Cleft Size and Maxillary Arch Dimensions in Unilateral Cleft Lip and Palate and Cleft Palate

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Dissertation presented at Uppsala University to be publicly examined in Skoogsalen, Uppsala University Hospital, entrance 79, Uppsala. Friday, December 9, 2011 at 09:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English.

**Abstract**


The wide variation in infant maxillary morphology and cleft size of children with unilateral cleft lip and palate (UCLP) and isolated cleft palate (CP) raise concerns about their possible influences on treatment outcome. The studies in this thesis aimed to investigate the relation between cleft size in infancy and crossbite at 5 years of age (Paper I); the impact of primary surgery on cleft size and maxillary arch dimensions from infancy to 5 years of age (Paper II); associations between cleft size, maxillary arch dimensions and facial growth in both UCLP and CP children (Paper III); and, to evaluate the relation between infant cleft size and nasal airway size and function in adults treated for UCLP (Paper IV).

In homogeneously treated groups of children with UCLP and CP, dental casts were used to measure cleft size and maxillary arch dimensions from infancy up to 5 years of age, and for crossbite recording at 5 years. Serial lateral cephalometric radiographs taken between 5 and 19 years of age in the same groups were used to study facial growth. Nasal airway size and function were evaluated by acoustic rhinometry, rhinomanometry, peak nasal inspiratory flow and odour test in a group of adults treated for UCLP.

The main findings were: crossbite was a frequent malocclusion at 5 years of age in children with UCLP and large cleft widths at the level of the cuspid points in infancy were associated with less anterior and posterior crossbite in this group (Paper I). Cleft widths decreased after lip closure and/or soft palate closure in both UCLP and CP children. Initially, UCLP children had wider maxillary arch dimensions, but after hard palate closure, the transverse growth was reduced, and at 5 years, they had smaller maxillary arch widths than CP children had (Paper II). Maxillary arch depths and cleft widths in infancy were correlated with maxillary protrusion and sagittal jaw relationships in both UCLP and CP children (Paper III), but cleft width in infancy was not correlated with nasal airway size and function in adults treated for UCLP (Paper IV).

**Keywords:** Unilateral cleft lip and palate, cleft palate, cleft size, maxillary arch dimensions, crossbite, facial growth, nasal function

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ISSN 1651-6206
urn:nbn:se:uu:diva-160178 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-160178)
To my parents Ingrid and Fred
List of Papers

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


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# Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AR</td>
<td>Acoustic rhinometry</td>
</tr>
<tr>
<td>BCLP</td>
<td>Bilateral cleft lip and palate</td>
</tr>
<tr>
<td>CB</td>
<td>Crossbite</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>CPo</td>
<td>Cleft palate only</td>
</tr>
<tr>
<td>ICC</td>
<td>Intra-class correlation coefficient</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>mm</td>
<td>millimetres</td>
</tr>
<tr>
<td>INSP</td>
<td>Nasal Airway Resistance during Inspiration</td>
</tr>
<tr>
<td>PNIF</td>
<td>Peak nasal inspiratory flow</td>
</tr>
<tr>
<td>PRS</td>
<td>Pierre Robin sequence</td>
</tr>
<tr>
<td>RM</td>
<td>Rhinomanometry</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</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 of the nose (0 - 2.2 cm from nostril rim)</td>
</tr>
<tr>
<td>Vol 2</td>
<td>Nasal volume, posterior part of the nose (2.2 - 5.4 cm from nostril rim)</td>
</tr>
<tr>
<td>3D</td>
<td>Three-dimensional</td>
</tr>
</tbody>
</table>

Additional abbreviations are explained in the associated text or figures.
Introduction

Clefts of the lip and/or palate are the most common congenital malformations in the cranio-facial region. Despite many improvements over the years the treatment of children with clefts remains a challenge. From birth until early adulthood, growth, aesthetics, function, and psychosocial development must be balanced during treatment, and many problems remain to be solved.

The infant maxillary morphology and cleft size of children with unilateral cleft lip and palate and isolated cleft palate present a wide variation in degree of severity. Standardised treatment programmes are common, but treatment outcome varies. This emphasises the need for evaluating specific morphologic relationships and their potential influence on treatment outcome. The studies that constitute this thesis represent an effort to add to the scientific knowledge in this field.

Embryology

The basic morphology of the face is created between the fourth and tenth weeks through development and fusion of five prominences: an unpaired frontonasal process, two maxillary processes and two mandibular processes (Marazita and Mooney, 2004).

During the fifth week, a pair of widely separated thickenings of ectoderm, the nasal placodes, develop on the frontonasal process. In the sixth week, the ectoderm at the center of the nasal placodes invaginates to form the nasal pits and divides the raised rim of the placodes into a lateral and medial nasal process. Meanwhile, the paired maxillary processes enlarge and grow ventrally and medially. The medial nasal processes migrate and fuse to form the intermaxillary process. Normally by the end of the seventh week, the tips of the maxillary processes meet the intermaxillary process and fuse with it to form the complete upper lip and premaxilla. This process occurs through mesodermal migration and merging, and failure of this process may result in a cleft of the lip and front of the palate that varies in severity.

The nasal pits deepen and fuse to form a single ectodermal nasal sac superior and posterior to the intermaxillary process. The floor and posterior wall of the nasal sac later develop into a thin membrane, the oronasal membrane, which separates the nasal sac from the oral cavity. This membrane ruptures during the seventh week and forms the primitive choana.
During the eighth and ninth weeks, the medial walls of the maxillary processes proliferate into a pair of thin medial extensions called the palatine shelves. These shelves grow downward parallel to the lateral surfaces of the tongue, but by the end of the ninth week, they rotate upwards into a horizontal position and fuse with each other and the primary palate to form the secondary palate. Clefts of the secondary palate form when the lateral palatal shelves of the maxillary processes are not fused.

While the secondary palate is forming, ectoderm and mesoderm from the frontonasal- and intermaxillary process proliferate to form the nasal septum. The nasal septum grows down from the roof of the nasal cavity and fuses with the primary and secondary palates along the midline, thus, dividing the nasal cavity into two nasal passages (Larsen, 1993; Wyszynski, 2002; Marazita and Mooney, 2004; Rice, 2005).

Cleft lip usually occurs at the junction between the lateral maxillary process and the intermaxillary process. The cleft may affect only the lip, or it may extend more deeply into the alveolar process and primary palate. Clefts of the secondary palate can appear separately or in combination with clefts of the lip and primary palate. Depending on the time of interference with embryonic development, different clefts arise, and various combinations of clefts can appear. The most common facial clefts are clefts of the lip and/or palate, and the cleft can be unilateral, bilateral, complete or incomplete.

Etiology

The causes of both cleft lip and palate (CLP) and isolated cleft palate (CP) are largely unknown. Etiology is considered multifactorial, with both genetic and environmental factors interacting (Cobourne, 2004; Rice, 2005; Mossey et al., 2009). Gene mapping of orofacial clefts by linkage and association methods have identified candidate loci or regions on seven chromosomes that have positive linkage or association in non-syndromic CLP, CP or both (Marazita and Mooney, 2004). Environmental factors associated with cleft lip and palate include maternal smoking (Little et al., 2004; Zeiger et al., 2005), alcohol (Romitti et al., 1999), drugs such as anti-epileptics and corticoids (Abrishamchian et al., 1994; Kallen, 2003), and low levels of folic acid (Bienengraber et al., 2001; Malek et al., 2004; Johnson and Little, 2008).

Epidemiology

The total incidence of CLP is reported to be about 1.5-2.0/1000 live births and is higher among males than among females (Henriksson, 1971; Jensen et al., 1988; Hagberg et al., 1997). The incidence varies with cleft type, sex and ethnic origin. In Sweden, the incidence of cleft lip (CL), CLP and CP is 0.6-
0.7/1000 live births, and the overall incidence for bilateral clefts is 0.3/1000 live births (Hagberg et al., 1997). CL and CLP are more prominent in boys and CP is more prominent in girls. Left-sided clefts are more frequent among patients with CL and CLP (Henriksson, 1971; Jensen et al., 1988). The highest total incidence is among American Indians and Japanese, with the lowest total incidence among Africans (Vanderas, 1987).

A large number of additional malformations and syndromes are associated with oral clefts, particularly in patients with CP (Stoll et al., 2000), and associated malformations are reported in 21 to 36.7 percent of children with clefts (Hagberg et al., 1997; Milerad et al., 1997; Stoll et al., 2000; Andersson et al., 2010; Chetpakdeeitch et al., 2010). A common malformation associated with isolated CP is the Pierre Robin sequence (PRS). PRS is characterised by mandibular micrognathia, cleft palate and various respiratory difficulties during the neonatal period (Lahtinen, 1998). The incidence of PRS is uncertain, but is estimated to occur in 1 in 8500 to 1 in 20,000 births (Bush and Williams, 1983; Tolarova and Cervenka, 1998). PRS in children can be divided into isolated PRS and PRS as part of a syndrome. PRS as part of a more complex syndrome is reported in about 40 percent of PRS children (Marques et al., 2001; van den Elzen et al., 2001).

Classification

Oral clefts are usually classified by anatomy and embryology. Fogh-Andersen (1942) divided oral clefts into three main groups: CL (cleft lip) including clefts of the lip and the alveolus; CL and CP (cleft lip and palate) including unilateral and bilateral cleft lip and palate; and, CP (isolated cleft palate) being median and not extending beyond the incisive foramen. To describe the extent of the cleft in cleft palate cases more specifically, Jensen et al. (1988) divided the cleft palate into four grades: grade 1 (soft palate); grade 2 (one-third of hard palate); grade 3 (more than one-third of hard palate); and, grade 4 (total). The Kernahan and Stark classification, the “striped Y” (Kernan and Stark, 1958; Kernahan, 1971), is one of the most frequently used classifications, although new classifications have been developed recently that provide more specific cleft descriptions and that are also based on degree of severity of the cleft (Friedman et al., 1991; Ortiz-Posadas et al., 2001; Rossell-Perry, 2009).

Anatomy of UCLP and CP

The complete unilateral cleft lip and palate (UCLP) is associated with certain anatomical defects. The lip, nose and alveolus have a cleft at the right or the left side. The cleft then continues into the palatal part of the maxilla and
separate the palatal bone at the level of the nasal septum. The alveolar arch and palate are separated into a large and a small segment. The segments are often laterally displaced and the anterior end of the larger segment protrudes, and there is a midline shift to the non-cleft side. The smaller segment is usually located dorsally and the anterior part is slightly curved upwards, compared to the larger segment (Prahl, 2008). UCLP is further associated with a characteristic deformity of the nose. Spina nasalis anterior and the cartilaginous nasal septum follow the larger palatal segment and often deviate to the non-cleft side. Conversely, the bony nasal septum often deviate to the cleft side (Verwoerd et al., 1995), giving rise to a more or less curved nasal septum. The dislocated cartilaginous nasal septum is responsible for a twist in the nasal tip. The columella is deflected and shortened and the alar cartilage on the cleft side is dislodged from its normal position. The medial crus is lowered into the columella, separated from the opposite alar cartilage, and the lateral crus is flattened, spread and stretched across the cleft at an obtuse angle. The alar base is rotated outwards in a flare and the alar rim often has a web, which further reduces the apparent length of the columella on the cleft side. The resulting nostril aperture on the cleft side is positioned along a horizontal axis rather than in a vertical direction as in the normal nostril aperture (Millard, 1976).

In isolated CP the extent of the cleft varies. The cleft can be submucous characterised by a bifid uvula, a notch in the posterior hard palate and a muscular sling that is not united. The cleft can extend only into the soft palate or extend with varying degrees into the hard palate. In complete cases, the cleft extends all the way to the incisive foramen. The attachment and orientation of the palatal muscle fibres in the soft palate are altered and the muscles normally joining at the midline are instead inserted along the posterior edge of the hard palate. Therefore, the velopharyngeal sphincter function is compromised, leading to velopharyngeal insufficiency and problems with speech development. In addition, the muscle control of the Eustachian tube is lost, often leading to chronic otitis media and risk of permanent hearing loss (van Aalst et al., 2008). Examples of the two different clefts types are presented in Figure 1.
Figure 1. Extraoral (A) and intraoral view (B) of a left sided unilateral cleft lip and palate and intraoral view of an isolated cleft palate (C).

