, which allowed everyone topresent and discuss cases, and this improved confidence infellows (n = 6). Learning from each other was also one of the important strengths, indicated by both Dutch and Ugandan participants (n = 5). The vast experience and knowledge of plastic surgery of team members, stimulating one to read more (n = 3) was an important strength.

Most important and frequently mentioned weaknesses were a suboptimal internet connection and poor-quality camera/microphone that hampered discussion of patient cases (n = 4). Two other professionals stated that a clear agenda/plan for the meetings was lacking and two participants liked to have more in-depth presentations for specific pathologies/surgical treatments. Participants indicated that the lack of a mutual database to register all the patients, allowing for structured follow-up on the outcome of patient cases, was a substantial disadvantage. After implementing the improvements, a second survey was sent in which we asked if participants would recommend this new type of patient discussion and if they would pose new improvements. The only recommendation from the second survey was the use of a database to reflect back on cases since this database was not fully completed yet. English was the chosen language. None of the respondents indicated that this has led to communication barriers.

DISCUSSION

The present study was designed to evaluate the success of weekly digital meetings. Our results show a strong interest and enthusiasm from plastic surgeons and residents from both countries who took part in weekly meetings to discuss difficult patient cases.

Substantial differences arise between the training of plastic surgeons and accessibility of (plastic) surgical care between Western Europe and Sub-Saharan Africa (one plastic surgeon per 9.4 million people) versus one plastic surgeon per 45,000 people in the Netherlands).[3,4] Consequently, the need for safe and accessible surgical care, nutritional health care and anesthesiology care remains unmet. By establishing a digital weekly opportunity to discuss difficult and/or successful patient cases between residents and plastic surgeons from both countries, a bilateral knowledge exchange is made possible.

One of the main weaknesses of the digital collaboration was the suboptimal internet connection. This was also found in a similar study.[5] Improving digital infrastructure for example by improving the internet in the hospital can solve this problem partly. Important aspects of improvement are displayed in Table 1.

Table 1. A list of suggestions for similar initiatives.

Suggested improvements
• Have a clear format (template) for patient discussion (in PowerPoint) • Appoint a moderator (plastic surgeon) per session • Appoint a resident from Uganda and the Netherlands to present a case every meeting • Improvement in internet connection • Create a database (after IRB approval), to assess the impact of the given suggestions to the patient cases by evaluation e.g. 3 months after surgery.

Abbreviation: IRB, Institutional Review Board.

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CHAPTER 10

SMART SURGICAL GLASSES FOR OROFACIAL CLEFT SURGERY TRAINING IN HIGH- AND LOW-INCOME COUNTRIES: A PROOF OF CONCEPT

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ABSTRACT

Introduction

The coronavirus 2019 pandemic urged us to find alternatives for education through remote proctoring and international surgical collaborations among high-, middle-, and low-income countries. Smart surgical glasses are promising for remote surgical education and international surgical collaborations.

Aims

This study aimed to assess the usability of smart surgical glasses during cleft surgery and explore their potential in remote surgical education and collaboration.

Methods

Six plastic surgical cases were randomly selected and recorded using the RODS&CONES glasses in 4K (3840 × 2160p). A 23-point questionnaire was sent to one plastic surgeon, one plastic surgery resident, and eight doctors who were not trained to critically appraise the video and audio quality of the smart surgical glasses and their applicability for remote surgical education.

Results

The participants indicated that the smart glasses had several significant advantages over conventional on-site education, such as facilitating a better view of the surgical field and providing possibilities for remote interaction. The audio quality was considered excellent. The main limitations were image stabilization issues and loss of video connection due to weak wireless fidelity.

Conclusions

All participants appreciated the use of smart glasses for remote education and considered them a promising tool for enhancing the quality of surgical education. The glasses can enable remote assistance and education of local surgical residents and may facilitate sustainable surgical collaborations among high-, middle-, and low-income countries.

Keywords

COVID-19; Cleft surgery; Remote surgical assistance; Smart surgical glasses.

INTRODUCTION

On March 11, 2020, the World Health Organization declared coronavirus disease 2019 (COVID-19) as a global pandemic.[1] Subsequently, multiple governments worldwide had to adopt extreme measures to restrain its spread. Social distancing, bans on live interaction, and lockdowns restricted the education of medical students and residents, and alternative remote approaches were sought.

Smart surgical glasses may be used for remote education and proctoring when on-site education is not feasible, as noted during the COVID-19 pandemic. These glasses are essentially web-connected wearable computers with the shape of conventional glasses that enable surgeons to record videos using a front-facing camera.[2] Moreover, these glasses enable remote assistance in the medical field and permit medical professionals to collaborate and interact with surgeons worldwide in real time.[3] The use of smart surgical glasses for educational purposes is relatively new.[4] However, smart surgical glasses may facilitate remote resident teaching by enabling the broadcasting of surgical procedures.[2] Furthermore, these glasses could enable remote surgical assistance and training between (plastic) surgeons from high-income countries (HICs) and those from low- and middle-income countries (LMICs) throughout theyear.[5] Traditional on-site missions are often limited in duration and not geared toward sustainable partnerships,[6] whereas smart surgical glasses may help establish sustainable collaborative practices that can improve global care quality.

This study aimed to test smart surgical glasses during cleft surgery to explore their potential in sustainable medical education and international collaborations. We described the limitations of the currently used smart glasses, proposed solutions to overcome them, and compared them with the limitations reported in the current literature. We hypothesized that smart surgical glasses would have several advantages over conventional on-site education, potentially improve local surgical education, and establish sustainable partnerships with healthcare personnel in LMICs. Finally, we compared the technical specifications of the RODS&CONES smart surgical glasses with those of the most frequently used smart surgical glasses (e.g., GOOGLE GLASSES, CRESCENT VISION LIVE, and WESTUNITIS INFOLINKER 3).

MATERIALS AND METHODS

In this cross-sectional survey study, the feasibility of using smart surgical glasses was tested by analyzing six cleft-related interventions broadcasted using smart surgical glasses. To measure the impact of the smart glasses, a 23-point questionnaire was sent to one plastic surgeon, one plastic surgery resident, and eight plastic surgery researchers (n = 10) after they virtually attended the cleft surgeries. All participants and the surgeon were situated in a high-resource setting in the Netherlands and had a minimal internet connection speed of 10 Mbps. The questionnaire was built using Castor electronic data capture and comprised two, eight, and five questions regarding respondent characteristics, video quality, and audioquality, respectively, and eight questions regarding general assessment questions (Supplemental Data Content 1). Six pediatric cleft cases were randomly selected from January 1, 2021 to March 31, 2022 (buccinator-based myomucosal flap, facial artery musculomucosal flap, mandibular distraction, pharyngoplasty, secondary cleft lip correction, and vomer flap). The patient demographics are listed in

Figure 1. Surgical setup with surgical assistance glasses, mounted on the right side of the surgeons' head, 4K optical zoom camera, built-in LED, speaker and microphone. Written consent was obtained from the recognizable individual (last author).

Table 1. The participants were provided a 10-day window to complete the questionnaire after the last surgery to reduce recall bias. Missing data were eliminated by making each question mandatory. Unfinished surveys were excluded from the analysis.

Table 1. Patient demographics

Type of surgery	Indication	Medical history	Age	Other remarks
BMF flap	Palatal fistula	UCLP right	17 years	NR
FAMM flap	Palatal fistula	BCLP	8 years	NR
Mandibular distraction	Micrognathia	Robin sequence	4 months	NR
Pharyngoplasty	VPI	BCLP; lip pits; closure lip vomer flap; BMF flap left	5 years	Cranial pharyngoplasty; no apneas
Secondary CL correction	Shortened scar tissue	UCL left	18 months	NR
Vomer flap and CL correction	UCLP left	UCLP left	4 months	NR

BCLP: bilateral cleft lip palate; BMF flap: buccinator-based myomuscosal flap; CL: cleft lip; CLP: cleft lip and palate; FAMM flap: facial artery musculomucosal flap; NR: not reported; UCL: unilateral cleft lip; UCLP: unilateral cleft lip palate; VPI: velopharyngeal insufficiency.

An encrypted video connection allowed participants to securely attend the six different surgical procedures. The latest smart surgical glasses RODS&CONES (RODS&CONES, Amsterdam, The Netherlands) were used to capture video in 4K (3840× 2160p). A built-in microphone and speaker enabled the surgeon to receive and respond to questions from the online audience (Figure 1). The smart surgical glasses were used for a maximum of two cleft surgeries per day. Batteries were changed between surgeries to ensure that the complete intervention could be broadcasted. Ordinal data were presented as means with standard deviations (SDs) to indicate variability. The requirement of ethical approval for this study was waived by the Medical Ethics Review Committee of the Academic Medical Center (W21_354 # 21.394), and parents provided consent for video recording and broadcasting. The study adhered to the STROBE checklist and conformed to the World Medical Association Declaration of Helsinki (1964) and its amendments.

RESULTS

The duration of surgeries ranged from 60 to 200 min. Battery life was sufficient to record full procedures. All 10 recipients responded to the questionnaire after attending a minimum of two surgical procedures (response rate, 100%). Overall, the participants gave the smart surgical glasses anaverage score of 77.5 out of 100 (SD 11.8). The video quality received an average rating of 72 out of 100 (SD 14.4; Table 2), and the audio quality received an average score of 73.5 out of 100 (SD 24.2; Table 3).

