Unilateral Cleft Lip and Palate

Quality of Life and Nasal Form and Function among Adults

MARIA MANI
Dissertation presented at Uppsala University to be publicly examined in Skoogsalen, Uppsala University Hospital, entrance 79, Uppsala, Friday, June 11, 2010 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract

Unilateral cleft lip and palate (UCLP) is a craniofacial malformation with functional and aesthetical impact on the face and the upper airways. The aims of the current thesis were to evaluate Quality of life (QoL) in adults treated for UCLP (I), to objectively evaluate nasal form and function and to search for possible differences in residual nasal deformity and impairment of function between patients operated according to one-stage and two-stage palatal closure (II) as well as to evaluate the relationship between professional and lay rating and patient satisfaction with nasolabial appearance (III) and to identify factors associated with lower levels of QoL and less satisfaction with nasal appearance among adults treated for UCLP (IV).

Analyses of data from a homogenous population of UCLP patients treated at Uppsala University Hospital form the basis of this thesis. The mean follow-up time after primary surgery was 35 years (20-47 years) and participation rate was 79% (n=86). An age and gender matched control group of 68 people without clefts were evaluated according to the same protocol. The evaluation protocol included the Short Form 36 questionnaire (SF-36), rhinomanometry, acoustic rhinometry, odor test, peak nasal inspiratory flow test and photographs of faces. For the SF-36 data, age- and gender-matched norm data of 1385 people from the Swedish population were used.

Unilateral cleft lip and palate affected QoL differently depending on gender and age of the patient. Younger patients were affected more negatively than older patients in several subscales. However, except for lower values in the Mental Health subscale, QoL was similar among UCLP patients and norm data. Objectively measured nasal function was extensively affected among adults treated for UCLP. No difference in impairment of nasal function was found between one-stage and two-stage palatal closure protocols on the cleft side. Judgment of nasolabial appearance differed between professionals, lay people and patients. Large infant cleft width was associated with less satisfaction with nasal appearance and male gender was associated with lower levels of mental QoL. Correlation between high nasal breathing resistance and low levels of physical QoL was found. In conclusion, this thesis provides a platform for future research for optimal evaluation of cleft treatment outcome.

Keywords: unilateral cleft lip and palate, quality of life, SF-36, nasal function, nasal breathing, nasolabial appearance, cleft width, long-term results

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To my princes and my king
Cover picture and illustrations: cleft malformation as interpreted by the author (Maria Mani).
List of Papers

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


IV Mani M, Reiser E, Andlin-Sobocki A, Skoog V and Holmström M. Factors Related to Quality of Life and Satisfaction with Nasal Appearance in Patients Treated for Unilateral Cleft Lip and Palate. *Manuscript.*

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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>Acoustic rhinometry</td>
</tr>
<tr>
<td>BP</td>
<td>Bodily pain</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CL</td>
<td>Cleft lip</td>
</tr>
<tr>
<td>CLP</td>
<td>Cleft lip and palate</td>
</tr>
<tr>
<td>CP</td>
<td>Cleft palate</td>
</tr>
<tr>
<td>Exp</td>
<td>Expiration</td>
</tr>
<tr>
<td>GH</td>
<td>General health</td>
</tr>
<tr>
<td>Insp</td>
<td>Inspiration</td>
</tr>
<tr>
<td>MCA-1</td>
<td>Minimal cross sectional area, anterior part of the nose (0 - 2.2 cm from nostril rim)</td>
</tr>
<tr>
<td>MCA-2</td>
<td>Minimal cross sectional area, posterior part of the nose (2.2 - 5.4 cm from nostril rim)</td>
</tr>
<tr>
<td>MCS</td>
<td>Mental cluster scale</td>
</tr>
<tr>
<td>MH</td>
<td>Mental health</td>
</tr>
<tr>
<td>NARExp</td>
<td>Nasal Airway Resistance during Expiration</td>
</tr>
<tr>
<td>NARInsp</td>
<td>Nasal Airway Resistance during Inspiration</td>
</tr>
<tr>
<td>PCS</td>
<td>Physical cluster scale</td>
</tr>
<tr>
<td>PF</td>
<td>Physical function</td>
</tr>
<tr>
<td>PNIF</td>
<td>Peak nasal inspiratory flow</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RE</td>
<td>Emotional role function</td>
</tr>
<tr>
<td>RM</td>
<td>Rhinomanometry</td>
</tr>
<tr>
<td>RP</td>
<td>Physical role function</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SF</td>
<td>Social function</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short form 36</td>
</tr>
<tr>
<td>SOIT</td>
<td>Scandinavian Odor Identification Test</td>
</tr>
<tr>
<td>UCLP</td>
<td>Unilateral cleft lip and palate</td>
</tr>
<tr>
<td>Vol-1</td>
<td>Nasal volume, anterior part (0 - 2.2 cm from nostril rim)</td>
</tr>
<tr>
<td>Vol-2</td>
<td>Nasal volume, posterior part (2.2 - 5.4 cm from nostril rim)</td>
</tr>
<tr>
<td>VT</td>
<td>Vitality</td>
</tr>
</tbody>
</table>
Introduction

Cleft care and cleft research have been of interest to mankind for long. The multiple aspects and concerns of this group of patients mean that, although a considerable amount of work has been done within the field, the remaining questions regarding this complex malformation are numerous. The studies that form the basis of the current thesis represent an effort to add to the scientific knowledge in this field.

Embryology and classification

During the fourth to ninth week of pregnancy the most important developmental steps of the face take place. By the eighth week the face is fully formed except for the palate, which is not completed until another three weeks. The face is formed from fusion of five different prominences (the paired maxillar and mandibular and the single nasofrontal prominences). Facial clefts have been considered a result of failure in this normal fusion and consequent obliteration of the grooves between the facial prominences. The obliteration is achieved by mesodermal migration and merging. The failure leads to an abnormal persistence of a groove, which produces a cleft (Stark and Kaplan, 1973). Depending on the time-point of interference with embryonic development, different clefts arise. Typical facial clefts include clefts of lip and/or palate, while median and oblique clefts are classified as atypical. The cleft can be unilateral, bilateral, complete or incomplete (Millard, 1976). Examples of different clefts are presented in Figure 1.

The nose arises from the nasal placodes during the fourth week of pregnancy. The nasal placodes are local thickening of the surface ectoderm on the lateral surface of the head of the embryo arising from the nasofrontal prominence. Hypertrophy of the tissue surrounding the nasal placodes creates nasal pits that divide each placode into medial and lateral nasal processes. The medial processes become the septum, the philtrum, and the premaxilla of the nose; whereas the lateral processes form the sides of the nose. The septum continues to grow posteriorly, reaching the palatine structures. Through this fusion the nasal and oral cavities as well as the right and left nasal chambers are formed. Chondrification and ossification of the nasal septum follows. During the sixth week of gestation, lateral nasal wall
development occurs. As the nasal cavity grows, ectodermal folds give rise to the superior, middle, and inferior concha (Daniel and Letourneau, 1988; Lanza et al., 1991).

Figure 1. Various cleft types; A) cleft lip; B) complete unilateral cleft lip and palate; C) bilateral cleft lip and palate; D) isolated cleft palate (printed with the kind permission of respective patient or parents).

The upper lip is derived from medial nasal and maxillary prominences. Failure of fusion between these at five weeks' gestation results in cleft lip (Wantia and Rettinger, 2002). Cleft lip usually occurs at the junction between the central and lateral parts of the upper lip on either side. The cleft may affect only the upper lip, or it may extend more deeply into the maxilla and the frontal, hard palate (i.e. primary palate), and thus the floor of the nose. Cleft of the primary palate always includes cleft lip and cleft of the alveolus. In contrast to this, cleft of the soft palate (i.e. secondary palate) can appear as a separate entity or combined with cleft of the primary palate and lip. This is a consequence of the development of the secondary palate by fusion of secondary palatal prominences beginning during eight weeks' gestation and continuing usually until twelve weeks' gestation. When fusion of secondary palatal prominences is impaired as well, the cleft lip is combined with cleft palate, forming the cleft lip and palate malformation, to which the patients of the present investigation belong (Wyszynski, 2002;
Bernheim et al., 2006). Schematic classifications have been developed over the years and the “striped Y” of Kernahan is internationally accepted, Figure 2 (Kernahan, 1971). This system is used for classification and registration of the patients at Uppsala University Hospital (Jakobsson, 1990).

Figure 2. Striped Y-classification of clefts. The letters indicates the cleft side and the extent of the cleft formation. For example a complete cleft of the lip and palate on the right side would be coded: ABCDIJK.

Etiology and incidence

Worldwide around one in every 600 newborn babies are born with a cleft malformation. Heterogenic reporting of cases and whether stillbirths are included or not make data difficult to interpret (Wyszynski, 2002). The incidents of clefts vary depending on ethnic origin, with the highest incidence being observed among Japanese (2.0/1000) (Natsume and Kawai, 1986), followed by American Indians, and Caucasians (Lowry and Trimble, 1977), while the lowest incidence has been reported among Africans (Vanderas, 1987). In Sweden the incidence is about 1.8/1000 newborns (Henriksson, 1971). Variations in incidence may reflect differences in both environmental and genetic factors affecting the risk of cleft formation. Among the different cleft forms cleft lip and palate (CLP) is the most common (approximately 50 % of the cases) while cleft lip (CL) and cleft palate (CP) are less common (approximately 25% each). There is a predominance of CLP in males and of CP in females (Fogh-Andersson, 1942). Cleft of the left side occurs twice as often as on the right side (Tolarova and Cervenka, 1998).
Clefts are like many other malformations caused by an interaction between genetic and environmental factors. In 1963, Falconer established the multifactorial threshold theory as an attempt to explain the etiology of facial clefting. This theory proposes that clefting is directly related to hereditary and environmental factors involved in the development and growth process (Falconer, 1965). Greater numbers of risk factors increase the probability of clefting. Examples of environmental factors known to influence cleft formation are maternal smoking (Kallen, 1997; Wyszynski et al., 1997), drugs like anti-epileptics (Hanson et al., 1976; Dansky et al., 1992) or low levels of folic acid (Czeizel et al., 1999).

Over the last decades, several genes that contribute to the etiology of orofacial clefting have been identified (Melnick, 1992; Vieira, 2008). Advances in modern technology have led to an understanding of the role of particular genes associated with embryonic cleft formation (Wantia and Rettinger, 2002; Bernheim et al., 2006), e.g. transforming growth factor-alpha (Ardinger et al., 1989).

Anatomy

The untreated nasal deformity associated with unilateral cleft lip and palate (UCLP) has a typical appearance. In UCLP the platform for the nose in the maxilla is cleft, with a subsequent skewed nose. The anterior portion of the septum tilts over the cleft with its base dislocated out of the vomerine groove and with the nasal spine in the floor of the normal nostril. This dislocation is responsible for a deviation of the nasal tip. The columella is deflected and shortened. The position of the maxillary segments defines the cleft size in the nasal floor from narrow to wide. The lateral alar cartilage is displaced with the medial crus lowered on the columella and the lateral crus laterally displaced resulting in a downward rotation of the nasal tip and alar cartilage. In conclusion the UCLP nose has a nostril aperture on the cleft side along a horizontal axis (whereas normal nostril aperture has a vertical direction). This is accompanied by a flat nasal tip on the cleft side, along with a webbed nostril arch and a deviated ala (Millard, 1976; Ahuja, 2001; Ahuja, 2002). After treatment, which optimally reverses this malpositioning of tissue, there are often residual malformations. These include alar lateral deviation and downrotation, nasal tip broadening and displacement, septum deviation and columella shortening, Figure 3.
In the Caucasian normal nose the narrowest portion of the nasal airway is at the level of the internal nasal valve. This involves the area bounded by upper lateral cartilage, septum, nasal floor, and anterior head of the inferior turbinate. It is usually located at approximately two cm from the nostril rim (Daniel and Letourneau, 1988). This becomes a critical area also in the cleft nose. The area in front of this narrowing is usually referred to as the anterior part of the nasal cavity, while the area behind is referred to as the posterior.

The normal development of the nose is connected to the facial growth with increment of nasal growth in puberty. The nasal growth is regarded as finished at the age of eighteen years. In the adult nose there is a significant increase of the nasolabial angle with age as well as an age related negative correlation of the nasal height/length ratio that can accentuate the drooping of the nose as it ages. These variables are not significantly changed in the age between 20 and 50 years (Edelstein, 1996).