Treatment of clefts in Uppsala, Sweden

The aim of CLP treatment is to achieve a normalisation of functions such as speech, growth of the naso-maxillary complex, and facial appearance. A wide variety of treatment protocols and surgical techniques are used by various cleft teams worldwide. Surgical techniques, timing and sequence of operations, the use of infant orthopaedics and secondary surgery vary between centres, both within the same country and between countries; as a result treatment outcome differs between centres. However, some important factors associated with good and poor treatment outcome of UCLP have been identified through large inter-centre studies (Asher-McDade et al., 1992; Mars et al., 1992; Molsted et al., 1992; Shaw et al., 1992a; Shaw et al., 1992b; Daskalogiannakis et al., 2011; Hathaway et al., 2011; Long et al., 2011; Mercado et al., 2011; Russell et al., 2011).

The cleft lip and palate team at Uppsala University Hospital, Uppsala, Sweden, is one of six centers in Sweden involved in care of cleft patients. The treatment of cleft patients at Uppsala University Hospital, is performed by a multidisciplinary cleft lip and palate team consisting of plastic sur-
geons, orthodontists, otolaryngologists and speech pathologists, and children with clefts began being treated at the Department of Plastic and Reconstructive Surgery in the 1960s. The current primary referral area for the cleft team in Uppsala is the middle part of Sweden and consists of 1.5 million inhabitants with approximately 40-50 new cases being presented to the unit each year. Documentation of data has been rigorous and meticulous, and has alleviated research in this field.

Surgery

At Uppsala University Hospital, lip closure is performed at about 3 months of age in children with UCLP, and according to the method by Skoog (1969). The principle procedure is an elongation of the philtrum through incision and the use of a triangular flap from the lateral segment to close the defect. Reorientation and suture of the lip muscle and adjustment of the base of the nasal wing is included. The method is a modification and enhancement of the Tennison principle.

Until 1977, the cleft palate was closed in one procedure at the age of 18-24 months. The palatal surgery was performed according to the methods described by Veau (1931), Wardill (1937), and Skoog (1974). In this operation, mucoperiosteal flaps are shifted medially and pushed backwards in order to elongate and close the palate. In 1977, a two-stage procedure for palatal closure was introduced and is still used. Between 1977 and 1985, the interval between the two operations gradually decreased, but since 1985, the timing and the interval between the two palatal operations have not been changed (Jakobsson, 1990). The soft palate is closed at the age of 6 months and the residual cleft in the hard palate is closed at 2 years of age. Between 1977 and 1989, the soft palate was closed by Z-plasty of the oral mucosa, rearrangement of the levator palatine attachments, and elongation of the nasal side through medial and backward rotation of soft tissue (Henriksson and Skoog, 2001). The surgical technique for closure of the soft palate was modified in 1990 to improve speech and reduce the need for pharyngeal flaps (Eriksson and Henriksson, 2001; Henriksson and Skoog, 2001). The method used from 1990 was inspired by the Sanvenero-Roselli principle and is an intravelar velopharyngoplasty. In this method, the levator palatine muscle is exposed by incisions along the cleft border and carried backwards into the superior parts of the posterior pillars to include the palatopharyngeal muscle. After release and backward rotation of the musculature, the palate is sutured and elongated beyond the uvula. During the last decade, a further modification of the soft palate closure has been introduced with an intravelar veloplasty according to Sommerlad (2003). The residual cleft in the hard palate is closed in the second procedure. In this procedure, the margins of the residual cleft in the hard palate are incised, and after sufficient subperiostal
dissection the nasal and oral mucoperiosteal membranes are mobilised and the cleft closed in two layers.

During the period from 1964 to 1976, the cleft in the alveolus was repaired by infant periosteoplasty before two years of age (Skoog, 1965). From 1977, infant periosteoplasty was no longer used, instead delayed periosteoplasty was recommended at an age of 5-6 years in small alveolar clefts. During the 1980s, secondary bone grafting to the residual alveolar cleft at the age of 9-11 years became an established procedure and is still used prior to eruption of the permanent lateral incisor and canine (Boyne and Sands, 1972; Bergland et al., 1986).

Minimal or no surgery is performed on the nose until adolescence. Therefore, all surgery on the nose is categorised as supplementary/secondary surgery. The secondary nasal corrections include external rhinoplastic procedures such as adjustment of the nasal tip projection and nostril symmetry: surgery of the inner parts of the nose is rarely performed. However, primary nasal corrections according to McComb (1985) at the time of the lip closure have been introduced to the treatment programme during the last decade.

Pharyngeal flaps for correcting velopharyngeal insufficiency are, if needed, performed after the speech evaluation at 5 years of age. However, this procedure was sometimes used before 3 years of age by one plastic surgeon at Uppsala (TG Henriksson) to assist in closing wide and difficult clefts. The current surgical protocol in Uppsala, Sweden, is presented in Table 1.

**Table 1. Current surgical protocol in Uppsala, Sweden**

<table>
<thead>
<tr>
<th>Age</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>Primary lip closure according to Skoog</td>
</tr>
<tr>
<td></td>
<td>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>9-11 years</td>
<td>Bone grafting to alveolar cleft</td>
</tr>
</tbody>
</table>

**Infant orthopaedics and orthodontics**

The orthodontic treatment of patients with cleft lip and/or palate aims at creating an aesthetically pleasant occlusion with an acceptable function.

Infant orthopaedics to facilitate feeding, reduce the cleft width and to normalize and maintain the shape of the upper dental arch, pre and post surgery in UCLP has not been a regular integrated part of the Uppsala treatment protocol over the years. During the last ten years infant orthopaedic plates have been used in UCLP and bilateral cleft lip and palate (BCLP) children with wide clefts as well as PRS children. Nasoalveolar moulding as described by Grayson et al. (1999), nose hooks and elastic stripes to mould the nasal alar cartilages, columella and lip are also used to some extent.
Orthodontic treatment is usually not introduced in the deciduous dentition to avoid long and tiring periods of treatment. In the mixed dentition, however, the maxilla might require some expansion and usually the upper incisors in UCLP and BCLP need alignment before bone grafting to the defect in the alveolar process. After bone grafting at the age 9-11 in UCLP and BCLP the lateral incisor and/or the canine move spontaneously into the previous cleft area and erupt. When all permanent teeth have erupted, final orthodontic treatment is carried out with fixed appliances.

Maxillary arch dimensions and occlusion

In cleft lip and palate research, a common approach for studying the effects of different treatment regimes is through evaluation of maxillary arch dimensions and occlusion from dental casts. Different surgical treatment protocols are frequently compared through the outcome of maxillary arch dimensions and occlusion (Dahl et al., 1981; Friede et al., 1991; Berkowitz et al., 2004; Kitagawa et al., 2004; Stein et al., 2007; Fudalej et al., 2011a). Maxillary arch dimensions are generally reduced in patients with clefts (Athanasiou et al., 1987; 1988; Nystrom and Ranta, 1989; da Silva Filho et al., 1992; McCance et al., 1993; Garrahy et al., 2005; Lewis et al., 2008), and are more reduced with complete clefts than with incomplete clefts (Derijcke et al., 1994). The primary surgical repairs affect maxillary arch dimensions in children with clefts. Lip repair in UCLP has a moulding effect on the forward and outward rotated segments, which creates a more normal alveolar arch shape and the surgical closure of the palate in both UCLP and CP children affects the growth of the maxillary arch in both the transverse and the antero-posterior dimensions (Kramer et al., 1994; Honda et al., 1995; Kramer et al., 1996; Huang et al., 2002). In patients with clefts, maxillary arch dimensions, such as arch widths and arch depths, are generally larger at birth, but smaller in the primary dentition than in normal children (Kramer et al., 1996; Heidbuchel et al., 1998).

As a result of the reduced transverse maxillary arch widths, crossbite is an early and common malocclusion in children with clefts (Athanasiou et al., 1986). For UCLP, reported frequency of anterior crossbite ranges from 7 to 64 percent and reported frequency of posterior crossbite ranges from 30 to 97 percent (Hellquist and Ponten, 1979; Molsted et al., 1987; McCance et al., 1990; Polaczek, 1992; Turner et al., 1998). In CP, the reported frequencies are lower, ranging from 14 to 27 percent for anterior crossbite and 22 to 37 percent for posterior crossbite (Ranta et al., 1974; Hellquist et al., 1978). However, the ages evaluated and the method of recording or classifying crossbite differs between studies. Crossbite in patients with clefts can be associated with speech problems such as defective articulation (Laitinen et al., 1999) and deviating masticatory muscle function (Li et al., 1998).
The most common methods to evaluate maxillary arch constriction and occlusion from dental models of the jaws in patients with clefts are the Goslon Yardstick (Mars et al., 1987) and the 5-Year-Old Index (Atack et al., 1997a; Atack et al., 1997b). However, there are drawbacks with these indices, as they are exclusively made for scoring patients with UCLP, there is an element of subjectivity in the assessment, and a calibration course is needed for those who wish to use the indices. Another approach to evaluate treatment outcome with respect to maxillary arch constriction in patients with clefts is the crossbite scoring method described by Huddart and Bodenham (1972). It is more objective and reliable, more sensitive to interarch discrepancies and also correlate well with the 5-year-old and Goslon indices (Mossey et al., 2003; Gray and Mossey, 2005). In addition, the crossbite scoring method developed by Huddart and Bodenham (1972) can be reliably applied to casts of BCLP and CP patients (Tothill and Mossey, 2007; Bartzela et al., 2011), and to digital photographs of study models from 5-year old UCLP patients (Ali et al., 2006).

Facial growth

Patients with clefts have a deviating facial morphology, compared to non-cleft individuals (Dahl, 1970; Paulin and Thilander, 1991; Semb, 1991; Corbo et al., 2005; Fudalej et al., 2008; Goyenc et al., 2008; Holst et al., 2009). The facial morphology in cleft patients is characterised by a larger cranial base angle, bimaxillary retrusion, a short and posterior positioned maxilla, a more open mandibular plane angle, a decreased vertical height of the maxilla, and increased lower face height (Dahl, 1970; Semb, 1991; Lisson et al., 2005; Fudalej et al., 2008; Nollet et al., 2008). Surgery, functional factors and intrinsic effects of the cleft itself are considered responsible for the different facial morphologies and facial growth in these individuals.

Surgery as a cause of disturbed facial growth is supported by studies on unoperated cleft patients. These studies indicate that unoperated cleft patients have the potential for normal growth of the maxilla (Ortiz-Monasterio et al., 1966; Mars and Houston, 1990; Shetye and Evans, 2006). Inter-center studies evaluating treatment outcome in UCLP, show craniofacial morphology to vary in relation to the surgical treatment protocol used (Brattstrom, 1991; Brattstrom et al., 1991; Friede et al., 1991; Molsted et al., 1992; Roberts-Harry et al., 1996; Daskalogiannakis et al., 2011). Lip repair affects dentofacial growth, particularly the anterior part of the maxilla and incisor inclination (da Silva Filho et al., 2003; Liao and Mars, 2005a). The effect of palate repair is reduced maxillary length and protrusion, and an impaired sagittal jaw relation (Liao and Mars, 2005b). However, there is controversy about the type and timing of palatal surgery and its effect on facial growth (Liao and Mars, 2006b; Yang and Liao, 2010). The cleft palate can be closed
in one stage or in two stages. Delaying surgery of the hard palate can reduce impairment of facial growth, but negatively affect speech (Rohrich et al., 2000; Liao and Mars, 2006a). According to Berkowitz et al. (2005), the timing of palatal closure should be based on the ratio of the area of the cleft to the palatal segments, and the best time to close the palatal cleft is when the cleft size is 10 percent or less of the total palatal surface area. This suggestion was based on evaluation of palatal growth in 242 individuals from different centres in America and Europe. In addition, both primary and secondary bone grafting in UCLP can have an inhibitory effect on maxillary development (Ross, 1987; Brattstrom et al., 1991).