The participants reported several advantages of using smart glasses over conventional education. In total, seven out of ten respondents indicated that the smart glasses provided a better view and understanding of the procedure than conventional education (i.e., hovering beside the surgeon and looking over their shoulder or even second-row views for medical students). The surgeon's point of view during surgery was appreciated by most participants (n = 9). Furthermore, direct interaction with the surgeon was possible through the built-in communication methods of the glasses (n = 2), even when the surgeon and resident were not in the same room. This, for instance, enabled one resident to operate independently with the knowledge that a senior

Figure 2. Broadcast of the surgical intervention (secondary cleft lip correction), as shown from the audience viewpoint. The visOR-V at the left displays the content of the smart surgical glasses. The panOR device 1 on the right-hand side displays camera built into the OR lights.

specialist was nearby. Moreover, three spectators appreciated the ability to annotate parts of the surgery, raise questions, and provide suggestions. Participants could snapshot specific parts of the video and annotate them to propose an incision technique, discuss anatomical landmarks, and ask specific questions about the procedure (Figures 2–3). These annotated photographs were sent to the operating room (OR) via the smart surgical glasses. Finally, the surgeon noted that the glasses offered the advantage of recording their own surgical interventions that could be reviewed later with peers, allowing easy quality evaluation and continuous improvement.

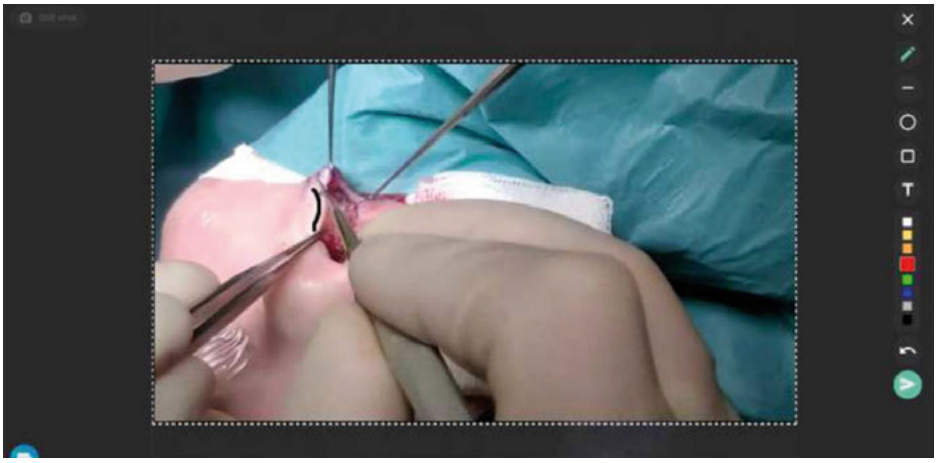

Figure 3. Host of the session can take real-time snapshots of the surgical intervention (secondary cleft lip correction) and annotate them by proposing incision lines (in black). These annotated pictures can be sent directly to the surgeon by pressing the green button in the lower-right corner.

Additionally, the use of remote surgical assistance glasses in the OR was associated with several disadvantages. Image stabilization was limited by mounting the camera onto the surgeons' head, which produced significant motion artifacts (n = 4). Furthermore, three participants noted that the location of the surgeons' hands limited the field of view of the viewer because the camera was mounted on the right side of the head. Moreover, the participants indicated that the surrounding noises in the OR, such as the beeping of monitors, radio, and non related conversations of surgical staff, were distractive (n = 3). The area of interest was also overexposed a few times during surgery, which had to be corrected by manually adjusting the white

balance of the camera (n = 1). Overall, the audio and video quality was also greatly dependent on the stability of wireless fidelity (Wi-Fi).

Table 2. Video quality

Video quality	Strongly disagree (*n*)	Disagree (*n*)	Neutral (*n*)	Agree (*n*)	Strongly agree (*n*)
The quality of the video was sufficientto follow the complete surgery	-	1	2	6	1
The area of interest was centered most of the time	-	1	2	7	-
The area of interest was focused (i.e. it did not focus on the surgeons' hands, and the area of interest was not blurry)	-	2	3	5	-
Zooming in and out provided optimal footage on the area of interest	-	2	4	3	1
Image stabilization was good	-	1	1	6	2
The area of interest was overexposed	-	5	5	-	-
The number of times video was lost per hour (estimation)		Never	1-3 times	4-6 times	>6 times
		2	8	-	-

Table 3. Audio quality

Audio quality	Strongly disagree (*n*)	Disagree (*n*)	Neutral (*n*)	Agree (*n*)	Strongly agree (*n*)
The audio quality was sufficient to attend this surgery	1	-	1	5	3
There were sufficient possibilities to discuss aspects of surgery with the surgeon	-	-	4	3	3
Background noises (e.g. radio, operation assistants) distracted me from th esurgery	1	3	3	3	-
The number of times audio was lost per hour (estimation)		Never	1-3 times	4-6 times	>6 times
		6	3	1	-

DISCUSSION

The smart surgical glasses enabled participants to remotely attend the surgery and interact with the surgeon. Overall, the participants strongly appreciated the added value of smart glasses in the OR owing to an improved view of the procedure, the ability to record surgical interventions, and annotate, fast forward, and rewind specific parts of the procedure at a later stage.

Recent studies have found that medical education through remote teaching and proctoring is safe and usable.[5,7] The smart surgical glasses facilitated a clear view of the surgical procedure and surgical anatomy from the surgeon's point of view. Orofacial cleft surgery presents unique challenges, and attending these types of surgeries (those performed inside a small oral cavity) without being the surgeon or assisting resident can be tedious and result in poor visibility and limited understanding of the procedure.[8] Smart glasses could substantially improve this by providing a better view and thus a better understanding of the surgery. This is in contrast to the well-established OR lights with integrated cameras that offer a general overview of the surgery but not visuals from the surgeon's vantage point. Although anatomical textbooks provide detailed illustrations, in vivo surgical anatomy is never entirely similar to textbook illustrations. The smart surgical glasses could help medical students learn surgical anatomy from a surgeon's point of view in a more efficient and clinically relevant manner. Furthermore, the glasses provided the senior specialists with the incredible advantage of supervising residents remotely during a procedure. This enables senior specialists to provide residents with greater autonomy while ensuring adequate supervision. Subtle differences could be identified in the responses of experienced surgeons compared with those of a resident in training. The resident in training appreciated the autonomy in the OR while knowing that experienced colleagues could guide and provide recommendations during surgery. Both resident and experienced surgeons appreciated the easy interface provided by RODS&CONES and the practicality of the smart surgical glasses. Smart surgical glasses could also be important in recording the procedure and subsequently enabling the division of the procedure into several trustable professional activities, which could improve the education of residents.[9] A competency assessment tool (CAT) is used to assess surgical performance by describing specific steps in the surgical process that cover specific tasks and evaluate the performance (instrument use, tissue handling,

and committed errors) and quality of the end product. These steps allow residents to perform parts of a surgical intervention and gradually gain autonomy to perform the complete intervention at the end of the residency.[9] Recording the surgery performed by the resident enables them to review their competence and reflect on their competence level with supervisors (e.g., surgeons). The CAT tool has been successfully applied to approve the quality of training in the English National Training Programme for laparoscopic colorectal surgery.[10]

Furthermore, smart surgical glasses may be used to facilitate supervision in the OR and may be applicable both locally and internationally because they allow surgeons to attend surgeries and advise colleagues from other hospitals and countries. A small pilot study, including three patients and two surgeons from Malawi and two patients and two surgeons from Uganda, was performed simultaneously with the present study in July 2021. The two doctors from HICs and two residents from Uganda attended the four surgical procedures live via the RODS&CONES virtual platform. Doctors from both HICs and LICs appreciated the possibility of discussing live surgery and proposing different treatment strategies. A recent systematic review indicated that surgical missions should develop into sustainable partnerships.[6] The importance and need for long-term and sustainable surgical collaboration over short-term missions have also been emphasized by healthcare providers from HICs and LMICs in recent survey studies.[6,11,12] To gain maximum impact via collaborations between HICs and LMICs, a transition of focus from surgical volume to training local team members and creating long-term relationships is required.[6,11,12] The present study and the concurrent pilot study indicate that surgical smart glasses may be applicable for international surgical collaborations that can facilitate long-term and sustainable partnerships.

Table 4. Technical specifications of smart glasses

	RODS & CONES	GOOGLE GLASSES	CRESCENT VISION LIVE	INFOLINKER 3
Battery life	2 – 12 h	3 – 5 h	3 – 5 h	Approximately 1 h
Operating system	Android 11.0	Android 4.4	Browser based	Android 4.2.2
Camera resolution	13MP (4K 60 fps)	5MP (720p)	8MP (1600x900p)	12MP (4K 30fps)
Display resolution	1920 x 1080p	640 x 360p	N/A	640 x 400p
Transparent screen	No	Yes	N/A	No
Compatible with other glasses *	Yes	No	Yes	Yes
Wi-Fi	802.11b/g/n 802.11a/ac	802.11b/g	2,4 GHz	802.11b/g/n 802.11a/ac
Mobile Phone Line	4G/LTE	N/A	N/A	4G/LTE
Bluetooth	Yes †	Yes † †	N/A	5.0 BR / EDR / LE
Microphone(s)	3	1	1	2
Speaker	Yes (97 dB)	Yes † †	Yes † †	Yes (1.0W)
Headlight	LED Flash	Yes † †	LED	Torch light
Weight in grams (oz)	85 (3.0)	46 (1.6)	450 (15.9)	150 (5.3)
Battery	1000 mAh	780 mAh	3350 mAh	4900 mAh
Ports	USB-C	Micro-USB	USB-C	USB / CTIA

Abbreviation: CTIA: Cellular Telecommunications and Internet Association; dB: decibel; fps: frames per second; LED: light emitting diode; mAh: milliampere-hour; MP: megapixel; N/A: not available; USB: universal serial bus; W: watt.
* e.g. surgical magnifying glasses, prescription glasses; †: not further specified.

Other smart glasses, such as the first-generation GOOGLE GLASSES, have been marketed, although they have not been implemented in surgical training. In Table 4, the technical specifications of the four most commonly used smart glasses in the medical field are listed (i.e., RODS&CONES, GOOGLE GLASSES, CRESCENTVISION LIVE, and INFOLINKER 3).[3,13–15] We excluded othertypes of smart glasses, such as META QUEST PRO glasses and EPSON MOVERION BT-40, because they are mixed virtual reality glasses and therefore could hamper comparability. An additional (systematic) review of all smart and virtual glasses with cost-effectiveness analysis and suitability for LMICs would add substantial value to the current literature.