**Surgical treatment of clefts**

There are records of attempts to repair a cleft in the Chinese literature from A.D. 390 but the first operations to repair a cleft of the palate surgically was performed in 1764 by Le Monnier, a French dentist. The operation was done mainly to facilitate eating and drinking (Millard, 1976). Since then major progress has been made and cleft care today is no longer only “closure of a hole” but rather a set of measures aimed to normalize function and appearance. These include surgery, but also e.g. speech therapy, orthodontic treatment, and psychological support.
Several different treatment protocols are used internationally. The timing and number of operations, the surgical protocol as well as the technique of the surgeon can vary. The first operation performed according to most protocols is a lip repair. The lip repair is usually performed as early as possible considering anesthetic safety. This usually means three to six months of age. Tennison and Randall described z-plasty repair of the lip (Tennison, 1952; Randall, 1959) and Millard presented a rotation advancement technique in the 1950’s (Millard, 1964). Skoog described his technique based on the z-plasty rational (Skoog, 1958).

Lately there has been greater focus on the nasal appearance and more primary surgery has been performed on the nose at the same time as the lip repair. Byrd and co-workers concluded that early surgery on 1200 cases had no negative effect on nasal growth (Byrd and Salomon, 2000). Others have also presented their techniques of early nasal surgery (Salyer, 1986; McComb and Coghlan, 1996; Sommerlad, 2006; Anderl et al., 2008). Presurgical naso-alveolar molding was introduced already in the 1950s. The presurgical treatment aims at retracting the premaxilla, elongating the columella, correcting the nasal cartilage deformity and subsequently facilitating primary surgery. Recently, the method has been modified in order to be more practically achievable and is being used in an increasing number of CLP centers (Grayson et al., 1999; Liou et al., 2007; Lee et al., 2008; Barillas et al., 2009; Kecik and Enacar, 2009).

For the closure of the palate von Langenbeck pioneered with the first bipedicle mucoperiosteal flaps and relaxing incisions for palate closure surgery in one stage in the 1950’s (Langenbeck, 1961). The vomer flap and suturing of velar muscles were presented by Veau aiming at lengthening the palate (Veau, 1931). Wardill and Kilner, independently of one another, added to the lengthening possibilities by the Veau-Wardill-Kilner “pushback” theory. This extensive V-Y retro positioning of the palate increases the length further (Wardill, 1937). A different approach was described by Furlow with the double-opposing z-plasty without relaxing incisions (Furlow, 1986). Closure of the palate can be performed in one stage or in two stages. The time points for surgery can vary from six months to 16 years. Closure of the palate in one or in two separate stages has been under discussion for several decades (Rohrich et al., 2000; Sommerlad et al., 2002). Furthermore bone transplantation to the alveolar cleft is mostly performed around the age of eight to ten years of age depending on the dental development of the upper lateral incisor or canine.

The need for secondary surgery depends on the residual deformities. For example, velopharyngeal insufficiency is corrected by pharyngeal flaps and nose deformities by rhino- and septoplasties. Secondary nasal surgery is performed to a varying extent in different parts of the world, much because
nasal correction has been of secondary concern after normalization of eating and speaking. The techniques used, the indications for surgery and the resource limitations differ between surgeons and between centers (Cohen et al., 2003; Wolfe, 2004; Wang, 2007; Kawamoto et al., 2008).

**Treatment of clefts in Uppsala**
Uppsala University Hospital is one of six centers in Sweden with cleft care. The current primary referral area consists of 1.5 million inhabitants and around 40-50 new cases are presented to the unit each year. The cleft patients have been cared for by a multi-professional cleft team consisting of orthodontists, plastic surgeons, oto-rhino-laryngologists and speech pathologists, since the beginning of cleft treatment at the department in the 1960’s. Documentation of data has been rigorous and meticulous over the years. Thanks to the Swedish National Birth registry the patients can be followed over time, also after terminating their treatment, as long as they remain Swedish citizens. The surgical treatment of the Uppsala cleft team went through a change in 1977 when the one-stage procedure was changed to the two-stage protocol (for details see below: Materials and methods). The current Uppsala protocol is presented in Table 1.

<table>
<thead>
<tr>
<th>Age</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>Primary lip closure according to Skoog and primary nose surgery according to McComb</td>
</tr>
<tr>
<td>6-7 months</td>
<td>Soft palate closure according to Sommerlad</td>
</tr>
<tr>
<td>2 years</td>
<td>Hard palate closure</td>
</tr>
<tr>
<td>8-10 years</td>
<td>Bone grafting to alveolar cleft</td>
</tr>
</tbody>
</table>

**The nose – a central problem**
The primary goal for treatment of CLP is normalisation of form and function of involved structures. Despite careful treatment during childhood and adolescence, adults with CLP are left with residual deformities – primary related to the malformation or secondary to earlier treatment. These can be airway obstruction, hearing impairment, recurrent ear infections, malocclusion and abnormal craniofacial growth, speech dysfunction e.g. hypernasality, asymmetric appearance and possibly psychosocial consequences.
The role of the nose is to optimize the quality of inspired air to the lower airways by humidification, temperature regulation and filtration. Other functions are olfaction and phonation (Howard and Rohrich, 2002). Any of these functions can be affected in the nasal cleft malformation. A range of clinical problems have been described, and in several studies the patients’ greatest concern was correction of the appearance and function of the nose (Asher-McDade et al., 1992; Anastassov et al., 1998; Marcusson et al., 2002; Oosterkamp et al., 2007; Chuo et al., 2008).

From earlier studies on nasal function it can be concluded that the cleft deformity has an impact on nasal breathing: the nasal deformities tend to reduce the dimensions of the nasal cavity (Warren et al., 1988; Hairfield and Warren, 1989; Fukushiro and Trindade, 2005), increase nasal resistance to airflow (Warren and Drake, 1993), and reduce nasal patency, all of which can lead to a high prevalence of compensatory oral respiration in this population (Hairfield et al., 1988; Warren et al., 1990; Warren et al., 1992), lower pulmonary function (Trindade et al., 1992), and altered speech production (Dalston et al., 1992). For example unilateral measurements of nasal resistance have shown higher values of the cleft side compared to the non-cleft side in CL (n=15) and UCLP (n=27) adolescents (Sandham and Solow, 1987). Further, Kunkel and co-workers showed a significantly decreased cross sectional area and nasal volume on the cleft side compared to the non-cleft side in a group of 23 UCLP patients (Kunkel et al., 1997). In patients operated for CLP, rhinomanometry has shown increased resistance to breathing on the affected side in both children (Drake et al., 1993) and in adults (Grossmann et al., 2005). In the same study by Grossman and co-workers, a higher smell threshold was identified although subjective perception of smell was not affected.

Quality of life

Cleft lip and palate, being a craniofacial malformation with both functional and aesthetical affection, has a large impact on a person’s life. It is evident in clinical work that the impact-level differs largely between individuals. Although the psychological status of those with CLP has been studied earlier (Richman and Eliason, 1982; Tobiasen and Hiebert, 1993; Ramstad et al., 1995; Turner et al., 1998; Bressmann et al., 1999; Endriga and Kapp-Simon, 1999; Marcusson et al., 2001a; Marcusson et al., 2002; Kapp-Simon, 2004; Noor and Musa, 2007), the extent to which the quality of life (QoL) of UCLP patients is affected is not fully known. Quality of life assessment is becoming a standard end-point in many clinical studies. It is a multidimensional construct that includes life satisfaction as well as health
and functioning during disease and/or treatment (Sullivan et al., 1995; Sullivan and Karlsson, 1998; Sullivan, 2002). In earlier studies, Sinko and co-workers suggest that facial esthetics is an important aspect of QoL in adults with repaired CLP (Sinko et al., 2005). When studying a group of bilateral CLP, Oosterkamp and co-workers found that satisfaction with facial appearance correlated positively with QoL (Oosterkamp et al., 2007). Marcusson and co-workers found that general QoL was satisfactory in a group of mixed CLP patients, however life meaning, family life and private economy was rated lower than in the control group. Females within the cleft group rated lower levels of QoL in global life, disturbed life and family life as well as their sociability and well-being scales (Marcusson et al., 2001a). Similarly, Cheung and co-workers studied a mixed group of adult cleft patients and found good level of QoL but low self-esteem (Cheung et al., 2007).

Background to the current thesis

Over time surgical procedures have developed and changed. Multi professional teams have evolved and are now part of high quality modern cleft care. This is an overall accepted strategy. However, consensus regarding which surgical technique to use and the optimal time-point for surgical treatment do not exist. Depending on what end-points are chosen for the evaluation, the impact of a certain surgical procedure varies. This puts the clinicians in the challenging situation of having to balance between advantages and disadvantages of different surgical protocols, which may never have been compared to one another. In general, considering the numerous surgical protocols being used over the world, few comparisons have been done. Earlier comparative studies have mainly focused on facial growth (Friede et al., 1999; Becker et al., 2001; Molsted et al., 2005; Nollet et al., 2005; Farzaneh et al., 2008b; Sinko et al., 2008), speech (Becker et al., 2000; Lohmander et al., 2006; Farzaneh et al., 2008a) and lip appearance (Asher-McDade et al., 1992). Over the last decade, more interest has been directed towards the form and function of the nose as well as the psychosocial aspects of living with a facial malformation. However, until now there is a lack of studies evaluating QoL among adults with clefts and the nasal form and function in homogenous populations of UCLP. The objective for the work of this thesis is to elucidate QoL among cleft patients and the importance of nasal form and function in cleft care.
Aims

The aims of the current thesis were:

to evaluate the level of QoL in adults treated for UCLP (I).

to objectively evaluate nasal form and function in adults treated for UCLP (II).

to evaluate possible differences in residual nasal deformity and impairment of function between patients operated according to one-stage and two-stage palate closure (II).

to evaluate the relationship between professional and lay rating and patients’ satisfaction with nasolabial appearance (III).

to identify factors associated with lower levels of QoL and less satisfaction with nasal appearance among adults treated for UCLP (IV).
Material and methods

Patients
All patients with a complete UCLP born between 1960 and 1987 who have been treated at the CLP Center, Department of Plastic Surgery, Uppsala University Hospital, Sweden, were invited to participate in the study. Patients with incomplete clefts and Simonart’s bands were not included. The material is based on the population in a region of approximately one point five million people where the CLP Center in Uppsala is responsible for all CLP surgery, with no private or alternatively funded hospitals that treat CLP. Of the 128 consecutive patients found, five patients with associated syndromes and/or other serious disease were not included. Another 14 patients were excluded due to death (n=6), living abroad (n=5), or because they were missing in the national population registry (n=3). The remaining 109 patients were asked to participate via a letter of invitation with information about the study. This was followed by a telephone call with further information to those who did not answer within the first two weeks. From the invited patients, 79% participated in the study (n=86). For paper I, age- and gender-matched norm data was retrieved from the Swedish national Short Form 36 (SF-36) database (n=1385). For papers II and III an age- and gender-matched control group was recruited from students, staff and friends (n=68).

Since 1960 a cleft team has cared for the patients according to specified protocols for operations, registrations and evaluations. The patients in this study were treated according to one of two different protocols for palatal closure, either a one-stage or a two-stage procedure. The one-stage procedure was used for patients born between 1960 and 1975. These patients were 33-47 years of age at the time of the study and are referred to as the “older age group” in paper I and “one-stage group” in paper II. Patients born between 1976 and 1987 were operated on according to the two-stage protocol and were 20-32 years of age at the time of the study. They are referred to as the “younger age group” in paper I and “two-stage group” in paper II. Patient data are presented in Table 2.
Table 2. Number (n), age and gender of patients, controls and norm data.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Older age group (33-47 years, mean 39)</th>
<th>Younger age group (20-32 years, mean 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>One-stage group</td>
<td>Two-stage group</td>
</tr>
<tr>
<td>Total number of</td>
<td>128</td>
<td>69</td>
<td>40</td>
</tr>
<tr>
<td>patients</td>
<td>-19</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>Invited to</td>
<td>109</td>
<td>69</td>
<td>40</td>
</tr>
<tr>
<td>participate</td>
<td>-23</td>
<td>Declined participation</td>
<td>-9</td>
</tr>
<tr>
<td>Participating UCLP patients</td>
<td>86</td>
<td>55</td>
<td>31</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>35 years (20-47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>Participating controls</td>
<td>68</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>33 years (20-53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>39</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Participating norm data</td>
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<td>919</td>
<td>466</td>
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<tr>
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<td>35 years (20-47)</td>
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<td></td>
</tr>
<tr>
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<td>757</td>
<td>451</td>
<td>306</td>
</tr>
<tr>
<td>Female</td>
<td>628</td>
<td>468</td>
<td>160</td>
</tr>
</tbody>
</table>

Surgical procedures

During the period 1960 to 1977 children with UCLP (born 1960 -1975) were treated according to a one-stage palate closure procedure at a mean age of two years. The palate closure was first described by Veau (Veau, 1931) and Wardill (Wardill, 1937), with a later modification by Skoog (Skoog, 1969). In this procedure mucoperiosteal flaps are shifted medially and pushed backwards in order to elongate and close the palate. This produces an area of exposed bone, which is left to heal by secondary intention. In some cases
modifications and additional steps were performed, such as island flaps to preserve the palate (Millard et al., 1970) and buccal flaps to cover exposed bone (Skoog, 1974).

