Cleft Lip and Palate - Epidemiology, Treatment and New Methods for Evaluation

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Cleft Lip and Palate

Epidemiology, Treatment, and New Methods for Evaluation

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Måns Cornefjord is a plastic surgeon at the Department of Plastic and Reconstructive Surgery, Skåne University Hospital, with a special interest in pediatric plastic surgery.

This PhD thesis focuses on cleft lip and/or palate, exploring the epidemiology of condition in Sweden and the occurrence of additional diagnoses among affected children. In addition, it examines different surgical methods for cleft palate repair and investigates the potential use of artificial intelligence in the follow-up and evaluation of speech outcomes.

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DOCTORAL DISSERTATION

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In Paper I, national registry data on over two million births in Sweden (2000–2020) was analyzed to determine the birth prevalence of CL/P and certain cleft subtypes, including temporal trends. The total CL/P birth prevalence during the studied period was 1.52 per 1,000 births, with declining trends for CL/P and all studied subtypes except cleft palate without cleft lip (CP).

Paper II used the same dataset as Paper I. Differences in birth prevalence of CL/P and subtypes between the six Swedish HC regions, and regional temporal trends, were analyzed. Birth prevalence was lower in the Stockholm HC region except for CP, higher for CP in the Northern HC region, and higher for cleft lip with/without cleft palate (CL±P) and bilateral CL±P (BCL±P) in the Southeastern and Southern HC regions. Declining trends were seen for all studied subtypes except CP.

In Paper III, medical records of 250 children with CL/P from the Southern HC region (born 2006–2016) were reviewed. One third (36.0%) had received an additional diagnosis by age 5, most commonly affecting the cardiovascular system (20.4%) and extremities and skeletal system (17.5%).

Paper IV was a systematic review comparing one- versus two-stage palatoplasty. No clear overall differences in outcome were found between the techniques. The certainty of evidence was highest for fistulae, facial growth, and speech outcomes.

Paper V explored AI-based assessment of velopharyngeal competence using audio recordings of children with cleft palate and perceptual speech assessments made by speech-language pathologists (SLPs). Two AI networks were developed, the best-performing agreeing with SLP assessments in 57.1% of recordings.

Overall, the thesis provides reliable updated estimates of CL/P birth prevalence in Sweden, new insights into additional diagnoses, an evaluation of palatoplasty techniques, and an initial exploration of AI-based methods for speech assessment.

Key words: cleft lip, cleft palate, epidemiology, Sweden, additional diagnoses, one-stage, two-stage, palatoplasty, artificial intelligence, speech

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MADE IN SWEDEN

To my mother and father,

Table of Contents

Original Papers

Paper I

Cornefjord M, Källén K, Klintö K, Stiernman M, Wiedel AP, Becker M. Birth prevalence of cleft lip and/or palate – a register study of all children born in Sweden years 2000–2020. J Plast Surg Hand Surg. 2025;60:120–6. doi:10.2340/jphs.v60.43739.

Paper II

Cornefjord M, Källén K, Klintö K, Stiernman M, Wiedel AP, Becker M. Regional differences in birth prevalence of cleft lip and/or palate in Sweden – a register study of all children born in Sweden between 2000 and 2020. J Plast Surg Hand Surg. 2025;60:196–203. doi: 10.2340/jphs.v60.44798.

Paper III

Aspelin E, **Cornefjord M**, Klintö K, Becker M. Additional diagnoses in children with cleft lip and palate up to five years of age. J Plast Surg Hand Surg. 2023;57(1-6):476–82. doi:10.1080/2000656X.2022.2164292.

Paper IV

Cornefjord M, Arnebrant K, Guné H, Holst J, Klintö K, Stiernman M, Svensson H, Wiedel AP, Becker M. A systematic review of differences in outcome between one and two stage palate repair in cleft lip and palate. J Plast Surg Hand Surg. 2023*;*58:132–41. doi:10.2340/jphs.v58.13368.

Paper V

Cornefjord M, Bluhme J, Jakobsson A, Klintö K, Lohmander A, Mamedov T, Stiernman M, Svensson R, Becker M. Using artificial intelligence for assessment of velopharyngeal competence in children born with cleft palate with or without cleft lip. Cleft Palate Craniofac J. 2025;62(10):1684–94. doi:10.1177/10556656241271646.

