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# Unilateral Cleft Lip and Palate

*Speech, Voice and Nasal Function in Adults*

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### **Abstract**

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Cleft lip and palate (CLP) is the most common craniofacial malformation. Even after repair of the cleft there may be persistent symptoms affecting speech, voice, nasal breathing, dentition, appearance and quality of life. The aims of the thesis were to: (I) investigate subjective nasal function and nasal airway at clinical examination, (II) evaluate speech by perceptual evaluation, (III) assess voice quality by perceptual evaluation and acoustic analysis and (IV) compare ratings of speech by naïve listeners, speech-language pathologists (SLPs) and patients.

All consecutive patients with complete unilateral CLP, born 1960-1987, and treated at Uppsala University Hospital were invited. A total of 83 (76%) (I) and 73 (67%) (II, III, IV) of the 109 eligible patients and non-cleft controls (n=63) participated. Patients had been treated in childhood with one- or two-stage palate closure. The participants underwent clinical examination, recording of speech and filled in questionnaires.

The results showed that: (I) Patients earlier treated for UCLP suffer from more nasal symptoms than controls. However, nasal symptoms were not associated with clinical findings or method of palate closure. (II) Seven patients (10%) presented with hypernasality, 12 (16%) had audible nasal emission and/or nasal turbulence, five (7%) had consonant production errors, one (2%) had glottal reinforcements/substitutions, and one had reduced intelligibility. Controls had no quantifiable problems with speech. (III) Among patients, the mean values for the 12 perceptual voice variables on a visual analogue scale (0 = no abnormality, 100 = maximal abnormality) ranged between 1 and 22 and the mean for all was 6 mm. Voice variables were similar between patients and controls except “vocal fry”; this and total mean of all the perceptual voice variables were slightly lower among patients ( $p = 0.009$  and  $p = 0.018$ ). No clear association was found between velopharyngeal insufficiency and dysphonia. (IV). There were positive correlations between speech ratings by naïve listeners and SLPs ( $r = 0.44$  to  $0.69$ ,  $p$  always  $< 0.001$ , Spearman). The correlations between ratings of any of these groups and the patients’ self-ratings were weaker ( $r < 0.40$ ). The patients were less satisfied with their speech and rated themselves to have more speech abnormalities than controls ( $p < 0.001$ ). There were no statistically significant differences in any of the variables regarding speech, voice or nose between patients treated with one-stage and two-stage palate closure in any of the studies.

This thesis shows that adults treated for unilateral CLP have more nasal symptoms and cleft related speech abnormalities compared to the controls, however the prevalence of speech abnormalities are relatively low. Voice quality is not affected. Speech quality is rated differently by naïve listeners, SLPs and patients.

*Keywords:* Adult, Cleft Lip, Cleft Palate, Cross-Sectional Studies, Control Groups, Dysphonia, Follow-Up Studies, Humans, Nasal Obstruction, Nose Deformities, Otolaryngology, Quality of Life, Reconstructive Surgical Procedures/methods, Retrospective Studies, Treatment Outcome, Voice Quality, Acoustic

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Non loquitur sine aere

*To Elina, Aura and Artur*



# List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Morén, S., Mani, M., Lundberg, K., Holmström, M. (2013) Nasal symptoms and clinical findings in adult patients treated for unilateral cleft lip and palate. *J Plast Surg Hand Surg.* Oct;47(5):383-9.
- II Morén, S., Mani, M., Stålhammar, L., Lindestad, P.Å., Holmström, M. (2017) Speech in Adults Treated for Unilateral Cleft Lip and Palate: Long-Term Follow-Up After One- or Two-Stage Palate Repair. *Cleft Palate Craniofac J.* Nov;54(6):639-649. doi: 10.1597/15-037. Epub 2017 Jan 31.
- III Morén, S., Lindestad, P.Å., Holmström, M., Mani, M. Voice quality in adults treated for unilateral cleft lip and palate; long-term follow-up after one- or two-stage palate repair. accepted 2017 for publication in *Cleft Palate Craniofac J.*
- IV Morén, S., Stålhammar, L., Lindestad, P.Å., Holmström, M., Mani, M. Speech in Adults Treated for Unilateral Cleft Lip and Palate as Rated by Naïve Listeners, Speech-Language Pathologists and Patients. *Manuscript*

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# Abbreviations

CLP	Cleft Lip and Palate
CL ± P	Cleft Lip with or without cleft Palate
CP ± L	Cleft Palate with or without cleft Lip
CL/P or CL(P)	Cleft lip and/or palate
CBCT	Cone Beam Computed Tomography
CPPS	Cepstral Peak Prominence (Smoothened)
CT	Computer Tomography
DSI	Dysphonia Severity Index
FET	Fisher's exact test
GRBAS	Grade, Roughness, Breathiness, Asthenia, Strain
GSS	Glottal Stop Substitutions
HNR	Harmonics to Noise Ratio
HRQoL	Health-Related Quality of Life
ICC	Intraclass Correlation Coefficient
LTAS	Long-Term Average Spectrum
MWU	Mann Whitney-U test
OR	Odds Ratio
SD	Standard deviation
SLP	Speech-Language Pathologist
SNR	Signal to Noise Ratio
SOIT	Scandinavian Odour Identification test
SVANTE	Swedish Articulation and Nasality Test
SVEA	Swedish Voice Evaluation Approach
UCLP	Unilateral Cleft lip and palate
UU	Uppsala University Hospital
VAS	Visual Analogue Scale
VPI	Velopharyngeal Insufficiency



# Introduction

Clefts of the lip and palate are among the most common malformations in the head and neck. The cleft can cause problems with speech, hearing, nasal function, appearance, quality of life, psychosocial issues and can also lead to increased mortality [Christensen et al., 2004, Berkowitz, 2013, Correa de Queiroz Herkrath et al., 2014]. Children with clefts need multidisciplinary care. There are many different treatment protocols used over the world and there is existing controversy on which is the optimal treatment. Despite many research efforts in this field there are still many unanswered questions. This thesis aims to add knowledge in the field of cleft lip and palate (CLP) focusing on the nasal airway, speech and voice

## Embryology of the face and palate

The most important steps in the development of the face take place between the 5<sup>th</sup> and 10<sup>th</sup> weeks of pregnancy. In the end of the 8<sup>th</sup> week the face is formed and the palate is closed by the 11<sup>th</sup> week. The cells that form the face come from the neural crest and migrate into the developing head and neck to form neural, skeletal and connective tissues. The face is formed by the fusion of five prominences surrounding the primitive oro-nasal cavity: the frontonasal prominence and the paired mandibular and maxillary processes. Anything that interferes with the fusion may cause a cleft.

At the beginning of the 5<sup>th</sup> week the frontonasal prominence divides its lower parts into paired lateral and medial nasal processes by formation of nasal placodes (ectodermal thickenings). The medial nasal processes fuse and form the columella of the nose, the anterior part of the nasal septum. The lateral nasal processes form the alae of the nose. The maxillary processes fuse in the midline with each other and with the frontonasal processes by the end of the 6<sup>th</sup> week and form the dental arch and the upper lip. The mandibular processes (the first branchial arch) develop into the mandible and lower lip.

The development of the palate can be divided into two steps: first, formation of the anterior part of the palate (premaxilla/primary palate) by the frontonasal process and the anterior parts of the maxillary processes. Second, the palate behind the premaxilla (secondary palate) is created when the palatal shelves from the maxillary processes fuse in the midline. Thereby the nasal

and oral cavities are separated from each other, by the end of the 10<sup>th</sup> week. [Watson et al., 2004]

## Incidence of CLP

Cleft lip and palate are among the most common congenital malformations. The incidence in Sweden is about 2/1000 births [Ollars Birgitta, 2004]. The world incidence is estimated to be between 1–2.21 cases per 1000 live births. There is variation in the incidence between countries, races and ethnic groups. The incidence is highest in Mongolians (1.3-3.18/1000 births) intermediate in Caucasians (0.69-2.35/1000 births) and lowest in Blacks of African descent (0.18-0.82/1000) [Gundlach and Maus, 2006]. There is a difference between sexes with 2:1, male:female ratio for CL/P, but an approximately 1:1, male:female ratio for cleft palate only (CP). The percentages of clefts depending on location are: Cleft lip and alveolus (CL) (26%), CP (31%) and CLP (43%). Left sided clefts are more common (52%) compared to right sided (24%) and bilateral (24%)[Gundlach and Maus, 2006].

## Etiology of CLP

Orofacial clefts are associated with other anomalies in about 30% for clefts in lip and/or palate and in about 50% in clefts in the palate only [Jugessur and Murray, 2005]. There are over 400 syndromes that have been associated with orofacial clefts. Syndromic clefts can be caused by chromosomal abnormalities, single gene disorders, teratogenic syndromes or syndromic clefts with unknown cause. Examples of syndromes associated with CLP are: Van der Woude Syndrome, Ectodermal Dysplasia Syndrome, X-Linked Cleft Palate and Ankyloglossia, Goldenhar syndrome, Treacher Collins syndrome, Aperts syndrome, Stickler syndrome and velo-cardio-facial syndrome.

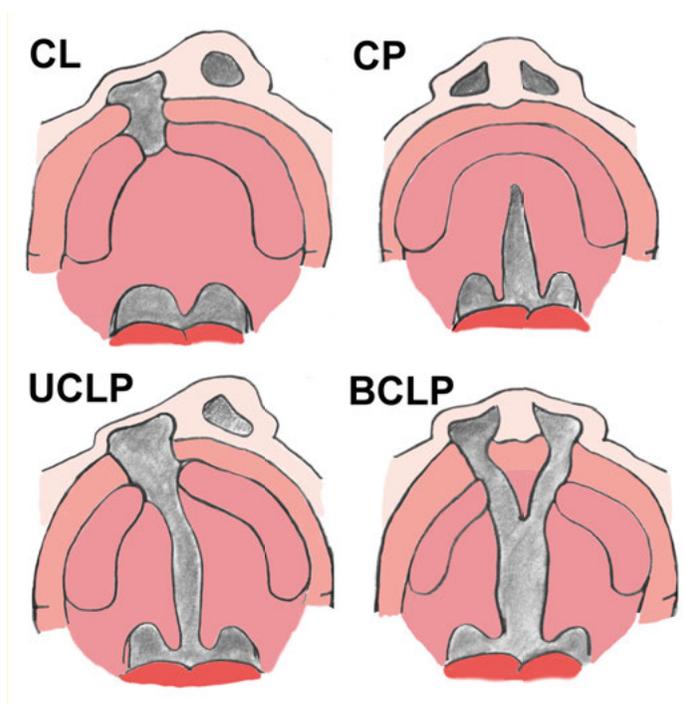
The majority of cases of CLP are non-syndromic and have multifactorial etiology. Environmental factors have been examined and shown to have influence on development of CLP. According to a review by Molina-Solana et al. [2013], examples of such factors are: tobacco (Odds ratio(OR)1.48), alcohol (OR 1.28), folic acid intake (OR 0.77), obesity (OR 1.26), stressful events (OR 1.41), low blood zinc levels (OR 1.82), and fever during pregnancy (OR 1.3). Fogh-Anderson [1942] came with the first population based evidence that genetics have an influence on the epidemiology of clefts. The genetics of non-syndromic clefts have been studied in recent "genome-wide association studies" and several genes have been identified [Mangold et al., 2011].

## Classification of cleft types

Clefts are classified according to localization and extent. Clefts can be partial or complete, unilateral, bilateral or median.

According to Fogh-Anderson [1942] there are three cleft types: (1) Cleft lip (CL) also including cleft lip and alveolus as far back as the incisive foramen, (2) Cleft lip and palate (CLP) and (3) Cleft palate (CP) with clefts as far forward as the incisive foramen. He showed that the etiologies of CL and CLP were different from CP. This has also been verified in further epidemiological and genetic studies. Consequently, one simple division in two cleft-types is often used: Cleft of the lip and/or palate “CL/P or CL(P)” and cleft palate (CP). Sometimes a U (unilateral) or a B (bilateral) and a C (complete) or I (incomplete) is added to the abbreviations to categorize further (figure 1).

A classification that has been commonly used is the one by Kernahan and Stark [1958]. They classified clefts anterior to the incisive foramen as clefts of the primary palate and clefts posterior to the incisive foramen as clefts of the secondary palate. This can be confusing as the lip is not part of the palate. Kernahan [1971] also proposed a symbolic method for classification, “the striped Y”, that has been later modified by others [Smith et al., 1998, Khan et al., 2013]. Tessier [1976] made a classification including also more rare craniofacial and laterofacial clefts.



*Figure 1.* Cleft types: CL – Cleft lip and alveolus, CP – Cleft palate, UCLP – Unilateral Cleft lip and palate, BCLP – Bilateral Cleft lip and palate. *Illustrations by Staffan Morén*

## Anatomy of UCLP

In the untreated complete UCLP there are certain typical anatomical features. There is a cleft from the lip through the alveolus, the hard palate and the soft palate. The cleft means not only separation of tissues that are normally connected but also a lack of tissue to varying degrees. In the lip, the orbicularis oris muscle is interrupted and fibres run upwards and insert in the margin of the cleft along with the vessels [Seagle and Furlow, 2004].

In the nose, the cleft in the floor of the nasal cavity causes distortion both of the exterior and interior parts of the nose. The entire nasal pyramid is wide, depressed and asymmetric. The lower part of the septum and the anterior nasal spine is deviated away from the cleft side with an angle up to 90 degrees from the vertical septum. More cranially there is deviation towards the cleft side. The columella is shortened and broadened by the downwards and laterally shifted medial crus of the alar cartilage. The nasal tip is blunt, downshifted, asymmetric and deviated to the non-cleft side. The base of the nasal ala on the cleft side is dislocated downwards, laterally and posteriorly by the separation of maxillary segments by the cleft, flattening the shape of the ala. The lower part of the lateral crus is buckled, collapsed and displaced [Ahuja, 2001, 2002]. The nasal bones are broad and there may be slight hypertelorism. Surgical repair of the cleft usually corrects some of the nasal deformities but some may remain. The collapse of the alar cartilage, septal deviation, alterations in the nasal floor and scarring can cause narrowing of the nostril and nasal cavity on the cleft side and asymmetric exterior nose.

The alveolus and palate in the unrepaired unilateral cleft is divided in two segments, one larger including the premaxilla and one smaller. The cleft in the alveolus is usually located between the lateral incisor tooth in the premaxilla and the canine in the lesser segment. There can be supernumerary teeth and the teeth can be dislocated or missing especially in the area close to the alveolar cleft. The premaxilla is displaced anterolaterally creating a protrusion and midline shift to the non-cleft side. The lesser segment is displaced dorso-laterally, and the anterior part is slightly curved upwards [Mishima et al., 2001, Berkowitz, 2013]. After lip repair the anterior dental arch width and the anterior and middle cleft width diminishes from the pressure of the lip [Kramer et al., 1994]. After repair of the palate cleft, the arch width and anterioposterior maxillary length is often diminished making less room for the tongue and affecting the bite.

In the soft palate the muscles (levator, tensor, palatoglossus, palatopharyngeus) are normally attached to each other in the midline to form muscular slings. These muscles can elevate, lower and lengthen the soft palate. The levator muscle together with the superior part of constrictor pharyngeus muscle makes velopharyngeal closure possible, thereby separating the oral and nasal cavities. In the cleft palate the velar muscles are dislocated anteriorly, attached to the sides of the cleft and the posterior rim of the hard palate. After repair of

the soft palate, there is a risk of velopharyngeal insufficiency i.e. inability to close the velopharyngeal sphincter completely. This may be related to inadequate length, configuration or movement in the soft palate.

## Surgical treatment of UCLP

There are records of cleft lip and palate in ancient cultures. The first description of cleft lip repair is from ancient China during the Chin dynasty, (317-420 AD) [Boo-Chai, 1966]. The first surgical repair of a cleft velum was described by a French dentist, Le Monnier in 1764 [Millard, 1980]. In 1828, Dieffenbach at Charité Hospital in Berlin, described elevation the mucosa on the hard palate to close the palatal cleft and in 1837 described relaxing incisions to ease palate closure [Peer et al., 1964]. Dr. von Langenbeck [1861], published on a reliable method for hard palate closure, which is still used nowadays in modified versions.



*Figure 2.* Child with UCLP before (left) and after (right) corrective surgery.

Since then, the surgery of cleft lip and palate has advanced from only closing the cleft to nearly restoring the shape and function of all the areas affected by the cleft. Evaluation of speech, facial growth and aesthetics is essential in assessing treatment outcome.

The cleft lip is usually repaired as early as possible considering safety of anesthesia, usually at 3-6 months of age. The closure of the lip can be made easier and with less tension on the tissues if the sides of the cleft are brought together closer before the operation. This can be achieved by using presurgical orthopedic splints, adhesive tape or by a simple preliminary operation called lip adhesion [Millard, 1976]. The lip can be closed with various methods using Z-plasty techniques [Tennison, 1952, Skoog, 1958, Randall, 1959] or by the rotation advancement operation by Millard [1976] that is more widely used.

Primary nasal correction can be accomplished simultaneous to the lip repair however, the use of presurgical repositioning of the cleft nose can reduce the need for surgery. Naso-alveolar moulding is a pre-surgical method aiming at repositioning the nose and alveolus by means of a palatal plate with support for the cleft nose [Maull et al., 1999]. The nose can also be repositioned with “the nasal alar elevator” - a hook pulling the alar cartilage upwards with adhesive tape to the forehead [Abdiu et al., 2009]. There are several methods for primary surgery of the nose and the most widely used is the one described by McComb and Coghlan [1996]. In many cases secondary surgery to the nose is performed during adolescence for both functional and aesthetic reasons.

Surgery to close the cleft palate can be performed in one or two stages. In one-stage closure the hard and soft palate are closed in one operation. In two-stage closure the soft palate is usually closed first followed by hard palate closure in a second operation. Two-stage closure with closure of the hard palate first by means of a vomer flap, followed by a soft palate closure is also practiced [Semb, 1991]. One-stage palatal closure by advancement of bipedicated mucoperiosteal flaps of the hard palate and relaxing lateral incisions was described by Bernhard von Langenbeck [1861]. The lateral incisions aid a tension free closure of the mucosa but leave areas of denuded bone to heal secondarily on the palatal surface. The original von Langenbeck method succeeded in closing the palate, however, resulting in short soft palate and poor speech. Victor Veau [1931] further developed the method by a V-Y pushback to add length to the soft palate to improve speech and also included a transverse closure of the levator muscle in the soft palate to improve velopharyngeal function. This method was adapted by Kilner [1937] and Wardill [1937]. A disadvantage is that the V-Y pushback leaves large raw surfaces of bone on the maxilla which may interfere negatively with maxillary growth in width, length and flattening of the arch anteriorly.

One way to reduce the raw palatal surface area in primary palatoplasty is by use of a vomer flap. A vomer flap may be used to close the anterior part of the maxillary cleft by single layer of mucosa to decrease the need for relaxing incisions. According to the method introduced by Pichler [1934], a cranially based flap is raised from the nasal septum and vomer extending to the posterior edge of the vomer. The flap is tucked under mucoperiosteum of the opposite edge of the palate cleft and fixed by mattress sutures. The septal raw surface is left for secondary healing. The vomer flap is often used at the time of lip closure (early hard palate closure) due to the good access to the septum before lip closure. The closure of the rest of the cleft palate is performed at a later stage. A favourable effect on maxillary growth in the long-term with the use of vomer flap has been reported in the Eurocleft and Americleft intercentre studies [Brattstrom et al., 2005, Daskalogiannakis et al., 2011]. However, some authors have suggested that the use of the vomer flap may hinder the forward growth of the midface due to scarring at the vomero-premaxillary suture [Delaire and Precious, 1985]. A recent study stated that there may be a

higher risk for complications in the subsequent full palate closure if the flap does not survive [Deshpande et al., 2015] and a recent review concluded that it is still unclear whether the vomer flap technique has more or less adverse effect on maxillary growth than the palatal flap [Lee and Liao, 2013].