From late 1977 and onwards, UCLP patients born 1976 to 1987 were treated according to a two-stage procedure where the soft palate was closed first and the residual cleft in the hard palate was closed in a second stage. This procedure reduces the subperiosteal dissection and the exposure of bone, and reduces the wounds left for secondary healing. The delay in the closure simplifies the closure of the hard palate and may reduce the disturbance to the growing maxilla (Widmaier, 1961; Perko, 1979; Friede, 2007). In the first operation, the soft palate is reconstructed by rearrangement of the levator palatini muscle attachments. In the second stage the margins of the residual cleft in the hard palate are incised, and after subperiosteal dissection the defect is closed. The timing of the two operations changed over time. From 1977 to 1983 the soft palate operation was performed at around 18 months of age and the second stage was performed between three and six years of age. Starting in 1983 the time-points for both operations were pushed forward, and from 1985 and onwards the soft palate closure was done at six months and the closure of the hard palate at two years of age.

From 1960 to 1987 the primary lip operations were unchanged. Minimal or no surgery was performed on the nose until adolescence. All surgery on the nose is therefore categorized as supplementary surgery. The nose corrections include rhinoplastic procedures like adjustment of the nasal tip projection and nostril symmetry and reduction of the wedges in the nasal vestibulum. Surgery on the inner parts of the nose was rarely performed: Only three patients had had septoplasties done at the time of the study. All supplementary surgery has been performed according to the treatment protocols of the Uppsala CLP-team and in agreement with the patient’s interest. The surgical procedures used for cleft surgery in Uppsala between 1960 and 1987 were described in detail by Jakobsson et al (Jakobsson and Ponten, 1990).

Primary nose surgery was not performed in any of the patients. Secondary lip and nose corrections as well as pharyngeal flaps were performed according to individual needs of the patient (Jakobsson and Ponten, 1990). Rhinoplasty had been performed in 65 of the patients (20 patients had three or more rhinoplasties done). Septoplasty had been performed only in three patients. Four different surgeons performed 95 percent of all surgical procedures. Secondary surgery is presented in Table 3.
Table 3. Number of patients with supplementary surgery including secondary palate surgery, pharyngeal flaps and nasal surgery. The rhinoplasties include mainly adjustment of nasal tip projection, nostril asymmetry and reduction of wedges in the nasal vestibulum. Surgery to the septum was accounted for separately (septoplasties).

<table>
<thead>
<tr>
<th>Surgery of the palate</th>
<th>Surgery of the pharynx</th>
<th>Surgery of the nose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palate reop.</td>
<td>Fistula op.</td>
<td>Pharyngeal flap</td>
</tr>
<tr>
<td>One-stage (n=55)</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>Two-stage (n=31)</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>

One-stage: closure of the palate in one stage
Two-stage: closure of the palate in two stages
Palate reop.: Number of patients with reoperation after palate closure
Fistula op.: Number of patients operated for palate fistula
Pharyngeal flap: Number of patients operated with pharyngeal flaps due to velopharyngeal insufficiency
Rhinoplasty: Number of patients with one or more rhinoplasties
Septoplasty: Number of patient with surgery to the septum

Methods

Papers I and IV

To evaluate QoL the SF-36 was used. The SF-36 is a generic, i.e. not disease specific, QoL instrument. The questionnaire was sent to participants to be answered at home. The SF-36 has been widely used internationally and has been validated in several studies, but never for Swedish cleft patients. However, it has been translated and psychometrically tested for the Swedish population with a large database of norm data for the Swedish population. It has been validated and tested for reliability (Sullivan et al., 1995; Sullivan and Karlsson, 1998; Sullivan, 2002). It consists of 36 different questions that address eight different aspects of health, Table 4. Each subscale has been coded and transformed into a scale from 0 – 100 according to the SF-36 manual (Sullivan, 2002). The subscales are further transformed into two health domains – physical health (physical component scores, PCS) and psychological health (mental component scores, MCS). The PCS and MCS scores were calculated using the standard scoring algorithms (Ware et al., 1995). Low scores imply poor health status and high scores imply good health status (see appendix: SF-36 Questionnaire).
Table 4. Short Form 36 subscales

<table>
<thead>
<tr>
<th>SF-36 subscales</th>
<th>Abbreviation</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Function</td>
<td>PF</td>
<td>Evaluates limitations in performing daily activities (i.e. climbing stairs,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>getting dressed, etc.) as a result of health problems.</td>
</tr>
<tr>
<td>Social Function</td>
<td>SF</td>
<td>Considers limitations in social activities like seeing relatives and friends.</td>
</tr>
<tr>
<td>Physical Role function</td>
<td>RP</td>
<td>Collects data on work or other daily activities as a result of health problems.</td>
</tr>
<tr>
<td>Emotional Role function</td>
<td>RE</td>
<td>Evaluates limitations due to emotional problems.</td>
</tr>
<tr>
<td>Mental Health</td>
<td>MH</td>
<td>Deals with questions about depression and nervousness.</td>
</tr>
<tr>
<td>Vitality</td>
<td>VT</td>
<td>Deals with feelings of energy or tiredness.</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>BP</td>
<td>Concerns amount of pain and limitations due to body pain.</td>
</tr>
<tr>
<td>General Health</td>
<td>GH</td>
<td>Measures the subjective evaluation of general health status.</td>
</tr>
<tr>
<td>Mental Component Scores</td>
<td>MCS</td>
<td>Cluster score of mental health based upon transformed subscale data (mental health domain).</td>
</tr>
<tr>
<td>Physical Component Scores</td>
<td>PCS</td>
<td>Cluster score of physical health based upon transformed subscale data (physical health domain).</td>
</tr>
</tbody>
</table>

Papers II and IV
Acoustic rhinometry (AR) and Rhinomanometry (RM) were performed using the RhinoMetrics SRE 2000 hardware platform (Interacoustics AS, Assens, Denmark) with different software modules (RhinoScan for AR and Rhinostream for RM). The instrument was calibrated before each test. All measurements were performed on both the right and left side. For the control persons, no side differences were detected with AR or RM and the mean of the right and left side was therefore calculated and used for the analysis.

Acoustic rhinometry is a well-established non-invasive method for measuring the volume and minimum cross-sectional area of the nasal passage (Cakmak et al., 2005). A noise signal is sent into the nose statically from a probe in the nostril and the reflected sound is analyzed and calculated. The registration is done for each side separately. These measurements are sensitive to changes in volume caused by congestion or
anatomical divergence. The calculated values are the minimum cross-sectional area (MCA, cm\(^2\)) and volume (Vol, cm\(^3\)) of the anterior and posterior nasal cavities, respectively. The calculated values describe the form of the nasal passage in the anterior (MCA-1, Vol-1) and the posterior (MCA-2, Vol-2) cavities (Ahman and Holmstrom, 2000).

Rhinomanometry is also a non-invasive technique. It evaluates nasal function by measuring airflow and pressure during nasal respiration. It is a dynamic process that registers the drop in pressure from the anterior to the posterior nose and based on this the resistance related to airflow is calculated. Registrations were done on one side while the other nostril was blocked. If the cross-sectional area of the nose is smaller than 0.05 cm\(^2\) no airflow can be registered. As the resistance becomes infinite in these cases, it was set at 10 Pa s/m\(^3\) for statistical reasons. Values for airflow resistance were registered separately for inspiration (NARInsp, Pa s/cm\(^3\)) and expiration (NARExp, Pa s/m\(^3\)). Nasal airway resistance was calculated according to the Broms technique (Clement and Gordts, 2005).

Airflow through the nose can also be evaluated by the peak nasal inspiratory flow meter (PNIF, l/min) measuring the total flow in both nasal passages at the same time. To assess peak flow (l/min), measurements were made with a Youlten nasal inspiratory peak flow meter (Airmed, London, England). Three measurements were made and the highest value was used for analysis (Wihl and Malm, 1988; Jones et al., 1991). A significant function of the nose is the sense of smell. Anatomical or mucosal changes in the upper airway could possibly disturb this function. The Scandinavian odor identification test (SOIT) was used to evaluate smell function. In this test subjects were exposed to 16 different odorous stimuli separately. Identification of each odor was done using four response alternatives (Nordin et al., 1998). The number of correct answers was collected and processed.

Before all measurements, acclimatization to indoor climate was done for a minimum of 15 minutes. This allowed for any adrenal effect on the mucosa to decrease. All measurements except the SOIT were performed in a sitting position, before and after decongestion with two nasal puffs of oxymethazolin 0.5 mg/ml on each side. After decongestion the patient waited 15 minutes before the second measurement was done. Values registered after decongestion are regarded as related to skeletal and cartilage conditions of the nose, while measurements before decongestion are influenced as well by mucosal swelling due to vascular dilatation. For this reason measurements after decongestion (except for SOIT) were used in the presentation of data. The tests were not done during the allergy season and if the patient had a common cold the tests were postponed for four weeks.
Papers III and IV
For self-evaluation of appearance the Satisfaction with Appearance scale (SWA), developed by the Psychology Special Interest Group of the Craniofacial Society of Great Britain and Ireland, was used (Emerson et al., 2004). The SWA reflects satisfaction with cleft-related and non-cleft-related parts of the face, speech, and overall appearance and extra oral visibility of the cleft. The SWA questions were answered with markings on a Visual Analogue Scale (VAS) extending from 0 to 10, where a score of 0 indicates a very high level of satisfaction with appearance and 10 a very low level. Example of question used in the current study was: How do you feel about the look of your nose? The answers could range from “I am very satisfied/happy” = 0, and ”I am very dissatisfied/unhappy” = 10. The questionnaire was tested before the study on a test panel for comprehensiveness and relevance. The 14 items version of the scale was used in the current study and six of the items of importance to the objectives of the study were selected for analysis: questions about the appearance of the lip and nose, and for comparison, questions about the degree of satisfaction with the appearance of the eyes, hair, face and general appearance. The SWA has been reported to possess satisfactory internal consistency and a coherent factor structure (Emerson et al., 2004). The instrument has similarities to the Cleft Evaluation Profile, which was developed by the Royal College of Surgeons Cleft Lip and Palate Audit group (Thomas et al., 1997; Noor and Musa, 2007). The SWA has previously been used in the Scandinavian population (Feragen et al., 2009). The SWA questionnaire was sent to the patients and the controls to be answered at home. At the follow-up visit arranged for the present study, the questionnaire was checked by a physician not participating in the study, in order to minimize unanswered questions and misunderstandings.

Professional and lay judgment
A professional photographer, at the UU Hospital, took all the photographs used in the present study under standardized and reproducible conditions. A yardstick with a colour palette was used for a colour and size calibration. The yardstick was placed in a holder at the level of the base of the nose. The frontal and profile photos were then cropped according to Asher-McDade et al (Asher-McDade et al., 1991) to include only the nose and upper lip and therefore avoiding the influence of the background facial appearance, Figure 4. The photos were rated according to the Asher-McDade et al index with four nasolabial components (nasal form, nose symmetry, vermillion border and nasal profile) and were rated separately on five point scales. For an individual with repaired UCLP, score 1 is a very good nasolabial appearance, score 2 a good appearance, score 3 a fair appearance, score 4 a poor appearance and score 5 a very poor appearance. Additionally a sum-score (mean) of the four parameters was calculated and analysed (Asher-McDade et al., 1991).
Figure 4. Cropped photo according to the Asher-McDade protocol in order to reduce the influence of the surrounding facial appearance (printed with the patient’s kind permission).

Before scoring all photos, a calibration test using ten randomly selected photos were scored by the panel members, to get familiar with the scoring scale. Then the cropped photos of all participants were run randomly in a power-point presentation and were rated firstly by a lay panel and later a professional panel. Ratings by each panel were performed at two different time-points with 4 weeks in between. One hundred and forty eight photosets were assessed each time. The pictures were randomly re-ordered between the first and second rating session. The professional panel consisted of two medical doctors and one orthodontist, none of whom had been involved in the treatment of the included patients nor in the present study, but with knowledge and experience of cleft care. The lay panel consisted of three acquaintances of the authors with no medical experience and with no connection to the present study. In order to assess intra-rater reliability a replicate scoring was made in ten randomly selected cases at both the first and second scoring session.