Abstract

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Key Insights of the Thesis

Paper	Study design	Population	Size	Key outcome	Key findings	Additional findings
I	Registry-based study	CL/P and subtypes	2,230,771	Birth prevalence in Sweden 2000–2020	CL/P birth prevalence: 1.52 / 1,000 births	Declining trends for CL/P and all subtypes except CP
II	Registry-based study	CL/P and subtypes	2,230,771	Regional birth prevalence in Sweden 2000–2020	Lower birth prevalence of CL/P in Stockholm HC region	Regional differences in prevalence per subtype. Declining trends for CL/P and all subtypes except CP in ≥2 regions
III	Retrospective cohort study	CL/P and subtypes	250	Additional diagnoses at age 5	36.0% had ≥1 additional diagnosis	Most common: extremities/skeletal, cardiovascular
IV	Systematic review	CP±L	14 original studies included in review	Overall advantages in outcome for one- vs. two-stage palatoplasty	No overall advantage for either approach	Highest certainty of evidence for outcomes fistulae, growth, speech (non-syndromic UCLP)
V	Methodological study	CP±L	449 audio recordings + speech assessments	AI assessment of VPC, accuracy compared with SLP assessment	Best ANN (VGGish): 57.1% accuracy	Not clinically applicable at this point

Table 1 – Key Insights.
Abbreviations: CL/P = cleft lip and/or palate. CP = cleft palate without cleft lip. HC region = health care region. CP±L = cleft palate with/without cleft lip. UCLP = unilateral cleft lip and palate AI = artificial intelligence. VPC = velopharyngeal competence. SLP = speech-language pathologist. ANN = artificial neural network. VGGish = one of the ANNs included in Paper V.

Abbreviations

AI	Artificial intelligence
ANN	Artificial neural network
BCLP	Bilateral cleft lip and palate
BCL±P	Bilateral cleft lip with/without cleft palate
BiLSTM	Bilateral long-short term memory layer
CCA	Complete-case-analysis
CNN	Convolutional neural network
CL	Cleft lip without cleft palate
CLP	Cleft lip and palate
CL/P	Cleft lip and/or palate
CL±P	Cleft lip with/without cleft palate
CP	Cleft palate without cleft lip
CP±L	Cleft palate with/without cleft lip
DL	Deep learning
FOK	Swedish National Register of Congenital Anomalies
GOSLON	Great Ormond Street, London and Oslo
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HC region	Health care region
HRQoL	Health-related quality of life
IRF6	Interferon regulatory factor 6
ICHOM	International Consortium for Health Outcomes Measurement
MAR	Missing at random
MCAR	Missing completely at random

MFR	Swedish National Medical Birth Register
ML	Machine learning
MNAR	Missing not at random
PCC	Percent consonants correct
PICO	Patient, Intervention, Comparison, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient-reported outcome measure
PRS	Pierre Robin Sequence
RCT	Randomized controlled trial
SLP	Speech-language pathologist
SoS	Swedish National Board of Health and Welfare
UCLP	Unilateral cleft lip and palate
VPC	Velopharyngeal competence
VPI	Velopharyngeal insufficiency

Introduction

Every other minute, a child with cleft lip and/or palate (CL/P) is born somewhere in the world[1], making CL/P the most common craniofacial malformation (3). When the cleft is diagnosed, the child embarks on a lifelong journey involving long-term treatment and follow-up, including surgical procedures, speech-language therapy, orthodontic care, and psychosocial support. Since surgical treatment of cleft lip was described as early as the 4th century in China (4), cleft care has come a long way. Nevertheless, more work is needed to achieve a better understanding of the underlying factors of CL/P and to improve treatment, follow-up, and outcomes for the affected children. This thesis will explore several aspects of cleft care, including birth prevalence, associated diagnoses, surgical treatment, and new methods for evaluating treatment outcomes. To introduce the subject, this section includes summaries of the embryology, etiology, epidemiology, symptoms, associated diagnoses, and treatment of CL/P, as well as methods for evaluation in CL/P care. An overview of CL/P care in Sweden is presented. Lastly, as one of the studies included in the thesis explored artificial intelligence (AI) as a method of evaluating treatment outcomes, a brief introduction to the concept of AI is also provided.

Cleft Lip and/or Palate at a Glance

CL/P is a congenital craniofacial malformation. Many different subtypes of CL/P exist, depending on whether the cleft affects the lip, alveolus, or palate, or a combination these structures. Different classification systems for cleft subtypes have been proposed, and classifications in this thesis are largely based on those suggested in the submission guidelines of the *Cleft Palate Craniofacial Journal* (5). The cleft subtype largely determines the symptoms that may occur, and hence also affects the treatment and outcome. This is outlined more thoroughly in the *Symptoms and Evaluation* and *Treatment* sections below. In the following sections, CL/P will most often be considered one diagnosis, but cleft subtypes such as cleft lip with/without cleft palate (CL±P) and cleft palate without cleft lip (CP) will also be discussed separately when relevant.

[1] Based on a global CL/P birth prevalence of 1.7 per 1,000 births (1) and a global annual number of births of 140,000,000 (2).