Function also influences facial growth direction in cleft patients. Nasal airway patency in cleft patients is influenced by adenoids and pharyngeal flaps. Large adenoids and pharyngeal flaps can compromise nasal airway size and affect facial growth, resulting in larger mandibular inclinations that are accentuated by age (Ren et al., 1993).

Cleft severity and maxillary morphology can also influence facial growth. Large clefts and small maxillae are generally associated with worse maxillary growth (Suzuki et al., 1993; Peltomaki et al., 2001; Honda et al., 2002; Liao et al., 2010; Chiu et al., 2011).

### Nasal airway size and function

Over the last decade, more interest has been directed towards the form and function of the nose in patients with clefts. The basic functions of the nose are respiration, humidification, temperature modification, particle filtration, olfaction, and phonation (Howard and Rohrich, 2002). Any of these nasal functions can potentially be affected in patients with clefts.

Adults with UCLP often present with residual nasal deformities that can be related to the original cleft malformation or to earlier treatment. Treated UCLP patients frequently have external asymmetries, stenosis of the vestibule on the cleft side, maxillary hypoplasia and collapse beneath the alar attachment on the cleft side, with asymmetry of the piriform aperture, underdevelopment of the maxilla and retroposition of the anterior nasal spine, and deviation of the cartilaginous and bony nasal septum and dorsum of the nose (Verwoerd et al., 1995). The nasal deformities tend to reduce the dimensions of the nasal cavity and increase nasal resistance to breathing. In UCLP patients, the nasal septal cartilaginous tip often deviates to the non-cleft side and the bony septum to the cleft side (Sandham and Murray, 1993). Reduced nasal volume and cross-sectional area and higher nasal resistance on the cleft side compared to the non-cleft side in UCLP are reported (Sandham and Solow, 1987; Sandham and Murray, 1993; Kunkel et al., 1997; Mani et al., 2010).
There are differences in nasal airway size among the cleft types and patients with bilateral and unilateral cleft lip and palate are reported to have the smallest nasal airway size (Warren et al., 1988; Fukushiro and Trindade, 2005). The nasal airway size in patients with clefts can also affect speech (Dalston et al., 1992; Warren et al., 1992), the smell threshold (Grossmann et al., 2005), and smell identification performance (Richman et al., 1988). In addition, a reduced nasal airway size has an impact on breathing mode and results in a higher frequency of compensatory mouth breathing (Warren et al., 1990; Drake et al., 1993), which in turn may affect dental and facial development (Linder-Aronson, 1970; 1979; Lofstrand-Tidestrom et al., 1999).

Cleft size

The size of the cleft at birth varies considerably (Aduss and Pruzansky, 1968; Hellquist and Skoog, 1976; Johnson et al., 2000; Peltomaki et al., 2001), and the extent of the tissue defect in infancy depends on the degree of separation of the segments and the degree of tissue deficiency. The width of the cleft in infancy influences the difficulty of surgical repair and, indirectly, the treatment outcome. There is no established method for measuring cleft severity in UCLP and CP. In children with CP, the size of the cleft is often categorised into groups by different anterior extensions in the palate. In children with UCLP, the method of measuring the cleft differs, some investigators only measure the separation between the two segments anteriorly, whereas, others measure the cleft width on several palatal levels or measure the cleft area in relation to the total palatal area. Both clinical measurements and measurements on dental casts are reported.

Cleft size and its relation to various treatment outcome variables in cleft patients have been evaluated earlier. These studies indicate that cleft size is related to arch dimensions and crossbite occlusion (Hellquist et al., 1978; Heliovaara et al., 1994), maxillary growth (Suzuki et al., 1993; Peltomaki et al., 2001; Liao et al., 2010; Chiu et al., 2011), certain speech variables (Lohmander-Agerskov et al., 1997; Persson et al., 2002), alveolar bone graft success (Long et al., 1995; Kawakami et al., 2002) and fistula formation (Parwaz et al., 2009).

Hellquist et al. (1978) grouped patients with CP according to the anteroposterior extension of the palatal cleft and found in the deciduous dentition the smallest intercanine and intermolar dimensions, as well as, the highest frequency of crossbite in patients with large palatal clefts. Similarly, Heliovaara et al. (1994) found larger palatal clefts in CP patients resulted in narrower palatal intercanine widths. However, Johnson et al. (2000), measured the cleft area in UCLP as a percentage of the total palatal area and correlated it to a 5-year-old index for dental arch relationship, but found no correlation between the size of the initial defect and the occlusal score at 6 years of age.
Peltomaki et al. (2001) found associations between the initial cleft extent and maxillary growth in children with UCLP. Patients with large clefts (measured as the degree of anterior segmental separation) and small arch circumference, arch length, or both demonstrated less favourable maxillary growth than those with small clefts and large arch circumference or arch length at birth. Chiu et al. (2011) and Liao et al. (2010) found large cleft areas in infancy to be related to a more retrusive maxilla at 9 years of age in UCLP.

Lohmander-Agerskov et al. (1997) measured the area, length, and maximal width of the residual cleft in the hard palate and correlated these with speech variables. The perceived oral pressure and resonance appeared related to the size of the residual cleft, whereas audible nasal escape and articulatory compensations were not. Persson et al. (2002) found the cleft extent in CP children to be related to retracted oral articulation. Haapanen and Ranta (1990), on the other hand, found no clear relation between cleft extent in CP subjects and degree of hypernasality at 19 years of age.

Long et al. (1995) measured cleft width on radiographs in UCLP and BCLP just before secondary bone grafting and identified a negative correlation between preoperative cleft width and alveolar bone attachment of teeth adjacent to the grafted cleft site after a mean follow-up of 3.1 years.

Parwas et al. (2009), studied cleft width on dental models in UCLP and CP patients before palatoplasty, and evaluated fistula formation after a mean follow-up period of 12.6 weeks. The width of the cleft affected the occurrence of postoperative palatal fistula formation. A width of 15 mm or more had a statistically significant risk of fistula formation. The strongest association was found for the ratio of the cleft width to the sum of the palatal shelf width. If this ratio was 0.48 or more, the risk of fistula formation was statistically significant.

Despite substantial work in this field, many questions are still unanswered, because methodology, cleft types and outcome measures varies greatly between studies.
Aims of the thesis

The overall purpose of the thesis was to study the influence of maxillary morphology and cleft size in infancy on various aspects of treatment outcome in UCLP and CP patients treated at the Cleft Lip and Palate Centre, Uppsala University Hospital, Uppsala, Sweden. In Papers I to III, the cleft groups UCLP and CP, were compared.

The specific aim of each separate paper was:

I  To investigate the relation between cleft size in infancy and crossbite at 5 years of age in UCLP and CP children.

II To study early changes in cleft size and maxillary arch dimensions and to evaluate these changes in relation to the primary surgical procedures performed on UCLP and CP children.

III To study the influence of cleft size and maxillary arch dimensions in infancy on facial growth between 5 and 19 years of age in UCLP and CP children.

IV To investigate the relation between cleft size in infancy and nasal airway size and function in adults treated for UCLP.
Materials and Methods

Subjects Papers I to III
All consecutive cleft patients, born between 1990 and 1999, and listed for primary palatal surgery at the Department of Plastic and Reconstructive Surgery, Uppsala University Hospital, Uppsala, Sweden, were originally included in the study. The material was based on the population in a region of approximately 1.5 million people and where the Cleft Lip and Palate Centre in Uppsala is responsible for all cleft lip and palate surgery. During the period 1990 to 1999, the primary surgical procedures were unchanged and there were few surgeons involved in treatment. The total number of patients listed for palatal surgery during this period was 204 patients. 28 were excluded because they had never attended the Department of Orthodontics and no lateral cephalometric radiographs or dental casts were available. 18 children were excluded because of bilateral cleft lip and palate. The medical records from the Departments of Orthodontics and Plastic Surgery and the availability of dental study casts and lateral cephalometric radiographs of the remaining 158 patients were carefully checked. UCLP and CP children were included in the study if they had the primary operations performed at the Cleft Lip and Palate Centre in Uppsala, were of Caucasian origin with no known major anomaly or syndrome and dental casts and lateral cephalometric radiographs were available. Children with combinations of different cleft types, UCLP children with an incomplete cleft of the alveolus and CP children with submucous clefts were excluded. Depending on the purpose of the study and the availability of study casts and lateral cephalometric radiographs, the number of subjects included in Papers I-III varied (Table 2). A small group of patients with nonsyndromic PRS were included and analysed separately in each Paper. The study subjects in Papers I and II are the same except for one UCLP girl later discovered diagnosed with a syndrome and therefore excluded in Paper II. The children were separated into the following groups in Papers I-III: UCLP, CPo (cleft palate only), PRS and CP (CPo+PRS).
Table 2. Number and gender of patients in Papers I-III

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>204</td>
<td>204</td>
<td>204</td>
</tr>
<tr>
<td>Never attended the Department of Orthodontics</td>
<td>-28</td>
<td>-28</td>
<td>-28</td>
</tr>
<tr>
<td>Bilateral cleft lip and palate</td>
<td>-18</td>
<td>-18</td>
<td>-18</td>
</tr>
<tr>
<td>Available for first assessment</td>
<td>158</td>
<td>158</td>
<td>158</td>
</tr>
<tr>
<td>Not fulfilling criteria</td>
<td>-78</td>
<td>-79</td>
<td>-61</td>
</tr>
<tr>
<td>Included</td>
<td>80</td>
<td>79</td>
<td>97</td>
</tr>
<tr>
<td><strong>UCLP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>29</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>Girls</td>
<td>20</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td><strong>CPo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>39</td>
<td>39</td>
<td>51</td>
</tr>
<tr>
<td>Girls</td>
<td>16</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>23</td>
<td>28</td>
</tr>
<tr>
<td><strong>PRS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>12</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Girls</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

No infant orthopaedic treatment or orthodontic treatment was performed before the age of five years in these children. However, 31 out of 33 UCLP patients and 39 out of 64 CP patients (Paper III) had had some type of orthodontic treatment at the time of the study (spring 2011).

**Subjects Paper IV**

The subjects in Paper IV were consecutive adult patients with complete UCLP, born between 1960 and 1987, and treated at the Cleft Lip and Palate Centre, Uppsala University Hospital, Uppsala, Sweden. Patients with incomplete clefts and Simonart’s band were excluded. Of the 128 consecutive patients found, five patients with associated syndromes and/or other serious disease were excluded. A further 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 sent a letter of invitation, with information about the study, asking them to participate in the study. After two weeks, non-responders were followed up by a telephone call with further information. Of the 109 patients, 83 (76 percent) agreed to participate in the assessment of nasal airway size and function. As an impression of the upper jaw had been taken routinely before each primary sur-
gical procedure, the dental casts of the upper jaw taken before the first surgical procedure, i.e. lip closure, were retrieved from the archive. Dental casts were retrieved for 53 (29 males and 24 females) of the 83 patients, and these 53 patients were included in the study.

Surgery

The children in Papers I to III were all treated with the same primary surgical protocol. The surgical protocol included lip closure in the UCLP according to Skoog (1969) at about 3 months. For palatal closure, a two-stage procedure was used: the soft palate was closed by intravelar velopharyngoplasty (Henriksson and Skoog, 2001) at about 6 months and the residual cleft in the hard palate was closed at about 2 years of age. Bone grafting was performed between 9-11 years of age according to the principles described by Boyne and Sands (1972) and Bergland et al. (1986). All primary operations were performed by a total of 5 surgeons, but two experienced surgeons performed 95-96 percent of the surgical procedures.