Paper IV

Upper jaw cleft width

Dental casts taken before lip-closure at 3 months of age were analysed. Reference points and linear measurements used have been described earlier (Hellquist and Skoog, 1976; Friede et al., 1993; Larson et al., 1998; Reiser et al., 2010). The cleft size was analysed by three measurements; cleft width at the level of the alveolar processes anteriorly (AntCleft), ratio of the cleft width related to the total alveolar arch width anteriorly at the level of the canine points (RelAntWidth) and posteriorly at the level of the tuberosity
The reliability of the recordings was good with Interclass Correlation Coefficients (ICC) of 0.97-0.99 (Reiser et al., 2010). In addition to the above mentioned evaluations background information including surgical history was retrieved from the patient records in the CLP archives and from a structured questionnaire with information on marital status, number of children and highest level of education (high school/elementary school or university/college) answered by the participants at the time of the study.

Figure 5. Schematic drawing of an infant maxillary dental cast with UCLP. Landmarks and distances used in the linear measurements are demonstrated. Cleft widths are marked with blue color (printed with kind permission of E. Reiser).

Linear dimensions measured on infancy dental casts:

- **D-E**: Cleft width at the level of the alveolar processes anteriorly (AntCleft)
- **D-E1**: Smallest cleft width at the level of the alveolar processes anteriorly
- **T-T1**: Posterior width of the alveolar arch in the tuber area
- **A-A1**: Width of the cleft at the level of T-T1
- **C-C1**: Anterior width of the alveolar arch in the canine region
- **B-B1**: Width of the cleft at the level of C-C1
- **B-B1/C-C1**: Ratio of the cleft width related to the total alveolar arch width anteriorly at the level of the canine points (RelAntWidth) and posteriorly at the level of the tuberosity points (RelPostWidth)
- **A-A1/T-T1**: Ratio of the cleft width related to the total alveolar arch width posteriorly at the level of the tuberosity points (RelPostWidth)
Statistical analysis

Papers I and II
Data from SF-36 and nose function evaluations were visualized with histograms and tested for normality with the Shapiro-Wilks test. The Mann-Whitney U-test was used for statistical analysis due to the skewed distribution of data. A p-value of <0.05 was regarded as significant. For Study I, all comparisons with controls were based on norm data matched for age and gender that were retrieved from the Swedish SF-36 database. For comparisons between subgroups of patients (men and women, and older and younger patients), the differences between the QoL results for each group and matched norm data were used in the analysis (ie the mean QoL value for the matched control group was subtracted from the QoL value of each UCLP patient).

Paper III
Non-parametric analyses were used since the data for ratings of nasolabial appearance were on ordinal scales. Correlations were tested with scatter plots and Spearman rank test. Weighted Kappa analyses were used to assess agreement between professional and lay ratings. Wilcoxon Signed Rank test and Mann Whitney U-test were performed to analyze differences between professional and lay rating and patient satisfaction and for differences between patient’s and control’s self-assessments. A p-value of <0.01 was regarded as significant.

To reduce variability, the scores of the three observers of each panel, were averaged for each individual nasolabial component as well as for the sum of the four sub-scores. To test for sufficient coherence among the observers Cronbach’s alpha was calculated panel-wise for each individual nasolabial component as well as for the sum of the four sub-scores. The calculated inter-rater coherence was good (laymen: 0.766-0.937; professionals: 0.881-0.960). Consequently the mean scores of the three observers were used for comparison between panels as well as when comparing the results of the panels to the SWA self-assessed scores. The intra-rater agreement of the panel scorings was calculated through cross-tabulations and weighted kappa analyses, and showed good to very good agreement among professionals and fair to good agreement among lay panel members (Altman, 1991). The intra-rater correlation between the first and second scoring session was good why further analysis were based upon scores from the first scoring session (laymen: 0.802-0.893; professionals: 0.895-0.920).
Table 5. Overview of variables.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Variables</th>
<th>Description</th>
<th>Scale/unit</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endogenous non-cleft related factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demo-graphics</td>
<td>Age</td>
<td>-</td>
<td>years</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-</td>
<td>Male/ Female</td>
<td>86</td>
</tr>
<tr>
<td><strong>Endogenous cleft-related factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleft size</td>
<td>AntCleft</td>
<td>Anterior cleft width at the level of the alveolar processes anteriorly</td>
<td>mm</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>RelAntWidth</td>
<td>Ratio of the cleft width related to the total alveolar arch width anteriorly at the canine points</td>
<td>ratio (percent)</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>RelPostWidth</td>
<td>Ratio of the cleft width related to the total alveolar arch width posteriorly at the tuberosity points</td>
<td>ratio (percent)</td>
<td>53</td>
</tr>
<tr>
<td>Nasal function</td>
<td>PNIF(before)</td>
<td>Peak nasal inspiratory flow before decongestion</td>
<td>l/min</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>PNIF (after)</td>
<td>Peak nasal inspiratory flow after decongestion</td>
<td>l/min</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>NARInsp(before)</td>
<td>Nasal airway resistance during inspiration before decongestion</td>
<td>Pa s/cm3</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>NARInsp (after)</td>
<td>Nasal airway resistance during inspiration after decongestion</td>
<td>Pa s/cm3</td>
<td>79</td>
</tr>
<tr>
<td>Aesthetics</td>
<td>Profpanel</td>
<td>Professional panel rating of nasal appearance</td>
<td>1-5 rating</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>NasalSWA</td>
<td>Self-evaluation of nasal appearance</td>
<td>VAS² 0-10</td>
<td>85</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>MCS</td>
<td>Mental component scores according to SF-36</td>
<td>0-100</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>PCS</td>
<td>Physical component scores (SF-36)</td>
<td>0-100</td>
<td>86</td>
</tr>
<tr>
<td><strong>Exogenous (non-cleft)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td>Education</td>
<td>Highest educational level</td>
<td>Categorized³</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Civil</td>
<td>Marital status</td>
<td>Categorized⁴</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>Child</td>
<td>Number of children</td>
<td>n</td>
<td>85</td>
</tr>
<tr>
<td><strong>Exogenous (cleft)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>Op</td>
<td>Palate closure</td>
<td>one- or two-stage</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>Rhinoplasties</td>
<td>Number of rhinoplasties performed</td>
<td>Categorized⁵</td>
<td>86</td>
</tr>
</tbody>
</table>

1) Number of patients/registrations included in analysis
2) VAS = visual analogue scale
3) Highschool/primary school or university/college
4) Cohabitant yes/no
5) 1, 2, 3 or more
In order to identify factors that might be related to QoL (MCS and PCS) and nasalSWA, stepwise regression was performed. Both forward selection and backward elimination procedures were performed. A criterion for being entered to or removed from the model was set to 0.05 ie in the final models all included factors had a p-value <0.05.

All variables considered along with the valid number of observations for each variable are presented in Table 5. Four of the variables stand out according to missing values; three for measurements of cleft width (n=53) and one for panel judgment of nasal appearance by professionals (n=73). As this will affect the number of observations for the statistical models the following models were used:

Dependent variable = nasalSWA, MCS or PCS (marked with *)

**Model 1a:** Gender, Age, Op, Rhinoplasties, Civil, Child, Education, PNIF(before), PNIF(after), NARInsp(before), NARInsp(after), AntCleft, RelAntWidth, RelPostWidth, Profpanel and nasalSWA*, MCS*, PCS*

**Model 1b:** Model 1a without Profpanel (ie without the ratings of the professional panel)

**Model 2a:** Model 1a without AntCleft, RelAntWidth, RelPostWidth (ie without the cleft size ratings)

**Model 2b:** Model 2a without Profpanel (see above)

The first model considered was model 1a. In case Profpanel was non-significant, model 1b was tested. The major aim of model 1a and 1b was to evaluate if cleft width was associated with any of the dependent variables. The same procedure was repeated for model 2a and 2b with the larger sample size (including also the patients without cleft width measurements). If any of the cleft width measurements for either model 1a or 1b were significant the results were presented along with model 2a or 2b, otherwise only results for model 2a or 2b were presented.

The model assumptions were checked using standard diagnostic checks such as evaluation of the distribution of residuals and influential observations. In the cases where model assumptions were violated (as were the case for PCS and MCS, where extremely low values were found) the values of the dependent variable have been transformed (using quadratic transformation) to better fit into the models. However, as the models remained the same as for the untransformed variable, only the estimates for
the analyses of untransformed data were presented for better interpretability. In addition to the checks of model assumptions checks for multicollinearity were performed.

For all studies, statistical evaluations were carried out with a computer software package (SPSS PC versions 14.0-17.0; SPSS, Chicago, IL, USA).
Results

Quality of life in UCLP (paper I)

Comparison of QoL between UCLP patients and norm data

Comparison of the whole group of patients with matched norm data is presented in Table 6. Overall, the QoL values for the UCLP patients were similar to the values of the norm population in six out of seven SF-36 subscales. Only the value of the Mental Health subscale was significantly lower for the whole patient group compared to norm data (p=0.005). When analyzing the results based on age, the older age group had a lower value in Mental Health subscale compared to matched norm data (patients’ mean 76 (SD 18); norm mean 81 (SD 19), p=0.007). There was no significant difference in any subscale between younger patients and matched norm data.

Table 6. Comparison of SF-36 subscales between UCLP patients and norm-data.

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Patients (n = 86)</th>
<th>Controls (n = 1085)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (Median)</td>
<td>SD</td>
<td>Mean (Median)</td>
</tr>
<tr>
<td>PF</td>
<td>93 (100)</td>
<td>17</td>
<td>93 (100)</td>
</tr>
<tr>
<td>SF</td>
<td>88 (100)</td>
<td>19</td>
<td>89 (100)</td>
</tr>
<tr>
<td>RP</td>
<td>87 (100)</td>
<td>29</td>
<td>88 (100)</td>
</tr>
<tr>
<td>RE</td>
<td>88 (100)</td>
<td>29</td>
<td>87 (100)</td>
</tr>
<tr>
<td>MH</td>
<td>78 (84)</td>
<td>18</td>
<td>81 (88)</td>
</tr>
<tr>
<td>VT</td>
<td>66 (70)</td>
<td>23</td>
<td>70 (75)</td>
</tr>
<tr>
<td>BP</td>
<td>77 (84)</td>
<td>28</td>
<td>78 (84)</td>
</tr>
<tr>
<td>GH</td>
<td>75 (77)</td>
<td>22</td>
<td>79 (85)</td>
</tr>
</tbody>
</table>


Data is presented as mean, median and standard deviation (SD) for each subscale. Comparison is done between all patients and all age- and gender-matched controls. Significant differences are marked with bold (p-value <0.01, Mann-Whitney U-test).
Analysis of the effect of UCLP on subgroups of patients: gender and age groups

Results of the analysis of how QoL of male vs female patients diverged from that of matched norm population are presented in Table 7. Women had a higher positive difference than men in the subscale Emotional Role function \((p<0.001)\). In the subscale Physical Role function, the mean and median values were not consistent; however, the \(p\)-value for the comparison of distribution between men and women was statistically significant \((p<0.001)\).

Table 7. Comparison of SF-36 subscales among unilateral cleft lip and palate patients based on gender and age (corrected for variation in norm population).