Embryology

After the fourth gestation week, five facial prominences, consisting primarily of cells derived from the neural crest, have formed: the frontonasal prominence, the paired maxillary prominences, and the paired mandibular prominences (6). The frontonasal prominence gives rise to the lateral and medial nasal prominences during the fifth week of gestation (6). The two maxillary prominences then grow and displace the medial nasal prominences toward the midline (6). By weeks six to seven, the medial nasal prominences fuse in the midline, forming the intermaxillary segment that develops into the central upper lip, alveolus, and primary palate (7, 8). At the same time, they fuse laterally with the maxillary prominences to create the lateral portions of the upper lip (6, 7). The lateral nasal prominences form the alae of the nose, whilst the mandibular prominences fuse to form the mandible (6). Meanwhile, the maxillary prominences continue to grow, and shelf-like prominences called the palatine shelves are formed during the sixth week (6). Initially, the two shelves are separated with the tongue located in between them. However, around weeks seven to eight, they elevate above the tongue and move toward the midline (6, 7). Fusion of the shelves progresses over the following weeks and is generally complete by week ten, creating the secondary palate (8-10). Some studies suggest that the process of palatal fusion is delayed in females compared with males (6, 8, 11). The primary and secondary palates then fuse at the incisive foramen (6), resulting in a complete palate.

A cleft affecting the lip, alveolus, or primary palate arises when the medial nasal prominences fail to merge with the maxillary prominences, whereas a cleft of the secondary palate results from failed fusion of the palatine shelves (6). This distinction is important when studying the etiology behind the different cleft subtypes. The affected anatomical structures arise from different embryonic tissues and are formed at different developmental time points, as the medial nasal prominences fuse before the palatine shelves. These embryological differences have led to clefts in the lip, alveolus, and/or primary palate being considered pathophysiologically and etiologically distinct from clefts involving the secondary palate (12). Nevertheless, a cleft lip is relatively frequently accompanied by a cleft palate (13), a phenomenon suggested to result from a severe cleft lip mechanically hindering palatal shelf fusion (14, 15). As a result, studies often separate clefts involving the lip (CL±P) from clefts only involving the palate (CP). However, cases of both CL±P and CP occurring in the same family challenge the notion that they are completely separate entities (16, 17).

Etiology and Risk Factors

Both genetic and environmental factors can increase the risk of a child being born with a cleft lip and/or palate (18).

Genetic Risk Factors

Advances within the field of genetics have opened new possibilities for identifying specific genetic variants that increase the risk of CL/P, and in some cases the mechanisms by which they act. Although most clefts do not occur as part of a syndrome (18, 19), so-called non-syndromic CL/P, over 500 syndromes that are associated with CL/P are known (18). Examples include van der Woude syndrome, Stickler syndrome, and 22q11 deletion syndrome (18, 20, 21). Reports regarding the frequency with which syndromes occur in CL/P vary significantly between studies (22, 23). One potential explanation is the fact that the number of recognized syndromes has increased over time. Hence, syndromes that are recognized today might have been overlooked in older studies, leading to smaller proportions of CL/P cases being reported as syndromic. Nevertheless, the occurrence of syndromic CL/P differs also between relatively recent studies. For example, a retrospective review of the medical charts of 1,127 American children with CL/P was published by Beriaghi et al. in 2009. In total, 229 cases (20.3%) were classified as syndromic (22). The patient selection process was not described in detail, making it unclear whether the study population was representative of the CL/P population in the area, and the relatively high proportion may partly reflect characteristics of the study cohort rather than the underlying population prevalence. Contrastingly, a Hungarian registry-based study from 2005 that included 3,110 children with CL/P reported that only 58 of them (1.9%) had clefts of syndromic or chromosomal etiology (23). However, it should be noted that data in that study were collected between 1973 and 1982.

One consistent finding, however, is that CP is more frequently associated with syndromes than is CL±P (19, 22, 24, 25). This has been shown for example by Calzolari et al. in two large European registry-based studies, one including almost 4,000 children with CP and the other more than 5,000 children with CL±P (19, 24). In the CL±P group, 619 of 5,449 cases (11.4%) were classified as part of "recognized conditions" (monogenic, chromosomal, or environmental syndromes, and sequences), whereas the corresponding numbers in the CP group were 1,046 of 3,852 cases (27.2%). When studying children with cleft lip without cleft palate (CL), the differences were even more pronounced, with only 153 of the 1,996 (7.7%) cases being classified as part of recognized conditions.

Many older studies have focused on specific genes, often associated with syndromic CL/P, and investigated whether certain genetic variations can also cause non-

syndromic clefts, so-called candidate gene studies. Genetic risk factors that have been identified through such studies include, for example, variants of transforming growth factor alpha (26) and interferon regulatory factor 6 (IRF6) (27, 28). In recent years, genome-wide studies, where the whole genome is analyzed, have become more prevalent. Such studies have identified other genetic risk factors such as variants in loci of genes 8q24 (29, 30), 17q22 (31) and 10q25.3 (31). However, the most obvious genetic risk factor for CL/P is male sex. The overall birth prevalence for CL/P is higher for boys than for girls (32-35), owing to higher birth prevalence of CL±P (32, 33, 36) and cleft lip and palate (CLP) (33, 37). The only cleft subtype consistently reported as more common in girls is CP (32-34, 36, 37). A possible reason for this is that the formation of the secondary palate takes longer in females, meaning the critical time when disruptions in the normal development can cause a cleft is longer (11), however sex-specific genetic factors have also been suggested as a potential explanation (38, 39).