Some limitations are inseparable from the application of smart surgical glasses in the OR. Because these glasses are head-mounted, every head movement produces movement artifacts. There is a learning curve for both surgeons and moderators to minimize these artifacts. This limitation was also noted in a previous study on head-mounted cameras.[16] Moreover, additional time is spent on setting up the system and examining the videos later. Furthermore, the point of view and focus, which are set on the surgeon's hands at thebeginning of the procedure, will not always show the area of interest, especially when the surgeons' hands block the view.[17] A fixed second camera could solve this problem. In addition, overexposure of light in the area of interest can be compensated by manually adjusting the white balance of the camera. Audio quality is mainly limited by background noise.[18] However, updates for introducing noise cancelation, which will significantly reduce background noise, are expected. In this pilot study, informed consent was obtained from the parents of the patients. After reviewing the videos, all files were deleted. Because these videos contain recognizable patients, further investigation and legislation are necessary to ensure privacy protection even when videos are stored and reviewed for a longer time. Finally, all live smart surgical glasses rely on a (wireless) internetconnection;[19] therefore, a stable infrastructure in the participating hospitals would facilitate the successful implementation of these devices in the OR for medical education and collaborations. Future software updates will enable users to broadcast high-quality audio and video by compressing data without compromising the quality. To ensure remote assistance, a network bandwidth of a minimum of 10 Mbps is required for both Wi-Fi and 4G connections. In cases of a suboptimal Wi-Fi connection, the 4G connection can ensure that proper remote assistance is available throughout the procedure. Internet speed must be checked before surgery. Broadcasting of video and audio must run through the RODS&CONES platform. Costs for technical support and training can be expected for the commercial use of the glasses. Although this was a pilot study, the authors used the smart glasses free of charge. In the future, costs will be associated with the use of these smart glasses. Moreover, the RODS&CONES smart glasses cannot be bought. However, healthcare professionals can lease the kits on a monthly basis (costs depend on the duration of the contract and the amount of kits leased), including the replacement of broken equipment, technical support, and training. Furthermore, for each lease by healthcare professionals in HICs, a kit may be donated to resource-limited areas to help doctors from

LMICs broadcast surgical interventions and gain experience using this new educational modality. In this proof of concept, we investigated the feasibility and viability of using smart glasses in the Netherlands. However, conducting a small pilot study in LMICs can pose challenges, such as cost implications, internet connectivity issues, and limited power supply. Cost implications are an important issue in similar projects. Several limitations are inherent to cross-sectional survey studies. In the current study, only 10 participants were included (all medically trained), which can result in selection bias, making it difficult to extrapolate the results to other research fields. Moreover, in all cross-sectional survey studies, response bias (more specifically courtesy bias) is difficult to eliminate. In this study, we (all six authors) tried to minimize bias by developing the questionnaire in a neutral, unambiguous language and encouraging students to be as critical as possible.

CONCLUSIONS

Smart surgical glasses are a promising tool for enabling remote surgical education that offers advantages such as an improved view of the procedure as well as the ability to record and virtually annotate the procedure. Furthermore, they may facilitate the shift toward sustainable partnerships between teams in HICs and LMICs by enabling real-time discussion of difficult cases with colleagues worldwide. In summary, this technology enables international interaction and the building of sustainable collaboration that can improve surgical education by facilitating remote proctoring of residents.

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CHAPTER 11

GENERAL DISCUSSION

Cleft lip and palate remain among the most common anomalies affecting the craniofacial region, yet substantial debate continues around their classification, etiology and optimal management. This thesis was initiated to contribute to improved treatment strategies for orofacial clefts (OFCs), particularly by reducing the incidence of velopharyngeal insufficiency (VPI) and the need for revision surgery. This revealed that many persistent challenges in cleft care (e.g. delay in diagnosis and inconsistent surgical results) arise from fragmented classification systems, different clinical approaches, and a lack of agreement among
(inter-)national cleft teams.

CLASSIFICATION: THE FOUNDATION OF COMMUNICATION AND RESEARCH

A recurring theme throughout this thesis is the need for a unified, standardized language to describe OFCs. As discussed in **Chapter 2**, the current landscape of classification systems is both diverse and inconsistently applied. While the Veau classification system is used frequently for cleft palate, it omits cleft lip.[1] And although the ICD-10 is essential for reimbursement purposes, it lacks the ability to capture laterality and specific phenotypes.[2] Meanwhile, LAHSHAL offers a highly detailed morphological classification (i.e. over 12,000 combinations are possible) but is infrequently used during outpatient consultation visits due to its complexity and limited awareness among clinicians.[3]

The lack of universal adoption hampers clinical communication and genetic investigations. If OFCs are grouped too extensively, we risk missing important patterns in genetic risk factors or treatment outcomes.[4] Conversely, if the classification systems are too detailed, there is a steep learning curve for individual healthcare providers and it is more difficult to compare more general data from years ago with the detailed information that will be logged afterwards. The value of classification is perhaps best illustrated by wide ranges of prevalence and different recurrence risks for all subcategories of orofacial clefts, an important aspect for proper genetic counseling.[5-6] In 1989, Kriens provided a new, extensive classification system to overcome shortcomings from previous classification systems.[7] Multiple aspects of a 'good' classification system were discussed in this chapter (i.e. 1. Simple, so as to be accepted. 2. Concise, for accurate recording. 3. Flexible, to account

for even rare presentations. 4. Exact, to facilitate research and statistics. 5. Morphological, to be able to visually assess. 6. Graphic, for clarity and to avoid ambiguity). The key of an optimal classification system lies in a difficult balance, developing a comprehensive yet user-friendly classification that integrates into existing clinical workflows and registries. A modified LAHSHAL system, harmonized with ICD-10 for compatibility with global health databases like the WHO's Global Burden of Disease, could be a valuable next step.[8-9]

Merely a new classification system is not sufficient. Both education and training in the 'new' classification system must accompany such transition to ensure uptake and consistency. Inter-rater and intra-rater reliability will remain low unless there is an orchestrated effort to unify not only classification systems, but also the criteria through which cleft anomalies are described and diagnosed.[10]

PALATAL FISTULAS: A PROBLEM OF RECURRENCE AND RECOGNITION

Chapters 3 and 4 dive into palatal fistulas, a complication that exemplifies many of the broader issues discussed in this thesis. Fistulas can have a significant burden on a patient's life, since they can cause VPI, nasal regurgitation, dental/oral hygiene problems, and halitosis (i.e. bad breath).[11-14] In terms of quality of life, a substantial recurrence risk after secondary surgery leads to even lower QoL.[15] The heterogeneity in classification again proves problematic. The Pittsburgh classification and anatomical description are often cited but used inconsistently, and even when adopted, inter-rater reliability remains poor.[15-20] The κ-values remain poor, even after the webinar with a targeted audience, demonstrating minimal agreement. This raised questions about the robustness of classification systems. National and international uniformity is lacking.

Surgical treatment for palatal fistulas shows similar fragmentation. Although oromucoperiosteal flaps and Furlow palatoplasties are associated with lower recurrence and therefore advocated in **Chapter 4**, the literature remains inconclusive, particularly in relation to staged versus single-stage repairs.[14,21-25]

The current study in **Chapter 4** lacks contextual and functional detail, which may significantly affect surgeons' decision-making and undermine the ecological validity of the results since the results are based solely on static images. Moreover, there is no long-term follow-up possible. Going forward, it is crucial to develop standardized, prospective data collection tools that consider cleft phenotype, patient factors, and surgeon experience. This is important not only to improve research, but also to enable personalized treatment planning that truly minimizes recurrence.

SUBMUCOUS CLEFT PALATE: THE CHALLENGE OF NUANCE

The results in **Chapter 5** demonstrate that subtle phenotypes of submucous cleft palate (SMCP) can hamper early detection, resulting in delayed diagnosis and associated developmental delays. SMCP was first described by Roux in 1825.[26] All subtypes are characterized by muscular diastasis of the soft palate with an intact oral and nasal lining and various combinations of anatomical abnormalities.[27] Although Calnan identified a triad of clinical criteria facilitating the diagnosis (bifid uvula, a notch in the posterior end of the hard palate and a zona pellucida in the midline of the soft palate), there are patients who suffer from velopharyngeal insufficiency in the absence of Calnan's triad.[28] The latter subgroup is classified as occult SMCP.[29] The subtlety of SMCP makes it a diagnosis that is often missed in initial birth screening.[30] While Calnan's triad has long served as a diagnostic cornerstone, the prevalence of occult SMCP and the average age of diagnosis (3.9 to 4.9 years of age) remain high across Europe, suggesting that current tools are not enough.[31-32]

Perhaps more concerning is the lack of data in **Chapter 5** on whether delayed diagnosis correlated with poorer long-term outcomes. Delays in speech, hearing, and feeding are commonly observed in SMCP. However, these associations remain largely speculative in the absence of longitudinal studies that track follow-up after treatment and developmental milestones. To address this gap, future research should focus on a prospective, patient-centered approach aimed at clarifying the optimal timing and methods for treating SMCP, as well as enhancing early detection, especially in settings where routine neonatal screening is not readily available.