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Men (n = 47)</th>
<th>Women (n = 39)</th>
<th>Men vs Women</th>
<th>Older (n = 55)</th>
<th>Younger (n = 31)</th>
<th>Older vs Younger</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>(p^1)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>(p^2)</td>
</tr>
<tr>
<td>PF 1 (4)</td>
<td>14 (14)</td>
<td>-2 (5)</td>
<td>0.060</td>
<td>4 (6)</td>
<td>9 (4 -7)</td>
<td>26 &lt;0.001</td>
</tr>
<tr>
<td>SF -2 (9)</td>
<td>19 (19)</td>
<td>-1 (7)</td>
<td>0.145</td>
<td>0 (11)</td>
<td>18 (-4)</td>
<td>23 0.009</td>
</tr>
<tr>
<td>RP 1 (8)</td>
<td>25 (15)</td>
<td>-3 (14)</td>
<td>&lt;0.001</td>
<td>0 (12)</td>
<td>31 (-2)</td>
<td>27 &lt;0.001</td>
</tr>
<tr>
<td>RE -6 (9)</td>
<td>34 (23)</td>
<td>9 (16)</td>
<td>&lt;0.001</td>
<td>2 (11)</td>
<td>30 (-3)</td>
<td>30 &lt;0.001</td>
</tr>
<tr>
<td>MH -4 (2)</td>
<td>19 (19)</td>
<td>-4 (0)</td>
<td>0.549</td>
<td>-5 (1)</td>
<td>19 (-1)</td>
<td>16 0.369</td>
</tr>
<tr>
<td>VT -2 (4)</td>
<td>22 (12)</td>
<td>-6 (-2)</td>
<td>0.452</td>
<td>-5 (-1)</td>
<td>23 (-1)</td>
<td>23 0.312</td>
</tr>
<tr>
<td>BP 5 (18)</td>
<td>22 (12)</td>
<td>-7 (-2)</td>
<td>0.495</td>
<td>0 (10)</td>
<td>28 (-2)</td>
<td>27 0.273</td>
</tr>
<tr>
<td>GH -3 (-1)</td>
<td>21 (11)</td>
<td>-3 (1)</td>
<td>0.860</td>
<td>-1 (-1)</td>
<td>20 (-6)</td>
<td>25 0.432</td>
</tr>
</tbody>
</table>


Values for each subscale is calculated as the difference between patient group and matched norm group (SF-36 subscale value for UCLP subjects subtracted by the mean value for the same SF-36 subscale of age- and gender-matched norm data) in order to correct for normal variation in subscale values in norm population due to gender and age differences. Data is presented as mean, median and standard deviation (SD) for each subscale. Comparison is done between men and women \((p^1)\) and older (33-47 years of age) and younger (20-32 years of age) patients \((p^2)\). Significant differences are marked with bold (\(p\)-value <0.01, Mann-Whitney U-test).

Results of the analysis of age groups are presented in Table 7. The younger age group consistently had a larger negative difference to matched norm data compared to the older age group in the subscales Social Function \((p=0.009)\), Physical Role function \((p<0.001)\) and Emotional Role function \((p<0.001)\). In the subscale Physical Function, the mean values were equal,
while the median value was negative for the younger age group and positive for the older age group (p<0.001).

Comments

Overall, the patients had a lower SF-36 value in the subscale Mental Health compared to norm data (difference of 4 units). While this difference was statistically significant, the clinical significance of this small difference is dubious. Earlier studies have stated that there is no universally accepted approach for determining the clinical significance of QoL data. The patients’ perspective will continue to be the key factor for interpreting the meaningfulness of the differences and changes found in QoL scores and results should be correlated to clinical experience or confirmed with other instruments (Marquis et al., 2004; Wyrwich et al., 2005). In this context, earlier studies of QoL of cleft patients with various instruments confirm the results of the current study (Bressmann et al., 1999; Marcusson et al., 2001a; Hunt et al., 2005; Sinko et al., 2005).

In the current study the younger age group was more negatively affected by UCLP compared to the older age group. Other studies identified lower values for facial satisfaction for younger patients (10-15 years) compared to older (older than 20 years) (Thomas et al., 1997). These studies could partly explain why younger patients score more negatively than older age groups in the current study. In contrast Cheung and co-workers found that adult patients (ages 17-40 years) tended to have greater satisfaction with life, higher social avoidance and lower parental and general self-esteem compared to adolescents (ages 10-16 years) (Cheung et al., 2007). No correction for normal age variation was done in the previous studies. In a review by Hunt and co-workers, which included more than 60 studies dealing with psychosocial aspects of CLP, there was limited indication that age influenced the level of psychosocial problems. However, the heterogeneity of the methodologies used in the studies made meta-analysis impossible (Hunt et al., 2005).

Nasal function (paper II)

There were no significant differences in nasal function (registered with AR and RM after decongestion) between patients who had undergone secondary external rhinoplasties, as presented in Table 3 above, and those who had not. Similarly, no differences were detected in any of the parameters between patients who were operated on with pharyngeal flaps and those who were not.
Nasal function on cleft side compared to non-cleft side in all patients

When comparing the two nasal cavities, the cleft side proved to have a smaller minimum cross sectional area and a smaller volume than the non-cleft side, both anteriorly and posteriorly (MCA-1, MCA-2, VOL-1 and Vol-2) (p<0.001). Rhinomanometric registrations identified increased resistance to nasal breathing during both inspiration and expiration on the cleft side compared to the non-cleft side (p<0.001), Table 8, p-values not shown.

Table 8. Acoustic rhinometry and rhinomanometry after decongestion - all cases compared to controls. Minimum cross-sectional area (MCA, cm²) and volume (Vol, cm³) of the anterior (1) and posterior (2) nasal cavities are presented as well as airflow resistance measurements with rhinomanometry (inspiratory and expiratory resistance, Pa s/cm³).

<table>
<thead>
<tr>
<th>Variable</th>
<th>All cases</th>
<th>All Controls</th>
<th>p₁</th>
<th>p²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cleft side</td>
<td>Non-cleft side</td>
<td>Mean of both sides</td>
<td></td>
</tr>
<tr>
<td>Acoustic rhinometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Area</td>
<td>0.43 (0.38-0.48)</td>
<td>0.64 (0.60-0.68)</td>
<td>0.61 (0.58-0.65)</td>
<td>0.000</td>
</tr>
<tr>
<td>(MCA-1, cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior Area</td>
<td>0.53 (0.42-0.63)</td>
<td>1.06 (0.96-1.17)</td>
<td>0.80 (0.73-0.87)</td>
<td>0.000</td>
</tr>
<tr>
<td>(MCA-2, cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Volume</td>
<td>1.70 (1.60-1.80)</td>
<td>2.05 (1.95-2.15)</td>
<td>2.07 (1.96-2.20)</td>
<td>0.000</td>
</tr>
<tr>
<td>(Vol-1, cm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior Volume</td>
<td>7.03 (5.56-8.49)</td>
<td>9.09 (8.26-9.93)</td>
<td>7.67 (6.71-8.63)</td>
<td>0.003</td>
</tr>
<tr>
<td>(Vol-2, cm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinomanometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inspiration</td>
<td>4.76 (3.88-5.65)</td>
<td>0.53 (0.47-0.60)</td>
<td>0.89 (80.75-1.04)</td>
<td>0.000</td>
</tr>
<tr>
<td>(Pa s/cm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expiration</td>
<td>2.77 (2.03-3.52)</td>
<td>0.95 (0.67-1.22)</td>
<td>0.70 (0.60-0.81)</td>
<td>0.000</td>
</tr>
<tr>
<td>(Pa s/cm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p₁: p-value for cleft side of all cases compared to the mean value of the control’s both nasal passages.
p²: p-value for non-cleft side of all cases compared to the mean value of the control’s both nasal passages.

For each parameter results of the cleft and the non-cleft side are presented and for controls the mean of both nasal passages (mean and 95% confidence interval). Significant differences are marked with bold (p<0.05, Mann-Whitney U-test).
Nasal function in all patients compared to age-matched controls
The cleft side was also significantly smaller (MCA-1, MCA-2, Vol-1 and Vol-2) \((p<0.05)\) and had higher resistance at inspiration and expiration \((p<0.005)\) compared to controls. The non-cleft side of the UCLP patients was significantly larger in the posterior part (MCA-2 and Vol-2) but not in the anterior part (MCA-1 or VOL-1) \((p<0.05)\). Furthermore, the non-cleft side demonstrated lower inspiratory resistance compared to controls \((p<0.001)\), Table 8. Nasal peak inspiratory flow was significantly impaired and lower values for SOIT were found among UCLP patients compared to controls \((p<0.005)\).

Nasal function of patients in the different surgical protocol groups compared to age-matched controls
Data for patients who had been operated according to the one-stage procedure, and for those who had the two-stage procedure, were compared separately with age-matched controls, revealing a smaller area and volume (MCA-1, MCA-2, Vol-1 and Vol-2) \((p<0.05)\) and higher inspiratory and expiratory resistance on the cleft side for both groups \((p<0.005)\). The same analysis of data for the non-cleft side showed lower inspiratory resistance among both groups of UCLP patients \((p<0.001)\) and, for the one-stage procedure, a larger MCA-2 and Vol-2 compared to controls \((p<0.05)\). The PNIF measurements revealed lower values for patients treated with both surgical protocols compared to controls \((p<0.005)\), while SOIT revealed lower values for patients who had undergone the two-stage protocol but not for those of the one-stage protocol \((p< 0.005)\).

Nasal function after one-stage compared to two-stage procedure
No differences were detected for any of the AR or RM variables when comparing the cleft side of the one-stage and two-stage patients. However, comparison of the non-cleft sides revealed a larger MCA-1, Vol-1 and Vol-2 after the one-stage compared to the two-stage procedure \((p<0.05)\). No differences were detected with PNIF or SOIT.

Comments
The present study shows that the objectively measured nasal function of UCLP patients is extensively impaired. The minimal cross sectional area as well as the nasal volume and nasal flow resistance are highly affected on the cleft side compared to the non-cleft side. These findings mirror the clinical situation we see among UCLP patients, where unilateral stuffiness is of concern to the patients (Warren et al., 1992; Hocevar-Boltezar et al., 2006). The current study also identifies the differences between UCLP patients and controls. Our findings confirm reports from earlier studies (Sandham and
Solow, 1987; Hairfield and Warren, 1989; Kunkel et al., 1999; Duskova et al., 2002; Fukushiro and Trindade, 2005). For example, earlier studies have used rhinomanometry to show increased resistance to breathing on the affected side in both children (Drake et al., 1993) and adults with CLP (Grossmann et al., 2005). Acoustic rhinometry has identified a decreased cross sectional area and lower volumes on the affected side (Kunkel et al., 1999). In the present study PNIF was tested as an easy alternative to measuring the flow through the nasal cavities, and impaired values were found in the cleft patients.

Surprisingly, odor identification was significantly impaired in the UCLP patients when comparing the whole group with controls and when comparing the two-stage patients with age-matched controls (p<0.005). There was no significant difference between patients in the one-stage group and age-matched controls. The mean value for the two control groups corresponds to expected values including higher values in the younger control group (Nordin et al., 1998). In the patient group the expected age-dependent decrease in the sense of smell was not seen (patients in the two-stage procedure group compared to those in the one-stage group). This might explain why no differences were detected when results for the one-stage group were compared with results for the controls (since the one-stage group was older than the two-stage group). Based on AR, RM and PNIF results, the decreased nasal breathing capacity among patients can explain the degree of impaired sense of smell compared to controls. Grossmann and co-workers (2005) tested smell thresholds in children treated for CLP with similar findings, and concluded that low airflow was related to a high smell threshold. The results of the present study confirm this conclusion.

Acoustic rhinometry as well as RM both show highly significant impaired conditions on the cleft side compared to the non-cleft side and compared to controls. The tests are congruent, which strengthens the findings. According to several authors the two tests should be used together at the same time to strengthen the findings (Numminen et al., 2002; Zhang et al., 2008).

Witsell and co-workers (Witsell et al., 1994) found in a small study that not all patients had decreased MCA after pharyngeal flap surgery. However, Yamashita et al (Yamashita and Trindade, 2008) found that measurements of posterior rhinomanometry were significantly decreased after pharyngeal flap surgery. In the current study the percentage of patients who had undergone a pharyngeal flap operation were similar in the two different surgical protocol groups (17% and 19%), and comparison of data for patients with pharyngeal flaps and those with no pharyngeal flap surgery revealed no significant differences in any of the parameters. These patients were therefore not excluded in the current study. Septoplasty was performed in three patients. The low number and the results from Rautio and co-workers (Rautio et al.,
2002), who found no differences in RM measurements before and after septoplasty in CLP patients, suggest that this supplementary surgery had little impact on the outcome of the current study.

Nasolabial appearance (paper III)
A high and significant correlation was found between the lay and the professional ratings of nasolabial appearance of patients with UCLP and of controls both at the first and second rating session. However, the Kappa analyses were poor to fair and mean ratings of nasolabial appearance were consistently rated as better (lower score) by professionals compared to lay people, although the differences were smaller for the second rating session (p<0.001).

Lay panel judgment and self-assessment by both patients and controls with SWA (based upon the question of nose appearance) showed low correlation to the different variables of the panel rating (Spearman correlation coefficient 0.467-0.509, p<0.01). Similar results were seen in the correlation analysis between professional panel judgment and the patients’ and controls’ self-assessment (0.475-0.527, p<0.01). Mean ratings of panel judgment and self-assessment of nose appearance with SWA showed significant differences (Wilcoxon Signed Rank test, p<0.001 for all values).