The adult study group (Paper IV) were not as uniformly treated surgically as the subjects of Papers I-III were, and there were many surgeons involved due to the longer period. During the period 1960 to 1987, the primary lip operation was unchanged and the lip was closed at about 3 months of age and according to Skoog (1969). In adults born with UCLP between 1960 and 1975, the palate was closed at about 2 years of age by a one-stage procedure according to Veau (1931) and Wardill (1937), which was later modified by Skoog (1974). In the adults born with UCLP between 1976 and 1987, the palate was closed by 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. Between 1977 and 1983, the soft palate was closed at about 18 months of age and the residual cleft in the hard palate was closed between 3 and 6 years of age. In 1983, the time for both operations was pushed forward, and from 1985 onwards, the soft palate was closed at 6 months of age and the hard palate at 2 years of age. Minimal or no surgery was performed on the nose until adolescence; therefore, all surgery on the nose was categorised as supplementary surgery. The secondary nasal corrections included external rhinoplasties, such as adjustment of the projection of the nasal tip, nostril symmetry, and reduction of the wedges in the nasal vestibulum. Secondary lip and nose corrections and pharyngeal flaps were performed according to the individual needs of the patient.
Methods

Dental cast measurements

Dental study casts from impressions taken of the maxilla under general anaesthesia immediately before each primary surgical procedure and dental study casts of the maxilla from the 5-year follow-up visit at the Department of Orthodontics were used for measuring the transverse and sagittal maxillary arch dimensions and cleft size. In Papers I, III and IV, only dental casts of the maxilla from the first surgical procedure were measured. In Paper II, all dental casts of the maxilla present up to 5 years of age for each individual were measured. The reference points and linear measurements used are established and have been previously described, but under various denominations (Sillman, 1964; Hellquist and Skoog, 1976; Friede et al., 1993; Huang et al., 1994; Kramer et al., 1994; Heidbuchel et al., 1998; Larson et al., 1998). However, reference points Q and Q1, marking the cleft edges at the level of the transverse distance G-G1 in CP patients, were created for the study. The reference points and linear distances are presented in Figure 2.

Maxillary arch widths were measured as the transverse distance between cuspid points (C-C1) and tuberosity points (T-T1), and maxillary arch depths were measured antero-posteriorly as the right angle distance between the incisal point (I) and a point on a line connecting C-C1 (I-CC1) or T-T1 (I-TT1). The cleft size measured on infancy dental casts was calculated as a ratio, where the transverse width/antero-posterior length of the cleft was related to the total alveolar arch transverse width/antero-posterior length:

Relative anterior cleft width (UCLP): $B-B_1$ ratio = $B-B_1/C-C_1$
Relative posterior cleft width (UCLP, CP): $A-A_1$ ratio = $A-A_1/T-T_1$
Relative middle cleft width (CP): $Q-Q_1$ ratio = $Q-Q_1/G-G_1$
Relative antero-posterior cleft length (CP): $H-T_c$ ratio = $H-T_c/I-TT_1$

In UCLP, the cleft was also measured anteriorly as the distance in millimetres (mm) between the segmental ends of the alveolar processes (D-E) and as the smallest cleft width at the level of the alveolar processes (D-E1). The dental casts were measured to the nearest 0.01 mm with digital callipers (Mitutoyo, Japan, 573-121, NTD12-15, 0.01-150 mm).
Figure 2. Schematic drawings of infant maxillary dental casts for CP and UCLP. The reference points and linear distances measured are indicated. C-C1 (anterior alveolar arch width in the cuspid region); G-G1 (middle alveolar arch width at half the distance between C and T points); T-T1 (posterior alveolar arch width in the tuber area); I-CC1 (anterior maxillary arch depth); I-TT1 (total maxillary arch depth); D-E (cleft width at the level of the alveolar processes anteriorly); D-E1 (smallest cleft width at the level of the alveolar processes anteriorly); B-B1 (width of the cleft at the level of C-C1); Q-Q1 (width of the cleft at the level of G-G1); A-A1 (width of the cleft at the level of T-T1); and, H-Tc (antero-posterior cleft length).

Crossbite scoring
Dental study casts from the 5-year follow-up at the Department of Orthodontics were used to study the occlusion for anterior and posterior crossbite (CB) (Paper I). The severity and location of crossbites were evaluated with a modification of the crossbite scoring method described by Huddart and Bodenham (1972). Each maxillary tooth was given a score according to the position relative to its opponent in the mandible (no CB = 0; edge-to-edge
relation = -1; CB = -2). Both maxillary lateral incisors were excluded from the analysis in all groups, as they were often missing or ectopically erupted in the UCLP group. If another tooth was missing, it was given a score corresponding to the mean value of the neighbouring teeth within the segment. A total crossbite score for the maxillary arch and the scores for the different segments (anterior, posterior, cuspid) of the maxillary arch were calculated.

Cephalometrics

Cephalometrics was used to study longitudinal facial growth between 5 and 19 years of age (Paper III) in UCLP and CP. Lateral cephalometric radiographs were recorded at 5-, 10-, 16- and 19-years of age, according to the treatment protocol of the Cleft Lip and Palate Centre at Uppsala University Hospital, Uppsala, Sweden. However, additional lateral cephalometric radiographs were retrieved from the medical records and digital archives that were recorded for the study subjects at other ages. Thus, a complete set of lateral cephalometric radiographs could be analysed for each individual: in total, 259 lateral cephalometric radiographs were included in the study. The radiographs were grouped according to the age levels 5-6 years, 7-8 years, 9-11 years, 13-14 years, 15-17 years and 18-19 years, however, the number of cephalometric radiographs available declined with age, and at 18-19 years, there were few recordings.

The lateral cephalometric radiographs were analysed with the cephalometric tracing program Facad 3.0, Ilexis, Sweden. The reference points and lines used in the cephalometric analysis are shown in Figure 3. The cephalometric analysis pertained to cranial base angle (NSBa), sagittal skeletal relations, including maxillary protrusion (SNA), mandibular protrusion (SNB) and sagittal jaw relation (ANB). The vertical skeletal relationships included maxillary angulation (NL/NSL), mandibular angulation (ML/NSL), vertical jaw relation (ML/NL), upper face height (UFH), lower face height (LFH) and the relation between upper and lower face height (U/L FH).
Figure 3. The cephalometric reference points and lines. Reference points: A (Subspinale, the deepest point in the concavity of the anterior maxilla between the anterior nasal spine and the alveolar crest); ANS (Anterior Nasal Spine, the tip of the anterior nasal spine); B (Supramentale, the deepest point in the concavity of the anterior mandible between the alveolar crest and Pogonion); Ba (Basion, the most inferior point on the anterior margin of the foramen magnum); Go (Gonion, a midplaned point at the gonial angle of the mandible, located by bisecting the posterior and inferior borders of the mandible); M (Menton, the lowest point on the lower border of the mandibular symphysis); N (Nasion, the junction of the frontal and nasal bones at the naso-frontal suture); PNS (Posterior Nasal Spine, the tip of the posterior nasal spine); S (Sella, the centre of sella turcica); and, Sp’ (Spina prim, a calculated point at the intersection between lines N-M and NL). Reference lines and distances: LFH (Lower Facial Height, the distance between Sp’ and M); ML (Mandibular Line, the tangent to the lower border of mandible through M and Go); NSL (Nasion-Sella Line, the line through points N and S); NL (Nasal Line, the line through points ANS and PNS); UFH (Upper Facial Height, the distance between N and Sp’); and, U/L FH (Facial index, UFH divided by LFH, in percent).
Nasal airway size and function

Nasal airway size and function were evaluated in 53 adults treated for UCLP (Paper IV).

**Acoustic rhinometry (AR)** was used for assessment of the internal size of the nasal passage. With this method, a noise signal is sent into the nose statically from a probe in the nostril, and the reflected sound is analysed and calculated. It is a well established non-invasive method for measuring minimum cross-sectional area and volume of the nasal passage. The registration was done for both right and left side as well as for anterior and posterior nasal cavity. The anterior cavity was measured from the nostril rim to 2.2 cm into the nose, including the inner valve and anterior part of the inferior turbinate. The posterior cavity was measured from 2.2 cm to 5.4 cm inside the nostril rim. The calculated values were 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.

**Rhinomanometry (RM)** was used to evaluate nasal function. RM is a dynamic process that registers the drop in pressure from the anterior to the posterior nose when breathing, and based on this, the resistance to breathing 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. In these cases, the resistance becomes infinite, therefore, resistance was set at 10 Pa s/m$^3$ for statistical purposes. The values for airflow resistance were registered for inspiration (INSP, Pa s/cm$^3$). Nasal airway resistance was calculated according to the Broms technique (Clement and Gordts, 2005).

For both AR and RM, RhinoMetrics SRE 2000 hardware platform (Interacoustics AS, Assens, Denmark) was used with different software modules (Rhinoscan for AR and Rhinostream for RM). The instrument was calibrated before each test.

**Peak nasal inspiratory flow (PNIF)** was used to evaluate maximum airflow through the nose. The total flow in both nasal passages was measured at the same time (l/min) with the Youlten nasal inspiratory peak flow meter (Airmed, London, England). Three measurements were taken and the highest value was used for analysis.

**The Scandinavian odor identification test (SOIT)** (Nordin et al., 1998) was used to evaluate smell function. In this test, the patients were exposed to 16 different odorous stimuli separately. The identification of each odour was through four response alternatives and the number of correct answers was collected for statistical analysis.

An experienced nurse at the Department of Otorhinolaryngology, Uppsala University Hospital, took all nasal measurements.
Reliability of the methods

Dental cast measurements

The reliability and intra-examiner reproducibility of the dental cast measurements were determined from duplicate recordings, 3-6 months apart, in 12 randomly chosen UCLP children and 19 randomly chosen CP children. Bland-Altman plots were created and intra-class correlation coefficients (ICC), and method errors were calculated. Method errors were calculated with the equation $\sqrt{\sum d^2/2N}$, where $d$ is the difference between two measurements and $N$ is the number of duplicate measurements. Systematic measurement errors were not observed. The ICC coefficients varied from 0.85 (I-TT1) to 1.00 (C-C1), with good correlation of repeated measurements. The method errors ranged from 0.14 (C-C1) to 0.87 (H-Tc) and were considered acceptable, as method errors of similar magnitude and range for dental cast measurements in patients with clefts have been reported (Seckel et al., 1995).

For crossbite scores, a kappa coefficient was calculated as the measurement of agreement. The kappa coefficient was 0.87 for the CP group and 0.82 for the UCLP group: the degree of agreement was considered good.

Cephalometric measurements

The reliability and intra-examiner reproducibility of the cephalometric measurements were determined from duplicate recordings, one month apart, in 10 UCLP children and 20 CP children, who were randomly chosen. In total, 74 lateral cephalometric radiographs were traced twice. Intra-class correlation coefficients (ICC) and method errors were calculated. The ICC coefficients varied between 0.90 and 1.00, except for NL/NSL (0.86): ICC of similar magnitude and range are reported for cephalometric analysis in cleft lip and palate children (Daskalogiannakis et al., 2011). The method errors ranged from 0.46 (LFH) to 1.90 (U/L FH).

Statistical analyses

Paper I

Descriptive statistics (mean, standard deviation, median and range) were calculated for all linear dimensions and crossbite scores. Differences in linear measurements between the CPo group and the PRS groups were evaluated graphically with histograms and an unpaired Students’s t-test, and differences in crossbite scores between the same two groups were assessed with the Chi²-test. The differences in crossbite scores between the combined CP group (CPo+PRS) and the UCLP group were tested with Chi²-test.
The association between cleft size in infancy and crossbite scores at 5 years was evaluated by linear regression analysis with the linear models:

\[ \text{Rang} = \text{Intercept} + (D-E) + (D-E1) + BB1/CC1 + AA1/TT1 \] for the UCLP group.

\[ \text{Rang} = \text{Intercept} + AA1/TT1 + HTc/I-TT1 + AA1/TT1: HTc/I-TT1 \] for the CP group.