ROBIN SEQUENCE: COMPLEXITY REQUIRES COORDINATION

Robin Sequence (RS), explored in Chapter 6, mirrors common challenges observed throughout cleft care: phenotypic heterogeneity, inconsistent diagnostics, and disparities in resource availability. Patients suffer from upper airway obstruction, micrognathia, and glossoptosis.[33] Although often associated with a U-type cleft palate, it is not necessary for the diagnosis of Robin Sequence.[33] The condition's variable severity, particularly with regard to upper airway obstruction (UAO), which ranges from 1.7% to 65%, necessitates accurate and timely diagnosis.[35-36] The level of UAO is important for determining the best surgical treatment.[36] However, diagnostic practices remain inconsistent across Europe. The significant variation in access to essential diagnostic tools, even within countries, raises serious concerns about equity in care and complicates international comparisons.[37]
Moreover, while the study in **Chapter 6** offered important insights into European countries with higher gross domestic products (GDPs) versus lower GDPs, its representativeness is limited due to a respondent pool skewed toward tertiary centers. Broader studies, involving both secondary and tertiary care providers, are needed to assess the true landscape of RS care in Europe. Only then can consensus meetings lead to meaningful, realistic, and affordable European guidelines that are feasible across high- and low-resource settings.

STRUCTURAL ANOMALY SCAN: ETHICAL AND CLINICAL IMPLICATIONS

The structural anomaly scan (SAS) at the 20th gestational week is a powerful tool in the diagnosis of cardiac or neural tube defects. Over time it has been frequently used to examine the fetal upper lip.[38] Due to the widespread use of the SAS, it is now rare for a baby in the Netherlands to be born with a cleft involving the lip that was not diagnosed prenatally.[39] Yet, as **Chapter 7** demonstrates, its increasing use also has societal and ethical implications, particularly in relation to terminations of pregnancies (TOPs). The percentage of terminations following prenatal diagnosis of isolated OFCs was 27.3% in South Korea and 93.3% in Israel.[40-41] The observed decline in children born with cleft lip following SAS implementation in the Netherlands may suggest

increased TOP, but without direct data on parental decision-making, such interpretations remain speculative.

This thesis emphasizes the need for prospective studies that explore both parental choices and the role of communication during counseling. The way a diagnosis is communicated, together with the time, support and how the diagnosis in framed, can significantly influence decisions regarding further testing or termination. Counseling strategies must therefore be carefully refined to ensure that expectant parents are making an informed and well-considered choice.

COVID-19 AND CLEFT CARE: RECONSIDERING PRIORTIES

On March 11, 2020, the World Health Organization declared COVID-19 to be a global pandemic, which classifies the outbreak as an international emergency.[43] **Chapter 8** examines the effects of the COVID-19 pandemic, which disrupted elective surgeries and forced cleft teams to rethink priorities. The proposed model offers a pragmatic approach to managing waiting times and ensuring critical cases receive timely care. However, these discussions are not limited to pandemics. For the future, the cleft community may benefit from establishing clearer frameworks for prioritizing surgical interventions, even outside of pandemic contexts. Moreover, healthcare systems continue to face pressures related to staffing, costs, and capacity. In case of a new pandemic, priority should be given to children with Robin sequence that suffer from obstructive sleep apnea and patients that require a craniosynostosis correction due to increased intracranial pressure. Primary cleft lip repair, bone grafting and implementing bone conductive devices can safely be postponed.

INNOVATIONS IN (SURGICAL) EDUCATION: TECHNOLOGY AS A BRIDGE FOR CLOSING THE GAP

Finally, the exploration of digital education and surgical collaboration (**Chapters 9 and 10**) highlights exciting possibilities but also important limitations. During COVID-19, physical restrictions hindered both (surgical)

care and education.[43] Moreover, access to surgical care in not equally distributed globally. Over 4.8 billion people do not have access to safe and affordable surgical care.[44] Restricted time and resources prevent proper training for physicians and surgeons.[45] Surgical education was often provided through traditional collaborative on-site missions, typically limited to two to three weeks.[46] In **Chapter 9** digital patient discussions between high- and low-income countries were assessed to establish year-round bilateral education and options for consultation. All participants involved appreciated weekly digital discussions and were better prepared for surgery. Due to the absence of measurable, clinical follow-up, the ability to demonstrate real-world impact (i.e. is the suggested surgical intervention was implemented and if for example length of stay in the hospital was reduced) is substantially limited. In **Chapter 10**, the collaboration between high- and low-income countries was reinforced by introducing smart surgical glasses in the operating room. The web-connected wearable computers allow surgeons to record videos using a front-facing camera.[47] It enables medical professionals to collaborate and interact with surgeons worldwide in real time.[48] Introduction of smart surgical glasses is a potential novel way of medical education and is geared towards sustainable partnership.[46] However, cost aspect of the surgical glasses creates a barrier for most cleft teams since there is no specific budget allocated.

Digital case discussions and smart surgical glasses offer new ways to build sustainable partnerships between high- and low-income countries, overcoming barriers of geography and time. However, reliable internet connectivity remains a major bottleneck, and the cost of high-tech devices may exclude many teams from participating. Furthermore, without robust clinical follow-up, the true impact of these interventions (e.g. on surgical outcomes, complication rates, or hospital stay) remains unknown.

Thus, while these technologies are promising, future studies must go beyond feasibility and explore long-term effectiveness, scalability, and integration into local health systems.

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CHAPTER 12

SUMMARY

This thesis was initiated to improve treatment strategies in patients with orofacial clefts (OFCs) so velopharyngeal insufficiency (VPI) and revision surgery could be minimized. Initial steps in classifying orofacial clefts were taken to better compare outcomes nationally and internationally. This improved outcome prediction and counseling for patients with OFCs and their families.

In **Chapter 2**, a summary is provided of the most frequently used classification systems globally. Multiple aspects of a 'good' classification system were discussed in this chapter (i.e., 1. Simple, so as to be accepted; 2. Concise, for accurate recording; 3. Flexible, to account for even rare presentations; 4. Exact, to facilitate research and statistics; 5. Morphological, to be able to visually assess; 6. Graphic, for clarity and to avoid ambiguity). The increasing use of elaborate classification systems, such as LAHSHAL, provided clinicians access to a more etiological diagnosis. During outpatient consultation visits, LAHSHAL, ICD-10 and Veau were most frequently used. The increased use of one classification system (e.g. LAHSHAL linked with ICD-10) provides clinicians better comparison of surgical outcome and reimbursement. Focusing more on the extensiveness of LAHSHAL and raising awareness should eventually result in an optimal classification in each individual patient with OFCs.

In **Chapter 3**, an overview is provided on all classification systems used in palatal fistulae by craniofacials specialists who attended the International Cleft Palate Master course in Amsterdam, 2021. The Pittsburgh classification and anatomical descriptions are both used frequently. However, the inter-rater reliability is low ($\kappa = 0.136$; 95% confidence interval 0.131 – 0.142). Consequently, confusion may occur in communication between different specialists when using the Pittsburgh classification. A standardized way of classification is crucial to identify certain risk factors for subtypes of OFCs. Training in the Pittsburg classification system is recommended.

Chapter 4 consists of a critical appraisal in terms of surgical approaches in palatal fistulae. Adequate planning and proper treatment of fistulae is very important since surgical treatment of fistulae may have a high recurrence rate of up to 33%. Two major cleft palate fistula repair techniques, the oromucoperisteal flap and the Furlow palatoplasty are being used in patients with palatal fistula. Controversy exists in terms of minimizing risk after a two-stage palatal repair compared to a single-stage repair. Most participants

advocated a two-layer closure (n = 124; 88.0%). Some even suggested a third layer (n = 7; 5.0%). Higher fistula rates (17%) were found when mucosal defects were covered with acellular dermal matrices (ADMs). In addition to the cost of ADM, another reason to avoid ADM is that it is a non-vascularized graft that could also potentially act as a foreign body nidus for infection in an environment with a high bacterial load.

Despite Calnans' triad (bifid uvula, a notch in the posterior end of the hard palate and a zona pellucida in the midline of the soft palate) facilitating the diagnosis of submucous cleft palate, **Chapter 5** demonstrated that age of diagnosis remained high at two years and nine months, suggesting substantial delay. Such delays are associated with impairments in speech and hearing. An overview of patient characteristics is presented in Chapter 5 to increase awareness in craniofacial specialists and therefore minimizing delay associated with developmental deficiencies in hearing, speech and feeding problems.

Although often associated with a U-type cleft palate, it is not a necessity for the diagnosis of Robin Sequence (upper airway obstruction, glossoptosis and micrognathia). Severe breathing difficulties range from 1.7 – 65%. Early and accurate diagnosis is important, to decrease chances of comorbidity (e.g. neurocognitive impairment, growth failure, pulmonary hypertension). However, diagnostic tools differ highly from country to country (even in Europe). In **Chapter 6** Europe was divided in two groups (higher gross domestic product [GDP] per capita versus lower GDP per capita). Especially CO_2 analysis and polysomnography were not available in all European countries. A uniform European protocol for diagnosis that is feasible for all countries involved could decrease comorbidity in Robin Sequence.

The structural anomaly scan (SAS) at 20 weeks of gestation is a highly effective diagnostic tool for detecting cardiac and neural tube defects. Over time, it has also been increasingly used to examine the fetal upper lip. As a result of the widespread availability of the SAS, it is now exceedingly rare for a baby to be born in the Netherlands with an OFC involving the lip that was not detected prenatally. However, the increased use of ultrasonography has also led to a rise in pregnancy terminations. The termination rates for prenatally diagnosed isolated OFCs vary widely, from 27.3% in South Korea to 93.3% in Israel.

In **Chapter 7**, the impact of the nationwide implementation of the SAS in January 2007 was explored. The study revealed a significant decrease in the prevalence of children born with cleft lip with or without alveolus (CL/A) ($P = 0.04$) and cleft lip and palate (CLAP) ($P = 0.01$) after 2007. However, the overall prevalence of OFCs remained unchanged ($P = 0.85$) due to an increase in cases of cleft palate (CP) without lip involvement ($P = 0.02$).