When analyzing the differences in self-assessment between patients and controls, a significant difference was found for the following parameters/questions (p<0.001): nose, face and general appearance (including face) but not for hair (p=0.368) or eyes (p=0.559).

Comments
Satisfaction with nasolabial appearance is one of the key end-points of cleft surgery. Perception of appearance may however vary between individuals. In the clinical setting, it is important to know if the health care professional’s judgment of appearance correlates with that of the patient’s and that of the society in general. The current study showed high correlation in judgment of nasolabial appearance of cleft patients between professionals and lay people. However, the professionals consistently rated nasolabial appearance as better than the laymen. Furthermore, the study implies that, self-assessment among patients with cleft and controls, does not correlate with lay and professional ratings.

A limitation of the present study is that different scales were used for self-assessment and panel judgment of nasolabial appearance, making comparison of results more difficult. Therefore non-parametric statistics based upon ranking, and not numeric values, were used. Self-assessment can
be influenced by factors such as generally inferior body image or opinion of one’s own appearance, confounding the results of the analysis. Yet the self-assessment among patients with UCLP for attributes not associated with the cleft (e.g. hair and ear) did not differ from the control group’s self-assessment for these attributes, indicating similar body-image perception among patients and controls. However, the self-assessment of the cleft related attributes like lip, nose, face and overall appearance, was affected negatively among patients with cleft.

The panel judgment procedure described by Asher McDade et al was chosen for rating of nasolabial appearance (Asher-McDade et al., 1991). This method has been used earlier in several studies (Asher-McDade et al., 1992; Nollet et al., 2007; Fudalej et al., 2009a). The current study confirmed that panel judgment is a reasonably reliable and reproducible method for evaluation of nasolabial appearance (Asher-McDade et al., 1992; Nollet et al., 2007; Fudalej et al., 2009a). While panel rating has the advantage of minimizing the influence of larger differences between individual raters, the difficulties in finding representative panel members may impose problems on the evaluation process.

Strong correlation of nasolabial rating was found between lay people and professionals though the results of the Kappa analyses showed that the professionals consistently rated nasolabial appearance as better than the lay panel. Furthermore, the lay panel rated the nasolabial appearance more favourably in the second session compared to the first session, while the professionals had less variation in their evaluation. This could be explained by the fact that health care professionals were more accustomed to the evaluation of cleft treatment outcome. However, as patients normally meet non-medically trained lay people in their daily life, the ratings of the first session were used in the analyses of the current study. In contradiction to previous studies (Eliason et al., 1991; Roberts-Harry and Stephens, 1991; Cussons et al., 1993), the current study showed a clear trend towards more unfavourable rating of nasolabial appearance (higher scores) by the lay panel compared to professionals.

Factors correlating to QoL and satisfaction with appearance (paper IV)

The statistical models chosen were significant for all dependent variables (p<0.011) with adjusted R-square varying from 13.7–27.7% ie with the explanatory percentage within this range. The analyses identified that larger posterior cleft width measure (RelPostWidth) was associated to less satisfaction with nasalSWA. Associations were further found between

40
nasalSWA and number of rhinoplasties performed (Rhinoplasties) where a larger number of rhinoplasties were associated to less satisfaction with nasalSWA. Less satisfaction with nasalSWA was also associated with lower levels of QoL (both mental cluster scales (MCS) and physical cluster scales (PCS)) and to female gender, Table 9.

Table 9. Multivariate regression analysis of variables related to variation in satisfaction with nasal appearance and quality of life in UCLP patients.

<table>
<thead>
<tr>
<th>Statistical Model</th>
<th>F(df)</th>
<th>p¹</th>
<th>R-square adjusted (%)</th>
<th>Independent variables</th>
<th>Coefficient (95%CI)</th>
<th>p²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self evaluation of nasal appearance (NasalSWA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b*</td>
<td>4.9</td>
<td>0.011</td>
<td>13.9%</td>
<td>Rhinoplasties</td>
<td>1.70 (0.30; 3.10)</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>(2,47)</td>
<td></td>
<td></td>
<td>RelPostWidth</td>
<td>0.13 (0.02; 0.24)</td>
<td>0.021</td>
</tr>
<tr>
<td>2b**</td>
<td>10.8</td>
<td>&lt;0.001</td>
<td>27.7%</td>
<td>gender</td>
<td>1.63 (0.51; 2.75)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>(3,74)</td>
<td></td>
<td></td>
<td>PCS</td>
<td>-0.08 (-0.14;-0.01)</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MCS</td>
<td>-0.12 (-0.17;-0.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Quality of life, mental (MCS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b**</td>
<td>9.6</td>
<td>&lt;0.001</td>
<td>18.3%</td>
<td>gender</td>
<td>6.00 (1.60;10.40)</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>(2,75)</td>
<td></td>
<td></td>
<td>nasalSWA</td>
<td>-1.63 (-2.43; -0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Quality of life, physical (PCS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b**</td>
<td>7.1</td>
<td>0.001</td>
<td>13.7%</td>
<td>NARInsp(after)</td>
<td>-0.63 (-1.09; -0.16)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>(2,75)</td>
<td></td>
<td></td>
<td>nasalSWA</td>
<td>-0.88 (-1.55; -0.22)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

* Backward regression analysis presented.
** Forward regression analysis presented.
Variance ratio (F) and degrees of freedom (df)
p¹=p-value for the model
p²=p-value for specific factor
R-square adjusted (R²-adjusted) explanatory percentage adjusted for multiple factor analyses
Coefficients (change corresponding to an increase of 1), 95% confidence interval (CI)
When analyzing the dependent variable MCS, an increase in MCS (ie higher QoL) was associated to female gender. For PCS, a higher level of PCS was associated to less resistance during nasal breathing (NARInsp(after)). Furthermore, the relation between MCS and PCS to nasalSWA was confirmed with an association of decreased MCS and PCS with less satisfaction with nasalSWA, Table 9.

**Comments**

In the current study the impact of endogenous and exogenous factors on QoL and satisfaction with nasal appearance was studied. An association between satisfaction with nasal appearance to cleft width, gender and the two QoL domains; mental and physical was identified. Male gender was found to be associated with lower levels of MCS and high nasal breathing resistance was associated with lower PCS.

Age and gender were chosen as plausible factors associated to MCS, PCS and nasalSWA as earlier studies have indicated such relationships (paper I). In the current study, age was not an explanatory factor for any of the dependents analysed. It cannot be ruled out that age was excluded due to the statistical analysis method where co-variation may lead to exclusion or non-inclusion of variables that would be included if analysed separately. Hunt and co-workers, in a review, concluded that with few exceptions, the age of the individual with cleft did not influence the occurrence or severity of psychosocial problems; that the methodology in earlier studies often varied; and that the studies often lacked control groups and were based on heterogeneous groups of patients (Hunt et al., 2005). Gender was represented as an associated factor for both MCS and nasalSWA. This is in line with paper I where female gender was found to be associated with higher levels of QoL. However, this is opposite to the gender differences in the Swedish norm population for SF-36, where male gender is associated to higher levels of QoL (Sullivan, 2002).

No study evaluating associations of cleft width to satisfaction with appearance or to QoL has been found. In the present study, correlation between larger posterior cleft widths and lower satisfaction with nasal appearance was found, indicating that larger cleft size could be a predictor for less satisfaction with appearance in adulthood. A high number of rhinoplasties were associated to low satisfaction with appearance. These findings are difficult to interpret, as one cannot know if a higher number of operations were performed due to a bad aesthetic result or if the bad aesthetic outcome is a result of several operations. In the current study a large number of the patients (65/86) had had rhinoplasties performed, however only three patients among these had septoplasties performed. The external rhinoplasties have not been studied in detail, thus there is in the current study no information on what specific procedure or correction has been done.
Educational level is known to influence level of QoL (Sullivan, 2002). Earlier studies on educational status and cleft patients have shown a delay in educational achievements and lower final educational level (Broder et al., 1998; Danino et al., 2005). Norm data of the Swedish population identifies a correlation between higher level of education and increased QoL (Sullivan, 2002). However, in the current study, educational level was not associated to either nasalSWA or QoL results. This data suggests that, among a UCLP population a higher educational level is not associated to an increase in QoL to a level where it is measurable with the SF-36 questionnaire. Marital status and number of children were chosen as potential factors influencing the QoL and possibly nasalSWA. The hypotheses is based on earlier studies identifying associations between having children and living longer as well as between higher QoL and being married/co-habitating with someone (Sullivan, 2002). However in the current study the number of children was not associated to any of the dependant variables. Similarly, no association was seen for marital status. Once again, as discussed above, the statistical method used, risks excluding co-varianting factors, such as in this case number of children or marital status. Furthermore, the number of cases may be too few to identify associations.

Interestingly the current study points out that there is no association between professional ratings and patients’ nasalSWA or QoL. Paper III, studying the relation between professional and lay panels and patient’s self-assessment, showed equivalent results. These findings are important, as the decision making process for surgical treatments is a combination of the patient’s wish, the reasonability of his expectations, what is feasible surgically and what is available within the patient’s health-care system.

Nose appearance and satisfaction with appearance is important to the cleft patients as shown in several studies (Tobiasen and Hiebert, 1993; Marcusson, 2001c; Semb et al., 2005; Chuo et al., 2008). The SWA scale has been reported to possess satisfactory internal consistency and a coherent factor structure (Emerson et al., 2004) with similarities to the Cleft Evaluation Profile, developed by the Royal College of Surgeons Cleft Lip and Palate Audit group (Thomas et al., 1997; Noor and Musa, 2007). Neither the current paper nor paper III could find a correlation between professional panel’s judgment and patient’s self-assessment of appearance. Furthermore, the current data showed association between satisfaction with appearance and QoL, but not between professional’s ratings of appearance and QoL. This indicates that the patients’ own opinion about appearance and their way of handling it is of greater importance to the well-being of the patient than the extent to which the malformation stigmata is apparent to the surrounding community and to professionals.
The current study has a relative large number of participating patients from a homogenous group of UCLP (as far as for cleft malformation description) but in a statistical perspective the number of patients is relatively few for multiple regression analysis. Generally, the number of explanatory factors in a model should be no more than n/10, where n is the sample size. In the final models in this study the maximum number of explanatory factors was three, and thus no problem for any of the models. In a multiple regression analysis a subject is excluded from the analysis if the subject has missing value for any of the variables. Obviously this will lead to a problem if any variable has a large amount of missing values, as the sample size for the analysis will be largely affected. In this study there were 4 variables that had a larger number of missing values and as these where highly important, the analyses were performed in different steps to get the most information.

When performing stepwise regression analyses with a large amount of potentially explanatory factors there is always a risk of performing Type I errors, i.e. some factors are significant just by chance. A very conservative way of dealing with this problem would be to adjust the p-values according to some pre-determined procedure. However, as this study is exploratory, the nominal p-values were chosen to be presented without adjusting for multiplicity. Another way of dealing with this issue is to evaluate the models in order to see if they seem plausible or not. If not (i.e. if the included factors are empirically hard to motivate), there is a large risk that the factor would have been included by chance only. As the included factors for all of the models can be motivated empirically this indicates that the risk of committing a Type I error is sufficiently low.
General discussion

The research behind the current thesis aims to broaden and deepen the knowledge within the area of cleft care. Over the past decades, cleft research has focused on evaluating functional aspects of the cleft malformation and its treatment. In the current thesis, an attempt was made to consider the “subjective” aspects of cleft including satisfaction with appearance and QoL, and to link these subjective aspects to objective measurements. Challenges remain in finding optimal evaluation instruments for measurement of outcome after cleft treatment.

What end-points should be evaluated?

A multi-professional approach to cleft care demands a multi-faceted evaluation of treatment. Normally, evaluation methods consider one or perhaps two end-points, but none can mirror all aspects of the malformation. Additionally, a good clinical result within one area of cleft care (eg facial growth) can be associated with negative effects in another area (eg speech). There is no way of deciding upon the most important end-point for treatment of cleft patients. In the current thesis focus was put upon nasal form and function as this has been shown to be of special concern to the patients both in earlier studies and in clinical work (Asher-McDade et al., 1992; Anastassov et al., 1998; Marcusson et al., 2002; Oosterkamp et al., 2007; Chuo et al., 2008).