An experienced statistician performed the calculations with the statistical program R version 2.4.1. P-values ≤ 0.05 were considered statistically significant.

**Paper II**

Descriptive statistics (mean, standard deviation, median and range) were calculated for all cleft dimensions and maxillary arch dimensions for the different ages and the separate groups UCLP, CPo and PRS. The individual levels and means were displayed by time in figures for each cleft size and maxillary arch dimension for the different groups (UCLP, CPo and PRS).

The differences between boys and girls and between CPo and PRS were studied by the figures showing individual values and mean lines for each variable over time.

Changes over time in cleft size and maxillary arch dimensions, for each group (UCLP, CPo and PRS) separately and for the combined CP group, were identified with linear mixed-effects models (Pinheiro and Bates, 2000). Each variable was modelled as a function of age (fixed effect) and individual (random effect). The model accounted for the design of repeated measurements by assuming a constant correlation between all measurements from the same patient (compound symmetry correlation structure). The importance of age was quantified with F-tests.

General differences between groups and differences in change over time between groups were analyzed with linear mixed-effects models and F-tests for each variable. In these models, age, group and the interaction between age and group were modelled as fixed effects, and a random effect of individual was included.

An experienced statistician performed all calculations with the statistical program R version 2.4.1. P-values ≤ 0.05 were considered statistically significant.

**Paper III**

Descriptive statistics (mean, standard deviation, median and range) were calculated for both dental cast measurements in infancy and for the cephalometric measurements at the age levels 5-6 years, 7-8 years, 9-11 years, 13-14 years, 15-17 years and 18-19 years. If a subject had had two cephalometric analyses within the same age level, the mean values of the two analyses
were used. The calculations were done for each separate group, UCLP, CPo and PRS. The distributions of the variables were determined as normal with the Shapiro-Wilk’s test. The differences in cephalometric measurements between the CPo and the PRS groups were analysed by unpaired Student’s t-test.

Pearson correlation coefficients were calculated for the separate groups UCLP, CPo, PRS, and the combined CP group to determine correlations between maxillary arch dimensions and cleft size in infancy and cephalometric outcomes at the various age levels.

The growth rates of individual cephalometric variables per year for each child were derived from a simple linear regression model. Pearson correlation coefficients were calculated to determine correlations between maxillary arch dimensions and cleft size in infancy and the growth rates of the cephalometric variables among the UCLP, CPo and PRS groups. The growth rates of individual cephalometric variables over time was further analysed for between group differences (UCLP vs. CPo and CPo vs. PRS) by unpaired Student’s t-test.

An experienced statistician performed all calculations with the SAS statistical program package, version 9.2. P-values ≤ 0.01 were considered statistically significant.

**Paper IV**

Descriptive statistics (mean, standard deviation, median and range) were calculated for all cleft dimensions and nasal airway parameters. Spearman correlation coefficients were used to determine the correlation between cleft dimensions in infancy and the nasal airway parameters in adulthood.

An experienced statistician performed all calculations with the SAS statistical program package, version 9.2. P-values ≤ 0.05 were considered statistically significant.
Results

Cleft size and crossbite (Paper I)

There was a large inter-individual range in cleft dimensions in infancy for all groups, UCLP, CPo and PRS. Cleft width at the level of the tuberosity points (A-A1 ratio) was larger in the UCLP group than in the CPo and PRS groups. Antero-posterior cleft extension (H-Tc ratio) was larger in the PRS group than in the CPo group (Table 3).

Table 3. Mean, standard deviation, median and range for cleft size measurements D-E and D-E1 in mm and cleft size ratios calculated on dental casts in infancy.

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D-E (mm)</td>
<td>29</td>
<td>7.66</td>
<td>3.50</td>
<td>6.79</td>
<td>2.04-14.4</td>
</tr>
<tr>
<td>UCLP</td>
<td>D-E1 (mm)</td>
<td>29</td>
<td>5.17</td>
<td>3.76</td>
<td>4.32</td>
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</tr>
<tr>
<td></td>
<td>B-B1 ratio</td>
<td>29</td>
<td>0.27</td>
<td>0.09</td>
<td>0.27</td>
<td>0.06-0.42</td>
</tr>
<tr>
<td></td>
<td>A-A1 ratio</td>
<td>24</td>
<td>0.28</td>
<td>0.06</td>
<td>0.27</td>
<td>0.19-0.36</td>
</tr>
<tr>
<td>CPo</td>
<td>Q-Q1 ratio</td>
<td>4</td>
<td>0.18</td>
<td>0.06</td>
<td>0.17</td>
<td>0.11-0.25</td>
</tr>
<tr>
<td></td>
<td>H-Tc ratio</td>
<td>30</td>
<td>0.24</td>
<td>0.16</td>
<td>0.21</td>
<td>0.00-0.61</td>
</tr>
<tr>
<td></td>
<td>A-A1 ratio</td>
<td>28</td>
<td>0.20</td>
<td>0.08</td>
<td>0.20</td>
<td>0.04-0.37</td>
</tr>
<tr>
<td>PRS</td>
<td>Q-Q1 ratio</td>
<td>2</td>
<td>0.08</td>
<td>0.01</td>
<td>0.08</td>
<td>0.07-0.09</td>
</tr>
<tr>
<td></td>
<td>H-Tc ratio</td>
<td>10</td>
<td>0.28</td>
<td>0.15</td>
<td>0.35</td>
<td>0.08-0.44</td>
</tr>
<tr>
<td></td>
<td>A-A1 ratio</td>
<td>10</td>
<td>0.21</td>
<td>0.06</td>
<td>0.21</td>
<td>0.15-0.36</td>
</tr>
</tbody>
</table>

Median total crossbite score at 5 years of age was -4 for the UCLP group and 0 for the CPo and PRS groups. Crossbite was recorded in 25 of 27 UCLP children and 18 of 50 children in the combined CP group. Anterior crossbite was most frequent in the UCLP group and least frequent in the PRS group. In all groups, the canine was the most frequent tooth in crossbite, and in UCLP children, the canine on the cleft side was often involved (Table 4).
Table 4. Frequencies of crossbite for different segments of the occlusion, separately for each group, UCLP, CPo, PRS, and combined CP group. The crossbite scores are dichotomized into 1= full crossbite or edge-to-edge relation and 0= normal transverse relation.

<table>
<thead>
<tr>
<th>Segment</th>
<th>UCLP</th>
<th>CP</th>
<th>CPo</th>
<th>PRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>16/27</td>
<td>8/50</td>
<td>7/38</td>
<td>1/12</td>
</tr>
<tr>
<td>Canine</td>
<td>25/27</td>
<td>13/50</td>
<td>11/38</td>
<td>2/12</td>
</tr>
<tr>
<td>Total</td>
<td>25/27</td>
<td>18/50</td>
<td>15/38</td>
<td>3/12</td>
</tr>
</tbody>
</table>

The UCLP group demonstrated significantly more crossbite compared to the combined CP group, tested with Chi²-test (p=0.002 for anterior occlusion and p<0.0001 for canine and total occlusion).

The linear regression analysis revealed no association between cleft size in infancy and crossbite scores at 5 years of age for the combined CP group. However, in the UCLP group, cleft width at the level of the cuspid points (B-B1 ratio) was negatively associated with total crossbite scores (p=0.0063), cleft side posterior crossbite scores (p=0.021), and anterior crossbite scores (p=0.012). This relation is illustrated in the 3D scatter plots in Figures 4 and 5.

![Figure 4. 3D scatter plot of the UCLP group showing the association between relative anterior cleft width at the level of the cuspid points (B-B1 ratio) at the time of lip closure, and total crossbite score and cleft side crossbite score at 5 years.](image-url)
Figure 5. 3D scatter plot of the UCLP group showing the association between the relative anterior cleft width at the level of the cuspid points (B-B1 ratio) at the time of lip closure, and total crossbite scores and anterior crossbite scores at 5 years.

Changes in cleft size and maxillary arch dimensions (Paper II)

The transverse cleft widths, both anteriorly and posteriorly, decreased after lip closure and soft palate closure in UCLP children. Anteriorly, at the time of hard palate closure, the cleft at the level of D-E1 was closed, but the distance between the segmental ends was still about 3 mm. In CPo and PRS children, the relative middle cleft width (Q-Q1 ratio) and the relative posterior cleft width (A-A1 ratio) decreased after soft palate closure: this change was significant for the A-A1 ratio. The relative antero-posterior cleft extension (H-Tc ratio) remained stable in the CPo group, but decreased in the PRS group after closure of the soft palate. The dimensional changes of the cleft in UCLP and CP are shown on photographs of dental casts in Figure 6 and 7.
Figure 6. Dental casts of a child with UCLP at lip closure (A), soft palate closure (B), hard palate closure (C) and occlusion at 5 years (D).

Figure 7. Dental casts of a child with CP at soft palate closure (A), hard palate closure (B) and occlusion at 5 years of age (C).
In UCLP children, the arch width at the level of the cuspid points (C-C1) decreased immediately after lip closure, increased after soft palate closure, and decreased again after closure of the residual cleft in the hard palate up to 5 years of age. There was no change in C-C1 over time. At 5 years, C-C1 was slightly less than at the first registration prior to any surgery. During the 5-year observation period, the arch width at the level of the tuberosity points (T-T1) increased; but was most marked during the first 2 years of life. Anterior arch depth (I-CC1) presented the same pattern of change over time as C-C1. The change over time was significant, and mean I-CC1 was slightly larger at 5 years than prior to any surgery. Total arch depth (I-TT1) decreased after lip closure, but then steadily increased up to 5 years: the increase was more marked during the period between soft and hard palate closure and the change in I-TT1 over time was significant.

In CPo and PRS children, the arch widths at C-C1, T-T1 and the total arch depth (I-TT1) increased from the time of the first registration prior to any surgery up to 5 years of age: the increase was more marked during the period between soft and hard palate closure. Anterior arch depth (I-CC1) increased after closure of the soft palate, but decreased after hard palate closure up to 5 years of age in both the CPo and PRS groups. However, the change in I-CC1 over time was only significant for the CPo group.

The A-A1 ratio was the only comparable cleft size measurement among the UCLP, CPo and PRS groups; however, there was no difference in A-A1 ratio or change over time in A-A1 ratio among the groups. Arch widths at the C-C1 and T-T1 levels differed over time both among the UCLP, CPo and PRS groups and between the UCLP and the combined CP group. Also the change in C-C1 and T-T1 over time was different between the UCLP, CPo and PRS groups as well as between UCLP and the combined CP group. In the UCLP group, the measured distances, C-C1 and T-T1, were larger in infancy and smaller at 5 years than in the combined CP group. The change over time in C-C1 and T-T1 for the UCLP and the combined CP group is illustrated in Figure 8 and 9.
Figure 8. The change over time in mean transverse distance between cuspid points (C-C1) for the UCLP and the combined CP (CP+PRS) group. First registration in UCLP before lip closure at about 3 months of age. First registration for the combined CP group before soft palate closure at about 6 months of age.

Figure 9. The change over time in mean transverse distance between tuberosity points (T-T1) for the UCLP and the combined CP (CP+PRS) group. First registration in UCLP before lip closure at about 3 months of age. First registration for the combined CP group before soft palate closure at about 6 months of age.
Maxillary arch dimensions, cleft size, and facial growth (Paper III)

In the UCLP group, anterior arch depth (I-CC1) was positively correlated to SNA at several age levels. At the older age levels (15-17 and 18-19 years of age), I-CC1 was positively correlated to SNB but negatively correlated to cranial base angle (NSBa) and maxillary angulation (NL/NSL). Total maxillary arch depth (I-TT1) was positively correlated to SNA and ANB at the younger age levels, but negatively correlated to the ratio of upper to lower face height (U/L FH) at 7-8 years of age and the cranial base angle (NSBa) at 15-17 years of age. The relative anterior cleft size (B-B1 ratio) in infancy was negatively correlated with SNA and SNB at 15-17 years of age.