Environmental Risk Factors

In addition to genetic predisposition, several environmental risk factors have been reported as associated with CL/P. Firstly, maternal smoking has consistently been shown to increase the risk (40-42). This has been demonstrated primarily for active smoking, but also for passive smoking (43). Another relatively well-established risk factor is the use of certain medications during pregnancy or in the periconceptual period, anticonvulsants in particular (44-47). Other medications for which an association with CL/P has been reported include certain antibiotics (44, 47, 48) and corticosteroids (49). Folate levels are a factor for which research findings have been conflicting. Folate deficiency has been reported as a risk factor for CL/P (50), whilst folate supplements have been shown to have a protective effect (51, 52). However, other studies have shown no effect of folate levels or supplements on the risk of CL/P (53-55). Supplementation with multivitamins, not only folate, has been shown to have a protective effect in multiple studies (54, 56), although a recent large Japanese study reported an increased risk of cleft formation associated with multivitamin supplementation during the first trimester (57). Other less well-established risk factors include, for example, low socioeconomic status or parental education level (58-61), high parental age (62, 63), and high maternal body mass index (64, 65).

As mentioned earlier, the fact that the upper lip/alveolus/primary palate and the secondary palate are formed through different embryological processes should be noted when discussing both genetic and environmental risk factors for CL/P. As a result, some risk factors might have a greater effect on the risk of CL±P than CP, and vice versa. For example, when it comes to parental age as a risk factor, a large Danish study showed that only high paternal age was associated with a higher risk of CP, whilst the age of both parents affected the risk of CL±P (63). Similarly, a

recent large American study showed that higher parental age increased the risk for CP, but not for CLP (62).

Studying the environmental risk factors for CL/P is challenging, mainly because many potential factors may have coincident risks. For example, maternal smoking may be associated with a low maternal level of education (66), or nutritional deficiencies with low socioeconomic status (67). Hence, the risk of confounding is high. Another complicating factor when discussing risk factors for CL/P is that there are genetic variants that accentuate the effects of certain environmental risk factors, so-called gene-environment interactions (68). Such examples include genetic variants affecting the production of the enzymes GSTT1 and GSTM1. These variants have been shown to markedly increase the effect of maternal smoking during pregnancy on the risk of CL/P development (69).

Epidemiology

CL/P is the most common craniofacial malformation globally, with a birth prevalence that is usually reported as between 1 and 2 per 1,000 births (1, 70, 71). The International Perinatal Database of Typical Oral Clefts (IPDTOC) Working group published a report in 2011, including data from 54 registries in 30 countries worldwide, regarding the birth prevalence of certain cleft subtypes. In the report, the global birth prevalence of CL±P, CL, and unilateral cleft lip and palate (UCLP) was 9.92, 3.28, and 6.64 per 10,000 births, respectively (corresponding to approximately 0.99, 0.33, and 0.66 per 1,000 births) (13). A meta-analysis from 2022 found the birth prevalence of CP to be 0.33 per 1,000, that of CL to be 0.30 per 1,000, and that of CLP to be 0.45 per 1,000 births globally (72). The IPDTOC report also noted that unilateral CL±P occurs more often on the left side compared with the right, and that bilateral clefts occurred in 10.3% of CL cases, and 30.2% of CLP cases (13). The left side predominance in unilateral clefts has been consistently reported (8, 37, 73, 74).

The birth prevalence of CL/P and its subtypes varies markedly between different geographical regions and ethnic groups. Large registry-based studies often mainly include data from Europe and North America (13), which should be considered when assessing the global prevalences. In regions where reliable registries are lacking, and reporting infrastructure is suboptimal, epidemiological data is likely to be less reliable (75, 76). The differences are most likely the result of not only environmental factors, but also genetic variation as it has been shown that the occurrence of CL/P differs between ethnic groups even when they live in the same geographical area (77). Generally, high birth prevalence has been reported in Native American and East Asian, for example Japanese and Chinese, populations, with African populations presenting with the lowest prevalence (8, 70, 71, 77).

Previous Swedish studies have indicated that the birth prevalence of CL/P in the country is within the range reported globally. A frequently referenced study was published by Hagberg et al. in 1998. There, all children born with CL/P in Stockholm between 1991 and 1995 were included, and the birth prevalence was 2.0 per 1,000 births (78). In an older study published in 1972, Beckman and Myrberg reported 124 cases of CL/P in 71,220 births (birth prevalence 1.74 per 1,000) in northern Sweden between 1958 and 1970 (79). A more recent study by Amini et al. from 2009 included data from four different Swedish registries. They reported a CL/P birth prevalence of 18.92 per 10,000 live births (corresponding to approximately 1.89 per 1,000 live births) (80). Chetpakdeechit et al. studied the birth prevalence of the CP subtype in southwestern Sweden between 1975 and 2005 and found it to be 0.64 per 1,000 (81). More recent studies regarding the overall birth prevalence of CL/P in Sweden are lacking, and with the exception of the study published by Amini et al. (80), they all focus on subgroups of the Swedish population based on geography. The study by Beckman and Myrberg indicated that there are geographical differences in birth prevalence within Sweden, as they noticed a higher prevalence of CP in the northern parts of the country (79). Interestingly, this has been seen also in Finland, with higher CP birth prevalence compared with the rest of Europe(19), and a larger proportion of the entire CL/P group consisting of CP (82). It has been suggested that this is a result of a higher occurrence of a single nucleotide polymorphism in the IRF6 gene in certain Finnish regions (83).