The soft palate closure has developed from only closing the palate to aim at restoring the function by repositioning the muscles. Braithwaite [1964] described the correction of the abnormally positioned cleft musculature during cleft palate repair with the levator muscle sling, later named intravelar veloplasty as described by Kriens [1970]. Sommerlad et al. [1994] further developed the method, added the use of an operating microscope and also described the method as a secondary palate operation “re-repair” although many use the method in the primary palate operation. Furlow’s double opposing Z-plasty is another technique for soft palate closure aimed at lengthening the soft palate [Randall et al., 1986]. To release tension in the soft palate the pterygoid hamulus process can be fractured [Billroth, 1889]. This relaxes the tensor veli palatini tendon which makes a turn under the hamulus. The same effect can be achieved by dividing the tensor tendon close to the hamulus [Kriens, 1969]. Both fracturing of the hamulus and tensor tendon transection may decrease Eustachian tube function with increased need for transmyringal tubes [Flores et al., 2010]. However, tensor veli palatini transection, is considered a critical step to reconstruct the muscular sling of the levator veli palatini during cleft palate repair as this is thought improve velopharyngeal function and produce low rates of pharyngeal flaps [Shi, 2013]. Tensor tenopexy at the time of tensor tendon transection may help preserving the Eustachian tube function [Flores et al., 2010].

The two-stage palate closure with soft palate closure followed by a hard palate closure in a second stage was proposed already in 1921 by Gillies and Fry [1921]. As the soft palate heals the tension of the muscles in the soft palate pulls the maxillary halves together and narrows the remaining cleft in the hard palate. This facilitates the closure of the hard palate which often can be done undermining of the mucoperiosteum of the free edges of the hard palate, without lateral relaxing incisions and more extensive dissection [Malek and Psaume, 1983]. The long delay of hard palate closure in Marburg until mean age 13.2 years showed beneficial long-term effect on maxillary growth [Schweckendiek and Doz, 1978] while assessment of speech development revealed significant speech impairment [Bardach et al., 1984]. In the Gothenburg team, delay of hard palate closure until  $8.2 \pm 1.2$  years revealed good maxillary growth and speech outcome at the age of 19 years [Friede et al., 2012, Lohmander et al., 2012].

The alveolar cleft is usually closed with bone transplantation when the permanent incisor tooth on the cleft side has descended, usually at 8 to 10 years of age [Abyholm et al., 1981, Jabbari et al., 2017].

## Treatment of UCLP in Uppsala

Uppsala University hospital (UU) is one of six hospitals in Sweden treating patients born with CLP. The plastic surgery department at UU opened in 1951 and planned follow up of cleft patients started in 1960. The cleft palate team consists of specialists in plastic surgery, orthodontics, phoniatics/otolaryngology, speech-language pathology, orthognathic surgery, a team-coordinating nurse and a dental nurse. The team also has close contacts with other specialties when needed. The child with cleft is treated and followed by the team from shortly after birth until approximately 18-20 years of age.

The current surgical protocol of UCLP at UU is shown in table 1. The surgical protocol has undergone changes since the sixties. However, the method for lip closure has remained grossly unchanged with closure according to Skoog [1958], [1969] which is a modification of the method described by Tennison [1952]. Until 1977 the hard and soft palate closure was done in one operation at approximately 18- 24 months of age according to Veau [1931] and Wardill [1937], modified by Skoog [1974]. Since 1977 the palate closure has been performed in two stages with soft palate closure first, followed by closure of the residual cleft in the hard palate. The reason for the change to the two-stage palate closure was the aim to reconstruct the soft palate including the muscle sling with a minimum of periosteal dissection and bone exposure in an attempt to improve dental occlusion and maxilla development. After soft palate closure, there is a narrowing of the residual cleft, and the hard palate can be closed without extensive dissection [Jakobsson and Ponten, 1990].

The technique for soft palate closure was modified in 1990 by intravelar veloplasty reinforced by including the superior part of posterior pillars and their palatopharyngeal muscle sheet. The aim was to increase the functional length and strength of the velum and to reduce nasal emission and the need for pharyngeal flaps [Henriksson et al., 2005]. After 2000 the soft palate closure technique was changed to intravelar veloplasty according to Sommerlad [2003]. The closure of the residual cleft in the hard palate is done by incision of the cleft margins, raising of mucoperiosteal flaps on the nasal and oral side of the cleft and suturing in two layers, without relaxing incisions in the mucosa. In the period 1964 to 1977 the cleft alveolus was repaired with periostoplasty according to Skoog [1965] at the time of lip repair before two years of age. Since 1977 the cleft alveolus is closed by secondary alveolar bone grafting from the hip at 8 -10 years of age, prior to the eruption of the lateral incisor and canine [Jabbari et al., 2017]. Secondary surgery to the lip or nose is provided if needed. Surgery with a superiorly based pharyngeal flap is usually performed at ages 5-6 years when necessary. In case of maxillary hypoplasia/retrognathia orthognathic surgery may be needed.

At UU, the use of nasoalveolar moulding was started more than a decade ago. Orthodontic treatment to expand the maxilla and align the upper incisors is performed before repair of the alveolus when needed. The final orthodontic

treatment with fixed appliances is done when the patients have their permanent dentition.

Speech is assessed by the team speech-language pathologists (SLPs) at team visits and when needed. Speech therapy is provided by SLPs in the hospital closest to the patient in cooperation with the team SLPs. The team SLPs and the SLPs at other hospitals have also regular meetings and educational activities together.

The responsibility for following otological status and hearing is shared by the cleft palate team and the hospital closer to the patient's home. The patients are provided with trans-myringal drainage tubes when needed.

Table 1. Current surgical treatment for UCLP at Uppsala University Hospital

Age of child	Surgical procedure
3 months	lip closure (Skoog) & nasal correction (McComb)
6 months	soft palate closure (Sommerlad)
24 months	hard palate closure
8-10 years	secondary bone grafting to cleft alveolus

## The Nasal airway

Cleft lip and palate may affect shape and function of the upper airways. Nasal deformities such as deviated nasal septum, stenosis of the nostrils, hyperplasia of conchae and nasal floor alterations tend to reduce the size of the nasal airway on the cleft side. According to Warren et al. [1992] nasal impairment is present in 70% of the adult cleft population and oral breathing pattern is frequent among CLP patients. Patients treated for UCLP have a high degree of nasal airway resistance measured with rhinomanometry and a reduced nasal volume measured with acoustic rhinometry [Sandham and Solow, 1987, Mani et al., 2010b]. Examinations with computer tomography (CT) have also revealed reduced nasal airway size in children treated for CLP [Suri et al., 2008]. In addition, the nasopharyngeal airway volume has been found to be lower in adult individuals treated for UCLP [Shahidi et al., 2016]. Maxillary sinus volume is also smaller in patients treated for UCLP compared to non-cleft individuals as examined by cone beam computed tomography (CBCT) [Demirtas et al., 2018]. An association between the severity of the cleft and the degree of the nasal septum deviation has been found in patients with UCLP examined by CT [Nagasao et al., 2008]. However, Reiser et al. [2011] found no correlation between initial cleft size and nasal airway size and airflow in patients treated for UCLP.

There are several studies on patient satisfaction with aesthetic results of the nose in patients treated for CLP [Anastassov et al., 1998, Marcusson et al., 2002, Sinko et al., 2005, Mani et al., 2010c]. However, studies reporting nasal symptoms and subjective nasal airway function in patients treated for CLP are few [Marcusson et al., 2002, Saito et al., 2006, Sobol et al., 2016]. To our knowledge no previous studies evaluating the association between nasal symptoms and clinical findings of the nasal airway among adults treated for UCLP have been published. A comparison between objective measurements of nasal function and self-assessed nasal symptoms and finding of septal deviation at anterior rhinoscopy among the same group of adults treated for UCLP as in the current thesis, was published by the UU research group in 2017 [Peroz et al., 2017].

## Speech

Individuals treated for UCLP can have affected speech. The primary goals of palatal closure are to provide an intact hard and soft palate and create a normally functioning velopharyngeal valve to promote proper speech development, while attempting to minimize problems with craniofacial growth [Chepla and Gosain, 2013]. Even after palatal repair, problems with speech, such as hyper- or hyponasality, audible nasal air emission, consonant production errors and reduced speech intelligibility can persist [Henningsson et al., 2008]. Velopharyngeal insufficiency (VPI), oronasal fistulas and yaw and dental anomalies and other factors may contribute to such speech problems [Watson et al., 2004]. Individuals treated for CLP also have a higher prevalence of abnormal middle ear status and decreased hearing abilities, [Flynn et al., 2012] which potentially could affect speech.

The current thesis reports the long-term outcome after different surgical protocols. This is important as a current belief is that the initial treatment concept will determine the patient's functional outcomes for the rest of their life span. However, the preferences of different surgeons for their treatment plans are probably largely based on personal experience and anecdotal evidence. Many different surgical techniques for palatal closure are being used [Shaw et al., 2001].

There is controversy about timing and operative technique and there is “no consensus in the literature regarding the proper timing of repair, number of stages, or surgical technique(s) to maximize speech outcomes and minimize the impact on long-term skeletal growth and facial development” [Chepla and Gosain, 2013]. Early closure of the palate appears to have a positive influence on the phonological development of children with cleft palate [Willadsen, 2012]. However, delaying the closure of the hard palate may be beneficial for midfacial growth [Friede, 2007]. Concern has been raised that delaying the closure of the hard palate may have a negative effect on speech outcome

[Bardach et al., 1984, Holland et al., 2007, Pradel et al., 2009, Willadsen, 2012, Berkowitz, 2013]. However, there are reports of speech outcome after two-stage palate closure which are as satisfactory as the outcome after one stage palate closure [Van Demark et al., 1989, De Mey et al., 2006, Yamanishi et al., 2011, Lohmander et al., 2012]. In a recent review of the literature a single-stage repair of the hard and soft palate at 9 to 12 months was advocated [Chepla and Gosain, 2013]. Another review suggested the optimal timing to be soft palate closure at 6 months of age and hard palate closure at 15–18 months of age [Rohrich et al., 2000]. In the case of two-stage palate surgery with delayed hard palate closure, closure of the residual cleft no later than 12 months of age has been recommended from a linguistic point of view [Willadsen, 2012]. A recent review found no conclusive evidence of a relationship between one- or two-stage palatoplasty and facial growth, speech and fistula formation in patients with unilateral cleft lip and palate [Reddy et al., 2017].

Speech outcome may change with growth and maturation of individuals with CLP [Lohmander et al., 2012]. Long-term follow up studies are needed to evaluate treatment outcomes in individuals with clefts. Ideally, long-term follow up should be done after the patients reach adulthood, when the growth of the anatomical region affected by the cleft is completed. So far, there are only few studies that evaluate speech in adult patients treated for CLP with speech outcome based on recorded speech material [Lohmander, 2011]. A literature review identified four recent studies that reported speech outcome in adults treated for UCLP [Van Lierde et al., 2004b, Farzaneh et al., 2008, Havstam et al., 2008, Lohmander et al., 2012]. The design and main results of these studies are summarized in Table 2. All four studies reported speech outcome based on audio-recorded material with blinded perceptual speech assessments and reported listener reliability. For quality reasons it has been stressed that speech outcome should be based on speech recordings and blinded individual assessments by multiple expert listeners instead of live single rater assessments [Sell, 2005]. Only two of these studies compared two different surgical protocols [Van Lierde et al., 2004b, Farzaneh et al., 2008]. None of these four studies included a non-cleft control group.

A non-cleft control group could serve as a reference for “normal non-cleft speech” for comparison as there may be a certain variation within normal limits. For example, perceived nasality in non-cleft individuals is reported to vary depending on the socioeconomic status of the speaker [Irvine, 1994].

The treatment goal for speech for individuals with CLP would preferably be speech perceived as “normal”, i.e. free of the cleft speech characteristics. Perceptual speech evaluation may characterize and grade speech but can we be sure that the variables used cover every aspect of cleft palate speech? The speech of an individual with cleft palate might be rated to have no cleft speech characteristics but still be distinguished, by a listener, from the speech of an individual without CLP.

Table 2. Previous studies on speech outcome in patients with UCLP older than 16 years at speech assessment (based on recorded speech material)

Study	Method of palatal surgery (n)	Age at palatal surgery	Age at speech assessment	Percentage of speech errors (mild to severe degree)					Secondary pharyngeal flap surgery %	
				hyper nasality	hypo nasality	audible nasal emission	consonant production errors	s- distortions		reduced intelligibility
Type of cleft (n)										
Van Lierde et al. 2004	One stage, WK (17)	1.2-2y	16-30y	24	NI	NI	NI	50	12	*
UCLP (18), BCLP (13)	Two stage, F (14) HPC:8-12y	SPC:13-28m, HPC:8-12y	16-30y	57	NI	NI	NI	53	21	*
Farzaneh et al. 2008	One stage, WK (27)	5-15m	median 21y	33	14	26	NI	29	0	15
UCLP (61)	One stage, vL (34)	4-15m	median 28y	20	3	6	NI	41	3	26
Havstam et al. 2008	One stage, WK (35)	9m	22-32y	33	14	43	3	37	NI	20
UCLP (25), BCLP (10)										
Lohmander et al 2012	Two stage, vomer flap (45)	SPC:7.5m, HPC:8.2y	19y	22	9	4	2	2	2	11

n = number of subjects, m = months, y = years, F = Furlow, vL = von Langenbeck, WK = Wardill Kilner, SPC = soft palate closure, HPC = hard palate closure, NI= not indicated, \*patients with pharyngeal flaps not included

One way to distinguish if the speech of the individual with cleft palate is perceived as “normal” could be to use blinded classification of speech recordings as coming from a cleft individual or a non-cleft individual. Recordings from individuals with cleft classified as coming from a non-cleft individual could then be considered “normal”.

## Voice

In addition to the previously mentioned speech abnormalities, studies suggest that individuals with CLP may have an increased risk for voice abnormalities (dysphonia) [Leder and Lerman, 1985, D'Antonio et al., 1988]. A dysphonic voice may be characterized by alterations in voice quality, pitch, loudness, and/or vocal flexibility [Aronson and Bless, 2009]. Dysphonia such as harshness, breathiness, strain, reduced loudness, deviant pitch and restricted pitch range have all been reported among individuals treated for CLP [McDonald and Koepp-Baker, 1951, Marks et al., 1971, D'Antonio et al., 1988]. However, the results from studies diverge considering the reported prevalence of dysphonia among both children and adults treated for cleft palate.

Studies on the prevalence of dysphonia in children report values ranging from 5.5 to 41% [Timmons et al., 2001, Hocevar-Boltezar et al., 2006, Hamming et al., 2009, Robison and Otteson, 2011]. In a study by Timmons et al. [2001] of 5-12 year old children (n = 44) treated for CP ± L, dysphonia was present in eight patients with CP (30%) and in seven of patients with CLP (41%). Hocevar-Boltezar et al. [2006] found a 12 % prevalence of dysphonia among 153 children (age < 12y) who had undergone treatment for CP ± L. A study by Hamming et al. [2009] of 185 children treated for different types of clefts found the prevalence of dysphonia to be 20% at age 3-4 years and 18% at age 6-7 years. Robison and Otteson [2011] found a 5.5% prevalence of dysphonia among 487 children treated for CP ± L (age < 10y). As a point of reference, children without cleft palate are reported to have dysphonia at rates of 6-38% [Mornet et al., 2014].

Among adults treated for cleft palate, results on the prevalence of dysphonia range from no differences in voice quality when compared to a non-cleft control group, to a prevalence as high as 47% [D'Antonio et al., 1988, Bressmann et al., 1998, Van Lierde et al., 2003, 2004b, Farzaneh et al., 2008]. One study of voice and laryngeal findings in 85 children and adults with VPI reported that 41% of the patients had perceivable voice symptoms and/or observable laryngeal abnormalities [D'Antonio et al., 1988]. In contrast, other studies report a low prevalence of dysphonia close to or within the range of that of the non-cleft population [Bressmann et al., 1998, Van Lierde et al., 2004b]. In a study by Van Lierde et al. [2004b], patients treated for CLP aged 16 – 23 years (n = 31), operated with one- or two-stage palate closure reported no difference in voice quality compared to age-related normative data. Another study by Bressmann et al. [1998] reported a

prevalence of severe dysphonia of 6.5% among 154 selected patients treated for CLP. However, none of the above mentioned studies included a control group, and only two made comparisons to normative voice data [Van Lierde et al., 2004a, 2004b]. It is noteworthy that reports estimated the prevalence of dysphonia at 0.65 to 15% among the general population of non-cleft adults [Roy et al., 2005].

The etiology of all dysphonia varies with different ages [Martins et al., 2016]. However, for children and adults treated for cleft palate, the etiologies of dysphonia are thought to be muscle tension both with and without benign vocal fold lesions. [D'Antonio et al., 1988, Robison and Otteson, 2011]. Already in 1951, McDonald and Koeppe-Baker [1951] found hyperemia or hyperplasia of the vocal folds in adult patients treated for cleft palate; the authors suggested that faulty phonation was an important contributing factor to the dysphonia.

Some studies suggest that VPI could contribute to dysphonia among patients treated for cleft palate [Leder and Lerman, 1985, D'Antonio et al., 1988, Van Lierde et al., 2004a]. These studies suggest that efforts to reduce involuntary air leakage to the nasal cavity could lead to inappropriately adducted vocal folds during speech production and a consequent straining of the vocal folds, thereby creating the mechanism for dysphonia. If this hypothesis is true, then VPI and the consequent hypernasality and/or excessive nasal airflow would impact the voice quality. The following two studies give some support to this theory. In a study by Aydinli et al. [2016] of 34 children treated for cleft palate, voice quality was significantly worse in the group with VPI and glottal stop substitutions (GSS) when compared to a group without GSS. Similarly, a study by Lewis et al. [1993], on aerodynamic measures of laryngeal function (transglottal pressure and airflow) found increased laryngeal airway resistance in 27 children treated for CLP compared to non-cleft controls. In contrast, in a retrospective study of 185 children treated for various types of cleft palate there was no correlation between VPI and hoarseness [Hamming et al., 2009].

The impact of the surgical method on outcomes in cleft palate treatment has been an ongoing debate. Studies have shown that various types of palatoplasties may affect dysphonia and its prevalence differently among patients treated for cleft palate [Musgrave et al., 1975, Farzaneh et al., 2008]. Musgrave et al. [1975] reported higher prevalence of dysphonia in 11 children treated for CP with von Langenbeck palatal closure compared to 9 children treated with V-Y palatal closure evaluated at mean ages 5 and 10 years. Farzaneh et al. [2008] reported abnormal voice quality in 47% of the patients treated for unilateral CLP (UCLP) operated with von Langenbeck palatal closure and in 33% of the patients operated with Wardill palatal closure evaluated at the mean age of 28 years and 21 years, respectively. In both these studies, the voice was analysed perceptually on a dichotomous scale only.