In the combined CP group, the transverse maxillary widths C-C1 and G-G1 in infancy were negatively correlated to sagittal jaw relationships (ANB) at age levels 5-6 and 9-11 years. Maxillary arch depths (I-CC1 and I-TT1) in infancy were positively correlated to sagittal jaw relationship (ANB) at all age levels up to 15-17 years: the correlation to ANB was stronger for anterior arch depth (I-CC1), especially at older ages. The posterior cleft width (A-A1 ratio) in infancy was negatively correlated with the cranial base angle (NSBa) and the sagittal jaw relationship (ANB) at 7-8 years of age. Relative antero-posterior cleft length (H-Tc ratio) in infancy was also negatively correlated with upper face height (UFH) at 9-11 years of age.

Growth rates for SNA and ANB differed between the UCLP and the CPo groups. The growth rates for SNA and ANB were more negative for the UCLP group. SNA and ANB were initially larger for the UCLP group than the CPo group, but after 9-11 years of age the opposite was found. The growth rate for SNA was also more negative for the PRS group than the CPo group. The development of SNA and ANB over time in UCLP and CPo is illustrated in Figure 10 and 11.
In the UCLP group, relative anterior cleft width (B-B1 ratio) was positively correlated with the growth rate of the cranial base angle (NSBa). In the CPo
group, no correlations were identified at the 0.01 level between maxillary arch dimensions, cleft size, and the calculated growth rates of cephalometric variables. In the PRS group, the transverse width at G-G1 in infancy was positively correlated to the growth rate of U/L FH, and the anterior maxillary arch depth (I-CC1) in infancy was negatively correlated to the growth rate of the vertical jaw relation (ML/NL). However, the number of individuals analysed was few, as the PRS group was small.

Cleft size and nasal function (Paper IV)

For the adult group of 53 subjects treated for UCLP, the measurements of cleft side nasal airway size and function were reduced, compared to the non-cleft side. The acoustic rhinometry measurements (MCA 1, VOL 1, MCA 2 and VOL 2) revealed lower values on the cleft side than on the non-cleft side. Inspiratory rhinomanometric measurements (INSP) were higher on the cleft side, indicating greater resistance to breathing.

Median smell performance was 14.0 and median peak nasal inspiratory flow was 100.0 l/min. The smell function in this group of adults treated for UCLP was close to normal for the age group (Nordin et al., 1998), but the range was considerable and in four individuals smell function was below cut-off levels for anosmia. Peak nasal inspiratory flow was lower than expected (Mani et al., 2010) (Table 5).

Table 5. Descriptive data for nasal airway size and function for both the non-cleft side and cleft side. SOIT and PNIF are bilateral values.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOIT (No)</td>
<td>53</td>
<td>13.5</td>
<td>2.5</td>
<td>14</td>
<td>5-16</td>
</tr>
<tr>
<td>PNIF (l/min)</td>
<td>51</td>
<td>107.5</td>
<td>49.3</td>
<td>100</td>
<td>30-250</td>
</tr>
<tr>
<td><strong>Non-cleft side</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA 1</td>
<td>51</td>
<td>0.63</td>
<td>0.19</td>
<td>0.61</td>
<td>0.3-1.2</td>
</tr>
<tr>
<td>VOL 1</td>
<td>51</td>
<td>2.09</td>
<td>0.47</td>
<td>2.02</td>
<td>1.3-3.3</td>
</tr>
<tr>
<td>MCA 2</td>
<td>51</td>
<td>1.09</td>
<td>0.51</td>
<td>1.04</td>
<td>0.3-3.6</td>
</tr>
<tr>
<td>VOL 2</td>
<td>51</td>
<td>8.99</td>
<td>3.81</td>
<td>8.37</td>
<td>3.4-26.5</td>
</tr>
<tr>
<td>INSP</td>
<td>50</td>
<td>0.57</td>
<td>0.33</td>
<td>0.56</td>
<td>0-1.3</td>
</tr>
<tr>
<td><strong>Cleft side</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA 1</td>
<td>51</td>
<td>0.46</td>
<td>0.23</td>
<td>0.44</td>
<td>0.08-1.0</td>
</tr>
<tr>
<td>VOL 1</td>
<td>51</td>
<td>1.77</td>
<td>0.48</td>
<td>1.73</td>
<td>0.7-3.4</td>
</tr>
<tr>
<td>MCA 2</td>
<td>51</td>
<td>0.59</td>
<td>0.52</td>
<td>0.42</td>
<td>0.2-4.2</td>
</tr>
<tr>
<td>VOL 2</td>
<td>51</td>
<td>8.32</td>
<td>7.89</td>
<td>6.25</td>
<td>0.02-42.7</td>
</tr>
<tr>
<td>INSP</td>
<td>50</td>
<td>4.86</td>
<td>3.99</td>
<td>2.52</td>
<td>0.34-10.0</td>
</tr>
</tbody>
</table>

No correlations between the size of cleft, measured from infancy dental casts, and any of the variables evaluating size and function of the nasal air-
way were identified. Similarly, there were no correlations between cleft size in infancy and nasal airway size and function when the groups (one-stage closure of the palate and two-stage closure of the palate) were analysed separately.
Discussion

Materials and Methods

For this thesis, an effort was made to study homogenous groups of subjects born with UCLP and CP. Children born between 1990 and 1999, and treated at the Cleft Lip and Palate Centre in Uppsala, were chosen for the studies in Papers I-III, because during this period the protocol for primary surgery was unchanged, and only a few experienced surgeons were involved in the treatment. To further increase the homogeneity of the groups, individuals with syndromes or major malformations, non-Caucasian origin, combinations of different cleft types and primary surgery performed at another hospital with another technique were excluded. Other individuals were also excluded due to missing records, especially missing or defective dental study casts. The 5 year dental model was often missing, probably due to 5 year old children being resistant to taking the impression, which would be postponed and taken when they were older.

Changes in cleft size and maxillary arch dimensions were evaluated longitudinally (Paper II). UCLP and CP children were compared, but no control group was available for evaluation of maxillary arch dimensions in non-cleft children of the same age. However, data for non-cleft subjects is reported in other investigations (Kramer et al., 1994; 1996; Heidbuchel et al., 1998), and can be used for comparison.

A small group of PRS children were included in the studies for Papers I to III, and this group was partly analysed separately from the CPo group. Differences between CPo and PRS were detected in some dental cast measurements and cephalometric measurements. Middle cleft width (Q-Q1 ratio) was larger in the CPo group, but arch widths at the level of the tuberosity points (T-T1) was larger in the PRS group. Mandibular angulation (ML/NSL) and vertical jaw relation (ML/NL) were larger in the PRS group at several age levels. Differences in craniofacial morphology and growth between PRS and CPo have been previously reported (Laitinen and Ranta, 1992; Laitinen et al., 1997; Hermann et al., 2003; Eriksen et al., 2006). The main differences are in the mandible length and position. Laitinen et al. (1997) found young adults with PRS have a more retruded and posteriorly rotated mandible, a shorter posterior cranial base, a shorter maxilla and a shorter mandibular ramus compared to CPo. However, Laitinen (1993),
found no differences in maxillary arch widths between PRS and CPo before palatal closure: this was in contrast to our findings.

The cephalometric data (Paper III) for boys and girls were pooled because most cephalometric variables do not exhibit gender differences until adolescence and groups were generally too small, especially the UCLP group, for separate gender analysis after 9-11 years of age. In addition, most cephalometric variables evaluated were angular and/ratio measurements, and earlier research has reported sex differences mainly in size reflected in linear variables during longitudinal cephalometric evaluations of both normal children and children with clefts (Krogman et al., 1982; Jain and Krogman, 1983; Semb, 1991; Thilander et al., 2005).

The dental casts were measured conventionally and directly with digital callipers, because although virtual 3D dental cast analyses techniques were available when the work for this thesis began, the reliability of the technique was uncertain and the measuring technique was cumbersome and time-consuming. In addition, the reliability of the measurements between reference points constructed outside the surface of the model (such as I-CC1 and I-TT1) is low on virtual 3D models (Oosterkamp et al., 2006).

Cleft size ratios were calculated, where possible, as the actual defect measured in mm is less important than the extent of the defect in relation to the total arch width or total arch depth. However, cleft size, as measured on a dental cast, is not the same as the true size of the cleft in a particular individual. Although cleft size is a 3D structure, it was measured in two dimensions with digital callipers at predetermined levels on the dental casts. Even so, the cleft presented on a dental cast can contain inherent faults, in that, defects in the plaster, due to difficulties during impression taking, can be misleading, and the model only reflects the soft tissue boundaries of the cleft: the defect in the hard tissues can be more extensive.

A modification of the crossbite scoring method developed by Huddart and Bodenham (1972) was chosen instead of indices such as the Goslon yardstick and the 5-year old index, because both UCLP and CP patients were to be evaluated and the method is objective, reliable and sensitive to interarch discrepancies (Mossey et al., 2003; Gray and Mossey, 2005).

Nasal airway size and function were evaluated with four different tests to assess different aspects of the nasal airway and nasal function (Paper IV), as there is no standardised test for nasal function. Airflow was measured by peak nasal inspiratory flow. Resistance to breathing was measured by rhinomanometry and minimal cross sectional area and volume of the nose were measured by acoustic rhinometry. Acoustic rhinometry and rhinomanometry are established clinical methods for evaluating nasal patency. The reproducibility of acoustic rhinometry and rhinomanometry measurements has acceptable levels of reproducibility if done by an experienced operator under controlled circumstances (Silkoff et al., 1999). Both acoustic rhinometry and rhinomanometry are sufficiently sensitive to reveal deviations in the anterior
part of the nose, but are less sensitive for disclosing deviations in the poste-
rior part and posterior to a narrowing (Hilberg et al., 1993; Szucs and Clem-
ent, 1998); therefore, posterior values should be interpreted cautiously, espe-
cially on the cleft side. Odour identification was measured with the Scandi-
navian Odor Identification Test (SOIT), which has satisfactory reliability, 
validity, sensitivity and specificity (Nordin et al., 1998).

Relations between variables were studied with both linear regression 
analysis (Paper I) and correlations coefficients (Papers III and IV). Linear 
regression analysis is useful for information about the nature of the relation-
ship between two variables, how one change with the other, but correlation 
coefficients also give the strength of the relation. However, proof of correla-
tion does not necessarily indicate a cause-and–effect relationship, but only 
co-occurrence.

Cleft size and crossbite (Paper I)

There was wide inter-individual variation in cleft size measured on dental 
casts in infancy of both UCLP and CP children; this finding has also been 
previously reported (Pruzansky and Aduss, 1964; Aduss and Pruzansky, 
1968; Hellquist and Skoog, 1976; Hellquist et al., 1978; Johnson et al., 2000; 
Peltomaki et al., 2001).

The CP group developed less crossbite at 5 years of age and no associa-
tion with cleft size in infancy was found. In the UCLP group, crossbite was 
more frequent at 5 years of age, especially on the cleft side. The canine on 
the cleft side was usually in crossbite and this was likely due to an inward 
rotation of the anterior end of the minor segment, leaving the posterior end 
of the segment in normal transverse relation.

The comparably high crossbite frequency reported in Paper I could be ex-
plained by the different methodologies used. All end-to-end relations be-
 tween teeth and full crossbite relations were classified into the crossbite 
group. Most studies do not classify end-to-end relations or crossbite on a 
single tooth, for example the canine, as belonging to the crossbite group 
(Athanasiou et al., 1986).

A wide cleft in an infant born with UCLP, potentially demonstrating a 
large degree of tissue deficiency and with a more difficult surgical closure, 
could be considered to result in a more marked transverse constriction and 
higher frequency of posterior crossbite. However, large cleft widths at the 
level of the cuspid points in UCLP were associated with less development of 
anterior and posterior crossbite in the primary dentition.