Lastly, birth prevalence differ by sex: CL/P, CLP, and CL±P occur more frequently in boys (32-37), whereas CP is more common in girls (32-34, 36, 37). This aligns with findings discussed in the *Etiology and Risk Factors* section, where both embryological timing and potential genetic mechanisms have been suggested as explanations.

Symptoms and Evaluation

In this section, the symptoms of CL/P are introduced. Different potential symptoms require different methods for follow-up and evaluation. Therefore, a brief introduction to the evaluation of certain outcomes is also given. For a more comprehensive walk-through of outcome measures in CL/P care, however, an article published by the International Consortium for Health Outcomes Measurement (ICHOM) working group in 2017 can be recommended (84). The effect of CL/P on speech, and the evaluation of speech, is described more in depth in the next section, due to its particular relevance to Paper V.

The symptoms caused by a cleft depend heavily on cleft morphology. Functional problems are mainly caused by a cleft palate, and include speech problems, affected

hearing, and nutritional difficulties in infancy (3). Affected hearing is commonly a result of secretory otitis media, which is more prevalent in children with cleft palate with/without cleft lip (CP±L) and tends to become less frequent with older age (85, 86). For CL, hearing and speech difficulties are not as prevalent (87). For most cleft types, dental issues are prevalent and can include missing teeth (hypodontia), supernumerary teeth (hyperdontia), or malformed teeth (88-90). Clefts involving the lip are visually apparent, and hence aesthetic considerations arise. Suboptimal facial growth, of the maxilla in particular, can cause both orthodontal and aesthetic problems. That children with CL/P can have affected maxillary growth has been shown in numerous studies (91-94). However, it is difficult to determine whether the cause is the cleft itself or the trauma and scarring that the surgery (further discussed in the *Treatment* section) entails. Supporting the latter claim is the fact that studies have shown that unoperated patients, or those operated at an older age, tend to show near-normal growth (91, 95). Clefts only affecting the lip do not normally cause significant deficits in maxillary growth (96), and studies on the matter tend to include children with CP or CLP (91-95).

Evaluation of hearing, facial growth, and dental development is preferably performed at regular follow-up visits to the multidisciplinary cleft team. Hearing can be evaluated through for example audiometry (84) and physical otologic examination. For the evaluation of dental development and facial growth, physical examination can be complemented by a variety of outcome measures. These measures could be based on measurements from for example cephalograms or dental casts (97). Several different indices are used to classify measurements regarding facial growth and dental relations, examples of which include the Great Ormond Street, London and Oslo (GOSLON) Yardstick index (98), the Huddart and Bodenham index (99) and the 5-year olds' index (100).

CL/P may not only cause functional problems but can also affect the child's psychosocial well-being (101, 102) and health-related quality of life (HRQoL) (103). Systematic reviews have suggested that, overall, persons born with CL/P do not seem to be experiencing major psychosocial difficulties compared with the non-cleft population (101, 102). However, negative effects of CL/P on certain aspects of psychosocial well-being have been reported (102, 104-107). It should be noted that findings are inconclusive (101, 102), and certain studies have even shown positive effects of CL/P on psychosocial domains (108-110). Understanding the psychosocial implications of CL/P is complex, and individual differences between affected persons most certainly exist. Individual factors that are believed to affect the psychosocial well-being of a child or adult born with CL/P include the ability to adapt to preserve well-being and quality of life despite adverse events (resilience), and the use of cognitive and behavioral strategies to manage stressful situations (coping) (111-113). Both resilience and the use of effective coping strategies are partial explanations for why most children and adults born with CL/P seem to fare quite well psychosocially (101, 113-116).

Evaluation of psychosocial well-being in children and adolescents with CL/P can be facilitated by the use of patient-reported outcome measures (PROMs). PROMs are used to measure the treatment outcomes from the patient perspective and are closely related to HRQoL. In order to capture the patient perspective, PROMs are usually based on questionnaires and/or rating scales that are completed by the patient. Both general and diagnosis specific PROMs exist. An example of a PROM that is specific to CL/P care is the CLEFT-Q questionnaire (117). It was recommended in the standard outcome set suggested by the ICHOM working group in 2017 (84).