The majority of previous studies evaluating voice with perceptual or acoustic measures in individuals treated for cleft palate have small group sizes, contain various cleft types and participants of different ages. Furthermore, a variety of

definitions of dysphonia cases, variables and methods are used for outcome assessment. Eleven previous studies on voice in patients treated for CP±L, evaluated using acoustic analysis, with and without perceptual rating of voice, are referred to in table 3 [Leder and Lerman, 1985, D'Antonio et al., 1988, Zajac and Linville, 1989, Lewis et al., 1993, Bressmann et al., 1998, Van Lierde et al., 2003, 2004a, 2004b, Niedzielska, 2005, Yang et al., 2014, Villafuerte-Gonzalez et al., 2015, Aydinli et al., 2016]. Seven of the 11 studies evaluated children/adolescents and four studies evaluated adolescents/adults. The GRBAS (Grade, Roughness, Breathiness, Asthenia, Strain) scale [De Bodt et al., 1997] was used in five out of the seven studies that reported on perceptual voice evaluation. Five of these seven studies had more than one speech language pathologist assessing perceptual voice quality and only three of the studies reported reliability measures. The perturbation measures jitter and shimmer were used for acoustic evaluation in six of the 11 studies. The large variation in methodology of voice assessment makes comparisons between these studies difficult.

Some studies in which measurements of acoustic variables were used, indicated a more disordered voice among patients treated for cleft palate compared to non-cleft individuals [Van Lierde et al., 2004a, Niedzielska, 2005, Yang et al., 2014, Villafuerte-Gonzalez et al., 2015]. Examples of acoustic variables that have been reported in patients treated for cleft palate are: jitter, shimmer, pitch (F0), signal to noise ratio (SNR), harmonics to noise ratio (HNR), and smoothed cepstral peak prominence (CPPS). However, findings are not consistent (table 3).

The composite score dysphonia severity index (DSI) has also been used in some studies. A study by Van Lierde et al. [2004a] found significantly lower DSI values in 10-year old children treated for cleft palate compared with normative data, suggesting more dysphonia in children treated for cleft palate. Interestingly, the pathological values on DSI were only found among the male children in the study. In contrast, two studies also by Van Lierde et al. [2003], [2004b] that evaluated the voice of 16-23 year old patients treated for UCLP or bilateral CLP with both perceptual (GRBAS) and acoustic measures (DSI) found the voice quality to be normal or near normal.

Despite earlier studies, it is still unclear whether adults treated for cleft palate have more dysphonia than individuals without cleft. A potential association between method of palate closure and dysphonia has not been evaluated in a longterm perspective, with a combination of perceptual and acoustic voice analysis. In addition, the relation between VPI and dysphonia has not yet been clarified.

Table 3. Previous studies on voice in patients treated for CLP/CP evaluated using acoustic analysis, with or without perceptual ratings of voice

Authors, Year	n	Cleft-type (n), symptoms	Control (n)	Age at evaluation (n)	Reliability (n)	Evaluation methods Perceptual	Acoustic	Results
Aydinli et al., 2015	17	CP, CLP with glottal stops	CP, CLP without glottal stops (17)	4-12y, median 6y	2 cons	GRBAS	F0, jitter, shimmer	Grade, roughness and jitter higher in patients with glottal stops than in patients without glottal stops.
Villafuerte-Gonzalez et al., 2015	14	UCLP with VPI	non-cleft (14)	7-9y, mdn 8y	-	-	F0, jitter, shimmer	F0 higher in male patients compared to male controls, shimmer higher in patients compared to controls.
Yang et al., 2014	40	CP with VPI	non-cleft (40)	6-9y, mean 7y	-	-	CPP	CPP lower in CP patients before and after VPI surgery, compared to controls. CPP normalized after postsurgical speech therapy.
Niedzielska, 2005	27	CP	non-cleft (31)	6-15y, mean 10	-	GRBAS	F0, jitter, shimmer, HNR, SNR	Higher F0, HNR and SNR in CLP patients compared to controls.
Van Lierde et al., 2004a	28	UCLP (16), BCLP (12)	age-related normative data	8-12y	2 cons	GRBAS	DSI	CLP children had lower DSI-value, lesser maximum pitch and lower intensity compared with normative data. Females had better voice quality than males.
Van Lierde et al., 2004b	31	UCLP (18), BCLP (13)	age-related normative data	16-30y	2	GRBAS	DSI	No significant difference between CLP patients and normative data
Van Lierde et al., 2003	14	UCLP (8), BCLP (6)	none	16-23y	3	GRBAS	DSI	Normal or slightly impaired voice quality.
Bressman et al., 1998	15 4	CP (18), UCLP (98), BCLP (37)	none	10-66y, mdn 17y	1	RBH	F0, jitter, shimmer	Prevalence of severe voice disorder 6.5%, moderate voice disorder 25.3%.
Lewis et al., 1993	27	CP, CLP	non-cleft (12)	4-16y	-	-	SNR, jitter, shimmer	No significant difference between CLP patients and non-cleft controls in jitter, shimmer and SNR.
Zajac and Linville 1989	10	CP, CLP with VPI	non-cleft (5)	6-11y	3 perc	hoarseness 5-p-scale	F0, jitter, shimmer	Positive correlations: jitter vs nasality, and shimmer vs hoarseness.
Leder and Lerman, 1985	10	CP, CLP	non-cleft (5)	14-47y	-	-	spectrograms	Spectrograms of patients with severe hypernasality had different characteristics compared to patients with mild hypernasality and non-cleft individuals.

A= Assessors of voice quality, CP = cleft palate only, CLP = cleft lip and palate, UCLP = unilateral CLP, BCLP = bilateral CLP, VPI = velopharyngeal insufficiency, DSI = dysphonia severity index, SNR = signal to noise ratio, HNR = harmonics to noise ratio, CPP = cepstral peak prominence, GRBAS = Grade, Roughness, Breathiness, Asthenia, Strain, FO = fundamental frequency, RBH = Roughness, Breathiness, Hoarseness, mdn = median, cons = consensus, perc = percent, - = not reported

## Speech ratings by naïve listeners and self-ratings of speech

The quality of a person's speech is essential for verbal communication. Speech may be affected among patients with cleft lip and palate (CLP) and as a consequence may influence quality of life [Bickham et al., 2017]. Speech is one of the main outcome measures in treatment of CLP [Shaw et al., 1992, Havstam et al., 2008]. The way we speak determines how we are perceived and judged. It may affect interpersonal and social encounters, occupational possibilities, and quality of life. A judgement of the personality and capabilities of a person can be formed after listening to 30 seconds of a voice recording [Ambady, 2006]. Negative attitudes towards speakers with hypernasal resonance [McKinnon et al., 1986, Lallh and Rochet, 2000] and other speech disorders [Allard and Williams, 2008] have been reported. Hunt et al. [2006] reported speech as the reason for being bullied among one third of the bullied/teased children treated for CLP.

It is important that the outcome measures used in cleft care are representative, valid and reproducible. Cleft palate speech is usually evaluated by speech-language pathologists (SLPs) [Lohmander, 2011]. These professionals are trained to identify specific speech abnormalities related to the cleft. However, it is unclear how well these assessments are representative of the people whom the patients interact with in their daily life. Assessments of naïve listeners have been suggested to add validity to the traditional speech assessments of SLPs [Bagnall and David, 1988, Tonz et al., 2002].

Several previous studies have evaluated cleft palate speech with naïve listeners and compared with ratings of SLPs [Starr et al., 1984, Bagnall and David, 1988, Witt et al., 1996, Witt et al., 1997, Tonz et al., 2002, Lewis et al., 2003, Brunnegard et al., 2009, Nyberg and Havstam, 2016]. Witt et al. [1996] found that naïve raters were insensible to differences between the speech of cleft patients and controls. This is in contrast to other studies where naïve listeners have been able to perceive cleft speech characteristics [Starr et al., 1984, Brunnegard and Lohmander, 2007, Nyberg and Havstam, 2016]. In a study by Starr et al. [1984] speech of children with cleft palate was rated on 8 point equal appearing interval scales for the variables nasality and articulation. The same scales were used for experts (SLPs in hospital and schools) and untrained listeners (children treated for CLP, peers and their parents). In their study, ratings did not differ extensively between raters but expert listeners were better at differentiating between nasality and articulation than naïve listeners.

Two studies by Witt et al. [1996], [1997] used different scales and variables in the analysis for naïve listeners and SLPs which complicates any comparison. Tonz et al. [2002] found that SLPs and untrained listeners agreed upon the improvement of speech on a group level, after pharyngeal flap surgery in 87% of the cases, however also this study analysed different variables for expert and naïve listeners. Brunnegard et al. [2009], used speech variables for naïve listeners that were related to the variables nasality, nasal emission and articulation rated on ordinal 5 point scales and a question of need for speech therapy. It was found that untrained listeners' ratings of the speech in ten-year-old patients mainly confirmed the ratings performed by SLPs.

Nyberg and Havstam [2016] investigated how peers described the speech of 10-year-old children treated for cleft palate. In their study, the SLPs and peers did not agree on minor signs of VPI, but agreed on what was normal and severely impaired speech respectively. None of the previous studies rated speech among adults treated for UCLP by naïve listeners, SLPs and the patients themselves.

Patient-reported outcomes are important in all aspects of cleft care outcomes [Ranganathan et al., 2015]. Several studies have examined self-ratings and satisfaction with speech in children as well as adolescents after treatment of cleft palate [Broder et al., 1992, Hunt et al., 2006, Van Lierde et al., 2012, Bickham et al., 2017]. The patient satisfaction with speech ranged from 50 to 90 percent in these studies. Broder et al. [1992] compared ratings of satisfaction with speech and appearance in 495 children (age 5 to 18 years) treated for CL/P and found that a higher percentage of the older children (around 70%) were very satisfied with their speech compared to the younger children (around 50%). There was a moderate agreement between the ratings of children and parents. Hunt et al. [2006] reported on psychosocial functioning and self-ratings including speech ratings in 8 to 21-year-old individuals treated for CL/P and a control group. They also found that 18% of the individuals treated for cleft and 4% of the non-cleft individuals were dissatisfied with their speech. Additionally, older individuals had more behavioral problems and were less satisfied with appearance and speech than younger individuals.

Van Lierde et al. [2012] studied satisfaction with speech and facial appearance in 11 to 17-year-old individuals treated for UCLP (n = 43) and a control group (n = 43). They reported that ratings of satisfaction with speech was on the same level (91-93%) for patients and controls as rated by the children themselves and their parents. However, children treated for UCLP rated themselves to have an articulation disorder in 42% and hypernasality in 49%, which was higher than in the control group. In a study by Bickham et al. [2017], speech and quality of life was studied in 108 children treated for CP±L (age 5 to 19 years). Patients, parents and SLPs had different perceptions of the quality of the CLP children's speech but the parents' and childrens' ratings correlated the most. About 30 % of the patients and parents expressed difficulties with the child's speech.

Studies on self-ratings of speech among adults are few [Oosterkamp et al., 2007, Havstam et al., 2008]. Havstam et al. [2008] studied self-reported satisfaction with speech compared with speech ratings by SLPs in 35 patients treated for UCLP or BCLP (age 22 -32 years). Seventy-seven percent of the participants classified their speech as normal and the SLPs rated 66% of the participants to give normal general impression of speech. Self-rated satisfaction with speech did not correlate significantly with the SLP's speech assessments. A study by Oosterkamp et al. [2007] evaluated satisfaction with treatment outcome in 43 adults (mean age 28 years) treated for BCLP and a control group. They found no differences in the quantitative measures of satisfaction with speech between patients and controls (mean 7.2 vs 7.7 / 10 on VAS). However, 44% of the patients expressed concerns about speech, for example articulation and nasality.

# Aims

The overall purpose was to study various treatment outcomes regarding the speech, voice and nasal function in adults treated for unilateral cleft lip and palate in childhood, by the cleft palate team, Uppsala University Hospital, Sweden.

The specific aim of each separate paper was:

- I to investigate the patients' subjective nasal function and their nasal airway, examined clinically and explore their potential association.
- II to assess speech in adult patients treated for UCLP with one-stage or two-stage palatal closure and compare their speech with non-cleft controls.
- III to assess voice in adult patients treated for UCLP with one-stage or two-stage palatal closure and compare their voice with non-cleft controls.
- IV to compare speech assessments by naïve listeners, speech-language pathologists and self-ratings by adults treated for UCLP and non-cleft controls.

# Materials and Methods

## Subjects

All consecutive, non-syndromic patients with complete UCLP, born 1960-1987 and treated at the cleft centre at UU were eligible to participate in the study. Patients with Simonart's band or incomplete clefts of the lip or palate were excluded. Of the 128 patients found in the hospital records 19 patients were excluded for the following reasons: syndromes and or other serious illnesses (n=5), death (n=6), living abroad (n=5) and missing in the national population registry (n=3). The remaining 109 patients were invited to participate in the study by letter containing information and a form for written consent. Those patients who had not answered after two weeks were contacted by telephone for further information. Eighty-three of the 109 patients (76% of those invited) participated (Figure 3). The participating patient group did not differ from the non-participating patient group regarding age and gender distribution. The mean follow-up time from the first operation to the participation date of the current study was 37 years.

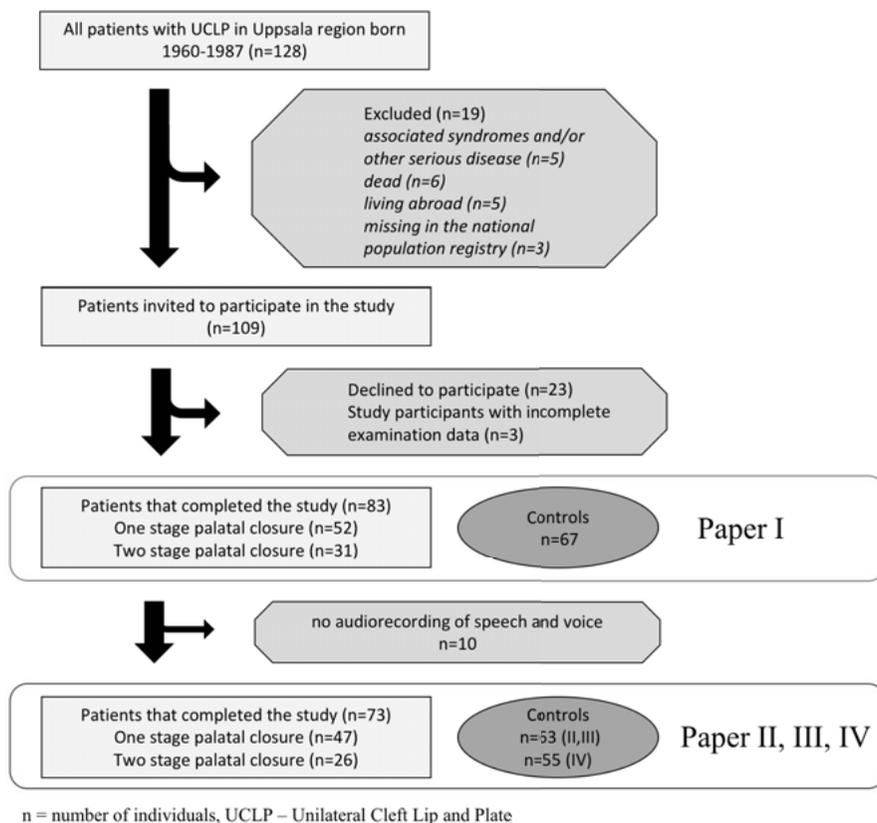
Eighty-three patients underwent clinical nasal examination and answered a questionnaire (paper I). Audio recording of speech was done in 73 of these patients (papers II, III, IV). In 10 patients, no speech recording was done due to technical or logistic problems.

The cleft team UU has cared for the patients with clefts according to specified protocols for surgery, evaluation and registration since 1960. The patients in this thesis were treated with two different methods of palatal closure. Patients born between 1960 and 1976 were treated with one-stage palatal closure and patients born between 1977 and 1987 were treated with two-stage palatal closure. To be able to compare results after these different methods of palatal closure patients are divided in two groups according to surgical method: "one-stage group" and "two-stage group". At the time of the study the patients in the one stage group were 31-47 years old and in the two-stage group 20-32 years old.

An age matched control group (n=67) (paper I), (n=63) (paper II, III), (n=55) (paper IV), was recruited among students and colleagues. This control group underwent the same investigations as the patients. The control group was divided in two groups in order to match the patient groups operated with one- or two-stage palate closure for age.

The study was approved by the Research Ethics Committee of Uppsala University (Reference number 2005:245). All participants gave their informed consent to the study.

Figure 3. Study population



## Surgical techniques

The surgical lip closure was performed at  $3.5 \pm 0.8$  months of age according to Skoog [1958]. The palate was closed either in a one-stage or a two-stage procedure. The one-stage procedure was used for patients born 1960-1976, whereas patients born 1977-1987 were operated on according to the two-stage protocol. Patients in the one-stage group underwent palatal closure in one stage at a mean age of 1.9 years as described by Veau [1931] and Wardill [1937] and later modified by Skoog [1974]. In the two-stage procedure the soft palate was closed first and the residual cleft of the hard palate was closed in a second stage [Jakobsson and Ponten, 1990]. The timing of the two operations changed, the child's age at operation decreasing with time; for the soft

palate from 18 to 6 months and for the residual cleft from 6 to 2 years. The alveolar cleft was closed either by periosteal flap at the time of lip operation or later at age 7-12 years with a periosteal flap or bone grafts.

Primary nasal surgery was not performed in any of the patients. Secondary lip and nasal corrections as well as pharyngeal flaps were performed according to individual needs of the patient [Jakobsson and Ponten, 1990]. Rhinoplasty including adjustment of the nasal tip projection and nostril symmetry and reduction of the wedges in the nasal vestibulum was performed in 65 out of 83 (78%) patients (20 patients had three or more rhinoplasties done). Septoplasty was performed only in three patients. Pharyngeal flap surgery had been performed in 15 of the 83 patients (18%) in paper I. In papers II, III and IV, pharyngeal flap surgery had been performed in 11 of the 73 patients (15%). Four different surgeons performed 95 percent of all surgical procedures.

## Speech therapy interventions

Speech was analyzed at multidisciplinary team follow-up conferences and speech therapy provided to the patients if needed. In the time period 1960–1983, speech therapy was provided mainly at UU where the patients were admitted for 1–2 weeks of speech analysis and therapy. Speech therapy was routinely administered once or twice a day during the hospital stay. The patients came from a large geographic region and, at that time, local speech therapy was only available to a limited number of the patients. From 1983 speech therapy was provided at a hospital or a school close to the patient. Clinical records reveal that speech therapy was given to 59 of the 73 patients. Forty-seven patients were admitted for speech therapy at the hospital at an average of 4.1 times (SD 2.7) over an average period of 3.5 years (SD 2.3). Twenty-nine patients received speech therapy at the local hospital or school. Ninety-three per cent of the patients with one-stage palate closure received speech therapy compared to 62 per cent of the patients with two-stage palate closure.

## Methods

### Questionnaire on nasal symptoms (paper I)

To evaluate subjective nasal symptoms, a questionnaire was used. Background information such as previous surgery or trauma to the nose, previous and current airway disease (allergic and non-allergic), current medication, and co-morbidities was covered in the first 16 questions. Subjective nasal symptoms were covered with the subsequent 20 questions. The questions were answered according to multiple-choice principle or by marking along a Visual

Analogue Scale (VAS). The VAS is a 100mm straight line, with two opposite points of view at each end (for example 0 = never, 100 = always). The VAS was used to grade nasal obstruction, ability to smell, headache, pressure or pain in the face, mouth breathing and also to rate quality of life and the influence of nasal symptoms on quality of life and daily activities. Two additional questions addressed the extent to which the subjects wanted to change the function or shape of the nose. The questionnaires were sent by post to participants to be answered at home and were checked at the time of the clinical examination in order to minimize misunderstandings and left-blanks.