In 2020, the World Health Organization declared COVID-19 to be a global pandemic. Medical services and supplies needed to be reprioritized when restrictions were terminated. Since oncology and emergency trauma surgeries are prioritized over elective (pediatric) surgical care, an excess of surgical patients has been added to the existing waiting lists from before the pandemic. To ensure optimum care in difficult circumstances and to minimize adverse consequences for patients, in **Chapter 8** a priority list of surgical interventions was proposed.

In **Chapter 9**, digital patient discussions between high- and low-income countries were evaluated to establish year-round bilateral education and consultation options. All participants involved appreciated the weekly digital discussions, which enhanced their performance (e.g., their know-how, tips and tricks, and their confidence) in surgery. In **Chapter 10**, the collaboration between high- and low-income countries was further strengthened by the introduction of smart surgical glasses in the operating room. These web-connected wearable devices allow surgeons to record videos using a front-facing camera, enabling real-time collaboration and interaction with surgeons worldwide. The introduction of smart surgical glasses represents a potential new approach to medical education and is aimed at fostering sustainable partnerships. The findings presented in this thesis represent a step towards more standardized diagnosis and treatment of cleft, ensuring that every patient, regardless of where they live, can rely on receiving the best possible care.

ADDENDUM

Samenvatting in het Nederlands
List of abbreviations
Portfolio: publications & presentations
Acknowledgements
About the author

SAMENVATTING IN HET NEDERLANDS

Dit proefschrift werd uitgevoerd om de behandelingsstrategieën bij patiënten met schisis te verbeteren, zodat velopharyngeale insufficiëntie (VPI) en re-operaties worden geminimaliseerd. De basis werd gelegd voor het ontwikkelen van een classificatie van schisis om de uitkomsten zowel nationaal als internationaal beter te kunnen vergelijken. Als een accurate vergelijking van operatietechnieken mogelijk is kan in de spreekkamer beter uitgelegd worden wat de voor- en nadelen zijn van verschillende operaties.

In **Hoofdstuk 2** wordt een samenvatting gegeven van de meest gebruikte classificatiesystemen voor patiënten met schisis in de wereld. Meerdere kenmerken van een goed classificatiesysteem werden in dit hoofdstuk besproken. Het systeem moet 1. Eenvoudig zijn, zodat het makkelijk kan worden geïmplementeerd; 2. Bondig zijn voor een nauwkeurige registratie; 3. Flexibel zijn om ook zeldzamere subtypen op te nemen; 4. Exact zijn om onderzoek en statistieken te vergemakkelijken; 5. Morfologisch zijn om visuele beoordeling mogelijk te maken; 6. Grafisch zijn voor duidelijkheid en om ambiguïteit te vermijden. Het toenemende gebruik van gedetailleerde classificatiesystemen, zoals LAHSHAL, geeft clinici toegang tot een meer etiologische diagnose. In de spreekkamer werden LAHSHAL, ICD-10 en Veau het meest gebruikt. Het gebruik van één classificatiesysteem (bijvoorbeeld LAHSHAL gekoppeld aan ICD-10) biedt clinici een betere vergelijking van chirurgische uitkomsten waarbij tevens vergoeding door zorgverzekeraars kan worden gerealiseerd. Meer focus op de uitgebreidheid van LAHSHAL en het vergroten van het bewustzijn zou uiteindelijk moeten leiden tot een optimale classificatie voor elke patiënt met schisis.

In **Hoofdstuk 3** wordt een overzicht gepresenteerd van alle classificatiesystemen die gebruikt worden door deelnemers aan de 'International Cleft Palate Master Course in Amsterdam in 2021' bij fistels in het gehemelte. Zowel de Pittsburgh classificatie als anatomische beschrijvingen worden vaak gebruikt. De inter-beoordelaarsbetrouwbaarheid (de mate van overeenstemming tussen verschillende beoordelaars) is echter laag (κ = 0,136; 95% betrouwbaarheidsinterval 0,131 – 0,142). Het gebruik van de Pittsburgh-classificatie kan leiden tot verwarring in de communicatie tussen specialisten door de lage inter-beoordelaarsbetrouwbaarheid. Een uniforme manier van classificeren is cruciaal om bepaalde risicofactoren voor subtypen van schisis te identificeren. Training in het Pittsburgh-

classificatiesysteem wordt aanbevolen. **Hoofdstuk 4** bestaat uit een kritische beoordeling van de chirurgische benaderingen bij gehemeltefistels. Goede planning en een gepaste behandeling van fistels is van groot belang, aangezien behandeling van fistels een hoog recidiefpercentage kent, tot wel 33%. Twee belangrijke technieken voor het herstellen van een gespleten gehemeltefistel, de oromucoperiosteale flap en de Furlow palatoplastiek, worden gebruikt bij patiënten met fistels in het gehemelte. Er bestaat controverse over het minimaliseren van het risico op re-operatie na herstel in één fase versus in twee fasen. Daarnaast pleitte de meerderheid voor een sluiting in twee lagen (n = 124; 88%). Sommigen stelden zelfs een derde anatomische laag voor (n = 7; 5%). Hogere fistelpercentages (17%) werden gevonden wanneer slijmvliesdefecten werden bedekt met niet-cellulaire dermale matrices (ADM), een type transplantaat zonder eigen bloedtoevoer. Naast het kostenaspect is de ADM een niet-gevasculariseerd transplantaat. Dit kan als vreemd lichaam fungeren en een infectiebron zijn.

Ondanks de triade van Calnan (gespleten uvula een inkeping aan het achterste gedeelte van het harde gehemelte en een zona pellucida in de midlijn van het zachte gehemelte) die de diagnose van een submuceuze gehemelteschisis vergemakkelijkt, werd in **Hoofdstuk 5** aangetoond dat de leeftijd waarop de diagnose gesteld werd hoog bleef (twee jaar en negen maanden) wat duidt op een aanzienlijke vertraging. Deze vertraging wordt geassocieerd met ontwikkelingsproblemen in spraak en gehoor. Het is de subtiliteit van de triade van Calnan en het lang asymptomatisch kunnen blijven van submuceuze gehemelteschisis waardoor clinici de diagnose pas laat stellen. In **Hoofdstuk 5** wordt een overzicht gegeven van patiëntkenmerken, om craniofaciale specialisten meer bewust te maken om zo de vertraging die gepaard gaat met ontwikkelingsstoornissen in gehoor, spraak en voedingsproblemen te minimaliseren.

Hoewel vaak geassocieerd met een U-vormige palatoschisis, is dit geen vereiste voor de diagnose van Robin-sequentie (gekenmerkt door bovenste luchtwegobstructie, glossoptosis en micrognathie). Ernstige ademhalingsproblemen komen voor in 1,7% tot 65% van de gevallen. Vroege en accurate diagnose is belangrijk om de kans op comorbiditeit (bijvoorbeeld neurocognitieve achterstand, groeibeperking, pulmonale hypertensie) te verminderen. Diagnostische instrumenten verschillen echter sterk van land tot land (zelfs binnen Europa). In **Hoofdstuk 6** werd Europa verdeeld in twee

groepen (hogere versus lagere bruto binnenlands product [BBP] per hoofd van de bevolking). Vooral CO_2-analyse en polysomnografie waren niet goed beschikbaar in alle Europese landen. Een uniform Europees protocol voor diagnostiek dat haalbaar is voor alle betrokken landen, zou comorbiditeit bij Robin-sequentie kunnen verminderen.

De 20-weken-echo is een zeer effectief diagnosticum voor het opsporen van cardiale defecten en neurale buisdefecten in de zwangerschap. In de loop der tijd is deze echo ook steeds vaker gebruikt om de bovenlip van de foetus te onderzoeken. Door de brede beschikbaarheid van de 20-weken-echo komt het nu zelden voor dat een baby in Nederland wordt geboren met een schisis (met lipbetrokkenheid) die niet prenataal is vastgesteld. Echter, het toegenomen gebruik van echografie heeft ook geleid tot een stijging van zwangerschapsafbrekingen. De percentages zwangerschapsafbrekingen bij prenataal gediagnosticeerde geïsoleerde schisis variëren sterk, (van 0% in landen waar abortus niet is toegestaan tot 93,3% in Israël (onder andere door culturele en religeuze factoren).

In **Hoofdstuk 7** werd de impact van de landelijke invoering van de 20-weken-echo in januari 2007 onderzocht. Uit de studie bleek een significante afname in de prevalentie van kinderen die werden geboren met een gespleten lip al dan niet met alveolus (CL/A) (P = 0,04) en een gespleten lip en gehemelte (CLAP) (P = 0,01) na 2007. De algehele prevalentie van schisis bleef echter onveranderd (P = 0,85) vanwege een toename in het aantal gevallen van gehemeltespleten (CP) zonder lipbetrokkenheid (P = 0,02). De toename in de prevalentie van CP-patiënten kan mogelijk verklaard worden door de toename in obesitas bij moeders in Nederland. Een hoger BMI bij moeder is in meerdere studies geassocieerd met een toegenomen risico op CP, mogelijk door een combinatie van metabole stress, tekorten in bepaalde micronutriënten en verstoringen in hormonale signalering tijdens de vroege embryonale ontwikkeling.

In 2020 verklaarde de WHO COVID-19 tot een wereldwijde pandemie. Toen de restricties werden opgeheven, moest de prioriteit van medisch personeel en materialen worden herzien. Aangezien oncologie en spoedtraumachirurgie voorrang kregen boven electieve (kinderplastische) chirurgische zorg, ontstond er een achterstand in de chirurgische behandeling van patiënten, bovenop de patiënten die al op de wachtlijst stonden vóór de pandemie.

Om optimale zorg te waarborgen in moeilijke omstandigheden en nadelige gevolgen voor patiënten te minimaliseren, werd in **Hoofdstuk 8** een prioriteitenlijst voor chirurgische ingrepen voorgesteld.