Speech in Cleft Palate

Speech deviations occur predominantly when the cleft affects the palate (CP±L). The anatomical abnormality that the cleft represents can cause difficulties for the child throughout the process of speech development, also after the palate has been surgically repaired (118). Some can be addressed with speech therapy, but it is important to note that others are the result of physical limitations, arising from the cleft, that cannot be treated through speech therapy but rather require secondary surgical intervention (119). Furthermore, speech deviations can also persist after both primary and secondary surgery (120). Hence, treatment strategies often need to combine both surgery and speech therapy in order for speech development to be optimal.

All spoken languages contain sounds that are realized both orally and nasally. Hence, the ability to conduct the air through the desired cavity, oral or nasal, is a prerequisite for adequate sound formation and speech (118). The primary reason behind speech abnormalities in CP±L is the inability to correctly close the velopharyngeal opening between the oral and nasal cavities. When velopharyngeal closure is difficult or sometimes even impossible to achieve, the resonance becomes nasal, the articulation weakened, and air flows through the nasal cavity involuntarily when the person tries to create an oral sound. This is called velopharyngeal insufficiency (VPI) (120). VPI causes the perhaps most typical speech deviation that is seen in cleft palate speech, hypernasality (118). Hypernasality is not the only speech deviation that is associated with cleft palate, though. In 2008, Henningsson et al. presented five universal speech parameters for reporting speech outcomes in individuals with cleft palate: hypernasality, hyponasality, audible nasal air emission and/or nasal turbulence, consonant production errors, and voice disorder (121).

Prior to cleft palate repair, a child born with CP±L will almost certainly experience both hypernasality and difficulties producing consonants requiring intraoral pressure (e.g. /p/, /t/, /k/) since the anatomical prerequisites for closure between the oral and nasal cavities are non-existent (120). Successful palatal surgery restores the anatomy in the sense that the cleft itself is closed. However, this does not necessarily bring with it normal function of the palate (122). For example, the repaired palate

might be short or scarred, and the muscular function suboptimal. A short or immobile palate, although intact, is not always able to lift and reach back to touch the posterior pharyngeal wall and achieve velopharyngeal closure. The result is VPI, which leads to passive speech deviations such as hypernasality, audible nasal air emission, and reduced pressure on consonants requiring high intra-oral pressure (120, 123, 124). However, VPI can also result in secondary active compensatory articulatory processes, through retraction of articulation to a place behind the air leakage (84, 123, 124). An example of such a process is glottal articulation, where articulation is retracted to the glottal region (123, 125). Such compensatory articulatory processes may affect the intelligibility of speech. Importantly, compensatory processes may become an acquired behavior, meaning that they can persist also after the VPI has been corrected by for example secondary palatal surgery (126). For this reason, it is important to ensure that VPI is present before surgical interventions are planned. Videofluoroscopy is a commonly used method, where dynamic x-ray imaging is used to visualize velopharyngeal anatomy and function after administration of a radiopaque material into the nasal cavity (127). In order to assess velopharyngeal function, it is important that the child articulates a few words orally, as sounds realized in the glottal region will not engage the velopharyngeal system. If compensatory articulatory processes are present, but there are no signs of VPI when words with oral sounds are produced during videofluoroscopy, speech therapy is needed to address the acquired articulatory behavior. Contrastingly, if there are signs of VPI, speech therapy alone will not suffice, and surgical intervention should be considered (119). For this reason, early detection and treatment of pronounced VPI is essential to ensure appropriate treatment and optimal speech development.

The current gold standard for speech assessment in CP±L care is auditory perceptual speech assessment by trained speech-language pathologists (SLPs) (128). These assessments require training of SLPs and are time-consuming (129). One commonly used measure that is recommended for perceptual speech assessment in CP±L care is velopharyngeal competence (VPC), which is an overall measure of the impression of hypernasality, nasal air emission, and weak pressurized consonants (84). It has been recommended by the ICHOM working group (84), and is measured on the three-grade scale VPC-R with scale values competent/sufficient, marginally incompetent/insufficient, and incompetent/insufficient (130, 131). Examples of other outcome measures that are based on perceptual speech assessment include percent consonants correct (PCC) (132) and assessment of hypernasality (133). Perceptual speech assessment is inherently subjective. Objective methods such as nasometry do exist, but no ideal instrumental tool exists as of today, as stated by Bettens et al. in a review from 2014 (134). The lack of an ideal instrumental tool underlines the need for exploring novel approaches such as AI.