### Nasal examination (paper I)

Clinical nasal examination by inspection of the exterior and interior parts of the nose is an essential part of an examination for finding signs of pathology in patients with nasal symptoms or complaints and to follow up treatment.

Anterior rhinoscopy allows for evaluation of the anterior part of the nasal cavity where structural/anatomical causes of obstruction can be identified as well as mucosal signs of disease. With nasal endoscopy it is possible to visualize the middle meatus and the ethmoid bulla as well as the posterior parts of the nasal cavity. Although anterior rhinoscopy has been practiced since historical times there is no standardized protocol and examiners reliability values are not very high. The valve area inside the nostril in the bony entrance of the nose is usually the narrowest part.

All subjects were examined at the Department of Otorhinolaryngology of the UU. One of three specialists in otorhinolaryngology performed the nasal examination which consisted of three parts: external inspection, anterior rhinoscopy and nasal endoscopy. External inspection of the nose was done to evaluate deviation of the bony or cartilaginous exterior part, or columellar luxation/ subluxation. Thereafter, an anterior rhinoscopy with Thudichum's nasal speculum was performed evaluating mucosal colour (pale, hyperaemic), mucosal swelling (uni-/bilateral), secretions (dry, watery, mucous, purulent) and nasal septum deviation (insignificant, mild unilateral, severe unilateral, moderate to severe bilateral). The middle meatus and the posterior part of the nose were examined by nasal endoscopy with a Hopkins rod optic 0° (Karl Storz, Germany) after two sprays of decongestant (naphazolini hydrochloridum 0,17 mg/ml) each side. Possible findings of nasal polyps, syneccias or crusts were noted. The examinations were done out of the pollen season. If the subject had a common cold or other upper airway infection the tests were postponed for four weeks.

### Inspection of tympanic membranes and oral cavity (paper II)

In order to investigate other possible contributing factors for speech outcome, presence of oronasal fistulas and hearing related measures was regitered.

One of three otorhinolaryngology specialists at the UU examined patients and controls the same day as the speech was recorded. Ears were examined by otoscopy and the tympanic membranes were evaluated. The tympanic membranes were classified as one of the following: normal, slightly retracted, retracted with decreased mobility  $\pm$  fluid in the middle ear or tympanic membrane adherent to the promontory of the middle ear. It was also noted if there was a perforation of the tympanic membrane or a trans tympanic ventilation tube in place. The oral cavity was inspected and possible oronasal fistulas in the hard or soft palate were registered.

### Satisfaction with hearing and hearing aid usage (paper II)

In connection with the visit for speech recording, patients and controls filled in a questionnaire and answered the following questions regarding hearing: "How satisfied are you with your hearing?" on a 100mm visual analogue scale (VAS) (0 = very satisfied, 100 = very dissatisfied) and "Do you use a hearing aid?". A similar question was used in a previous study [Palmer et al., 2009]: "On a scale from 1 to 10, 1 being the worst and 10 being the best, how would you rate your overall hearing ability?" and the answers on that scale was a strong predictor of hearing aid purchase.

### Speech and voice assessments (paper II, III, IV)

#### **Audio recordings of speech and voice (paper II, III, IV)**

Most recordings were made in a soundproof studio equipped with a microphone (Sennheiser mke2-p) placed on constant distance from the patient, connected to a digital recording system (VoiceJournal™). Eight of the recordings were made in a non-soundproof room due to technical problems with the studio. The sound quality of these recordings was considered to be sufficient for evaluation. The speech recording samples included three parts: 1. Reading of a set of standardised sentences from the Swedish Articulation and Nasality Test (SVANTE) including six sentences with high pressure oral consonants, four sentences with oral and nasal consonants and one with only nasal consonants [Lohmander A et al., 2005]. 2. Reading of a story ("The man who wanted to borrow a spade"), which is routinely used for recording of speech for perceptual analysis of speech and voice in many hospitals in Sweden. 3. Retelling of the story with own words. The recordings were coded and transferred to a compact disc for computers in a randomised order. Ten of the patient recordings and five of the recordings of the control group were duplicated to allow for calculation of intra-rater agreement.

### **Perceptual assessment of speech and resonance by SLPs (paper II & IV)**

Five experienced speech language pathologists (SLP A-E) assessed the recordings individually. Two of the SLPs were from the UU cleft palate team and three of the SLPs were recruited externally. The SLPs listened to the recordings individually with headphones connected to a computer. Hypernasality, hyponasality, audible nasal airflow (nasal escape or/and velopharyngeal friction sounds), glottal reinforcement and/or glottal stop substitutions, low pressure articulation and articulation errors were assessed perceptually on five-point scales. The steps on the scale were: 0 = normal, 1 = slight/single occurrence, 2 = mild/some occurrences, 3 = moderate/frequently occurring, 4 = severe/occurring always. Articulation errors included errors such as retracted oral articulation and distorted s, r, l sounds but excluded non-oral articulation errors. Intelligibility was assessed on a 3-point scale (0 = normal, 1 = mildly/moderately reduced, 2 = severely reduced). The SLPs also indicated whether they thought the recording came from a patient or control.

### **Perceptual assessment of voice (paper III)**

Two speech-language pathologists from Uppsala University Hospital, with > 10 years of experience in voice assessments, performed perceptual voice analysis independently of each other, using headphones connected to a computer. These two SLPs had not been members of the cleft palate team and none of the patients were known to the two SLPs. No special instructions or training were given for the study, however, the SLPs had long experience (>10 years) with the scale used. Twelve voice variables according to Swedish Voice Evaluation Approach (SVEA) were assessed using the Visual Analog Scale (VAS) 100 mm, (0 = no abnormality, 100 = maximum abnormality) [Hammarberg, 1986]. The variables were: intermittent aphonia, breathiness, hyperfunction/strain, hypofunction, vocal fry, hard vocal onset, roughness, vocal scrape, instability, register breaks, diplophonia and pitch. Pitch was assessed on a 200mm scale (0 = no pitch deviation, range:  $\pm 100$ ). The median VAS value was calculated from the ratings of the two SLPs for each variable and for each participant. Inter- and intra-rater agreement was calculated.

An overall rating of voice abnormality was assessed on a 3-point scale (0= no voice abnormality, 1= mild abnormality, 2 moderate/severe abnormality) by four SLP's at the same time as perceptual speech assessment described in study II. The four SLPs were experienced in cleft palate speech. Two belonged to the cleft palate team of the hospital and two were from cleft teams of other hospitals. These four SLPs were different from the two SLPs specialized in voice. The median ratings of these four SLP's were rounded to the closest integer scale step.

### **Acoustic assessment of voice (paper III)**

The blinded and randomized voice samples were analyzed using the computer software Praat version 5.4.21 ([www.praat.org](http://www.praat.org)), [Boersma and Weenink, 2015]. The sound files were analyzed for mean pitch in read passages and spontaneous speech. For acoustic analysis two consecutive standard sentences from SVANTE were chosen: “Titti tittar på TV” (Titti is watching TV) and “David å du leder” (David oh you are leading). The files were edited to only contain these two sentences in order to have a uniform speech material for acoustic analysis. The signal to noise ratio (SNR) was measured for all voice samples. The recordings with  $SNR < 30$  were excluded since SNR with a minimum of 30 is considered to be required for acoustic measures to be reliable [Deliyski et al., 2005]. The unvoiced segments of the files were removed according to the PRAAT script written by Maryn et al. [2010]. The following analyses were run for each sound: tilt of long-term average spectrum (LTAS), slope of LTAS [Maryn et al., 2010] and Cepstral Peak Prominence (Smoothened) (CPPS), as these are components in a multiparametric model of acoustic voice analyses [Maryn and Weenink, 2015].

### **Assessment of speech by naïve listeners (paper IV)**

Fourteen listeners (4 males, 10 females) without formal training in assessing or rating speech were recruited for the study through personal contacts of the authors. The mean age was 35 years (range 11 to 71). None of the naïve listeners had undergone any listening training or education about cleft speech. Each listener received a USB memory stick containing information about the listening procedure and the rating task, the randomized and coded recordings and a rating’s registration form. The listeners were instructed to listen to the recordings with headphones connected to a computer in a silent environment and rate each recording one by one. They were informed that replaying the recording of a subject was allowed if needed. The questions for speech assessment by naïve listeners were selected to match the SLPs speech rating format for comparison. The questions were chosen from the questionnaire of Brunnegard et al. [2009].

The following questions were rated on a five-point scale: “Do you think the person speaks through the nose?” (0 = No, 1 = Yes, slightly, 2 = Yes, a little, 3 = Yes, moderately, 4 = Yes, very much) “Does it sound like airflow noise/snort from the nose?” and “Do you notice any deviations in the articulation?” (0 = No, 1 = Yes, once or twice, 2 = Yes, some occurrences, 3 = Yes, frequently occurring, 4 = Yes, almost occurring always). The listeners were informed that “speak through the nose” also can mean “stuffy/obstructed nose” in this context. The question: “Is the speech intelligible?” Was rated on a three- point scale (0 = Normal, 1 = mildly reduced, 2 = much reduced). The listeners also answered the question: Do you think the recording comes from

an individual with cleft? yes/no. The listeners received a small gift of approximately 30 Euro as an appreciation.

### **Self-rating of speech by patients and controls (paper IV)**

At the time of the speech recording the participants answered a questionnaire regarding their own speech. The following questions were included: Do you speak through your nose (leak)? Do you sound like you have a congested nose? Do you have difficulties to articulate certain speech sounds? Do other people understand what you say? How satisfied are you with your speech? The questions were answered on a 100mm visual analogue scale (VAS). The question “Do you experience your speech as abnormal?” was answered with yes or no.

### **Statistical Analyses**

The computer software IBM Statistical Package for the Social Sciences statistics 20.0, (paper I,II,III) and 24,0 (paper IV) (IBM Corporation, Route 100, Somers, NY 10589, USA) was used in all analyses. Normality of data was tested with the Shapiro-Wilk Test. As data were not normally distributed, non-parametric tests were used. Comparisons were made with Fishers exact test (FET) ( $p < 0.05$ ) for categorical data including group comparison of data from clinical examination of the nose and nasal symptoms questionnaire (I) and voice-ratings on three-point scale (III). Mann Whitney-U test (MWU) ( $p < 0.05$ )(I,III,IV) and ( $p < 0.025$ )(II) was used for group comparisons on VAS in questionnaires (I,II,IV) and voice ratings (III) and for comparisons of ratings of speech on three to five point scales (II,IV). For comparison between Naïve listeners' and SLPs' classification of the recording as coming from a patient or not, the McNemar's test ( $p < 0.05$ ) was used (IV). For comparison of differences between naïve listeners' and SLPs' ratings the Wilcoxon signed rank test ( $p < 0.05$ ) was used (IV).

Correlations were made by Spearman's rank correlation coefficient (I,II,IV). For speech variables (II), the interrater agreement (degree of agreement among raters) and intrarater agreement (agreement at repeated ratings by the same rater/rater's self-consistency) were calculated as percentages of absolute agreement for ratings of speech (II) as well as intraclass correlation coefficient (ICC) with a mixed two-way model for single measures of absolute agreement (II) or mixed two-way model for average measures and consistency (IV). ICC was also used for calculation of inter- and intra-rater agreement for ratings of voice (III) with a two-way mixed model, consistency and average measures. The cut-offs and interpretation for rater reliability measures by ICC according to Cicchetti [1994] are; ICC  $< 0.40$  = poor, ICC  $0.40-0.59$  = fair, ICC  $0.60-0.74$  = good and  $0.75 - 1.00$  = excellent.

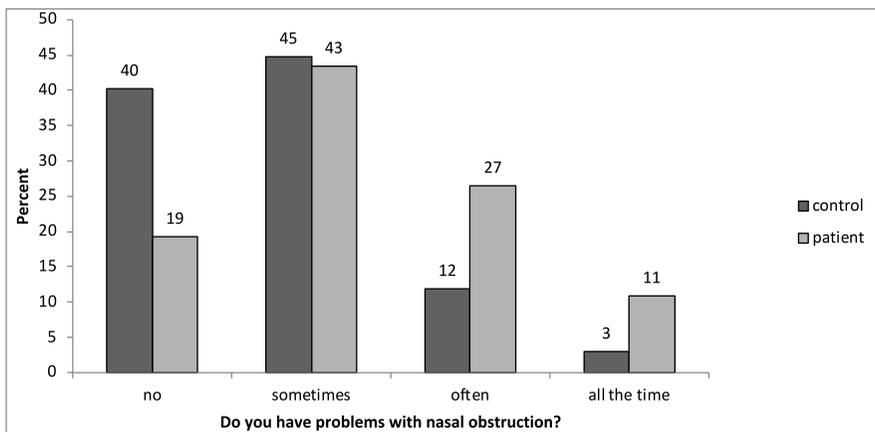
# Results

## Nasal symptoms and clinical findings (paper I)

### Questionnaire

Study population characteristics are presented in Table II/paper I. Medication use was lower in the patient group than in the control group. The most common medications were for asthma and allergy, contraceptives and antidepressants. Reported nasal obstruction is presented in Figure 4a.

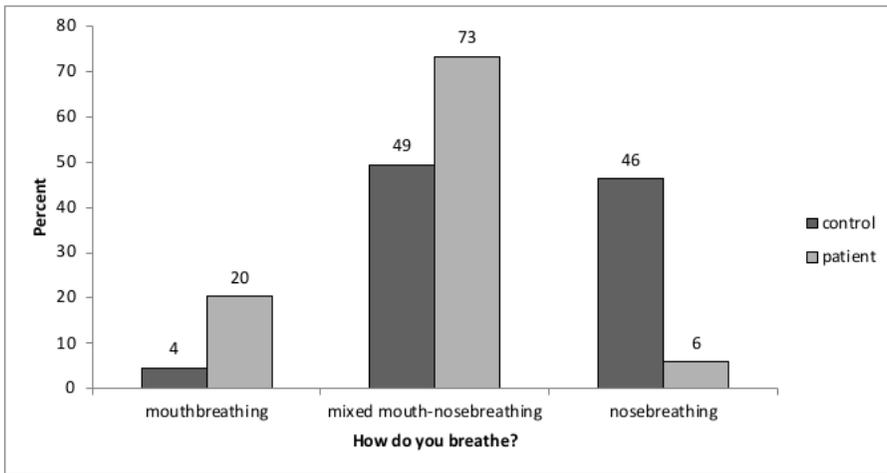
Figure 4a. Reported nasal obstruction in patients and controls



UCLP patients (n=83) and controls (n=67) (%). Fisher's exact test, p=0.005.

Out of the 67 patients who reported nasal obstruction, 52% had unilateral nasal obstruction on the cleft side, 3% on the non-cleft side, 24% had bilateral and 21% had side changing nasal obstruction. Mouth breathing and mixed oronasal breathing were more common among the patients compared to controls (Figure 4b).

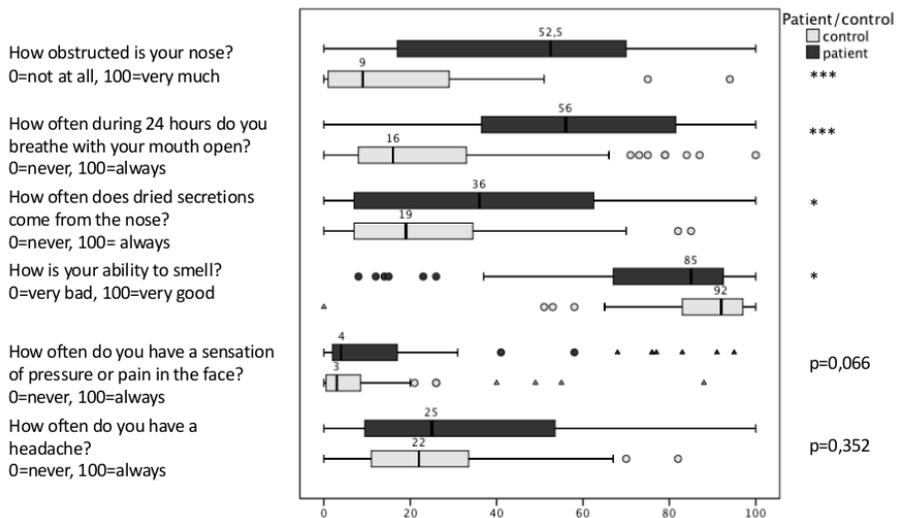
Figure 4b. Frequency of mouth-, nose-, or mixed mouth-nose breathing



UCLP patients (n =83) and controls (n=67) (%). Fisher's exact test, p<0.001

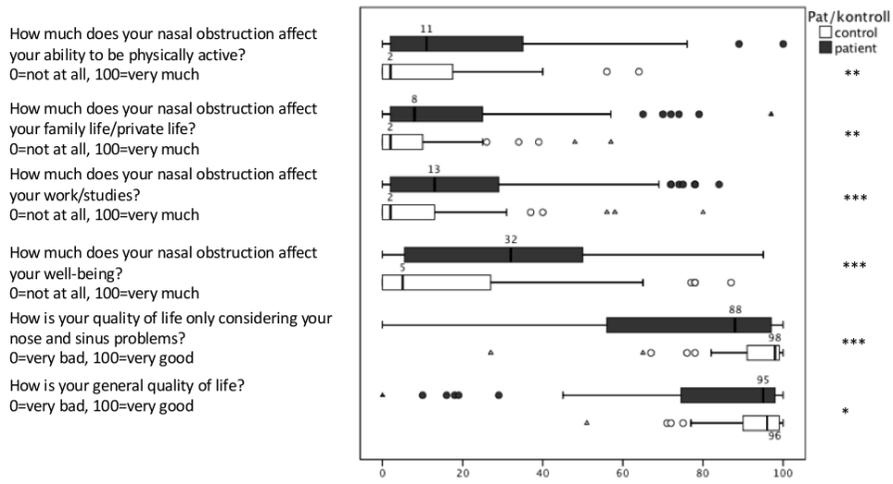
Nasal symptoms are presented in Figure 5a. Patients rated higher on VAS than controls for nasal obstruction and mouth-breathing, but lower for ability to smell.

Figure 5a. Nasal symptoms in patients and controls



UCLP patients (n =83) and controls (n=67). Questions answered by VAS scale as box plot with median values. ○=outlier, △=extreme outlier, Mann Whitney U test, \* p<0.05, \*\* p<0.01, \*\*\* p<0.001

Figure 5b. Nasal obstruction and quality of life in patients and controls



UCLP patients (n=83) and controls (n=67). Questions answered by VAS as box plot with median values. O=outlier, Δ=extreme outlier, Mann Whitney U test, \* p<0.05, \*\* p<0.01, \*\*\* p<0.001

Nasal obstruction negatively affecting well-being, professional life, private life and physical activity was reported to a greater extent among the patients compared to controls (Figure 5b). General quality of life was rated slightly lower among patients compared to controls. The patients had a stronger wish to change the appearance and the function of the nose by surgery compared to the control group ( $p < 0.001$ ). General quality of life correlated inversely with desire for surgical correction of nasal function ( $\rho = -0.249$ ,  $p = 0.023$ ) and appearance ( $\rho = -0.381$ ,  $p < 0.001$ ) in the patient group, indicating that patients with lower general quality of life tend to have a higher desire for surgical correction than patient with higher general quality of life. However, when analysing men and women separately the correlations were significant only for men (nasal function ( $\rho = -0.349$ ,  $p = 0.019$ ) and appearance ( $\rho = -0.593$ ,  $p < 0.001$ )).