In **Hoofdstuk 9** werden digitale patiëntbesprekingen tussen hoge- versus lageinkomenslanden geëvalueerd om het hele jaar door onderwijs- en consultatiemogelijkheden op te zetten. Alle betrokken deelnemers waardeerden de wekelijkse digitale besprekingen, die hun prestaties tijdens de chirurgie verbeterden. In **Hoofdstuk 10** werd de samenwerking tussen hoog- en laaginkomenslanden verder versterkt door de introductie van geavanceerde chirurgische brillen in de operatiekamer. Deze draagbare apparaten stellen chirurgen in staat om video's op te nemen met een camera, waardoor wereldwijde samenwerking en interactie tussen chirurgen in real-time mogelijk wordt. Geavanceerde chirurgische brillen bieden een nieuwe benadering van medische opleiding en zijn gericht op het bevorderen van duurzame partnerschappen. Door de beperkte internetsnelheid in laaginkomenslanden en het kostenaspect van de bril is de toepassing van de chirurgische bril beperkt gebleven tot studieverband. De bevindingen uit dit proefschrift vormen een stap richting meer gestandaardiseerde diagnostiek en behandeling van schisis, zodat elke patiënt, ongeacht waar ter wereld, kan rekenen op de best mogelijke zorg.

LIST OF ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
AAS	Advanced anomaly scan
ABG	Arterial bloodgas analysis
ACPA	American Cleft Palate-Craniofacial Association
ADM	Acellular dermal matrix
BCD	Bone conducting device
BCLP	Bilateral cleft lip and palate
BMF	Buccinator mucosal flap
CAT	Competence assessment tool
CL/A	Cleft lip with or without alveolus
CLP	Cleft lip and palate
CO_2	Carbon dioxide
COST	European Cooperation in Science and Technology
COVID-19	Coronavirus disease 2019
CP	Cleft palate
CRANE	Cleft registry and audit network
CTIA	Cellular Telecommunications Industry Association
DB	Decibel
ECCE	European Cleft and Craniofacial Initiative for Equality in Care
ECPCA	European Cleft Palate Craniofacial Association
EDC	Electronic data capture
EHR	Electronic health records
ENT	Ear, nose and throat
FAMM	Facial artery musculomucosal
FGFR2	Fibroblast growth factor receptor 2
FPS	Frames per second
GBD	Global burden of disease
GDP	Gross domestic product
HHEC	Higher-health expenditure countries
HIC	High-income country
HIPAA	Health Insurance Portability and Accountability Act
ICD	International classification of diseases
ICP	Intracranial pressure
IRB	Institutional Review Board
IRF6	Interferon regulatory factor 6
IQR	Interquartile range

LED	Light emitting diode
MAH	Milliampere per hour
MP	Megapixel
MSX1	MSH Homeobox 1
N/A	Not avalaible
NPT	Nasopharyngeal tube
NVSCA	*Nederlandse vereniging van schisis en craniofaciale Afwijkingen*
NR	Not Reported
OR	Operating Room
LASHSHAL	Lip, alveolus, soft palate, hard palate, soft palate, hard palate alveolus, lip
LHEC	Lower-health expenditure countries
LMIC	Low- and middle-income countries
MDO	Mandibular distraction osteogenesis
OFC	Orofacial cleft
OSAS	Obstructive Sleep Apnea Syndrome
PCFC	Pakistan Comprehensive Fistula Classification
PPP	Purchasing Power Parities
PSG	Polysomnography
PVRL1	Poliovirus receptor-related 1
QoL	Quality of life
RS	Robin sequence
SAS	Structural anomaly scan
SABG	Secondary alveolar bone grafting
SDC	Supplemental data content
SMCP	Submucous cleft palate
SPSS	Statistical Program for Social Sciences
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TLA	Tongue-lip adhesion
TOP	Termination of pregnancy
TPP	Tuebingen palatal plate
UAO	Upper airway obstruction
UCLP	Unilateral cleft lip and palate
US	Ultrasound
USB	Universal serial bus
VPI	Velopharyngeal insufficiency
W	Watt
WHO	World Health Organisation

PHD PORTFOLIO

Name PhD student: Hans Smit
PhD period: January 15, 2020 until January 28, 2026
Names of PhD supervisor(s) & co-supervisor(s): Prof. dr. C.M.A.M. van der Horst, prof. Dr. C.C. Breugem, dr. B.S. de Bakker

1. PhD training

	Year	ECTS
General courses		
- Advanced Trauma Life Support, ASGL	2023	1.5
- Systematic Approach of Medical Emergency Situations	2023	1.5
- Clinical Epidemiology: Observational Epidemiology	2022	0.6
- BROK course	2021	1.5
- Clinical Epidemiology: Evaluation of Medical Tests	2021	0.9
- Clinical Epidemiology: Randomized Clinical Trials	2021	0.6
- Clinical Epidemiology: Systematic Reviews	2021	0.7
- Entrepreneurship in Health and Life Sciences	2021	1.5
- MRI: basic understanding for (bio)medical research	2021	1.0
- Peer to peer group coaching	2021	0.5
- Scientific Writing in English	2021	1.5
- Research Data Management	2021	0.5
- Laboratory Safety	2020	0.3
- The AMC World of Science	2020	0.7
Seminars, workshops and master classes		
- ECCE – Equality of Care training school	2022	1.0
- International Cleft Palate Master Course Amsterdam	2021	2.0

Oral presentations

-	"Het onderwijzen en assisteren in plastische chirurgie middels smart surgical glasses in Nederland en daarbuiten: een proof of concept" NVPC Research autumn meeting, Nijmegen, the Netherlands	2023	0.5
-	"Treatment of cleft palate fistulas: a cross-sectional questionnaire study 37th NVSCA autumn meeting, Zwolle, the Netherlands	2023	0.5
-	"Smart glasses in paediatric plastic surgery during the COVID-19 pandemic" 14th International Cleft Congress, Cleft 2022. Edinburgh, Scotland, UK.	2022	0.5
-	"Decrease in prevalence of cleft lip, alveolus and palate after nationwide introduction of the second-trimester anomaly scan in the Netherlands. 32nd EURAPS annual meeting Naples, Italy.	2022	0.5
-	"Het effect van de 20-weken echo op de incidentie van schisis in Nederland: een retrospectieve multicentre cohortstudie" NVPC Research autumn meeting, The Hague, the Netherlands	2022	0.5
-	"Smart glasses voor chirurgische hulp en onderwijs op afstand tijdens de COVID-19 pandemie" NVSCA Research autumn meeting, digitally.	2022	0.5
-	"Classification systems of cleft lip, alveolus and palate: results of an international survey" ECCE Meeting Tallinn, Estonia.	2022	0.5
-	"Incidentie van submuceuze palatoschisis in Nederland: een retrospectieve cohortstudie" NVSCA Research autumn meeting, digitally.	2022	0.5
-	"Het effect van de 20-weken echo op de incidentie van schisis in Nederland" NVSCA Research autumn meeting, digitally.	2021	0.5
-	"Anterior versus posterior scoring of cartilage in otoplasty: a retrospective patient-related outcome measurement study" Virtual Plastic Surgery the Meeting (ASPS), digitally.	2020	0.5

Poster presentations

- "Decrease in prevalence of cleft lip, alveolus and palate after nationwide introduction of the second-trimester anomaly scan in the Netherlands" 14th International Cleft Congress, Cleft 2022. Edinburgh, Scotland, UK.	2022	0.25
- "Treatment of cleft palate fistulas amongst craniofacial specialists: a cross-sectional survey study" 14th International Cleft Congress, Cleft 2022. Edinburgh, Scotland, UK.	2022	0.25
- "Identification of risk factors for recurrence after cubital tunnel release: a retrospective cohort study" FESSH (ON)line week, digital	2020	0.25

(Inter)national conferences

- NVPC Research autumn meeting, Nijmegen, the Netherlands	2023	0.25
- 37th NVSCA autumn meeting, Zwolle, the Netherlands	2023	0.25
- 14th International Cleft Congress, Cleft 2022. Edinburgh, Scotland, UK.	2022	0.5
- 32nd EURAPS annual meeting Naples, Italy.	2022	0.5
- ECCE Meeting Bucharest, Romania	2022	0.5
- NVPC Research autumn meeting, The Hague, the Netherlands	2022	0.25
- 36th NVSCA autumn meeting, digital	2021	0.25
- ECCE Meeting Tallinn, Estonia	2021	0.5
- International Cleft Palate Master Course Amsterdam	2021	0.5
- 35th NVSCA autumn meeting, digital	2020	0.25
- FESSH ON(line) week	2020	0.25
- Virtual Plastic Surgery the Meeting (ASPS)	2020	0.25

2. Teaching

	Year	ECTS
Lecturing		
- Residents in training cleft lip/palate pre-exam tuition "Embryology of the face and congenital anomalies"	2023	0.25
- Cleft lip/palate mini symposium bachelor Medicine "Embryologie van het aangezicht"	2022	0.25
- Global health week bachelor Medicine "Future solution: Distance proctoring"	2022	0.25
- Cleft lip/palate mini symposium bachelor Medicine "Embryologie van het aangezicht"	2021	0.25

Tutoring, Mentoring

-	Christian Petit (bachelor Medicine)	2022	0.5
-	Nathaniel Sullivan (master Medicine)	2022	0.5
-	Ruben Houkes (MD)	2022	0.5
-	Floris Broecks (master Medicine)	2021	0.5
-	Puck Mulder (bachelor Beta-gamma)	2020	0.5

3. Parameters of Esteem

Grants **Year**

- Innovation Impulse Amsterdam UMC 2020
  Title: "Augmented Reality voor onderwijs, diagnostiek en counseling bij schisis"
  Amount: €194.272

4. Publications

Peer reviewed **Year**

- Improving Patient Care by Virtual Case Discussion Between Plastic Surgeons and Residents of Uganda and the Netherlands 2023
- Using Smart Surgical Glasses for Training in Orofacial Cleft Surgery in High- and Low-Income Countries: A Proof of Concept 2023
- Differences in Analysis and Treatment of Upper Airway Obstruction in Robin Sequence Across Different Countries in Europe 2023
- Unraveling a Major Burden of Orofacial Clefts Analyses: Classification of Cleft Palate Fistulas by Cleft Surgeons 2023
- Decrease in Prevalence of Cleft Lip, Alveolus and Palate After Nationwide Introduction of the Second-Trimester Anomaly Scan in the Netherlands 2022
- A three-dimensional analysis of the development of cranial nerves in human embryos. 2022
- Identifying Risk Factors for Recurrence After Cubital Tunnel Release. 2022
- Imaging fetal anatomy. 2021
- Classification Systems of Cleft Lip, Alveolus and Palate: Results of an International Survey. 2021
- Incidence of Symptomatic Submucous Cleft Palate in the Netherlands: A Retrospective Cohort Study Over a Period of 22 Years. 2020
- Anterior versus Posterior Scoring of Cartilage in Otoplasty: A Retrospective Patient-Related Outcome Measurement Study. 2020
- Prioritizing Cleft/Craniofacial Surgical Care after the COVID-19 Pandemic. 2019
- Metastasis of colorectal carcinoma in the testis: first sign of peritoneal disease.