Two-stage palatal surgery is usually considered associated with more fa-
vourable dental arch relationships than one-stage closure is (Nollet et al., 
2005; Stein et al., 2007; Fudalej et al., 2011b). The two-stage surgical 
method used for palatal closure, and the fact that the majority of clefts were
incomplete in the CP group, may explain the lower frequency of crossbite and the lack of an association between cleft size measurements in infancy and crossbite scores at 5 years in this group. The lower frequency of crossbite in the CP group could also be explained by the less severe type of clefting and the smaller number of operations for this group.

Besides the cleft itself and the surgical repair of the cleft, environmental factors can contribute to early crossbite development in these children. Tongue position, mouth breathing and jaw-posture, and non-nutritive sucking (such as digit or pacifier sucking) can contribute to the development of posterior crossbite in the primary dentition (Lofstrand-Tidestrom et al., 1999; Warren and Bishara, 2002; Malandris and Mahoney, 2004; Melink et al., 2010). In this retrospective study, these factors could not be reliably controlled, but there was no reason to consider pacifier sucking as over expressed in these children, compared to normal children.

Changes in cleft size and maxillary arch dimensions (Paper II)

The transverse cleft widths in all three groups (UCLP, CPo and PRS) decreased after lip and/or soft palate closure; however, antero-posterior cleft length in CPo remained relatively stable after soft palate closure. In UCLP children, the narrowing of the cleft after lip closure was in accordance with several other investigators (Mazaheri et al., 1971; Kramer et al., 1994; Braumann et al., 2003). Closure of the soft palate in CPo and PRS children was followed by a spontaneous reduction in the width of the remaining cleft in the hard palate: this finding was in agreement with Larson et al. (1998). At the time of hard palate closure, D-E1 (the smallest distance between the segments anteriorly) was generally closed, but D-E (the distance between the segments anteriorly) was almost 3 mm wide at this time, indicating some degree of overlapping of the segments occurred anteriorly at this stage. Mazaheri et al. (1993) evaluated early changes of maxillary alveolar arches in operated UCLP from 1 months to 4 years of age, and found the percentage of children with contact between the segments and overlap of the segments anteriorly steadily increases after lip and palatal surgery.

The antero-posterior extension of the cleft (H-Tc ratio) remained stable in the CPo group, but decreased to some extent in the PRS group after soft palate closure. In contrast to these findings, Rintala and Ranta (1987) found a 7 percent decrease in the relative antero-posterior cleft length in CP children between the age of 2 and 17 months, although it is unclear from their study whether the children received palatal surgery during this period and whether PRS children were included.
The UCLP group had wider maxillary arches in infancy, but narrower maxillary arches at 5 years of age, especially at the level of the cusp points, than the CPo and PRS groups. Anterior and total arch depths were larger in the UCLP group before lip closure, but after lip closure, presented the same pattern of change as the CPo and PRS groups. Similar changes in arch dimensions over time and in relation to the surgical procedures performed are reported (Mazaheri et al., 1971; Kramer et al., 1994; Honda et al., 1995; Kramer et al., 1996; Huang et al., 2002). The effect of lip closure on UCLP was a medial repositioning of the laterally displaced segments and a posterior levelling of the protruded larger segment to a narrower and shorter anterior maxillary arch. The closure of the soft palate did not appear to influence maxillary arch dimensions. Both transverse and sagittal arch dimensions increased after soft palate closure. However, the closure of the residual cleft in the hard palate at 2 years of age in UCLP children appeared to affect the transverse growth at the level of the cusp points (C-C1) and, to some extent, the anterior arch depth (I-CC1). These findings support the opinion that a one-stage closure of the soft and the hard palate before 2 years of age could restrict the transverse and anterior sagittal growth at an earlier age and result in a narrower and shorter maxillary arch in UCLP children.

The dimensional changes of the maxillary arch in the CPo and PRS children mimicked the reported changes in maxillary dimensions of non-cleft children (Kramer et al., 1994; 1996; Heidbuchel et al., 1998).

Initial maxillary transverse dimensions were larger in the UCLP group than in the CPo and PRS groups, and was probably due to the absence of arch continuity and a lateral displacement of the segments in UCLP. Lip closure slightly reduced the arch width at the level of C-C1, but this was later outweighed by transverse growth in the period between the soft- and hard palate closure. However, after hard palate closure in UCLP children, the transverse growth at the level of C-C1 decreased again up to 5 years of age. In UCLP, the width at the level of T-T1 continued to increase after hard palate closure, but the increase was less than in the CPo and PRS groups. The differences in maxillary arch widths between the UCLP group and the CPo and PRS groups support the earlier results on transverse occlusion in the same groups of children at 5 years of age (Paper I).

It can be tempting to speculate that the increased tension from the reconstructed lip after lip closure in UCLP is the most contributing factor behind the reduced maxillary arch development in this group compared to the CPo and PRS groups. However, the results of our study clearly demonstrate that the lip closure only has a temporary and limited constricting effect on the maxilla. Instead, the closure of the residual cleft in the hard palate seems to give some reduction of the transverse growth of the maxilla in the UCLP group compared to the CPo and PRS groups. However, the maxillary arch constriction in UCLP should not solely be interpreted as a consequence of primary surgery. An intrinsic tissue deficiency (Lo et al., 2003), medial dis-
placement of the segments, especially the minor segment (da Silva Filho et al., 1992), and mode of breathing and resting posture of the oral cavity (Kozelj, 2000) can also influence maxillary arch dimensions in UCLP.

Aside from delaying an inhibitory effect on the transverse growth of the maxilla, a two-stage closure of the palate allows spontaneous narrowing of the cleft in the hard palate, thereby minimising the technical difficulties during surgery and also secondary fistulae formation (Jakobsson and Ponten, 1990; Parwaz et al., 2009). However, a two-stage closure of the palate with late closure of the hard palate may compromise speech development (Lohmander-Agerskov et al., 1995; Lohmander-Agerskov et al., 1996; Van Lierde et al., 2004).

Maxillary arch dimensions, cleft size, and facial growth (Paper III)

The evaluation of facial growth from 5 to 19 years of age in UCLP and CP children and the relationship between maxillary arch dimensions and cleft size in infancy and facial growth revealed consistent associations between maxillary arch depths (I-CC1 and I-TT1) in infancy and sagittal skeletal relations (SNA, ANB) in both UCLP and CP children.

In UCLP children, a short maxilla in infancy appeared associated with a lower degree of maxillary protrusion, impaired sagittal jaw relation, and a larger cranial base angle. A large initial cleft width at the levels of the cupids was associated with lower values of maxillary and mandibular protrusion, suggesting a short maxilla, and especially a short anterior arch depth, and a wide cleft at the level of the cuspids in infancy were factors related to less favourable sagittal growth of the maxilla. This finding was in agreement with Peltomaki et al. (2001) who found UCLP patients with wide clefts and small arch length in infancy have less favourable maxillary protrusion at 5-6 years of age. Similar findings are also reported by Honda et al. (2002) who used surface laser scanning to determine palatal surface area and volume in infancy and correlated this to facial growth at 16 years of age in UCLP children. Larger palatal surface areas and volumes in infancy (i.e. larger maxilllas) were associated with larger SNA and ANB values in their study.

In the combined CP group, large maxillary arch depths and more constricted arches appeared associated with larger ANB values. Wide clefts at the level of the tuberosities in infancy were associated with decreased cranial base angles and ANB values. Clefts with a large antero-posterior extension into the hard palate were also associated with lower values of upper face height, indicating CP children with short and wide arches and a wide cleft at the level of the tuberosities in infancy were at risk of developing less favourable sagittal jaw relations during subsequent growth. Cleft extent is reported
to have an impact on facial morphology in CP patients (Jakobsson, 1990; Heliovaara and Ranta, 1993), but different measuring methods inhibited direct comparison of data with our study.

During the observation period of 5-19 years of age, mean annual growth rates for maxillary protrusion (SNA) and sagittal jaw relation (ANB) were more negative in the UCLP group than in the CPo group. Reduced maxillary growth and successive impairment of sagittal jaw relationships during growth in UCLP is previously reported in several studies (Paulin and Thilander, 1991; Semb, 1991; Corbo et al., 2005; Fudalej et al., 2008; Nollet et al., 2008). The growth rate for maxillary protrusion (SNA) also appeared more negative for the PRS group than for the CPo group. The reason is unknown, but it can be assumed that a larger antero-posterior cleft extension in the PRS group may have affected the sagittal growth of the maxilla more (Heliovaara and Ranta, 1993).

Earlier studies on the relationship between maxillary morphology in infancy and outcome in terms of craniofacial growth in UCLP (Suzuki et al., 1993; Peltomaki et al., 2001; Liao et al., 2010; Chiu et al., 2011) have all used an early evaluation point (4-9 years), presurgical orthopaedics, and a one-stage closure of the palate at 1 or 2 years of age. Various methods of measuring cleft size have been applied, and there are differences in the cephalometric analysis used. Despite this, they all report negative relations between cleft size measurements in infancy and facial growth parameters, which are in accordance with the findings in Paper III.

**Cleft size and nasal function (Paper IV)**

In adult patients with UCLP, the clinically measured minimal cross sectional area, volume, and resistance to breathing were impaired on the cleft side compared with the non-cleft side. PNIF was lower than expected. In a normal control group, mean PNIF values were 159 l/min (Mani et al., 2010). Median smell function evaluated with SOIT (14 correct smell identifications) was normal for the age group when compared with normative data for the same age group (12-16 correct smell identifications) (Nordin et al., 1998). In contrast to our findings, studies on children and adolescents show higher smell threshold in UCLP on the cleft side (Grossmann et al., 2005) and marked lower olfactory scores in boys with cleft lip and/or palate compared with a normal control group (Richman et al., 1988).

Side differences and reduced airway size and function on the cleft side in UCLP is previously reported (Sandham and Solow, 1987; Grossmann et al., 2005; Mani et al., 2010), and the most likely explanation for the side difference in size and function is the frequent deviation of the nasal septum in UCLP patients (Sandham and Murray, 1993).
Size and function of the nasal airway in adulthood was not correlated with the measured extent of the defect in infancy. Despite this lack of association, the study provided value information, as there is a lack of data on the relation between cleft size in infancy and objectively measured nasal airway size and function in patients treated for UCLP.

The strength of the data on the outcome of internal size and function of the nose in this adult group of UCLP patients was that none of the patients had had secondary internal nasal surgery or septoplasty. In addition, several methods were used for objectively recording the different nasal variables: neither the variables measuring size nor those measuring function were correlated with initial size of cleft.

A potential shortcoming of this study was the wide age range (19-45 years) for assessing the size and function of the nasal airway. Other limitations included the different treatment protocols used for palatal closure within the group, the different protocols for alveolar bone grafting, various orthodontic treatments, and supplementary treatments, such as pharyngeal flaps and orthognathic surgery, and that many surgeons were involved in the treatment. Thus, many potential factors could affect treatment outcome in in this group of adult subjects treated for UCLP.

General discussion

Treatment outcome in patients treated for clefts can be evaluated from many aspects: surgery, speech, appearance, psychological well-being, facial growth, maxillary arch dimensions and occlusion, and nasal airway size and function. Despite numerous scientific reports, there is still incomplete understanding of the factors affecting outcome of treatment in patients treated for clefts. In a broader context, potential factors influencing outcome are intrinsic, functional and iatrogenic (factors related to the treatment given) (Ross, 1987). The iatrogenic factors have received most attention over the years. Several large inter-center studies evaluating dental arch relationships, craniofacial morphology and nasolabial appearance (Asher-McDade et al., 1992; Mars et al., 1992; Molsted et al., 1992; Shaw et al., 1992a; Shaw et al., 1992b; Daskalogiannakis et al., 2011; Hathaway et al., 2011; Long et al., 2011; Mercado et al., 2011; Russell et al., 2011) have shown treatment outcome to vary with treatment protocol used. Although intrinsic factors such as initial maxillary morphology and size of the cleft in infancy and its effect on treatment outcome have been evaluated, the studies use different methodology and outcome measures. The majority of the more recent studies in the field focus on the relation between cleft size in infancy and facial growth in UCLP children (Suzuki et al., 1993; Peltomaki et al., 2001; Liao et al., 2010; Chiu et al., 2011).
The studies comprising this thesis aimed to expand knowledge on how cleft size and maxillary arch dimensions in infancy were influenced by primary surgical procedures and how they could affect treatment outcome with respect to crossbite, facial growth, and nasal airway size and function. The evaluation of treatment outcome in relation to the extent of initial deformity in cleft patients is vital for making early decisions about treatment prognosis and for better allocation of treatment resources to those in greatest need.