The subgroup of 15 (18%) patients with pharyngeal flaps showed a tendency towards more subjective nasal problems compared to patients without pharyngeal flaps. However, the difference was significant only for extent of mouth-breathing which was higher in the patients with pharyngeal flaps compared to patients without ( $p < 0.05$ ). No significant differences were found in the questionnaire results between patients treated for UCLP with one-stage and two-stage protocol.

## Nasal examination

Findings at nasal examination are summarised in table 4. In summary, the patients presented with significantly more deformities of the exterior as well as interior parts of the nose compared to controls ( $p < 0.001$ ). One patient had nasal

polyps but none of the controls. In 15% of the patients, the nasal opening on the cleft side was too narrow for the 4.0 mm rod optic endoscope to be inserted. The 15 patients with pharyngeal flaps had similar distribution of findings at nasal inspection as patients without pharyngeal flaps except for nasal septal deviation where 4 (26%) had no deviation and 11 (74%) had severe unilateral deviation and no patient had mild unilateral or severe bilateral deviation.

Table 4. Findings at nasal examination

	Controls		All patients		p	One stage		Two stage		p
	n	%	n	%		n	%	n	%	
<b>Exterior nose</b>										
Deviation of bony part	1	2	9	11	*	5	10	4	13	0.72
Deviation of cartilaginous part	2	3	43	52	***	24	46	19	61	0.26
Web/ inward rotation of alar cartilage	0	0	28	33	***	17	33	11	36	0.8
Subluxation/ luxation of anterior border of septum					***					0.78
Subluxation	1	2	13	16		7	14	6	19	
Luxation	0	0	26	31		17	33	9	29	
Alar insufficiency at calm respiration	0	0	2	2	0.18	0	0	2	7	0.36
Septum short not reaching columella	0	0	20	24	***	11	21	9	29	0.60
<b>Interior nose</b>										
Nasal septal deviation					***					0.35
Mild unilateral	19	28	23	28		13	25	10	32	
Severe unilateral	1	2	37	45		21	40	16	52	
Moderate to severe bilateral	3	5	8	10		7	13	1	3	
Insignificant	44	66	15	18		11	21	4	13	
Concha hypertrophy					***					0.81
Unilateral compensatory for septal deviation	4	6	44	53		27	52	17	55	
Bilateral	1	2	4	5		2	4	2	7	
Mucosal swelling					0.08					0.57
Unilateral	0	0	4	5		2	4	2	6	
Bilateral	4	6	10	12		5	10	5	16	
Hyperaemic mucosa	25	37	26	31	0.17	14	27	12	39	0.27

Clinical examination of controls, all UCLP patients (All), one- and two-stage palatal closure groups (one and two). n = number of individuals, Fisher's exact test, \* p < 0,05, \*\* p < 0.01, \*\*\* p < 0.001

The findings at nasal inspection (concha hypertrophy, nasoseptal deviation and mucosal swelling) did not show any positive correlation to the subjective symptoms reported, i.e. patients with more severe findings at nasal inspection did not have higher rating for subjective symptoms (table III/paper I). However, there were negative associations indicating that more extensive mucosal swelling was associated with reduced mouth breathing, and more extensive concha hypertrophy was associated to less effect on physical activity. Patients treated with one-stage or two-stage palate closure did not differ regarding findings at nasal examination or regarding subjective symptoms.

## Speech (paper II)

### Speech outcome: patients vs. controls

Median scores for speech variables for all the patients and the one-stage and two-stage groups are presented in Figure 6. The patients had higher scores compared to controls for the following variables: hypernasality ( $p < 0.001$ ), hyponasality ( $p < 0.001$ ), audible nasal emission and/or nasal turbulence ( $p < 0.001$ ) and consonant production errors ( $p < 0.001$ ). The specific consonant production errors noted among patients included retracted oral articulation in 3% (two patients operated on with two-stage palate closure), s-distortions in 15% (11/73) (lateral or interdental/dental stigmatism) and r-distortions in 3% (two patients operated on with one-stage palate closure). Mild glottal reinforcement and/or glottal stop substitutions were found only in one patient and one other patient had mildly/moderately reduced intelligibility due to retracted articulation. The controls had normal speech variables except one who was assessed to have slight audible nasal emission and/or nasal turbulence and one who was assessed to have slight consonant production errors (s-distortion).

Based on the recordings, the SLPs (A, B, C and E) unanimously indicated 33 of the 73 patients correctly as patients (45%). The remaining 40 patients' recordings were indicated as coming from a control by one or more SLPs. Five per cent of the controls (3/63) were indicated as patients by two SLPs.

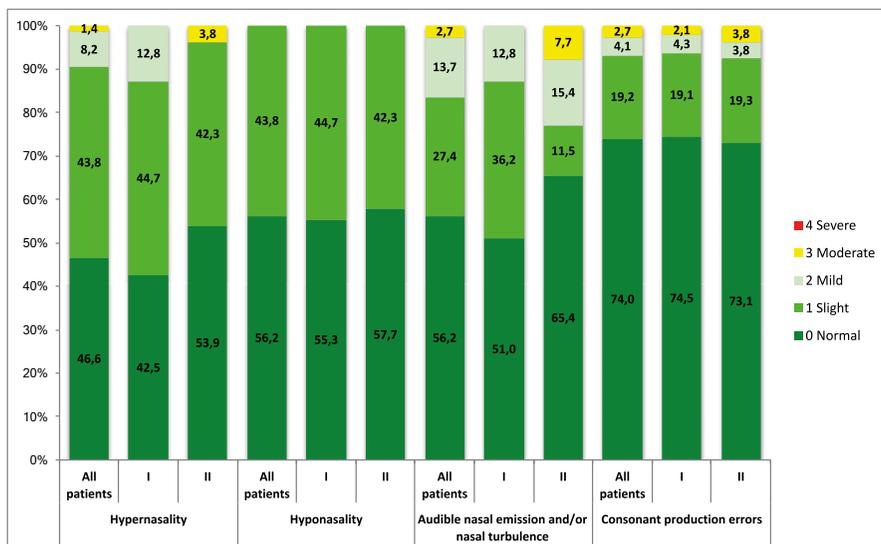
### Speech outcome: one-stage vs. two-stage palatal closure

Speech variables in patients operated with one- or two-stage palate closure are presented in Figure 6. There were no statistically significant differences between the patient groups in any of the six speech variables ( $p = 0.2 - 0.9$ ). No patient was rated to have severe abnormality (i.e. grade 4 of 4) for any of the speech variables.

### Inter- and intra-rater agreement for speech

The inter-rater agreement and intra-rater agreement is presented in Table 3/paper II. The mean inter-rater agreement for the SLPs (A, B, C and E) was 77.6% for the six speech variables and was lowest for audible nasal emission and/or nasal turbulence (57%). If a difference of one scale step was accepted, the mean inter-rater agreement was 94% with over 90% agreement for all variables except for audible nasal emission and/or nasal turbulence (80%).

Figure 6. Prevalence of speech errors in adult patients born with UCLP (n =73)



I = patients operated with one-stage palate closure (n = 47), II = patients operated with two stage palate closure (n = 26). Median values of ratings by four raters rounded to closest integer numbers. There were no statistically significant differences between the one-stage and two-stage groups (p-value 0.2-0.9, Mann Whitney U test). The colors refers to the color coding system “the traffic light system” [Harland, 1996].

The mean intra-rater agreement for SLPs (A, B, C and E) was 87, 87, 89 and 93% respectively, with a range of 67 – 100%. If a difference of one scale step was accepted, the mean intra-rater agreement was 94%. The speech ratings of the SLP D were excluded from the analysis of data and presentation of speech ratings. This SLP had lower (mean 71%) intra-rater agreement than the other SLPs. The lowest value of this SLP’s intra-rater agreement was for the variable hypernasality (40%). In contrast to the other SLPs this SLP rated many of the non-cleft controls to have several cleft speech characteristics (hypernasality, hyponasality, audible nasal emission and/or nasal turbulence) and indicated 70% of the non-cleft controls as patients.

### Fistulas in the palate

At inspection of the oral cavity, small oronasal fistulas were found in 24 out of 73 patients (33%). Fistulas in the hard palate were found in 22 out of 73 patients. All except one had been operated on with palate closure in one stage according to the patient charts. Ten patients had previously undergone secondary surgery for fistulas and twelve patients had not undergone fistula surgery. Fistulas in the soft palate were found only in two out of the 73 patients at oral inspection. According to patient charts, both patients had undergone palatal closure in one stage as well as fistula repair surgery. At oral inspection, 49 of 73 patients (67%) had no fistula. However, 19 of these patients had previously undergone fistula surgery according to the patient charts.

## Otoscopic findings and hearing satisfaction

Among the 73 patients, otoscopic findings were available for 119 of the patients' 146 tympanic membranes. Twenty-seven tympanic membranes were not examined. The inspection of tympanic membranes was added to the examination protocol just before the study started. However, by mistake, an earlier version of the examination protocol was used when the first patients were examined. Therefore the tympanic membranes of 8 patients were not examined (6 in the two stage group and 2 in the one stage group). Eleven tympanic membranes could not be evaluated due to cerumen in the external auditory canal (both ears in three patients, one ear in five patients).

Seventeen tympanic membranes were slightly retracted, one was strongly retracted, one was retracted and adhered to the promontory of the middle ear and one had a persisting perforation. Eighty-six per cent of the examined patients had at least one normal tympanic membrane. In the control group, one individual was found to have both of the tympanic membranes slightly retracted. All the other controls had normal tympanic membranes.

Patients tended to be slightly more dissatisfied with their hearing compared to controls and rated a mean value of 25 (SD = 29) on a 100mm VAS compared to mean 17 (SD = 18) in the control group (0 = very satisfied, 100 = very dissatisfied). However, the difference (MWU) was not statistically significant ( $p = 0.34$ ). Moreover there was no significant difference in hearing satisfaction between the two surgical groups ( $p = 0.46$ ).

Three patients were using hearing aids but had no signs of tympanic membrane pathology. Of the three patients with hearing aids, two had normal speech and one had mild hypernasality and audible nasal airflow together with a moderately deviated articulation. No one in the control group was using a hearing aid.

## Possible relations between speech outcome and other variables

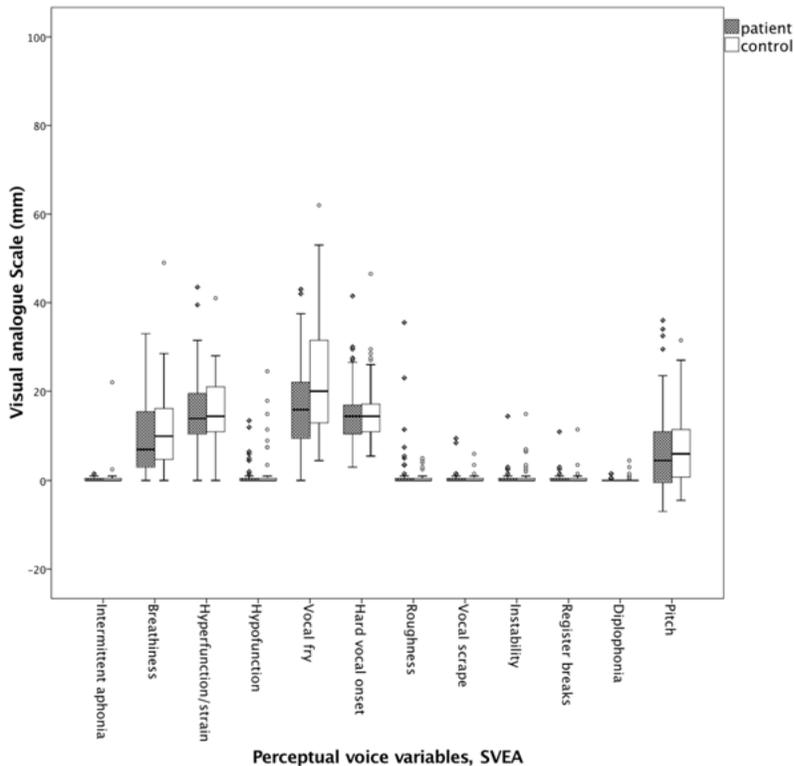
No statistically significant difference was found between the six speech variables and dichotomized outcome of tympanic membrane pathology, oronasal fistulas at inspection of the oral cavity or pharyngeal flap. Furthermore, when the one stage and the two stage groups were analyzed separately, no statistically significant correlation was found between age at hard or soft palatal closure and any of the speech variables (Spearman's rho: -0.26 to -0.02,  $p = 0.2-0.8$ ). No statistically significant correlation was found between the six speech variables and satisfaction with hearing (Spearman's rho: -0.20 to 0.20,  $p = 0.1-0.9$ ).

## Voice (paper III)

### Voice perceptual ratings of patients and controls

Perceptual assessments of voice according to the SVEA protocol (SLP A & B): Perceptual rating values are shown in figure 7. Ratings of the severity of the different voice variables did not differ significantly between patients and controls except for “vocal fry” which was rated lower among patients compared to controls ( $p = 0.009$ , MWU).

Figure 7. Perceptual assessments of voice according to the SVEA protocol



Median ratings of SLP A and B shown as boxplot. Patients treated for UCLP ( $n = 73$ ), Non-cleft controls ( $n = 63$ ). Significant difference in vocal fry ( $p = 0.009$ , Mann-Whitney U test).

The total mean of all 12 variables on VAS scale was lower (less severe) among the UCLP group ( $5 \pm 2$ ), compared to the non-cleft controls ( $6 \pm 2$ ) ( $p = 0.018$ , MWU). The following seven variables; intermittent aphonia, hypofunction, roughness, vocal scrape, instability, registry breaks and diplophonia had a rating on VAS very close to zero (no abnormality) among both patients (rating for all seven variables  $< 1.7$ ) and controls (rating for all seven variables  $< 1.8$ ). The mean of the remaining five variables (hyperfunction, breathiness, hard

vocal onset, vocal fry, pitch) was  $14 \pm 5$  among the UCLP group and  $16 \pm 5$  among non-cleft controls.

Perceptual assessment of voice on 3-point scale (table 4/paper III): No individual was rated to have moderate to severe abnormality. The number of individuals rated to have a mild voice abnormality was 10/73 patients and 7/63 controls. The difference was not significant ( $p = 0.80$ , FET).

### Voice ratings among patients treated with palatal closure in one versus two stages

Perceptual assessments of voice according to the SVEA protocol (SLP A & B): There was no significant difference in any of the 12 perceptual voice variables ( $p = 0.08 - 0.90$ , MWU) or in the total mean of all 12 variables ( $p = 0.21$ , MWU) between patients operated with one- or two-stage palate closure.

Perceptual assessment of voice on three-point scale (table 4/paper III): There was a tendency for patients operated with one-stage palate closure to be rated with a mild abnormality more frequently with 19% of the cases (9/47), compared to 4% (1/26) in patients operated with two-stage palate closure ( $p = 0.085$ , FET).

### Voice ratings among patients with hypernasality/audible nasal emission versus patients without

Perceptual assessments of voice according to the SVEA protocol (SLP A & B): There were no significant differences in the variables in SVEA between the seven patients with mild ( $n=5$ ) to moderate ( $n=2$ ) hypernasality when compared to the rest of the patients ( $p = 0.11$  to  $0.94$ , MWU). Additionally, there were no differences in the variables of SVEA when comparing the 12 patients with mild ( $n=10$ ) to moderate ( $n=2$ ) audible nasal air emission and/or nasal turbulence to the rest of the patients ( $p = 0.22$  to  $0.99$ , MWU).

Perceptual assessment of voice on three-point scale (table 4/paper III): There was a higher proportion of patients rated to have a mild voice abnormality among patients with hypernasality ( $p = 0.049$ , FET) and audible nasal emission ( $p = 0.008$ , FET) compared to the rest of the patients.

### Acoustic measurements of voice

There were 55 recordings from patients and 51 recordings from controls with  $\text{SNR} > 30$ . The results of the acoustic measurements are shown in table 5. There were no statistical differences between patients and controls for any of the

Table 5. Acoustic voice variables in patients, controls and patients with one and two stage palate closure. Recordings with SNR > 30.

Variable	Patients (n = 55)	Controls (n = 51)	Patients with one stage palate closure (n = 36)	Patients with two stage palate closure (n = 19)	U <sup>†</sup>	p <sup>†</sup>	U <sup>††</sup>	p <sup>††</sup>
	M ± SD (min to max)	M ± SD (min to max)	M ± SD (min to max)	M ± SD (min to max)				
Pitch (Hz)	164 ± 44 (98 to 251)	166 ± 46 (98 to 256)	168 ± 42 (98 to 245)	157 ± 48 (104 to 251)	1397	0.97	277	0.25
Slope of LTAS	-21 ± 3 (-27 to -16)	-21 ± 3 (-28 to -14)	-21 ± 2 (-27 to -17)	-21 ± 3 (-27 to -16)	1429	0.87	374	0.57
Tilt of trendline through LTAS	-12 ± 1 (-14 to -10)	-12 ± 1 (-14 to -11)	-12 ± 1 (-14 to -10)	-12 ± 1 (-14 to -10)	1463	0.70	377	0.53
CPPS	12 ± 2 (9 to 16)	12 ± 2 (8 to 15)	13 ± 2 (9 to 16)	12 ± 2 (9 to 16)	1611	0.19	261	0.15

M = mean, SD = standard deviation, LTAS = Long term average spectrum, CPPS = Smoothened cepstral peak prominence, SNR = signal noise ratio  
 Statistical comparisons by Mann Whitney U test, p < 0.05: U<sup>†</sup> & p<sup>†</sup> = All patients vs control, U<sup>††</sup> & p<sup>††</sup> = one stage vs two stage

acoustic voice variables ( $p > 0.19$ , MWU). Additionally, there were no statistical differences between male patients and male controls or female patients and female controls. There were no statistical differences in the acoustic variables between patients with one or two stage palate closure ( $p > 0.15$ , MWU).

Subgroup analysis showed that there were no statistical differences for any of the acoustic variables when the seven patients with hypernasality were compared to the rest of the patients, ( $p > 0.51$ , MWU). Furthermore, there were no statistical differences in any of the acoustic variables when comparing the 12 patients with audible nasal air emission and/or nasal turbulence to the rest of the patients ( $p > 0.20$ , MWU).

### Inter- and intra-rater agreement of ratings

Perceptual assessments of voice according to the SVEA protocol (SLP A & B): As expressed by ICC, the following five perceptual variables had a mean inter-rater agreement of 0.72, range (0.71-0.82): (hyperfunction, breathiness, hard vocal onset, vocal fry, pitch). The remaining seven perceptual voice variables had too limited variability for calculating ICC (figure 7). The mean intra-rater agreement as ICC was 0.43 for SLP A and 0.81 for SLP B for the 15 duplicated recordings.

Perceptual assessment of voice on 3-point scale: The inter-rater agreement was 0.73 and the intra-rater agreement was 0.60 and 0.65 for two of raters. For the other two raters the intra-rater agreement could not be calculated since one variable was constant.

## Rating of speech by naïve listeners, SLPs and patients (paper IV)

### Inter- and intrarater agreement

The inter-rater agreement for naïve listeners as ICC, average measures ranged between 0.83 and 0.91. The inter-rater agreement for SLPs the ICC average measures ranged between 0.65 and 0.89. The intra-rater agreement for naïve listeners as ICC ranged from -0.25 to 0.98 and the mean values for the intra-rater agreement for each variable ranged from 0.47 to 0.73. However, 27/70 (39%) ICC calculations were not possible when at least one of the variables were constant.