Certain clinical research has specific and easily quantified end-points such as survival rate, time to recurrence or flap loss. In the case of cleft research these kinds of more easily quantified end-points are lacking, or as discussed above, cannot be distinguished as the most important. Instead subjective evaluations of good or bad results are often used (Al-Omari et al., 2005; Hunt et al., 2005). The current thesis aims to quantify certain of these subjective aspects, such as QoL, satisfaction with appearance and nasal form and function. Objective quantification of data is important in order to perform evaluations and comparison of protocols. Optimal end-points should be easily quantified and thus comparable, as well as truly reflect reality. In clinical studies of CLP patients, long-term follow-up is necessary in order to
evaluate the final results of earlier surgery and the impact of the remaining deformity. The equation is challenging.

**Who is to decide about treatment?**

Especially in the case of secondary surgery one should consider the potential decision makers regarding the need for further treatment. Naturally, the patient should be highly involved in the decision regarding further corrective surgery. However, the decision making process can also involve the patient’s close surroundings such as friends, parents and other people of the society who may influence the patient. Health care professionals influence the decision of the treatment process to a varying degree.

The second question, after asking who decides on treatment, is what ground the decision is based upon? A reasonable scenario is that the satisfaction of the patient and in the long-term the QoL of the patient is the ultimate end-point. If the patient is satisfied – and lives a good life – the caregivers should be content and no further intervention should be made. On the other hand it is not obvious that further treatment is motivated in patients who are unsatisfied and experience low QoL. The risks of increased burden of care with additional treatments need to be considered (Semb et al., 2005).

In paper IV, the results indicate that QoL and satisfaction with nasal appearance of cleft patients are highly multifactorial.

The current thesis (papers III and IV) identified discrepancy between professional panel judgment and the patient’s self-assessment of appearance. Furthermore, the current data showed association between satisfaction with appearance and QoL, but not between professionals’ ratings of appearance and QoL. This tells us that the patient’s own opinion about his/her appearance is of greater importance for QoL than the health professionals’ opinion.

Although the patient’s opinion regarding further treatment is crucial, in a world with ending resources for health care it is not obvious that all patients who demand further treatment should be obeyed. It is the health care professionals’ responsibility to prioritize health care resources and use these resources soundly. To evaluate and prioritize between treatment options, transparent and comparable end-points are crucial and can help the health care professional in decision-making. As an example, much effort has been made to quantify lip and nose appearance (Becker et al., 1998b; Al-Omari et al., 2005; Edler et al., 2010). It is essential to reach concensus upon what end-points for cleft care to evaluate and base decisions upon.
Are we comparing apples and pears?

To draw conclusions from data one must be aware of the individual differences between patients in what is often referred to as homogenous groups. For the current thesis an effort was made to study a homogenous population based upon the original cleft type. On the other hand one cannot know if the cleft type is the correct factor to differentiate between patient groups. Theoretically, it is possible that categorization of patients based on cleft size or other factors (eg genetic etc) would be more adequate.

In earlier studies the patient groups have been more heterogeneous, smaller or randomly selected compared to the material in the present thesis (Sandham and Solow, 1987; Hairfield and Warren, 1989; Kunkel et al., 1999; Duskova et al., 2002; Fukushiro and Trindade, 2005). A participation rate of nearly 80% in the current thesis can be considered high, as the mean follow-up time was 35 years.

Does surgical treatment make a difference?

As a surgeon one would like to think that surgical treatment makes a difference. Considering what the situation would be like if no surgery at all was done on cleft patients, it is obvious that surgical treatment has a positive impact. On the other hand it is utterly difficult to distinguish the effect of one operation method from another. The effect of a certain surgical procedure is dependent not only upon the involved surgical steps but also the technique and experience of the surgeon, the surrounding facilities, non-surgical treatment etc. Due to these confounding factors, it can be difficult to distinguish the effect of specific surgical methods on outcome. This should be born in mind when interpreting the results of the current thesis where the operation method influenced the analysed end-points only slightly (papers II and IV). The treatment protocol for UCLP including the choice of surgical method has been debated extensively (Rohrich et al., 2000; Shaw et al., 2005; Holland et al., 2007; Stein et al., 2007). More conclusive data are still needed on outcomes of various surgical treatments in UCLP (Friede et al., 1999; Becker et al., 2000; Brattstrom et al., 2005; Molsted et al., 2005; Fudalej et al., 2009b).
The current results in a broader context

Quality of life

To the authors’ knowledge, there is no optimal instrument for evaluating disease-specific QoL in adults with UCLP. Many questionnaires have been introduced. However, these have either been constructed for use in children or adolescents (Bressmann et al., 1999; Edwards et al., 2005; Patrick et al., 2007), for other special circumstances and are therefore not applicable in the current studies (Jokovic et al., 2002; Warschausky et al., 2002) or have not been validated in a Swedish population. The QoL instrument used by Marcusson and co-workers was considered as an alternative when planning the current studies (Marcusson et al., 2001a; Marcusson et al., 2001b), however the SF-36 questionnaire was chosen as it is an internationally well-documented QoL instrument with a large norm-data base from the Swedish population (Sullivan et al., 1995; Sullivan and Karlsson, 1998; Sullivan, 2002). The SF-36 questionnaire has limitations in being a general QoL questionnaire. Consequently, the SF-36 questionnaire risks not to be specific enough to identify disease specific QoL factors. However, the data from paper I, still give valuable information; in a general QoL perspective the patients living with UCLP are doing well. There are large individual differences at least partly depending on gender and age. It is reasonable to assume that SF-36 due to its generic format rather underestimates QoL variations in the studied populations.

To answer the hypotheses regarding the potential effect of UCLP on QoL depending on gender and age a subtraction of means of gender and age matched norm data from individual patient results was done. This method may have limitations if norm data is not correctly matched. Although the norm data was matched for age and gender, other confounders such as differences in socio-economic status or education between the norm data and patient group could potentially affect the results.

Gender

In the present population, the low QoL scorings within the male group were due to extremely low values for nearly 1/5 of the male patients. When studying these patients’ files they were young men who often described a bothersome childhood with teasing and bullying as well as ongoing frustration over the current life situation (data not presented). Based upon the current results in papers I and IV, male gender could be used as predictive for lower levels of mental QoL among adults treated for UCLP. This emphasizes the importance of early identification of boys born with UCLP who may need special attention and support. Female gender was associated with less satisfaction with nasalSWA. Earlier studies show that female patients with
cleft deformities are less content with their facial appearance and rate lower levels of QoL compared to men (Berscheid and Gangestad, 1982; Broder and Strauss, 1989; Marcusson, 2001a). Other studies have found no differences between men and women when comparing level of satisfaction and psychosocial adjustment (Broder et al., 1994; Cheung et al., 2007).

Why are women and men affected differently by UCLP? Danino and co-workers identified differences in educational attainment and employment between adults with CLP and non-cleft individuals. Fewer individuals with CLP married, but when they did marry they did so later in life. They also found a significant delay in educational achievement and in living independently on their own among cleft patients. Income levels were substantially lower among CLP patients compared to controls. They concluded that, CLP patients as a group had a significant delay in the process of becoming independent (Danino et al., 2005). In a study by Persson et al, adolescents with cleft had lower body weight, stature and muscle strength. A possible correlation with lower achievement in physical education at school was seen (Persson et al., 2007; Persson et al., 2008). One might speculate that being physically strong is of greater importance to men than to women, and that being employed and having financial independence is similarly a more important factor for men.

Age
A potential drawback is the large age range in the study group. However, all patients were adults below 50 years of age. Regarding the function and appearance of the nose, patients in this age group have a fullgrown nose while the degenerative aging process of the nose has not yet started (van der Heijden et al., 2008). In addition, age-matched controls were used with nasal function values well corresponding to normal values in the literature (Millqvist and Bende, 1998; Ottaviano et al., 2006; Straszek et al., 2007).

In paper I the older age group had higher values in several HRQoL subscales. These findings correspond well with earlier studies where lower values for facial satisfaction were seen in youths (Thomas et al., 1997; Cheung et al., 2007). A possible reason for this is that acceptance and maturation increase over time in people living with a malformation. Maturation can also increase over time in a non-cleft population; however, the data in the current study indicate that this is a greater factor in a cleft population than in a non-cleft population.

Nasal function
Since there is no standardized test for measuring nasal function, four different tests that assess different aspects of the airway and nasal function, i.e. nasal dimensions, breathing and sense of smell were used (papers II and
IV). Peak nasal inspiratory flow measures flow, RM evaluates resistance to nasal breathing, AR detects acoustic reflections for mapping of the nasal cavity with calculations of minimal cross sectional areas and volumes in selected parts of the nose, and SOIT deals with odor identification. Although none of the tests is ideal for translating patient symptoms into numeric values, there is a high degree of correlation between the methods, and they provide consistent evidence of impaired nasal breathing and smell function in the UCLP patients in this study. Both AR and RM are reliable techniques for detecting skeletal deviations in the anterior part of the nose, while they are less sensitive in disclosing deviations in the posterior part or posterior to a narrowing (Hilberg et al., 1993). Therefore, posterior values on the cleft side must be considered with caution if significant obstruction has been measured in the anterior part of the nose (Szucs and Clement, 1998).

No studies were found where objectively measurable functional impairment of the cleft nose is compared to QoL levels. In paper IV, higher nasal breathing resistance was linked to lower PCS which indicates impaired airflow of the cleft nose to a degree where physical aspects of QoL is affected. These data support the expressed wish among patients to improve nasal function and should motivate the consideration of such surgery in cases of affected nasal function in preoperative ratings (Chuo et al., 2008). However, it has not been clearly evaluated if secondary rhinoplasties and septoplasties actually improve nasal function among patients with UCLP, and if these potential improvements increase physical QoL, as would be expected based upon paper IV.

**Finding the key factors**

In paper I a diverse distribution of QoL values among adults treated for UCLP was demonstrated. This resulted in an interest to identify factors of importance to the QoL outcome. These factors can either be endogenous or exogenous and cleft or non-cleft related, Table 5. Thus through paper IV a search for key factors correlating to cleft outcome – defined as QoL and satisfaction with appearance – was designed. Preferably, one would find factors that are strongly correlating to either very good or very bad outcome with a large explanatory percentage, and which are possible to influence or learn from. Furthermore, these factors should ideally be easily identified and quantified.

In the search for predictive factors for variation in QoL and satisfaction with appearance the following factors have been studied before: Emotional well-being (Feragen et al., 2009), cognitive function (Nopoulos et al., 2002), general bodyweight (Bowers et al., 1987), birth weight (Becker, Svensson et al. 1998; Wyszynski, Sarkozi et al. 2003), intellectual status (Wyszynski et al., 2006; Persson et al., 2008) and physical characteristics (Persson et al., 2007).
In addition to factors discussed in the result section, cleft width of infant maxillary study models before primary lip closure was analysed as a potential predictive factor for QoL and satisfaction with appearance in adults treated for UCLP. Analysis of cleft width at infancy and correlations to surgical outcome has been performed recently (Parwaz et al., 2009; Reiser et al., 2010). However, no study evaluating associations of cleft width to satisfaction with appearance or to QoL have been found. In the present study, correlation between larger posterior cleft widths and lower satisfaction with nasal appearance was found, indicating that larger cleft size could be a predictor for less satisfaction with appearance in adulthood. It is reasonable to think that more severe cleft malformations may lead to surgical difficulties.

In the current study, number of rhinoplasties was an explanatory factor only to nasalSWA. In general, the number of rhinoplasties performed is a factor difficult to interpret. Conclusions should be made with cautiousness, as it cannot be determined whether the number of operations and the total burden of care affect the outcome parameters or if dissatisfaction with nasal appearance results in more rhinoplasties.

As was hypothesized the factors identified in paper IV with correlation to QoL and satisfaction with appearance were not necessarily possible to influence by caregivers, but they may help us identify patients with a potentially greater need of support (eg affected nasal function, male gender, low satisfaction with nasal appearance etc).

Clinical implications

An early hypothesis, in the work of the current thesis was that palate closure in one or two stages would affect end-points such as nasal function. In the studies of this thesis little differences were seen between the two different operation protocols. This gives future caregivers information and support to decide between one-stage or two-stage closure of the palate based upon other end-points, e.g. outcome during earlier ages etc. This means that, as closure of the palate in one or two stages did not affect the nasal functional outcome, nor was a factor in the variation of QoL and satisfaction with nasal appearance, one does not have to consider these end-points when choosing operation method for palate closure.