The endpoint for evaluation of treatment outcome is often difficult to decide. The advantage of early evaluation during childhood is to determine the outcome of primary surgical treatment before additional treatments, such as orthodontics, secondary surgery or orthognathic surgery is performed. Therefore, early outcome studies provide immediate feedback on primary surgery. The disadvantage of early evaluation is that growth is not finished and the influence on the outcome after finished growth cannot be evaluated.

Clinical implications

UCLP patients with wider clefts at the canine level had less anterior and posterior crossbite at 5 years of age, suggesting that if a wide cleft is encountered at the canine level and appropriate atraumatic surgical care is provided; satisfactory arch form and occlusion may result at the age of 5 years. It would also suggest that moulding with the aim of narrowing the cleft through infant orthopaedics prior to surgery, could increase the probability of crossbite development in the primary dentition.

After lip and/or soft palate closure, cleft widths decreased in both UCLP and CP children. This facilitates palatal repair and presurgical orthopaedics to encourage lateral palatal shelf growth by stopping the tongue from sitting within the cleft site appear unnecessary.

The lip closure in UCLP resulted in a medial repositioning of the laterally displaced segments and a posterior levelling of the protruded larger segment to a narrower and shorter anterior maxillary arch. The closure of the soft palate did not have a major influence on maxillary arch dimensions in both UCLP and CP, but closure of the residual cleft in the hard palate appeared to reduce the transverse growth of the maxilla in the UCLP group. Thus, it would be reasonable to suggest that a one-stage closure of the soft and the hard palate before the age of 2 years would lead to an earlier restriction of transverse growth in UCLP, and a narrower maxillary arch and more crossbite in the primary dentition.

A short maxilla and a wide cleft at the level of the cuspids in infancy were factors associated with less favourable sagittal growth of the maxilla in UCLP children. In CP children, both a short and a wide arch, and a wide cleft at the level of the tuberosities in infancy were factors associated with less favourable sagittal jaw relations during subsequent facial growth. There-
fore, in UCLP and CP patients born between 1990 and 1999 and treated at the Cleft Lip and Palate Centre in Uppsala, Sweden a wide cleft in infancy appeared to be positive for occlusion, but negative for growth. Further studies are needed, but possibly in the future, early presurgical measurement of maxillary arch depth and cleft width may help predict maxillary growth and decisions of treatment needs on an individual basis.

As nasal airway size and function in adults treated for UCLP was not correlated with size of the cleft in infancy, other parameters must have been involved. Thus, future research in the field should focus on identifying early predictors of nasal form and function in patients with clefts in order to prevent or minimise the impairment of the nasal function associated with this deformity.
Conclusions

The main conclusions from this thesis are:

Cleft sizes vary considerably between individuals in infancy.

Crossbite is a frequent malocclusion at 5 years of age, especially in children with UCLP.

In UCLP children, but not in CP children, there appears to be an association between cleft width in infancy and crossbite at 5 years. Large cleft widths at the level of the cuspid points in infancy are associated with less anterior and posterior crossbite at 5 years in UCLP children.

Cleft widths decrease after lip and/or soft palate closure in both UCLP and CP children. During the first years of life, UCLP children have wider maxillary arch dimensions than CP children have, but after hard palate closure, the transverse growth reduces more in UCLP children than in CP children. At 5 years of age, UCLP children have smaller maxillary arch widths than CP children have, especially at the level of the cuspids.

Maxillary arch depths and cleft widths in infancy appear associated with maxillary protrusion and sagittal jaw relationships in UCLP and CP children. Maxillary protrusion and sagittal jaw relation develop less favourably in UCLP than in CPo.

In adults treated for UCLP, nasal airway size and function seems reduced on the cleft side compared to the non-cleft side, but cleft width in infancy is not correlated with nasal airway size and function in adulthood.
Läpp-, käk- och/eller gomspalt (LKG) är den vanligaste medfödda missbildningen i huvud/halsområdet och i Sverige drabbar ca 1 barn på 600 födda av någon form av LKG. Utan behandling får dessa individer uttalade funktions- och estetiska avvikelser. Behandlingen syftar till att normalisera funktion och utseende till största möjligaste mån. Trots ett omfattande multidisciplinärt omhändertagande med både kirurgiska och icke-kirurgiska behandlingar under uppväxten har de ofta kvarstående funktionella och estetiska avvikelser efter avslutad behandling. Forskning inom området syftar ofta till att hitta de behandlingar som på bästa sätt balanserar funktion och estetik till bästa möjliga behandlingsresultat.

Spaltens storlek vid födseln kan se mycket olika ut mellan olika individer med samma typ av spalt. Målet med den aktuella avhandlingen är att studera hur spaltens storlek och överkäkens dimensioner förändras under de första åren under påverkan av de kirurgiska ingreppen som görs och att studera om ursprunglig spaltstorlek påverkar graden av korsbett i mjölk tandsbettet vid 5 års ålder, tillväxten i käkarna mellan 5 och 19 år och näs ans inre form och funktion i vuxen ålder.


På de barn som ingår i delarbete I-III har spaltens storlek och överkäkens bredd och längd har mätts med ett digitalt skjutmått på gipsmodeller av överkäken tagna i samband med läppoperationen, slutning av mjuka gommen, slutning av hårda gommen och vid 5 års ålder. På gipsmodeller av käkarna från 5 år har också graden av korsbett poängbedömts. Käkarnas och ansiketoids tillväxt har analyserats med kefalometrisk analys av samtliga profilröntgenbilder tagna på barnen mellan 5 och 19 år.

På de vuxna som ingår i delarbete IV har spaltens storlek och tandbågsdimensioner mätts med ett digitalt skjutmått på gipsmodell av överkäken tagen i samband med läppoperationen. Näsans inre form och funktion i vuxen ålder har sedan utvärderats med akustisk rhinometri, rhinomanometri, luftflödesmätare och ett lukttest.
Utifrån de mätningar som gjordes på de första gipsmodellerna av överkäken kunde det konstateras att spaltens storlek varierade mycket mellan individer från början.

I delarbete I fann vi att korsbett och frontal invertering var vanligt vid 5 års ålder och att barnen med enkelsidig LKG hade mer korsbett och frontal invertering jämfört med barnen med isolerad gomspalt. Inget samband fanns mellan ursprunglig spaltstorlek och korsbett eller frontal invertering vid 5 år för barnen med isolerad gomspalt. För barnen med enkelsidig LKG däremot fann vi att spaltbredden i hörntandsnivå hade ett negativt samband med förekomst och grad av korsbett och frontal invertering. En bredare spalt från början var associerat med mindre korsbett och frontal invertering vid 5 år.

I delarbete II fann vi att spaltens bredd minskade efter läppslutning och/eller slutning av spalt i mjuka gommen hos både spaltgrupperna. Spaltens längd hos barnen med isolerad gomspalt var oförändrad. Barnen med enkelsidig LKG hade bredare överkäkstandbåge jämfört med barnen med isolerad gomspalt under de första 2 åren, men efter slutning av spalten i hårdagommen hämmades den transversella växten av överkäken mer hos dessa barn och vid 5 års ålder hade de smalare överkäkstandbåge, framförallt i hörntandsområdet, jämfört med barnen med isolerad gomspalt.

I delarbete III fann vi ett flertal positiva samband mellan överkäkens ursprungliga längd och överkäkens protrusionsgrad och käkarnas sagittala relation på profilröntgen från flera åldrar. Dessutom fann vi negativa samband mellan ursprunglig spaltstorlek och vissa skelettala parametrar utvärderade på profilröntgen mellan 5 och 19 år. Överkäkens protrusionsgrad och käkarnas sagittala relation utvecklades mindre gynnsamt för gruppen med enkelsidig LKG jämfört med gruppen med isolerad gomspalt.

I delarbete IV fann vi hos vuxna behandlade för enkelsidig LKG att näsans inre form och funktion var försämrad på spaltsidan jämfört med icke-spaltsidan. Luktformågan låg dock inom ramen för vad som anses normalt för åldersgruppen. Inget samband fanns mellan spaltens ursprungliga bredd och näsans inre form och funktion i vuxen ålder.

Detta avhandlingsarbete har genom att använda samma mätmetod och utvärderingsanalys på två vanligt förekommande spalttyper (enkelsidig LKG och isolerad gomspalt) visat att både typ av spalt och spaltens storlek vid födseln kan ha betydelse för behandlingsresultatet när det gäller ocklusjon och käkarnas tillväxt. Däremot verkar inte spaltens ursprungliga storlek hos vuxna behandlade för enkelsidig LKG ha betydelse för näsans inre form och funktion.
Acknowledgements

This thesis would not have been possible without the help and commitment of many persons. In particular, I want to thank:

Anna Andlin-Sobocki, my principal supervisor and co-author of all the papers. You have given me never ending support, encouragement, and much valuable advice over the years. I am deeply impressed by your brilliant mind, your experience and knowledge in the field, and your enthusiasm and generosity. I am most grateful for all the hard work you have put in over the years to teach me how to become a scientist.

Valdemar Skoog, my co-supervisor and co-author in Papers I and II, for sharing your great experience and knowledge of patients with clefts, teaching me basic principles of plastic surgery, and finally, for believing in me and helping me advance in my professional career.

Bengt Gerdin, my co-supervisor and co-author in Paper I, for your invaluable support, great ideas and practical help with the frequent enquiries encountered in the world of science. Thank you also for the excellent schematic drawings of maxillary dental casts.

Tor-Göran Henriksson, my former co-supervisor, for initiating this project and generously sharing research data.

Mats Holmström, my co-author in Paper IV, for sharing your great knowledge of the nose, and for your friendly support.

Maria Mani, my co-author in Paper IV, for generously sharing research data, encouragement, and for inspiring me to keep up with you.

Andreas Svee, my co-author in Paper III, for fast and precise delivery of extensive amounts of data.

Malin Hakelius, for taking excellent care of me during my time at the department of plastic and reconstructive surgery, for trying to teach me some basic principles of plastic surgery, and for a never ending friendly support.
Birgitta Henricsson and Karolin Gazharian, for all help over the years collecting/searching for medical records, dental casts and lateral cephalometric radiographs.

Caroline Andlin-Sobocki, for retrieving dental casts from the archives and assisting in dental cast measurements.

Ingrid Lönnstedt and Lars Berglund, for valuable statistical advice, discussions, and analyses.

Henrik Raber and Doris Berentsson, for giving me time off from the clinic whenever needed, for believing in me, and giving me the opportunity to grow professionally as well as academically.

My former and current colleagues at the department of orthodontics: Viveca Brattström, Olle Malmgren, Lars Goldson, Malin Karlsson, Ingrid Jönsson-Ring, Lars Petrini, and Kjell Palm, for your encouragement, and for taking care of my orthodontic patients while I was away writing this thesis.

My orthodontic assistants: Kajsa Lacorazza and Kerstin Heinemo, for the care of my orthodontic patients, for putting up with me during stressful days, and for making my work such fun.

My dear parents Ingrid and Fred Lindroth (to whom I dedicate this thesis), who despite having little academic education, have always inspired me to educate myself, and fully supported me in my educational choices. Thank you for teaching me to believe in myself and for your constant love and support.

My fantastic husband Mikael, and my wonderful girls Julia and Nellie, for your love and patience, and for always reminding me of what is most important in life.

The Thuréus foundation, the Public Dental Health Service, and Uppsala County Council, Uppsala, Sweden are acknowledged for financial support and grants during the work of this thesis.
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