## Correlations and differences between naïve listeners, SLPs and self-ratings

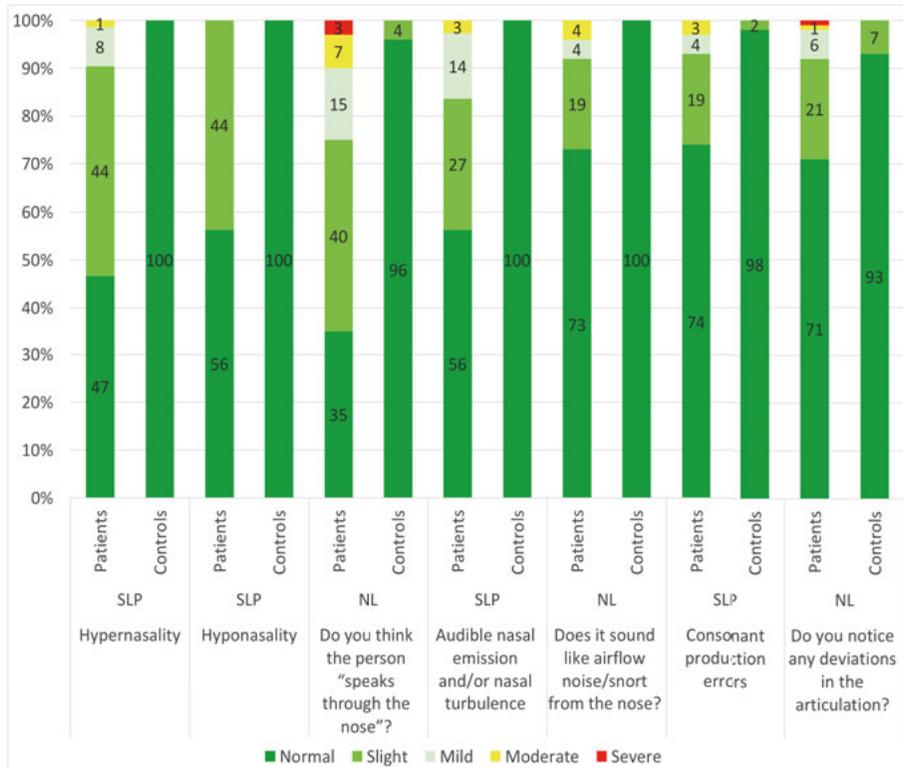
The correlations between the ratings of naïve listeners and SLPs as Spearman's rank correlation coefficient ranged between 0.44 and 0.71. The correlations between ratings of naïve listeners and self-ratings as Spearman's rank correlation coefficient had a range from 0.10 to 0.40. The Spearman's rank correlation coefficient between ratings of SLP and self-ratings as had a range of -0.10 and 0.41. There were statistically significant differences between the ratings by naïve listener and SLPs for all the compared speech variables ( $p = 0.039$  to  $p < 0.001$ , Wilcoxon signed rank test)

## Ratings of speech by naïve listeners, SLPs – patient vs controls

Ratings of speech by naïve listeners and SLPs are shown in figure 8.

There were significant differences between the ratings of speech in patients and controls for all speech variables rated by naïve listeners and SLPs ( $p < 0.001$ , Mann Whitney U test). Intelligibility was rated to be mildly reduced in five patients by naïve listeners and in one patient by the SLPs. None of the controls were rated to have reduced intelligibility. No patient or control was rated to have much reduced intelligibility. On the question: Do you think the recording comes from an individual with cleft? Naïve listeners rated 28 (38%) of the patients' speech recordings as coming from a patient and none of the controls' speech recordings as coming from a patient. The SLPs rated 56 (77%) of the patients' speech recordings as coming from a patient and 2 (4%) of the controls' speech recordings as coming from a patient. The difference was significant ( $p < 0.001$ , McNemar's test)

Figure 8. Ratings of speech in patients treated for UCLP by naïve listeners and SLPs

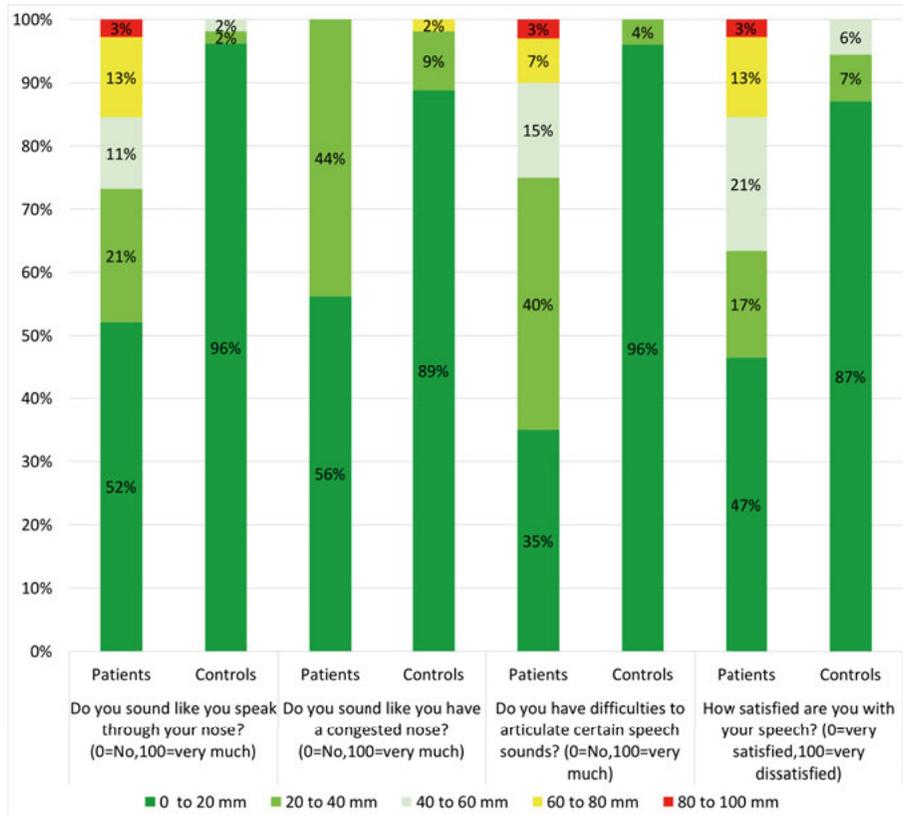


Ratings of speech in 73 patients treated for UCLP and 55 non-cleft controls by 14 naïve listeners and 4 SLPs. Ratings on a five-point scale. Median values of all raters in each group respectively for every subject rounded to integers. There were significant differences between the ratings in patients and controls for all variables ( $p < 0.001$ , Mann Whitney U test). SLP- speech-language pathologists, NL- naïve listeners

### Self-ratings of speech by patients and controls

The self-ratings of speech by patients and controls are shown in figure 9. There were significant differences between patients and controls for all ratings for the questions rated on VAS ( $p < 0.001$ , Mann-Whitney U test). The median rating for satisfaction with speech was 23 (interquartile range: 41) in patients and 3.5 (interquartile range: 12) in controls on the 100mm VAS (0 = very satisfied, 100 = very dissatisfied). On the question: "Do you experience your speech as abnormal?" 16/70 (23%) patients answered yes, and three of the patient answers were missing. None of the controls answered yes on the same question.

Figure 9. Distribution of self-ratings of speech in patients and controls on VAS



The figure shows the percentage of rating values on VAS within the following intervals: 0 to 20 mm, 20 to 40 mm, 40 to 60 mm, 60 to 80 mm and 80 to 100. VAS 100mm (0mm = Not at all, 100mm = very much for all variables except “How satisfied are you with your speech”:0= very satisfied,100=very dissatisfied) There were significant differences between patients and controls for all the variables ( $p < 0.001$ , Mann-Whitney U test)

# Discussion

## Nasal symptoms and clinical findings (Paper I)

In this study patients reported increased nasal symptoms compared with the control group including more nasal obstruction, more mouth-breathing and decreased ability to smell. The patients' nasal symptoms had a negative effect on daily life and physical activities to a greater extent than among controls.

Allergic rhinitis, rhinosinusitis and nasal polyposis, which are common causes of nasal congestion, were not more frequent among patients compared to controls. The patients had only little sinus problems compared to a study by Anastassov et al. [1998], which reported history of chronic sinusitis in 30% of their UCLP patients.

Additional corrective surgery may decrease or increase nasal obstruction in patients treated for UCLP. Septoplasty can improve the nasal function in patients with CLP [Trindade et al., 2009]. In paper I, only three patients had undergone septoplasty and their outcome did not differ from the rest of the patients. Surgery to expand and move the maxilla forward could improve nasal function [Trindade et al., 2003, Saito et al., 2006]. Two patients had undergone osteotomy of the maxilla with forward movement of the maxilla, however no rapid maxillary expansion was performed. Pharyngeal flap surgery can affect the nasal airway size and resistance negatively [Yamashita and Trindade, 2008]. The subgroup of 15 patients with pharyngeal flaps (18%) showed a tendency towards more subjective nasal problems compared to patients without pharyngeal flap. However, the difference was significant only for extent of mouth breathing. The distribution of findings at clinical nasal examination in this subgroup was similar for all variables except for nasal septum deviation. The limited number of patients in this subgroup of patients might explain why few differences were detected.

The frequency of nasal obstruction (37% reported "often" or "always") is in line with an earlier study where 34% of patients with UCLP reported reduced nasal breathing [Marcusson et al., 2002]. Patients reported more nasal obstruction than controls which supports the fact that the nasal airway of patients treated for UCLP has a higher airflow resistance [Mani et al., 2010b] and may induce mouth-breathing. Almost all patients (94%) reported habitual oral or mixed oro-nasal breathing patterns.

Self-assessed olfactory function was lower among the patients than the control group. This is in line with a previous report where olfactory function was

tested using the Scandinavian odour identification test (SOIT) [Mani et al., 2010b]. Grossmann et al. [2005] reported an elevated smell threshold but no difference in odour identification and Anastassov et al. [1998] found self-reported impaired olfactory function in 15% of the UCLP patients. The impaired olfactory function is thought to be a result of decreased nasal airflow [Anastassov et al., 1998, Grossmann et al., 2005, Mani et al., 2010b].

In non-cleft individuals, chronic nasal obstruction may have a negative impact on quality of life [Udaka et al., 2007]. In paper I, the patients reported their nasal symptoms to have a greater negative impact on daily life and physical activities than controls. The ratings for these two questions related to quality of life was slightly lower among patients compared to controls, which is in line with earlier studies [Marcusson et al., 2001, Sinko et al., 2005, Mani et al., 2010a].

Many patients expressed a desire to change the function and the shape of the nose through surgery. Interestingly, correction of nasal appearance seemed to be a greater concern compared to correction of nasal function. Marcusson et al similarly reported a frequent desire among CLP patients for surgical correction of the nasal appearance [Marcusson et al., 2002]. We found a correlation between lower rating of general life quality and a desire for nose surgery to improve the aesthetics. This is in line with a previous study by Sinko et al. [2005]. Sinko et al also pointed out the importance of the aesthetics of the face and especially the nose for social success and self-esteem.

Nasal inspection revealed nasal septum deviation as well as other deformities of the external and internal part of the nose in patients treated for UCLP, in line with previous studies [Warren et al., 1992]. Nasoseptal deviation and stenosis of the nasal valve area can affect nasal airflow resistance. Signs of disease of the nasal mucosa were not more frequent among the patients compared to controls, which corresponds well to asthma, allergy and sinus problems not being overrepresented among the patients.

There was no positive correlation between findings from nasal examination and nasal symptoms. Subjective nasal symptoms are not only influenced by the actual nasal impairment but also by psychological factors, personality and coping strategies, which might explain the lack of positive correlation. Others have reported poor relationship between nasal symptoms and rhinoscopic findings in non-cleft individuals [McCaffrey and Kern, 1979]. Paper I illustrates the difficulties in evaluating and quantifying the nose form and function of people treated for UCLP. Patients presenting with nasal symptoms are normally subject to nasal inspection as well as more objective methods such as acoustic rhinometry, rhinomanometry and peak nasal inspiratory flow. However, as any treatment aims to reduce symptoms, an appropriate evaluation of the self-perceived symptoms is important. Structured self-reported nasal obstruction symptoms has been shown to be useful in evaluating surgical outcomes both in patients with [Chaithanyaa et al., 2011] and without [Kahveci et al., 2012] CLP. Andre et al showed poor correlation between subjective and

objective measurements [Andre et al., 2009]. Adaptation to impaired nasal breathing since birth could be a reason for lack of correlation between objective and subjective measures in patients with congenital nasal obstruction.

The surgical method used for palate closure in UCLP can affect maxillary growth [Friede, 2007] and potentially the clinical findings and nasal symptoms. We found no differences in subjective nasal symptoms or findings at nasal inspection related to previous operation with one or two stage palatal closure. These findings are in agreement with previous study by the authors where no difference in level of impairment measured with acoustic rhinometry and rhinomanometry was found between one-stage and two-stage protocols, except for the findings on the non-cleft side [Mani et al., 2010b].

## Speech (Paper II)

The present study compared adults treated for UCLP to controls with regard to perceptual speech variables evaluated by four SLPs. The study also compared two subgroups, UCLP patients treated with either one-stage or two-stage palate closure. In contrast to controls, approximately half of the patients had at least slight hypernasality, hyponasality, audible nasal emission and/or nasal turbulence and approximately one fourth had at least slight consonant production errors, as expected. However, the results showed acceptable speech for the vast majority of UCPL patients regardless of surgical method of palatal closure.

The speech outcome measures evaluated in the paper II are well established and similar measures have been used in previous studies [Farzaneh et al., 2008, Havstam et al., 2008, Lohmander et al., 2012]. Perceptual assessments are considered as gold standard for speech evaluation of CLP patients [Sell, 2005] but as it is a subjective measure, outcomes should be interpreted with some caution. Approximately half of the patients had completely normal speech at the blinded speech assessment. Consequently, 55 per cent of the patients were classified as non-UCLP controls by one or more of the four raters.

Only 10 per cent of the patients had mild to moderate hypernasality, which is considerably lower than in previous studies that reported mild to severe hypernasality in 20–57 percent of adult UCLP patients [Van Lierde et al., 2004b, Farzaneh et al., 2008, Havstam et al., 2008, Lohmander et al., 2012]. An audible nasal emission and/or nasal turbulence was noted to a mild to moderate degree in 16 per cent of the patients, which is also in the lower range compared to previous studies (4–43%) [Van Lierde et al., 2004b, Farzaneh et al., 2008, Havstam et al., 2008, Lohmander et al., 2012]. Interestingly, more patients were perceived as having audible nasal emission and/or nasal turbulence than hypernasality. This might be explained by that the perception of hypernasality in speech requires a certain size of the velopharyngeal port [Bunton, 2015]. The audible nasal emission and especially nasal turbulence

may be perceived at very small velopharyngeal port sizes [Scarmagnani et al., 2015] as the sound of nasal turbulence is thought to be due to the friction of the air being forced through a small velopharyngeal gap [Kummer et al., 1992].

Patients with symptomatic velopharyngeal insufficiency after primary palatal closure are normally treated with secondary surgery, e.g. pharyngeal flap. The percentage of patients that need secondary surgery may be used to measure the success rate of the primary surgery. For the vast majority of patients in our study, the primary surgery was sufficient, as only 15 per cent of the patients underwent pharyngeal flap surgery. This is well within the range of previously reported percentages (11–26%) [Farzaneh et al., 2008, Havstam et al., 2008, Lohmander et al., 2012].

Paper II revealed that 44 percent of the patients presented with slight hyponasality and this finding corroborates prior data published for the same UCLP population, which revealed decreased nasal volume and airflow measured with acoustic rhinometry and rhinomanometry [Mani et al., 2010b]. In accordance with this, in paper I we found that patients with UCLP self-reported more nasal obstruction than the controls did. No patient in paper II was rated with a higher than slight (grade > 1 on the 5-point scale) degree of hyponasality, consistent with previous reports [Farzaneh et al., 2008, Havstam et al., 2008, Lohmander et al., 2012].

In studies of children with CLP, consonant production errors are usually transcribed phonetically. In this study involving adults with UCLP we choose not to use transcription since consonant production errors, except for sigma-tism, are rare among adults treated for cleft [Van Lierde et al., 2004b]. However, the SLPs were asked to note if a certain consonant production error occurred. The most frequent consonant production error was s-distortion/sigmatism, which was found in 15 percent of the patients, and which is within the lower range of prevalences reported in previous studies (2–53%) [Van Lierde et al., 2004b, Lohmander et al., 2012]. Henningson et al. [2008] categorized s-distortions as belonging to “other oral articulation errors” related to dentofacial or oral structural deviations.

Non-oral compensatory articulation errors like glottal stops and pharyngeal fricatives often reduce speech intelligibility and are challenging to treat with speech therapy. In this study population, where speech therapy was provided to more than half of the patients, only one patient presented with glottal reinforcement and/or glottal stop substitutions, while another single patient had reduced intelligibility. This is in line with previous studies that reported low prevalence of non-oral articulation errors in adult UCLP patients [Van Lierde et al., 2004b, Farzaneh et al., 2008, Lohmander et al., 2012]. As expected, there were almost no speech deviations among controls.

In paper II there were no significant differences in speech outcome between patients operated on with one- or two-stage palate closure. These findings are contradictory to the study by Van Lierde et al. [2004b] where patients who

received two-stage Furlow palatoplasty with hard palate closure at ages 8–11 years had higher nasal scores as measured by nasometry, than patients with one-stage Wardill-Kilner palatoplasty. Holland et al. [2007] found poorer speech and orthodontic outcome after two-stage palate repair, with soft palate closure at one year and hard palate closure at seven years of age, compared to one-stage von Langenbeck repair at one year of age. A recent study by Kappen et al. [2017] evaluated speech outcomes in 48 patients (mean age 21 years) treated for UCLP with two-stage palatoplasty, with hard palate closure at a mean age of 3 years. They found moderate intelligibility scores, a relatively high incidence of articulation errors and mild hypernasality. In addition, 42% of the subjects needed speech-improving surgery and 25% had a history of clinically significant fistulas. In contrast, the cleft centre in Gothenburg have reported better velopharyngeal function and orthodontic results after two-stage [Lohmander et al., 2012] than after one-stage palate closure [Havstam et al., 2008] among adults treated for UCLP.

The measures of inter- and intra-rater agreements in our study were comparable with those reported in previous studies [Farzaneh et al., 2008, Lohmander et al., 2012]. Unfortunately, one of the external SLP's ratings were considerably different from those of the others and therefore not considered reliable enough to be included in the analysis. This rater had not been active in clinical practice with CLP patients for several years prior to the study. This could explain the differences in ratings and also points out the need for continuous clinical practice for the accuracy of perceptual ratings of speech.

One notable difference between the groups was a higher fistula rate among patients operated on with one-stage palate closure, compared to patients who had had the two-stage operation. On the contrary, Holland et al. [2007] reported higher fistula rates after two-stage palate closure compared to one-stage palate closure. The overall rate of oronasal fistulas in the current study was within the range of what has been previously reported [Hardwicke et al., 2014]. The fistulas noted in paper II were small and did not seem to influence speech variables.

Speech therapy is likely to influence speech quality [Van Demark and Hardin, 1986]. A higher proportion of the patients operated on with one-stage palate closure received speech therapy according to the chart review, but the data was too limited to draw any conclusion. Quantitative measures of hearing like audiometric data were not available for this study, either. However, indirect measures like self-reported satisfaction with hearing, use of hearing aids and tympanic membrane pathologies were not associated with speech outcome.

## Voice (Paper III)

In paper III, voice of adults treated for UCLP was analysed and compared to that of a non-cleft control group. No differences were found in perceptual or acoustic voice variables between patients and controls, except for a slightly lower mean of the total of the perceptual variables and a lower rating of vocal fry among patients. No differences were seen between the two palate closing procedures. The perceptual voice ratings for both patients and controls were close to “no abnormality” except for the few outliers (figure 7).