Differences in ratings of nasal appearance between laymen, professionals and patients where the patient’s opinion correlates best to QoL give support to the caregivers when involving the patients in the discussions regarding secondary surgery.
Large infant cleft width and male-gender were associated to less satisfaction with nasal appearance and lower levels of mental QoL respectively. These factors can be identified at birth and special attention should be given to the potentially increased need of support over time especially among young men. The correlation between increased resistance during nasal breathing and low levels of physical QoL indicates impairment of nasal function to an extent where objective measurements can detect changes in resistance corresponding to changes in QoL of the patients. Patient’s satisfaction with nasal appearance and QoL did not correlate to operation method nor to professional’s ratings of nasal appearance. This indicates that the associated factors identified, are not easily improved by surgical professionals.
Conclusions

Unilateral cleft lip and palate affected QoL differently depending on gender and age of the patient. Younger patients were affected more negatively than older patients in several subscales (I).

However, except for lower values in the Mental Health subscale, QoL was similar among UCLP patients and norm data (I).

Objectively measured nasal function was extensively affected among adults treated for UCLP (II).

No difference in impairment of nasal function was found between one-stage and two-stage palate closure protocols on the cleft side (II).

Judgment of nasolabial appearance differed between professionals, lay people and patients (III).

Large infant cleft width was associated with less satisfaction with nasal appearance and male gender was associated with lower levels of mental QoL (IV).

Correlation between high nasal breathing resistance and low levels of physical QoL was found (IV).
Future perspectives

Despite generally good results of cleft care there are considerations to be made for future caregivers. Among the patients participating in the current study one third asked for a specific follow-up appointment with a surgeon in order to discuss possibilities for secondary surgery, mainly rhino- and septrTOPlasties. Based upon the results in Study IV, where associations were seen between nasal form and function and QoL there is an indication for a concealed need within cleft care. Hence, evaluation of nasal form and function as well as of QoL should be considered a part of the standard continuous evaluations of UCLP patients performed over time – equivalent to dental casts, photos, speech registrations etc.

Nasoalveolar molding has been introduced (Grayson and Maull, 2004) and recently more follow-up studies are available (Maull et al., 1999; Bennun and Langsam, 2009; Mulliken and Sullivan, 2009; Nakamura et al., 2009) making this a potential supplementary treatment. The effect of nasoalveolar molding treatment on QoL and SWA should be evaluated in a long-term perspective.

Focus is easily put on the problems experienced by cleft patients, but the evaluation of factors with a positive effect on the well being of a person treated for UCLP should perhaps receive greater attention. What can we learn from those that are satisfied and happy? (Strauss, 2001; Strauss and Fenson, 2005; Feragen et al., 2009; Strauss and Cassell, 2009). This question is of course not only relevant to the cleft patients but to all of us!
Populärvetenskaplig sammanfattning
(Summary in Swedish)

I Sverige drabbas ca 1 av 600 födda barn av någon form av läpp-, käk- och gomspalt (LKG). Läpp-, käk- och gomspalt medför funktionella och estetiska avvikelser trots kirurgiska och icke-operativa åtgärder under uppväxtåren. Målet med den aktuella avhandlingen är att utvärdera livskvaliteten och näsans form och funktion hos vuxna personer behandlade för enkelsidig total LKG. Korrelationen mellan professionellas, lekmäns och patienternas egen skattning av näsens utseende utvärderas och faktorer av potentiell betydelse för hur patienterna skattar sin näsas utseende samt sin livskvalitet utvärderas.

Läpp-, käk- och gomspalt har behandlats vid Akademiska sjukhuset i Uppsala sedan 1960-talet. Samtliga, i övrigt friska, vuxna patienter (födda 1960 -1987) med total enkelsidig LKG behandlade på Akademiska sjukhuset inbjöds att delta i studien. Av de 109 tillfrågade patienterna deltog 86 personer (79%) i medel 35 år efter första operationen. Patienterna har antingen genomgått gomslutning i en eller i två seanser; fram tills 1977 genomfördes gomslutningen i en seans, därefter i två seanser. Övrig kirurgi utöver gomslutningen följer gemensamt protokoll för de två olika grupperna. Följande utvärderingar utfördes; näsfunktion (rhinomanometri och akustisk rhinometri, peak nasal inspiratory flow mätare och lukttest), utseende (fotografier och egenskattning) samt enkäter; tex Short Form 36 (SF-36). Resultaten från dessa data utvärderades i fyra olika delarbeten. Tidigare data från journalarkiv samt bettavtryck insamlades och bearbetades i analyserna.

I delarbete I fann vi generellt god livskvalitet hos patienterna jämfört med norm data men att LKG förekomst påverkar en person olika beroende på ålder och kön: Unga män hade signifikant lägre värden för frfa emotionella subskalar av SF-36. Delarbete II påvisade kraftigt påverkat andningsmotstånd och innervolym på LKG näsens spaltsida, både i jämförelse med icke-spaltsidan och i jämförelse med kontroll personer. Däremot fann vi ingen skillnad i näsfunktionen på spaltsidan mellan de olika operationsmetoderna. I delarbete III identifierades stora skillnader mellan LKG patienters egenskattning av sin näsas utseende och panel bedömningarna av densamma där patienterna generellt skattade utseendet som sämre. I delarbete IV identifierades korrelationer mellan bred spalt vid
födseln och låg egenskattning av näsans utseende i vuxen ålder. Manligt kön var associerat till låga värden för mental livskvalitet och ökat luftflödes motstånd vid inandning genom näsan var associerat till lägre fysisk livskvalitet.

Utvärdering av behandlingsresultat vid LKG missbildning innebär flera utmaningar – behandlingen pågår under flera år hos växande individer vilket gör att slutresultaten inte kan utvärderas förrän efter många år. Därtill har det visat sig vara svårt att finna objektiva mätmetoder att utvärdera behandlingseffekten samt att besluta om vilka aspekter som skall utvärderas. I det aktuella avhandlingsarbetet är uppföljningstiden lång (20-47 år) och vi har använt oss av objektiva mätmetoder för att utvärdera näsans form och funktion, livskvalitet samt nöjdhet med utseende.
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My princes Filip and Oscar; for being just as wonderful as only you can be; for showering me with your love and affection; for making me feel happy, complete and warm inside! And to you little man – at the time of writing this dedication within me, but by the time of the celebration hopefully in my arms! Thank you for keeping me company day and night through this last path of the journey – you have kept me calm!

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Appendix

SF-36 Questionnaire
Swedish version
**Instruktion:** Detta formulär innehåller frågor om hur Du ser på Din hälsa. Informationen skall hjälpa till att följa hur Du mår och fungerar i Ditt dagliga liv. Besvara frågorna genom att markera det svarsalternativ Du tycker stämmer bäst in på Dig. Obs! Fyll i hela cirkeln, så här ✗. Om Du är osäker, markera ändå cirkeln som känns riktigast.

<table>
<thead>
<tr>
<th>1. I allmänhet, skulle Du vilja säga att Din hälsa är:</th>
<th>Utmärkt</th>
<th>Mycket god</th>
<th>God</th>
<th>Någorlunda</th>
<th>Dålig</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. De följande frågorna handlar om aktiviteter som Du kan tänkas utföra under en vanlig dag. År Du på grund av ditt hälsotillstånd begränsad i dessa aktiviteter nu? Om så är fallet, hur mycket?</td>
<td>Ja, mycket begränsad</td>
<td>Ja, lite begränsad</td>
<td>Nej, inte alls begränsad</td>
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<tr>
<td>a. <strong>Ansträngande aktiviteter</strong>, som att springa, lyfta tunga saker, delta i ansträngande sporter</td>
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<td>✗</td>
<td>✗</td>
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<tr>
<td>b. <strong>Måttligt ansträngande aktiviteter</strong>, som att flytta ett bord, dammsuga, skogspromenader eller trädgårdsarbete</td>
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<td>c. Lyfta eller bära matkassar</td>
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<td>d. Gå uppför <strong>flera</strong> trappor</td>
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<td>e. Gå uppför <strong>en</strong> trappa</td>
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<tr>
<td>f. Böja Dig eller gå ner på knä</td>
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<tr>
<td>g. Gå <strong>mer än två kilometer</strong></td>
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<td>h. Gå <strong>några hundra meter</strong></td>
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<td>i. Gå <strong>hundra meter</strong></td>
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<td>j. Bada eller klä på Dig</td>
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</tr>
</tbody>
</table>
4. Under de senaste fyra veckorna, har Du haft något av följande problem i Ditt arbete eller med andra regelbundna dagliga aktiviteter som en följd av Ditt kroppsliga hälsotillstånd?

   a. Skurit ned den tid Du normalt ägnat åt arbete eller andra aktiviteter

   b. Uträttat mindre än Du skulle önskat

   c. Varit hindrad att utföra vissa arbetsuppgifter eller andra aktiviteter

   d. Haft svårigheter att utföra Ditt arbete eller andra aktiviteter (t.ex genom att det krävde extra ansträngning)

5. Under de senaste fyra veckorna, har Du haft något av följande problem i Ditt arbete eller med andra regelbundna dagliga aktiviteter som en följd av känslomässiga problem (som t.ex nedstämdhet eller ångslan)?

   a. Skurit ned den tid Du normalt ägnat åt arbete eller andra aktiviteter

   b. Uträttat mindre än Du skulle önskat

   c. Inte utfört arbete eller andra aktiviteter så noggrant som vanligt

6. Under de senaste fyra veckorna, i vilken utsträckning har Ditt kroppsliga hälsotillstånd eller Dina känslomässiga problem stört Ditt vanliga umgänge med anhöriga, vänner, grannar eller andra?

7. Hur mycket värk eller smärta har Du haft under de senaste fyra veckorna?

8. Under de senaste fyra veckorna, hur mycket har värken eller smärtan stört Ditt normala arbete (innefattar både arbete utanför hemmet och hushållssysslor)?
9. Frågorna här handlar om hur Du känner Dig och hur Du haft det under de senaste fyra veckorna. Ange för varje fråga det svarsalternativ som bäst beskriver hur Du känt Dig.

<table>
<thead>
<tr>
<th>Hur stor del av tiden under de senaste fyra veckorna...</th>
<th>Hela tiden</th>
<th>Största delen av tiden</th>
<th>En hel del av tiden</th>
<th>En del av tiden</th>
<th>Lite av tiden</th>
<th>Inget av tiden</th>
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</thead>
<tbody>
<tr>
<td>a. ...har Du känt Dig riktigt pigg och stark?</td>
<td>☐</td>
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<tr>
<td>b. ...har Du känt Dig mycket nervös?</td>
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<td>c. ...har Du känt Dig så nedsämd att ingenting kunnat muntra upp Dig?</td>
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<td>d. ...har Du känt dig lugn och harmonisk?</td>
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<td>e. ...har Du varit full av energi?</td>
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<td>f. ...har Du känt Dig oyster och leden?</td>
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<td>g. ...har Du känt Dig utsätten?</td>
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<td>h. ...har Du känt Dig glad och lycklig?</td>
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<td>i. ...har Du känt Dig trött?</td>
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</tbody>
</table>

10. Under de senaste fyra veckorna, hur stor del av tiden har Ditt kroppsliga hälsotillstånd eller Dina känslomässiga problem stört Dina möjligheter att umgås (t ex hålsa på släkt, vänner, etc)?

<table>
<thead>
<tr>
<th>Hela tiden</th>
<th>Största delen av tiden</th>
<th>En del av tiden</th>
<th>Lite av tiden</th>
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</table>

11. Välj det svarsalternativ som bäst beskriver hur mycket vart och ett av följande påståenden STÄMMER eller INTE STÄMMER in på Dig.

<table>
<thead>
<tr>
<th>Stämmer precis</th>
<th>Stämmer ganska bra</th>
<th>Osäker</th>
<th>Stämmer inte särskilt bra</th>
<th>Stämmer inte alls</th>
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<table>
<thead>
<tr>
<th>a. Jag verkar ha lite lättare att bli sjuk än andra människor</th>
<th>Stämmer precis</th>
<th>Stämmer ganska bra</th>
<th>Osäker</th>
<th>Stämmer inte särskilt bra</th>
<th>Stämmer inte alls</th>
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<th>b. Jag är lika frisk som vem som helst av dem jag känner</th>
<th>Stämmer precis</th>
<th>Stämmer ganska bra</th>
<th>Osäker</th>
<th>Stämmer inte särskilt bra</th>
<th>Stämmer inte alls</th>
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<tr>
<th>c. Jag tror min hälsa kommer att bli sämre</th>
<th>Stämmer precis</th>
<th>Stämmer ganska bra</th>
<th>Osäker</th>
<th>Stämmer inte särskilt bra</th>
<th>Stämmer inte alls</th>
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<thead>
<tr>
<th>d. Min hälsa är utmärkt</th>
<th>Stämmer precis</th>
<th>Stämmer ganska bra</th>
<th>Osäker</th>
<th>Stämmer inte särskilt bra</th>
<th>Stämmer inte alls</th>
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