Acted as reviewer

- Cubital Tunnel Release Surgery: Understanding Risk Factors for Clinical Failure 2023
  Journal of Hand Surgery: American Volume
- A WAP-based Concept Acquisition Teaching Model in Cleft Lip and Palate Phenotype and Embryonic Development: Functionality and Usability Study 2023
  Cleft Palate-Craniofacial Journal
- Cephalometric soft tissue morphology of adults with unoperated submucous cleft palate 2022
  Cleft Palate-Craniofacial Journal

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Geachte **prof. Breugem,** beste **Corstiaan**. We gaan inmiddels alweer even terug, in Amersfoort begon het met een coschap en een onderzoekje naar oorcorrecties, waarna ik direct door jou geënthousiasmeerd raakte om meer onderzoek te doen naar schisis. Ik blijf het bewonderenswaardig vinden hoe jij ironmans loopt, fulltime professor bent en meerdere promovendi begeleidt, over de hele wereld spreekt en opereert en dan ook nog tijd hebt voor je gezin. Daarnaast ben je super laagdrempelig en ben ik je na alle jaren samenwerking echt als een vriend gaan zien. Bedankt daarvoor, zonder jou was dit proefschrift niet mogelijk geweest.

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Geachte leden van de leescommissie, **prof. Van Karnebeek**, **prof. Becking**, **prof. Bleys**, **dr. Nolte**, **dr. Paes**, **prof. Van Woensel** en **prof. Reitsema**. Wat fijn dat jullie mij kritisch aan de tand willen voelen op de dag des oordeels. Hopelijk kan ik jullie van goede repliek dienen en zullen jullie (niet te) kritisch, maar rechtvaardig naar mijn proefschrift kijken.

Lieve **Marloes**, lieve **Loes**. Achter elke sterke man staat een sterke vrouw. Ik twijfel aan deel één van die zin maar deel twee is zeker waar. Je bent mijn steun en toeverlaat. Vaak had ik lichte stress of was ik chagrijnig, al zou ik dat zeker ontkennen. Jij bleef altijd rustig en ondersteunde me waar nodig was. Ondertussen zijn we getrouwd en op het moment van schrijven sta je op het punt te bevallen van onze zoon! Ik heb heel veel zin in het leven met je na dit proefschrift (mogelijk dat dit proefschrift mij wel wat jaren levensverwachting heeft gekost en wat grijze haren heeft opgeleverd).

Lieve **pap** en **mam**, **Miek** en **Loes**. We gaan inmiddels alweer eventjes terug, een goede 31 jaar. Ik ben jullie heel erg dankbaar voor het steunen in wat ik graag wil doen, zonder me te sturen! **Pap,** je bent mijn paranimf en dat vind ik extra bijzonder. Je hebt ook veel van mijn artikelen taalkundig doorgespit en zelfs toen je 39,5 graden koorts had was je niet te beroerd om mijn artikelen met me door te nemen. Je hebt me geïnspireerd om huisarts te worden en ik hoop mijn vak met net zoveel plezier te blijven beoefenen zoals jij dat doet. **Mam,** fijn om met jou altijd te kunnen relativeren. Er is meer dan geneeskunde en werk! Jullie zijn me heel dierbaar! Na dit proefschrift is er meer dan voldoende tijd voor gezellige avondjes met één man meer!

Yorick, **Yor, Majoor,** waar moet ik beginnen? Ook wij gaan wat jaren en nachtjes doorhalen terug. We hebben heel wat mooie en emotionele momenten meegemaakt samen. Daarnaast hebben we cumulatief al gauw één maand achtereen gefilosofeerd over ons leven en onze toekomst. Wat mooi dat je vader bent en nu in opleiding tot MDL-arts. Voor mij zal je altijd de vriend zijn die in de onderbroek van je vader Rogier frikandellen staat te bakken om 04:00 uur 's nachts. En wat fijn dat je mijn paranimf op deze bijzondere dag bent! En **Frederike**, waar zullen we onze maatschap vestigen?

Chris, Crippie, mede keientrekker. Mijn sportievere evenknie. Hoe mooi vond ik het hoe je laatst onze vriendschap omschreef als 'lineaire vriendschap': in je leven heb je veel vrienden die komen en gaan en maar een paar vrienden zie je je hele leven. Dat is precies wat ik zo waardeer in onze vriendschap en hoop je nog veel te zien! Lieve **Alex**, onze ouders kennen elkaar ook al ruim honderd jaar. De heerlijke open gesprekken met je zijn geestverruimend en op naar veel gezellige borrels samen!

Michel, **Mies**, ook wij hebben al een hele geschiedenis. Al in groep 3 konden we het met elkaar vinden. Vaak zien we elkaar op de Putterweg 43 (Cafe de Hazenburg) voor een versnapering of twee. Ik zal nooit vergeten dat je daar van het dak bent 'gewaaid' haha, op naar de volgende 25 jaar vriendschap!

Bart/Bert, in Azië hadden we elkaar beloofd dat als we op ons 30e nog vrijgezel zouden zijn, we samen nog een keer het continent zouden aandoen. Ik heb me niet helemaal aan die afspraak kunnen houden, maar het lijkt me smullen om nog een keer dit kant met je op te gaan met jou. *What happens in Asia, stays in Asia, except for ..*

Elsa, **dr. Ronde**, allebei deden we onderzoek in de kinderplastische wereld en allebei zijn we begeleid door Corstiaan. We hebben daardoor veel samengewerkt, in Nederland maar ook in Milaan en Boekarest. We hebben veel gefilosofeerd 'wat als plastische niet zou lukken of als we het niet leuk zouden vinden'. Ik heb de jaren samen als heel gezellig ervaren en ben benieuwd waar je uiteindelijk plastisch chirurg gaat worden!

Jess, slechts kort hebben we samengewerkt maar als opvolger ga je een hele mooie tijd met mooi onderzoek in een fantastisch team tegemoet! Heel veel succes en plezier!

Ruben, Houky, ook jij bent niet te beroerd om wat te doen voor onze gezamelijke artikelen. Als 'de Corst' vroeg of jij 1000 artikelen plus wilde doorspitten dan deed je dat rustig naast een voltijdbaan bij de chirurgie, het liefst in de nacht volgens mij. Vrij episch dat je van plan was om naar Kyoto te gaan voor het *Cleft congress*, vervolgens te laat bent voor *abstract submission* en alsnog gaat maar dan niet voor de wetenschap maar gewoon lekker op vakantie. Laten we snel een pilsje pakken om het leven en je vakantie in Japan door te nemen!

Abbas Peymani, herr Madelung, je ongevraagde wijze raad was altijd vermakelijk. Als ik even snel wat aan je wilde vragen eindigde het vaak in een twee uur durende koffiesessie, want 'promoveren was af en toe wat onderzoek doen tussen het koffie drinken door'. **Anne** 'ik haat vakantie' **Fledderus**, wat heb ik gelachen om je in Napels. Meermaals kabouter Wesley citeren wekte bij meerdere Nederlandse professoren wat verbaasde blikken op maar daar zat je niet mee. Samen met **Max** ben jij volgens mij begonnen met mij 'zoon van Corstiaan' te noemen. **Kenneth** en **Sybren**, wanneer gaan we weer eens naar Sea Palace *for old times sake*?

Nathaniel, volgens mij ben jij de enige Nederlander die ik in het buitenland vaker heb gezien dan in Nederland. Meerdere mooie congressen hebben we samen bezocht waarbij Tallinn toch wel de kroon spande. Iets minder vonden we dat congres toen we onze vlucht (07:30 uur) hadden gemist omdat we na enkele biertjes met professor Martin Persson het verstandig vonden om om 05:30 uur 'even naar onze hotelkamer te gaan voor een kleine powernap'. Jij had je wekker voor de week erna gezet en ik had mijn telefoon op stil. Pas drie congressen later heb ik dat aan Corstiaan durven vertellen, haha. Heb je de gemiste vlucht nog kunnen declareren bij het AMC?

Mario Montes Klaver, altijd gezellig om even bij jou te buurten op de afdeling. Een lekker koffietje van de koffiebar om je zoon en de honden door te spreken. Ik heb veel verzoekjes bij je neergelegd maar je was nooit te beroerd om wat voor me te doen! Bedankt daarvoor, wanneer gaan we nog eens bij je BBQ'en?

Nadia, ook zonder jou was dit proefschrift niet mogelijk geweest. Naast feedback op onze artikelen heb je ook heel veel voor me gedaan wat betreft dataopslag, METC-aanvragen en randvoorwaarden waar minstens zoveel tijd in gaat zitten. Niet zelden hadden we vijftien minuten *quality time* met elkaar voordat Corstiaan in de Zoom aansloot.