There was more vocal fry among controls compared to patients. Sporadic vocal fry is frequently occurring in voices without pathology [Hollien et al., 1966]. Vocal fry is normally produced with lower or equivalent lung pressures compared to modal phonation, typically at the end of phrases when subglottic pressure is lowered [Murry, 1971]. In a recent study by Behrman and Akhund [2016], vocal fry in conversational speech was reduced by louder and clearer speech. In hypernasal speech the height of the second formant for resonance is lowered due to the acoustic features of the nasal cavity [Kataoka et al., 2001]. This may dampen the acoustic output of the voice. In accordance with this, one could speculate that if patients treated for cleft palate use increased efforts to produce a clearer and louder speech in order to compensate for the reduced resonance of the second formant, then this could also reduce the amount of vocal fry even to a level below that of non-cleft controls.

Previous studies on individuals treated for CLP show that dysphonia is more common among 10-year olds compared to 16 to 23 year olds [Van Lierde et al., 2003, 2004a, 2004b]. This may indicate that dysphonia can diminish or vanish after puberty and may partly explain the findings of the present study, where no differences were found in the acoustic voice variables nor in perceptual voice analysis between adult patients treated for CLP and controls.

Prevalence of dysphonia among patients treated for CLP have been reported to differ between different types of palatoplasty [Musgrave et al., 1975, Farzaneh et al., 2008]. These findings are contradictory to the findings of paper III where no differences in voice variables were found between different palatoplasties. The low rate of dysphonia for all patients in paper III may explain why no differences in dysphonia could be detected between the two different palate closing procedures.

We hypothesized that patients with hypernasality or audible nasal air emission would have more perceptual and acoustic signs of dysphonia than the patients without. However, no such difference was found in perceptual voice characteristics on the SVEA scale or for the acoustic variables. Only in the ratings of voice abnormality on a 3-point scale, patients with hypernasality and or audible nasal air emission were rated to have proportionally more dysphonia than the patients without these audible signs of VPI. These findings

are contradictory and cannot conclude whether VPI related speech abnormalities influence voice quality or not. Moreover, the number of patients presenting with hypernasality or audible nasal air emission in paper III was low and the degree of abnormality was mild to moderate. As such, more studies are needed to explore this hypothesis further. Glottal stop substitutions have been suggested to increase the risk of dysphonia in children treated for CLP [Aydinli et al., 2016]. In the present study population, however, only one patient had glottal reinforcement and/or glottal stop substitutions, which made such analysis not meaningful.

Perceptual voice analysis is a key element for evaluation of vocal impairments although validity and reliability will never be perfect [Kempster et al., 2009]. Acoustic measures provide an objective and non-invasive way to evaluate vocal function. A combination of perceptual and acoustic methods are recommended for evaluation of dysphonia [Dejonckere et al., 2001, Barsties and De Bodt, 2015]. Perceptual voice analysis usually includes judgment of different voice characteristics by a trained listener using a protocol or scale. Internationally, the most commonly used rating scale is the GRBAS scale. In paper III the SVEA [Hammarberg, 1986] was used because it is partly based on acoustic correlates, it is relatively detailed and is in clinical use for voice assessment in Sweden. It contains variables corresponding to the variables in GRBAS except for “grade”. In paper III two different sets of SLPs evaluated perceptual voice variables: two SLPs specialized in voice and four SLPs specialized in CP speech. The raters individually evaluated blinded and randomized recordings from patients and controls. The inter-rater agreement was good and the intra-rater agreement fair to excellent.

Acoustic voice analysis can provide quantitative measurements of dysphonia by various analytical methods. Some studies of voice in patients treated for cleft palate have used measurements of voice perturbation, e.g. variations of frequency (jitter) and amplitude (shimmer) as acoustic voice variables [Zajac and Linville, 1989, Lewis et al., 1993, Bressmann et al., 1998, Niedzielska, 2005, Villafuerte-Gonzalez et al., 2015, Aydinli et al., 2016]. These measures are analyzed only from sustained vowel phonation and the clinical validity as measurement of dysphonia has been questioned due to limited correlation to perceptual measures and reliability [Rabinov et al., 1995, Maryn et al., 2009, Barsties and De Bodt, 2015]. Measures of voice perturbation were not used in paper III due to these limitations and the fact that the recorded voice material of the study did not contain extended vowel phonation.

Paper III used spectral and cepstral measures of connected speech samples with unvoiced segments removed. Spectral and cepstral measures may be more adequate acoustic measures of dysphonia as these do not rely on the periodicity of the signal and can be analysed from samples of connected speech [Lowell et al., 2011]. The spectrum of the voice signal can be calculated with Fourier analysis, and illustrated as a graph showing the frequency

content of the sound. The shape of the long-term average spectrum (LTAS) of the voice can vary with voice quality [Leino, 2009, Lowell et al., 2011]. A way to measure the periodicity of the signal spectrum of a voice sample is the Cepstral Peak Prominence (CPP) developed by Hillenbrand et al. [1994]. The Cepstrum is the calculated Fourier transform of the logarithm of the power spectrum of the sound signal. The CPP is the difference in amplitude between the cepstral peak (i.e. the highest harmonic) and the background noise level in the cepstrum. The smoothed CPP (CPPS), that was used in the present study, has been shown to have a high correlation to perceived breathiness in the voice [Hillenbrand and Houde, 1996]. Several studies have found correlations between CPP and perceptual measures of dysphonia [Heman-Ackah et al., 2003, Halberstam, 2004, Maryn et al., 2009].

Connected speech samples contain both voiced and unvoiced segments. The removal of unvoiced segments may improve the quality of the acoustic analysis [Lowell et al., 2011, Lowell et al., 2013]. A recent review suggested the use of multiparametric models of voice samples containing both connected speech and extended phonation in acoustic measurement of dysphonia. These models show diagnostic accuracy, concurrent validity and reliable acoustic correlates of perceived overall voice quality [Barsties and De Bodt, 2015]. However, it was not possible to use multiparametric models in paper III as the voice material did not contain extended phonation.

The only previous study found in the literature, evaluating patients treated for cleft palate with CPPS, reported lower CPPS values in patients before and after surgery compared to controls. The values were normalized after speech therapy [Yang et al., 2014]. The CPPS and LTAS measures are derived from the frequency spectrum of the voice and hypernasality influences the spectrum [Vogel et al., 2009, de Boer and Bressmann, 2016]. Therefore, the CPPS and LTAS are products of both the voice source and the resonance. However, in paper III there were no differences in the acoustic variables between patients and controls. This may indicate normal voice and resonance by acoustic measures among patients, although specific acoustic tests for hypernasal resonance were not performed. In spite of this, perceptual speech evaluation in paper II showed mild hypernasality in 10% of the patients.

The majority of previous studies have smaller group sizes and are heterogeneous with respect to cleft type and age. Most studies lack a control group, however, normative voice data are sometimes used [Van Lierde et al., 2004a, 2004b]. In the present study the patient group was homogenous including only complete UCLP patients. All participants were adults and had been treated at the same centre during childhood and adolescence. At the time of the study all participants, patients and non-cleft controls, were examined by the same set of professionals. These aspects of the study make it unique.

## Naïve listeners and self-ratings (Paper IV)

Paper IV assessed speech among seventy-three adult patients treated for UCLP and fifty-five non-cleft controls by fourteen naïve listeners, four SLPs and self-ratings by patients and controls. The correlations between the ratings between these four groups of raters were investigated. The hypothesis was that there would be differences between the ratings but also positive correlations. Although there were significant differences between ratings of naïve listeners and SLPs for all the rated variables their ratings correlated positively. In contrast to what was hypothesized, correlations were stronger between naïve listeners and SLPs compared to correlations between self-ratings and ratings by naïve listeners or SLPs. To our knowledge, paper IV is the first study to compare speech assessments performed on adults treated for UCLP and non-cleft controls by naïve listeners, SLPs and self-ratings by patients and controls and in addition, to compare self-ratings of patients with those of non-cleft controls

The speech in adults treated for UCLP assessed by SLPs was found in paper II to be good/fair. In paper IV, the same group of patients was also assessed by naïve listeners, representing people who the patients interact with in their daily life. The naïve listeners were well able to differentiate between cleft patients and non-cleft controls, as none of the speech recordings from controls was classified as coming from a patient. They were also able to identify cleft-associated speech abnormalities, as there were significant differences between the ratings of speech among patients and controls. The current findings confirm that speech may affect the way individuals treated for CLP are perceived by other people.

Significant differences between the ratings of speech by naïve listeners and SLPs were expected due to the difference in knowledge and experience in evaluating the characteristics of cleft palate speech. The naïve listeners did use the highest score for “speak through the nose” while the SLPs never used the highest score for “hypernasality”. This is in accordance with a study by Lewis et al. [2003] where untrained listeners rated hypernasality higher than SLPs. This may be explained by the experience among SLPs including a wider spectrum of speech abnormalities and severe cases. It is interesting to note that even though the naïve listeners used the higher rating scores for “speak through the nose”, naïve listeners rated fewer of the patients’ recordings to actually come from a patient compared to the SLPs. A reason for this may be that SLPs perceive the more subtle speech abnormalities typical to the CLP population.

The positive correlation between ratings by naïve listeners and SLPs in the current study is in accordance with some previous studies that used assessments made by naïve listeners [Starr et al., 1984, Tonz et al., 2002, Brunne-gard et al., 2009, Nyberg and Havstam, 2016]. The high correlation between the ratings of the naïve listeners and the SLPs indicates that the experts’ assessments of speech may also be representative of the people who the patients

meet in their daily life. Our study indicates that the SLPs' evaluations can be considered relevant in assessing speech also from a broader perspective.

In the current study, patients rated their satisfaction with speech in comparable levels with previous studies on patients treated for CLP [Broder et al., 1992, Hunt et al., 2006, Oosterkamp et al., 2007, Havstam et al., 2008, Van Lierde et al., 2012, Bickham et al., 2017]. Additionally, patients rated lower on satisfaction with speech compared to controls. This is in agreement with a study by Hunt et al. [2006] where adolescents treated for CP±L were less satisfied with speech compared to controls. Opposite results were presented in a study by Van Lierde et al. [2012] where children as well as their parents had similar high satisfaction rates with speech among both patients and controls. In addition, the study by Oosterkamp et al. [2007] found no differences in quantitative measures of satisfaction with speech between patients and controls, however the patients expressed more concerns about their speech.

The correlations between self-ratings of speech and SLPs' ratings were low in the current study. This is in concordance with earlier studies of self-ratings and experts' ratings for cleft populations [Havstam et al., 2008, Mani et al., 2010b]. Nevertheless, self-reported outcomes are considered important as these are known to be associated to quality of life [Mani et al., 2013, Bickham et al., 2017]. A study by Bickham et al. [2017] showed that children treated for CLP who perceived more difficulty with speech also experienced worse scores on depression scales compared to those with less speech impairment. The same study also showed that patients whose speech was rated lower by the SLPs reported higher levels of anger, more depression, and more difficulty with peer relationships. Speech is one of the most important means to communicate and one's self-perception of speech may affect the ability and self-confidence to speak. These results should increase the awareness among health care personnel of speech abnormalities and self-perception in adult patients treated for UCLP.

## Strengths and weaknesses

The group of patients involved in the thesis was a relatively homogeneous group of UCLP patients in contrast to many previous studies including groups with patients of mixed cleft types. One of the main aims of the thesis was to compare outcome after two different surgical methods. Great differences at baseline would have affected the outcome more than the surgical method itself. Therefore, the fact that all included patients were Caucasians, non-syndromic and had complete unilateral clefts was important in reducing the confounding by these factors. On the other hand, the homogeneous sample limits the possibility of generalizing the results to other cleft types or ethnic groups.

A control group was included for comparison, which strengthens the study. There is a considerable variation in the variables studied: subjective nasal

symptoms, nasal configuration, voice and speech as rated by SLPs, naïve listeners, the patients themselves and the non-UCLP population. Assessment of non-cleft controls, using the same methods for comparison, is essential when interpreting the relevance of any result in patients with clefts.

The current thesis studied patients 35 years after initiation of treatment which can be considered a very long time. Information about treatment was collected retrospectively and depended on the accuracy and detail of the medical records available. This limits the ability to control data and there is a higher risk for missing data than in prospective studies. However, at UU, the cleft team has evaluated, and followed up cleft patients since 1960 and this allowed for a lot of the data to be collected. Over time, methods and routines may change. However, the surgical methods and cleft care protocols at UU are relatively well documented.

Patients were invited to participate in the study long after the regular team follow ups had stopped. Twenty-four percent of the 109 invited patients did not participate in the study. There is a risk for selection bias if participating patients differed from the non-participating. It is possible that patients with less favorable outcome would be more inclined to participate in order to get a new assessment and or further treatment. The opposite is also possible if the patients with less favorable outcome/ large burden of care would be tired of previous treatment and declined participation for this reason. However, the participating and non-participating patients did not differ from each other with respect to surgical procedures, gender distribution or age at the time of operations.

A large proportion of the variables analysed in the current thesis are generated from ratings by various scales. The scales used were dichotomous scales, ordinal scales and VAS. It is not yet clear what type of scale is most valid and reliable in assessing psychometric measures in medical research [Guyatt et al., 1987, Harland et al., 2015], also including perceptual cleft speech evaluation [Castick et al., 2017] and perceptual voice evaluation [Yu et al., 2002]. In paper II, the ordinal scales of the SVANTE protocol [Lohmander A et al., 2005] was used for speech evaluation by SLPs. The Cleft Audit Protocol for Speech-Augmented (CAPS-A) [John et al., 2006] is another example of a protocol that uses ordinal scales. For voice evaluation in paper III, the SVEA protocol was used including ratings on VAS. Comparisons between VAS and ordinal scales in perceptual judgement of cleft speech showed similar results for both scales indicating that both types of scales may be used. Regarding voice, a study by Yu et al. [2002] showed that compared with a conventional ordinal scale, the ratings on VAS correlated better with acoustic, aerodynamic, and physiologic parameters of voice evaluation.

It is important that protocols and questionnaires used in scientific research have a high reliability and validity [Kimberlin and Winterstein, 2008]. A limitation in the current thesis is that not all of the protocols and questionnaires used had been formally validated. For example at the time of the study there

was no validated questionnaire for evaluation of nasal symptoms prepared to suite the Swedish speaking population. The questionnaire used in paper I was developed by professor Björn Petruson, an otorhinolaryngologist in Gothenburg in the 1980s. It was accepted by the Swedish Rhinological Society for research purposes and some questions were added to that questionnaire by our group. A validated Nasal Obstruction Symptom Evaluation (NOSE) Scale was published in 2004 and has been frequently used in the United States [Stewart et al., 2004]. The majority of the questions of the NOSE scale and the questionnaire used in paper I overlap. However, for international comparisons it would have been more advantageous to use the NOSE scale.

There is a risk of over-reporting nasal symptoms due to patient's concerns of the facial aesthetics or underreporting due to adaptation during life. Nasal inspection may depend on the skill of the examiner and other factors not related to the nasal findings as there is no standardised protocol for clinical examination of the cleft nose. The examiner could not be blinded for if the subject is a patient or a non-cleft control. The inter- and intra-rater reliability of the nasal examination was not evaluated.

In the literature, heterogeneity in methodology, mixed patient groups and non-unified surgical techniques make comparison of speech results of different studies difficult. To facilitate comparisons, several quality requirements have been proposed [Lohmander, 2011]. Paper II complies with most of these requirements: speech assessment from blinded recordings of speech, multiple raters including external raters with reliability measures reported and utilization of standardized material for speech evaluation.

A more complete evaluation of speech would have included systematic phonetic testing, narrow transcription and acoustic analysis. For example quantitative measurement such as nasometry to evaluate hypernasality, but this was not available at UU at the time of the study. Instrumental assessment of velopharyngeal function with video-nasopharyngoscopy or videofluoroscopy could also have added useful information.

As the study was not prospective, several of the factors potentially affecting speech outcome could not be controlled for. The retrospective data on speech therapy interventions and audiometry data in the medical journals was limited and orthodontic status infrequently reported. The patients came from a large geographical region and audiometry data in the UU medical journals was sparse much due to the otological care of CLP patients is traditionally provided by the otolaryngology clinics at the local hospitals and not at UU. Audiometries of the adult patients at the time of the study would have added important information but was not feasible for logistic reasons. We compensated this by studying the variables related to current hearing status: occurrence of tympanic membrane pathology, patient reported satisfaction with hearing and the use of hearing aid. However, this can obviously not substitute audiometry data.

A potential limitation of the present thesis is also the relatively large age range of the participating patients. It is unclear how much speech variables change with age in young to middle-aged adults, but since the anatomical structures of the cleft affected area can be considered fully-grown at 20 years of age, it is unlikely for speech to be affected by age in the patients of the current study.

Due to the retrospective nature of the study it is difficult to estimate the impact of other surgery-related factors which may have influenced the speech results. Efforts were made to control for as many of these factors as possible. Nevertheless, the conclusion as for the impact of two surgical protocols (one- or two-stage) is challenging to interpret. The comparisons in paper II should be interpreted with caution: the experience and skill of the surgeon may influence the outcome as much as the timing or method of surgery [Shaw et al., 1992]. Surgical skills develop and techniques may be modified over time and the surgeons in the current thesis were not calibrated for the surgical method. However, the number of surgeons was limited to four and all of these had relevant surgical training and worked at the same hospital. In future prospective international multicentre studies – like the ongoing Scandleft [Lohmander et al., 2009] – these factors can be better controlled for, which increases the chances of results with a higher level of accuracy.

The third study had the following limitations. The quality of audio signal of voice recordings was not analysed specifically prior to the perceptual voice assessments. If the audio signal is of inferior quality this may affect the judgment. However, the skilled SLPs were experienced to evaluate the recordings under the current circumstances. Standardized microphone-to-mouth distance and calibration to sound pressure level could have improved the quality of the acoustic signal. A broader voice assessment in terms of vocal capacities such as determination of a voice range profile, maximum phonation time would be a merit. However, these data were not available for the study population.

Paper III used no specific method for acoustic detection of vocal fry as for example used in a recent study [Abdelli-Beruh et al., 2016] as this was beyond the scope of the thesis. When perceptually evaluating speech and voice there is always a risk of other speech abnormalities affecting the judgment of voice and vice versa. The SLPs were therefore asked to ignore these other characteristics when judging voice. It is unknown how the subspecialisation of SLP in voice or cleft speech affects the judgments of voice quality.

No laryngoscopy was performed in this study. However, the low ratings on all voice variables indicate a low probability of laryngeal pathology. Patient reported voice handicap can be valuable when reporting voice outcome in the population of patients treated for cleft palate [Cavalli, 2011] and could have added validity to study III.

One SLP rating voice had fair intra-rater reliability according to Cicchetti [1994] while the other SLP had an excellent level. As the number of duplications was low, this may affect the intra-rater reliability to a great extent. With

a larger number of duplicated ratings this intra-rater reliability would probably have been higher. Specific calibration training for the SLPs before the study, would most probably have increased the inter- and intra-rater reliability. However, this was not performed as no such voice evaluation training program was available at the time of the study. Another alternative to improve rater reliability would have been to use consensus amongst raters prior to undertaking perceptual evaluation through discussion and agreements amongst raters.

A detailed presentation on lifestyle factors, which may influence voice, is presented in table 2/paper III. There are of course other factors potentially affecting voice quality where data was incomplete or not available for the participants such as vocal load and life style habits concerning voice use.