In childhood, a relatively large proportion of children with CP±L present with speech deviations (120). The extent of the cleft has been reported to affect speech

outcomes, with children with milder clefts acquiring better speech at 5 years of age (135). This relatively high occurrence of speech deviations was illustrated for example in the Scandcleft randomized controlled trial (RCT), which included children with UCLP. Several different outcome measures were used in the trial, but examples of findings presented include sufficient VPC in 38.3–64.6% and age-appropriate consonant proficiency in 50–73% of children at age 10 (122). However, long-term speech outcomes have been reported as good (136, 137). This may be the result of successful speech therapy and surgery, but even without secondary intervention, speech is expected to improve as a result of the child's general development during childhood (136). Nevertheless, the relatively high proportion of children requiring speech-improving secondary palatal surgery – 29.6% at age 10 in the Scandcleft study (UCLP), 25.6% at age 13 in a recently published Swedish study of children with CP±L, and 33.3% at a median follow-up of 14.5 years in a Finnish study of children with CP (122, 138, 139) – highlights that primary palatoplasty is not always completely successful and underscores the need for improvement of surgical strategies and techniques.

Additional Diagnoses in Cleft Lip and/or Palate

CL/P can be associated with additional diagnoses and/or syndromes. One notable example is Pierre Robin sequence (PRS), which is typically associated with CP and characterized by micrognathia, glossoptosis (displacement of the tongue towards the pharynx), and upper airway obstruction (140, 141). PRS is clinically important both because of the immediate challenges it poses in the neonatal period and because it is frequently recorded alongside cleft diagnoses in registries. Examples of syndromes that are associated with CL/P are given in the *Etiology and Risk Factors* section, whilst this section focuses on associated additional diagnoses that are not part of a syndrome. A large British registry-based study published in 2023 included almost 10,000 children with CL/P. Among them, 38.8% had an additional congenital malformation (142). Other examples of large registry-based studies include two published by Calzolari et al. in 2004 and 2007, both including more than 3,500 children. One of the studies included children with CP, and reported that 54.8% were isolated cases, meaning that 45.2% had an associated malformation (19). The other, which included children with CL±P, reported that 70.8% were isolated, and hence 29.2% had additional diagnoses (24). Although several studies have demonstrated the fact that children born with CL/P relatively frequently also have additional diagnoses, the exact proportion is difficult to estimate. In the available literature, the proportions range from below 5% to above 60% (143, 144), although many studies report percentages between 20% and 40% (22, 23, 78, 142, 145-148). Factors affecting the numbers include patient selection, study population characteristics, reliability of medical records and/or registries, categorization of

additional diagnoses, and follow-up time. Hence, it is plausible that the discrepancies between studies largely reflect methodological differences rather than true variation between populations.

There are a few previous studies that have reported the occurrence of additional diagnoses in Swedish children with CL/P. Milerad et al. conducted a prospective study of children born in Stockholm, including 616 children born with CL/P between 1977 and 1992 (146). They found that 127 of the children (20.6%) had an additional diagnosis. Hagberg et al. studied 251 children born between 1991 and 1995 in Stockholm and the rate of additional diagnoses was reported as 22.3% (78). Few studies of from outside the Stockholm area exist. However, Chetpakdeechit et al. published a study in 2010 which included children born with CP in southwestern Sweden between 1975 and 2005 (children treated at Sahlgrenska University Hospital, Gothenburg) (81). Of the 343 included children with CP, 33.8% had additional congenital malformations.

In the available studies, additional diagnoses are often categorized based on the affected organ/system, and the systems most commonly affected differ between studies. Commonly affected structures include the musculoskeletal system/extremities (23, 24, 142, 145-147), cardiovascular system (142, 147, 148), central nervous system (23, 24, 144, 146), and craniofacial area (22, 144, 145).

Overall, previous research shows wide variation, and from a Swedish perspective, robust population-based data from outside Stockholm have been scarce.

Treatment

Treatment of CL/P almost always includes surgery. An exemption is sometimes made for mildest forms of cleft lip, where the tissue is not entirely separated, but a discreet furrow can be seen along the philtral column (3). Since cleft lip surgery was first described, a plethora of different surgical techniques have been introduced (149, 150). In general, surgical procedures aim to restore anatomy and provide normal function. For a cleft lip, this usually means that the lip is repaired in layers; mucosa, orbicularis oris muscle, and skin (151-153). Surgical techniques all focus on trying to make the postoperative signs of the cleft as inconspicuous as possible. Nevertheless, a scar is always present, and additional findings may include, for example, a suboptimal nasal shape (154, 155) or a short lip (156). Regarding the palate repair, the aim is to create an intact palate that is long and mobile enough to allow normal speech development. This is either done by using the existing palatal tissue to perform a layered repair (157), or in some cases by tissue replacement with for example buccal flaps from the inside of the cheek (158). Alveolar cleft repair typically has less impact on appearance and function than primary cleft lip or palate repair, as an alveolar cleft is neither as visually apparent as a cleft lip nor as

functionally impairing as a cleft palate. However, repairing the cleft is a prerequisite for optimal orthodontic treatment (159). Additionally, an unrepaired alveolar cleft that extends into the nasal cavity and results in a persisting anterior oronasal fistula can cause both nasal regurgitation and speech deviations. These symptoms can be improved by closure of the alveolar cleft and oronasal fistula (160, 161). Usually, a cleft alveolus is repaired through a free transplant of cancellous bone from for example the iliac crest or the tibia (162). In addition to the primary surgical interventions described above, secondary surgery may also be required. This can include, for example, speech-improving surgery, corrections of the lip or nose, or orthognathic surgery in the case of maxillary retrusion (122, 163, 164).