Karl, jouw eindeloos enthousiasme voor onderzoek en anatomie is aanstekelijk. Helaas hebben we weinig samengewerkt maar ik heb veel met je gelachen! **Yousif** en **Marieke**, mede TOP-teamleden, samen hebben we een hele mooie Biobank database opgezet. Ik was niet altijd te porren voor een nachtelijke dissectie of fixatie maar we hebben wel voor unieke data gezorgd. **Jaco**, jij enorm bedankt voor alle technische en Amira-vragen. **Maurice** uiteraard ook jij bedankt voor de feedback en gezelligheid in de Biobank meetings. **Quinn**, labwerk is niet helemaal mijn ding maar je was nooit te beroerd om me te helpen liters PFA te maken, waarvoor dank!

Aart, **Marjan**, **Sas** en **Tim**, bedankt voor alle steun en gezelligheid. Jullie zijn mijn favoriete (en enige) schoonfamilie en ik voel me (soms iets te) thuis bij jullie, waarvoor dank! Saskia, jij in het bijzonder bedankt voor de auteursfoto achterin dit proefschrift. Op veel mooie en gezellige momenten met Milou en onze zoon in de zeer nabije toekomst!

Lies en **Corb**, bedankt voor alle gezellige borrels bij jullie en bij ons met enkele speciaalbiertjes. De BBQ-sessies en spontane dinertjes zorgden voor de nodige ontspanning gedurende dit promotietraject, waarvoor dank!

Martin Persson, thank you for all your non-PhD related advice. Your nickname for me (posterboy) is still haunting me every day. We had a couple of drinks in Tallinn and you are the reason I missed my flight for which I am thankful. I hope to see you soon to have a beer (or two) and a pizza!

Roberto, jij enorm bedankt voor alles wat je voor mij en mijn familie hebt betekend, zowel op medisch vlak als ter voorbereiding op de opleiding. Je bent een heel bijzonder persoon en een bron van inspiratie!

Leden van **JC Pachacuti,** hoewel we gaandeweg wat leden zijn verloren in de strijd is het altijd gezellig als we samen zijn. Regelmatig nam ik de zogeheten rattentaxi (wat me niet altijd in dank werd afgenomen), maar de borrels in Groningen en Amsterdam zijn altijd genieten!

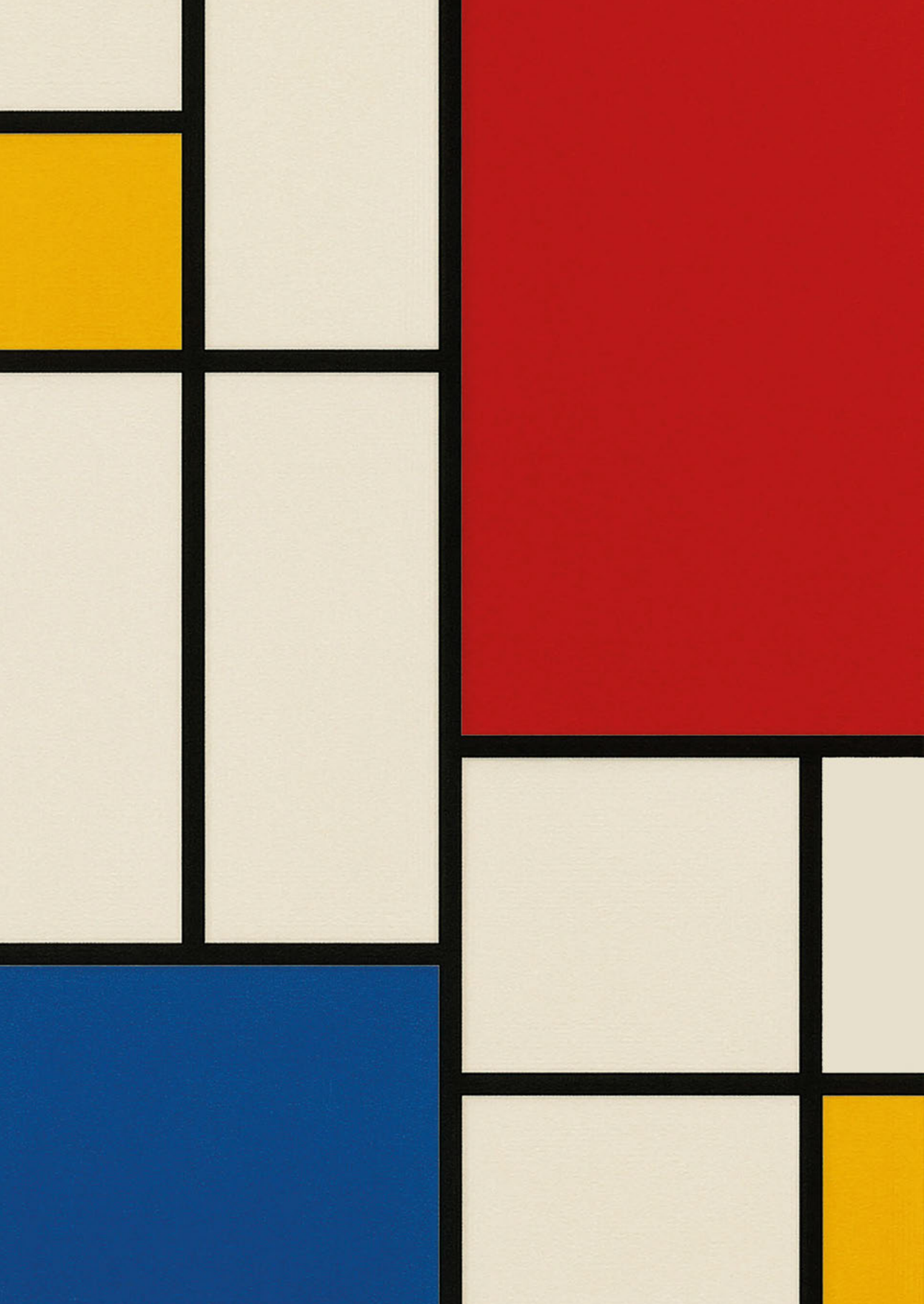
AIOS van 25-2A, **Ilona** en **Erik**, gedurende mijn tijd bij de chirurgie en plastische chirurgie kon ik alleen maar dromen van de hoeveelheid tijd voor intervisie en rondjes lopen rond slot Zeist. Inmiddels zijn we bijna klaar met het eerste jaar en moeten we in het volgende jaar los van elkaar verder. Ik zal volgend jaar met weemoed terugdenken aan de gezellige dinsdagen! **Graziëlla**, jij in het bijzonder bedankt voor het carpoolen en alle gezellige momenten. Het lijkt me top om later samen met je te werken!

Beste **Marieke,** het is fijn om met jou te werken en ik heb een heel prettig eerste jaar met je. De spreekuren samen, de gezellige leergesprekken en de diensten op de post onder het genot van een melanzane maakten dit tot een top jaar! We hebben nog maar een paar weken samen maar ik hoop je na dit jaar ook nog veel te zien en met je samen te werken!

Beste **Wim**, wat een prettige opleider ben je. Onuitputtelijke kennis van de huisartsgeneeskunde, wetenschappelijk zeer sterk (en neemt alle patiënten ook mee in counseling met NNT), kent alle patiënten van haver tot gort en kan naast het medisch inhoudelijke ook feilloos vertellen waar iedereen woont en wat hij/zij voor auto rijdt. Dan ben je een echt goede huisarts, haha! De praktijk, je patiënten en ik gaan je erg missen op het Vondelplein!

ABOUT THE AUTHOR

Johannes Adrianus Smit was born on July 31, 1994, in Amersfoort, the Netherlands, son of Hans Smit and Femmy Groenewegen van Wijk. The son of a general practitioner and a nurse, and brother to two older sisters, Annemieke and Marloes, it was anticipated that he would pursue a career in healthcare. His interest in the human body, inspired by his father's medical office, where ambulances often picked up patients, and his passion for caregiving, motivated him to pursue a degree in Medicine at the University of Groningen in 2013, after completing pre-university education in Utrecht. During his clinical rotations, he gained experience in multiple hospitals (e.g., Martini Hospital in Groningen, Isala Hospital in Zwolle, and Meander Medical Center in Amersfoort). During his final rotations at the Department of Plastic and Reconstructive Surgery, he met Prof. Dr. C.C. Breugem, with whom he had an instant connection both in clinical and scientific work. They collaborated on a manuscript on anterior versus posterior scoring of otoplasties, which served as the foundation for his PhD thesis at Amsterdam University Medical Center.

The research initially aimed to investigate embryology of the head and neck to support craniofacial surgery for cleft lip and palate patients. The hypothesis suggested that cleft surgeons were overly cautious when dissecting the tensor and levator veli palatini muscles, contributing to an increased rated of secondary surgeries. Prof. Dr. C.M.A.M. van der Horst was invited to the research team because of her extensive experience and being an expert in the field of cleft lip and palate surgery. Dr. B.S. de Bakker, a clinical anatomist and pioneer in fetal anatomy and dissections, immediately joined the team and included Hans as a member of the Dutch Fetal Biobank team, enabling him to study and dissect fetal specimens from terminated pregnancies. At that time, the COVID-19 pandemic was spreading globally, preventing the team from making micro-CT scans (high-resolution scans) of these fetuses.

Thus, the team shifted its focus to imaging and remote education on cleft lip and palate. After two and a half years of working as a full-time PhD candidate and attending numerous congresses, both national and international, Hans started to work in Zwolle, the Netherlands, under the supervision of Dr. V.B. Nieuwenhuijs at the Department of General Surgery in November 2022. After twelve months of intense training and caring for general surgery patients, he focused on plastic surgery patients in Enschede. Subsequently, he began working in geriatric medicine as preparation for General Practitioner (GP) training. Currently he is working in the General Practicioner office of dr. W. Opstelten and drs. M. Scholten.