In study IV, gender was not evenly distributed within the groups of raters. The four SLPs were all females. The group of naïve listeners consisted of 71% women (10/14). Whether this affects the ratings is unknown. Furthermore, the rating forms of the naïve listener and the questionnaires to the patients were not validated. The naïve listeners and the SLPs did not have any calibration or training sessions prior to the ratings. Calibration or training of listeners can increase rater agreement [Oliveira et al., 2016]. For some of the variables and naïve listeners an intra-rater reliability could not be calculated due to absence of variability for the variable. This could probably have been avoided if more of the recordings had been rated twice by the raters in addition to the 15 duplicated recordings in this study. The possible effect of the order of recordings presented to the listeners was not evaluated. Recordings of patients and controls were in mixed order and the order was the same for all raters. However, in a study by Brunnegard et al. [2009] the order of recordings presented to the untrained listeners did not change the ratings significantly.

It is challenging to compare assessments made by different groups of raters when the outcome cannot be on identical scales due to different background/experience of the raters. In paper IV, we used similar variables assessing the speech outcomes for each group of raters. To achieve comparable rating scales a translation of the professional terms and conditions was made into phrases expressing the conditions in laymen terms as in the study by Brunnegard et al. [2009]. To make a good comparison between ratings of different groups of raters or scales for outcome of cleft speech, the rated speech material should cover the full range of the rating-scale and have an even distribution of speech abnormalities. A good example of this is the study by Castick et al. [2017]. This was not completely the case in the paper IV where speech outcome from consecutive cases of UCLP was evaluated. According to the ratings of the SLPs, the speech abnormalities did not cover the full range as the most extreme ratings of speech abnormalities were missing and ratings were more concentrated on the lower range of the scale. This may have affected the ratings by naïve listeners. However, study IV had a relatively large group of study participants which should at least partly compensate for this.

## General discussion

### Evaluation of treatment outcome in CLP

CLP is a challenging area for scientific research partly due to the low number of patients and the long time needed before final results can be evaluated. Long term outcome in the adult individual is at least 18-20 years after primary palate surgery.

The current thesis evaluates outcome after treatment given many years earlier. Studies performed in a retrospective manner are limited with respect to the number of factors that can be analyzed and controlled for. There is still a low scientific evidence for current practice in treatment and follow-up of children and adults with clefts as stated in a report from the Norwegian Institute of public health [Forsetlund et al., 2009]. Prospective randomized controlled studies (RCT) can provide a higher level of evidence than retrospective studies. To be able to evaluate a sufficient number of individuals, collaboration between different cleft-care centers is necessary.

Multicentre prospective international studies are needed regarding the outcome of cleft palate treatment, and some studies have already been carried out: Eurocleft, Americleft and Scandcleft. Recently data from the international multicentre study Scandcleft of at 5 years follow-up was published. The study compares treatment outcome of four different protocols for palatal closure. A common protocol (A) with lip and soft palate closure at 3-4 months and hard palate closure at 12 months of age, is compared to three other protocols: (B) 'Long delay hard palate closure': Lip and soft palate closure at 3-4 months and hard palate closure at 36 months; (C) 'Simultaneous hard and soft palate closure': Lip closure at 3-4 months, hard and soft palate closure at 12 months; and (D) 'Early hard palate closure with vomer flap': Lip closure at 3-4 months combined with a single layer closure of the hard palate using a vomer flap, soft palate closure at 12 months.

Regarding maxillary growth, results show no significant differences in dental arch relationships [Heliövaara et al., 2017] or occlusion [Karsten et al., 2017] between the methods. Regarding speech, there were no significant differences between the methods regarding velopharyngeal competence or hypernasality [Lohmander et al., 2017], but scores for percentage of correct consonants for method A was higher compared to B and burden of care (number of secondary pharyngeal surgeries, fistulae and speech therapy visits) differed between methods [Willadsen et al., 2017]. Hopefully the Scandcleft project will continue to follow the cohort and report outcome until adulthood to add valuable information about long term outcome in cleft care.

## Patient reported outcome in cleft research

When evaluating outcome after treatment of CLP it is important to cover all aspects. Focus has historically been on esthetics and function but a growing number of studies now focus on the psychosocial effects of clefts [Hunt et al., 2005, Feragen and Stock, 2017] and health-related quality of life (HRQoL) [Sischo et al., 2017]. Objective evaluations by clinicians have traditionally been the primary way to assess outcomes in CLP care, with little patient input.

However, as the goal of treatment is to improve the patients' health and quality of life (QoL), the patients' own perspective is also needed. The World Health Organization's international consensus meetings on craniofacial anomalies 2000 and 2001 called for outcome measures that matter to people, and with relevance in everyday life [WHO, 2001]. Such patient-reported outcomes (PROs) needs to be standardized, and should focus on psychological, QOL measures and economic outcomes [Mossey et al., 2009].

Recently an instrument for PROs have been developed especially for evaluation of outcomes of cleft care: the CLEFT-Q [Wong Riff et al., 2017]. The CLEFT-Q has been validated [Tsangaris et al., 2017b] and so far been translated from the English language to Spanish [Tsangaris et al., 2017a]. Hopefully translations to other languages, including Swedish, will follow.

The outcomes in the present cohort of patients treated for UCLP have previously been evaluated considering HRQoL with the Short Form-36 (SF-36) questionnaire [Mani et al., 2010a]. HRQoL of the adults treated for UCLP was similar to that of the norm population, but men were affected more negatively by UCLP than women in emotional role function, and younger patients were more negatively affected than older patients. In another study of the same population, with the aim to identify factors related to HRQoL and satisfaction with nasal appearance, there was an influence of gender and infant cleft width [Mani et al., 2013]. Additionally, there was a correlation between nasal function impairment measured with rhinomanometry and decreased physical health as measured by SF-36. In the current thesis patient reported outcome was used for nasal symptoms (paper I), hearing (paper II) and speech (paper IV). These questionnaires were not validated and this has to be taken into account when interpreting the results.

## Clinical implications

In paper I a relatively high proportion of the patients treated for UCLP had nasal symptoms which could have a negative effect on QoL and daily life activities. This underlines the importance of nasal form and function for patients treated for UCLP and calls for an increased awareness of nasal problems. A standardized evaluation of nasal form and function including self-evaluated symptoms and the possibility for evaluation with objective methods such as rhinomanometry [Mani et al., 2010b] and computer tomography [Friel et al.,

2015, Massie et al., 2016] could help caregivers to select treatment more adequately and to better evaluate outcome of treatment of nasal airway problems. This would hopefully help patients treated for UCLP to receive good and individualized treatment for their nasal problems.

The prevalence and degree of speech abnormalities were rather low and similar in patients treated for UCLP with one- or two-stage palate closure (paper II). Individuals born with CLP are at risk for developing speech impairment. Regular monitoring of speech function by SLPs during team follow up is an important aspect of care for optimal speech development. Regular follow ups give the possibility of early intervention if difficulties with speech occur and probably aids in the prevention of compensatory speech errors. The current thesis showed that speech was relatively good in the majority of the treated patients, which is important information for patients under treatment, parents and caregivers, in order to be able to give an appropriate level of expectations on speech outcome after treatment.

Paper III revealed that adult patients treated for UCLP with low occurrence of speech abnormalities related to VPI after cleft team treatment and follow up, seem to have normal voice characteristics. This is important when informing parents and patients about what to expect considering voice and cleft when patients grow up to adulthood. Regular follow up of speech in the care of individuals born with CLP include evaluation of voice quality by the SLPs.

In paper IV there was a relatively good correlation between professional and untrained listeners' ratings of speech of patients treated for UCLP. This indicates that the speech ratings by SLPs also may be representative of people that patients are exposed to outside the healthcare system. The patients' ratings of their own speech did not correlate well with SLPs' ratings. The patients' self-ratings reflects the patients' perspective of what is relevant for them but are influenced by factors not directly associated with speech, for example psychosocial factors. This should be taken into consideration when assessing speech after CLP treatment and in the discussions and decisions on further treatment.

## Future Perspectives

The current thesis has studied different aspects of outcome in adults after treatment of UCLP. Previous studies have shown that the nasal airway is more narrow, especially on the cleft side. Paper I in this thesis found that patients had more nasal symptoms and abnormalities at nasal inspection than non-cleft individuals. The relation between the nasal symptoms and objective nasal function has also been studied among the same patients and smaller area and volume of the anterior nasal cavity correlated with more nasal obstruction an increased wish for correction of the nasal function [Peroz et al., 2017]. It would be interesting to study if the nasal symptoms correlate with the patient's quality of life.

The nasal airway is affected by the anatomical features of the cleft, with lack of tissue and hypoplasia of the maxilla [Dec et al., 2013]. Hopefully, in the future, with tissue engineering [Moreau et al., 2007] the lack of tissue can be compensated for with improved functional and aesthetic treatment result. With the means of stem cells, new tissues can be created, although the amount of tissue that can be created is currently limited to small grafts [Bajestan et al., 2017]. The mechanic strain in the tissues around the cleft also has to be considered if tissue engineering is considered [Brouwer et al., 2015].

In the future, imaging technologies will probably play an even greater role in diagnostics and treatment planning than today, both for primary and secondary surgery of the cleft deformity. The development in imaging technologies during the last decades is promising both regarding the quality and possibilities of documentation of the anatomic features and functional treatment outcome. With 3D imaging in radiological [Farzal et al., 2016] and photographic (stereophotogrammetry) methods [Al-Rudainy et al., 2017] the cleft nasal deformity before and after surgery can be objectively evaluated. With 3D printed scaffolds, implants could be tailored individually to the patient's cleft defect [Hixon et al., 2017].

Individuals born with a cleft are at risk of developing speech impairment. The current thesis confirms earlier studies which showed that speech impairment may persist into adulthood among individuals treated for UCLP [Farzaneh et al., 2008, Lohmander et al., 2012]. The primary palatal closure is reported to provide acceptable velopharyngeal function in about 70% of individuals after different surgical protocols [Lohmander et al., 2017, Naran et al., 2017]. Secondary procedures for VPI can improve speech in approximately 70% of individuals that have insufficient velopharyngeal function after primary surgery. However, there is still a lack of consensus in the literature to guide procedure selection for patients with VPI [Blacam et al., 2017] and with secondary speech surgery there is a risk for additional airway narrowing and obstructive sleep apnea [Yamashita and Trindade, 2008].

If the primary palate closure would be sufficient for all patients, secondary surgery would not be needed. Is it possible to find an optimal protocol for primary palatal closure and treatment? The current thesis found no difference in speech outcome between individuals treated with two different surgical protocols. Prospective multicenter studies are needed to further evaluate the effect of surgical techniques for palatal closure, timing as well as the adjunct health care on speech outcome. The technique for closure of the soft palate has improved with increased knowledge about velopharyngeal function and anatomy [Shi, 2013], and can hopefully further improve based on results from continuing studies of velopharynx in individuals with and without cleft [Perry et al., 2018]. Perhaps the surgical method can be more individualized to the anatomical conditions of the patient.

The quality of outcome is also dependent on large enough treated number of CLP of patients in a clinic. The centralization with dramatic decrease of the

number (57 to 11) of centers treating cleft palate in the UK improved speech outcome [Sell et al., 2015].

Perceptual speech evaluation is the gold standard method for evaluation of cleft palate speech. According to current understanding, in evaluation of speech outcome for research purposes, blinded assessments of speech should be performed by at least two trained SLPs. This approach is resource consuming and a recent study found that if the raters are well calibrated, the rating by one SLP may be sufficient [Ahl and Harding-Bell, 2018]. Even if raters have acceptable values for inter- and intra-rater reliability and use validated rating scales, perceptual speech analysis remains a subjective method and needs to be complemented with objective methods. There are objective methods for evaluation of hypernasality like the nasometry [Larangeira et al., 2016] and acoustic measures [Golabbakhsh et al., 2017], or those measures combined in a multiparametric method like the Nasality index [Bettens et al., 2016]. Objective alternatives for the other relevant speech variables are needed. Automated cleft speech evaluation using speech recognition may be a possibility to reduce bias [Vucovich et al., 2017] but further research is needed.

The use of patient reported outcome in cleft care has been advocated [Mossey et al., 2009]. The current thesis used patient reported outcome to some extent. It would be interesting to further study the relationship between self-ratings of speech in the current study and HRQoL in the form of SF-36 from the same population. The use of validated PROs in both research and clinical work is needed and hopefully the newly developed CLEFT-Q [Tsangaris et al., 2017b] will be available also in Swedish and a variety of other languages to make international inter-center comparisons possible. In clinical care and research, documentation of outcome is important. However, a large number of questionnaires and other evaluations could add to the burden of care for the patients, which needs to be taken into consideration when choosing outcome measures.

An important finding was that the voice quality in adults treated for ULCP was not different from that found in individuals without cleft. The relation between dysphonia and VPI-related speech abnormalities is still unclear. Further studies is needed to evaluate the possible relation between dysphonia and VPI in individuals treated for CLP. Further studies on voice in individuals treated for CLP should include perceptual ratings on validated voice scales and acoustic voice analyses in addition to patient reported voice handicap. Multiparametric models for acoustic voice analysis like the Acoustic Voice Quality Index (AVQI) [Barsties and Maryn, 2016] would be interesting to use in this context.

# Conclusions

The main conclusions are:

Adult individuals treated for UCLP had more subjective nasal symptoms and more signs of nasal obstruction at nasal examination compared to non-cleft controls. There were no significant differences regarding subjective nasal symptoms or findings at nasal examination in individuals treated with palatal closure in one or two stages. (paper I)

The number of adult individuals treated for UCLP with affected speech was low, but it was higher than the number of individuals without cleft. There were no significant differences regarding speech variables in individuals operated with palatal closure in one or two stages. (paper II)

Voice characteristics among adults treated for UCLP were not different from those in individuals without cleft. Findings on VPI related speech abnormalities and their correlation to dysphonia were not conclusive. The surgical method for palatal closure was not associated with voice characteristics. (paper III)

Adults treated for UCLP during childhood generally rated their speech as fairly good. However, these adults rated their speech as worse and their satisfaction with speech was lower compared to the non-cleft cohort. (paper IV)

The agreement on speech variables between naïve listeners and expert listeners were relatively good. However the agreement between these two rater-groups respectively and self-assessment of speech was lower. (paper IV)

# Sammanfattning

## *Enkelsidig Läpp-, käk-, och gomspalt – tal, röst och nässymptom hos vuxna*

Läpp-, käk-, och/eller gomspalt (LKG) är den vanligaste medfödda missbildningen i huvud-hals området. Det föds i Sverige ca 200 barn med LKG per år dvs ca 2 per 1000 födselar. Spalten kan ha olika utbredning och i ca en tredjedel av fallen finns spalten endast i gommen, i en fjärdedel i läpp och käke. Resten, dvs knappt hälften är genomgående LKG som kan vara antingen enkel eller dubbelsidiga. LKG kan medföra både utseendemässiga och funktionella avvikelser och svårigheter med bland annat tal, sväljning, bett, näsandning och hörsel. Behandlingen innebär både kirurgisk slutning av spalten och icke kirurgisk behandling av bl.a. tal och tänder. Behandling och uppföljning via ett multidisciplinärt team pågår från födsel upp till ca 20 års ålder. Målet är normaliserat utseende och funktion.

Trots behandling kan det dock finnas kvarstående utseendemässiga och funktionella avvikelser relaterade till spalten. Hos patienter behandlade för enkelsidig LKG, har tidigare undersökningar visat att näsan är trängre speciellt på spalt sidan, jämfört med personer utan spalt. Talet kan också vara påverkat, bl.a. om mjuka gommen inte förmår att sluta tätt upp mot näshålan vid tal och sväljning. Detta kallas ”gominsufficiens” eller ”velofarynxinsufficiens” (VPI). VPI innebär att luften läcker upp i näsan och all talet låter hypernasalt för att röstklängen ekar i näsan. Ca en tredjedel av personer med LKG kan ha VPI trots operation av spalten. Om VPI är tillräckligt uttalad kan man gå vidare med talförbättrande operation (svalglambå). Det är fortfarande oklart vilken operationsmetod och operationsålder som ger de bästa chanserna till välfungerande tal. Rösten kan också vara påverkad (t.ex. heshet) vid LKG och det har föreslagits vara kopplat till VPI.

Målen med denna avhandling var att utvärdera näsfunktion, tal och röst hos vuxna individer behandlade för LKG i barndomen.

Samtliga 109 patienter födda 1960-1987 med enkelsidig LKG, behandlade vid Akademiska sjukhuset i Uppsala kallades för uppföljande undersökning anordnad för forskningsstudien. Åttiotre av dessa patienter samt en åldersmatchad kontrollgrupp genomgick undersökning innefattande klinisk undersökning av öron-näsa-hals, näsfunktionsundersökningar och röstinspelning. Alla deltagarna fyllde i frågeformulär och gav sitt skriftliga godkännande till att

delta. I delarbete I ingick 83 patienter och i delarbete II, III och IV ingick 73 patienter.

I delarbete I fann vi att egenskattade näsbesvär som t.ex. nästäppa, och näsundersökningsfynd är mer uttalade hos tidigare behandlade patienter jämfört med personer utan LKG. Dock sågs ingen skillnad mellan patienter opererade med gomslutning med en eller två seanser i egenskattade besvär eller undersökningsfynd. Vi fann inget tydligt samband mellan nässymptom och näsundersökningsfynd. Det fanns inga skillnader i symptom eller näsundersökningsfynd mellan patienter opererade med gomslutning i en eller två seanser.

Delarbete II undersökte förekomst av talavvikelser hos tidigare behandlade patienter och kontroller. Fyra logopedier gjorde lyssnarbedömning av talet från anonymiserade ljudinspelningar enligt Svenskt Artikulations- och Nasalitetstest (SVANTE). Bland patienterna hade 7 (10%) hypernasalitet, 12 (16%) hörbart luftflöde genom näsan vid tryckstarka konsonanter, 5 (7%) artikulationsavvikelse, en (2%) hade glottala förstärkningar (artikulation med struphuvudet) och 1 (2%) nedsatt förståelighet i talet. Ingen av personerna i kontrollgruppen hade dessa talavvikelser. Det fanns inga skillnader avseende talet mellan patienter opererade med olika gomslutningsmetoder.

I delarbete III gjordes undersökning av röstkvalitet hos tidigare behandlade patienter och kontroller. En lyssnarbedömning gjordes enligt Swedish Voice Evaluation profile (SVEA) av två logopedier, från anonymiserade ljudinspelningar. Det gjordes också en akustisk röstanalys. Det fanns en låg förekomst av röstavvikelser hos patienter och kontroller. Förekomsten av röstavvikelser var inte högre i patientgruppen. Röstknarr var något vanligare hos kontrollpersonerna.

I delarbete IV bedömdes talet av vanliga personer, otränade i att lyssna på talinspelningar. Deras bedömning jämfördes med logopedernas talbedömningar och patienters och kontrollers bedömning av sitt eget tal. De otränade lyssnarnas och logopedernas bedömningar överensstämde relativt väl. Patienternas egenbedömning av talet stämde mindre väl överens med de naiva lyssnarnas och logopedernas bedömningar. Patienterna var mindre nöjda med sitt tal än kontrollpersonerna.

Sammanfattningsvis visar detta avhandlingsarbete att vuxna patienter efter behandling för enkelsidig gomspalt har mer nässymptom, näsavvikelser, talavvikelser och är mindre nöjda sitt tal jämfört med personer utan spalt. Röstkvaliteten verkar inte vara påverkad av spalten. Otränade lyssnare och logopedier och patienter bedömde talet olika. Dock ter sig talet hos dessa patienter vara relativt bra jämfört med många andra centra som behandlar LKG.

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