One of the more long-lasting debates in CL/P care concerns whether the primary repair of the palate should be done in one or two stages. One stage repairs were performed already in the 19th century (157), whilst a staged approach was described in 1921 (165). Commonly used one-stage techniques include that introduced by Von Langenbeck in 1861 (157), the Veau-Wardill-Kilner VY-pushback technique from the 1930s (166-168), and the Furlow double opposing Z-plasty introduced in 1986 (169). Over the years, several modifications to these techniques have been introduced, such as the intravelar veloplasty which was described by Kriens in 1969 (170) and later refined by Sommerlad (171). Two-stage approaches usually entail repair of the soft palate in the first stage, followed by the hard palate. The aforementioned one-stage techniques are not seldomly used also for staged repair, but new methods have also been developed. One example is the method developed in Gothenburg, Sweden, which involves early soft palate closure and delayed hard palate closure (the timing of which has varied) (172). Another example is hard palate closure using a vomerine flap during the lip plasty and soft palate closure at a second stage. This technique has been used by for example the cleft team in Oslo, Norway (173). The vast variation in techniques and protocols in CL/P surgery was illustrated in a survey from 2001 which was part of the Eurocleft Project, where 194 different protocols were used for UCLP surgery by the 201 participating centers (174).

The main rationale for a staged repair is that scarring of the hard palate at a young age negatively affects maxillary growth (175). In 1978, Schweckendiek published a report regarding children who had undergone hard palate repair as late as at 12–14 years of age, and the group had nearly normal facial growth (95).This is usually not seen when the hard palate is repaired at an early age (93, 94, 165, 176-178). The findings were confirmed by Bardach et al. in 1983, when they examined a selection of Schweckendiek's patients at a mean age of 17 years. However, while facial growth was satisfactory, the speech outcomes were suboptimal (179).

Today, most centers agree that at least the soft palate needs to be repaired by approximately 12–18 months of age to support speech development (180-183). Between 2000 and 2009, our department published three studies comparing the timing of palate repair: at 7 versus 18 months in CP, 8 versus 18 months in UCLP, and 14 versus 18 months in bilateral cleft lip and palate (BCLP) (184-186). Long-

term speech outcomes did not differ significantly in the CP or BCLP groups (184, 186). In UCLP, palate repair at 8 months produced slightly better long-term speech results but, although it was associated with a higher frequency of speech improving secondary palatal surgery (185). It should be noted that not only the timing, but also the surgical techniques (both one-stage) used, varied between the groups.

To ensure timely closure of the soft palate, staged techniques usually involve early soft palate repair, followed by a delayed hard palate repair. However, the exact age at which the hard palate repair needs to be prepared for both adequate speech development and facial growth remains unclear (136). Systematic reviews regarding facial growth were published by Liao and Mars in 2006 and by Salgado et. al in 2019 (97, 187). However, the small number of available studies, the heterogeneity between them, and conflicting results prevented meta-analysis and reliable conclusions. Regarding speech, Willadsen et al. published a study in 2012, including children from the Scandcleft RCT (188). All had undergone repair of the lip, soft palate, and posterior hard palate at 4 months. At 36 months, speech outcomes were compared between children who had received complete hard palate repair at 18 months and those with unrepaired hard palates. The latter group showed worse speech outcomes, suggesting that early hard palate closure benefits early speech development, although long-term follow-up was not included. In 1998, Lohmander-Agerskov highlighted the difficulties in assessing the effects of timing of hard palate closure in two-stage protocols, due to the heterogeneity between the studies available at the time (189). For example, the timing of delayed hard palate closure differed between 3 and 12 years of age in the available studies.

Overall, advocates of one-stage repair techniques argue that complete early closure of the palatal cleft benefits speech, while proponents of two-stage repair emphasize the advantages for facial growth. While studies have reported results in favor of both these claims, no definite answer to the question whether one- or two-stage palate repair should be preferred has been presented (127, 136, 190-193). The long follow-up times that are required for adequate evaluation of both speech and facial growth pose a key difficulty when attempting to evaluate the "final" results of different surgical strategies. As a result, the discussion has is ongoing, and surgical protocols remain largely shaped by local traditions and individual surgeon preference.

Non-surgical treatment of CL/P includes for example speech therapy, orthodontics, treatment for secretory otitis, and psychosocial support. Speech therapy plays a central role, especially for children with CP±L, who often have delayed or deviant speech development (136). However, it cannot always address deviations caused by anatomical limitations, which may require secondary surgery (119). Regular follow-up visits are therefore essential to identify children in need of secondary surgery and ensure timely care, as outlined in the *Speech in Cleft Palate* section.

Cleft Lip and/or Palate Care in Sweden

CL/P care in Sweden is carried out by six multidisciplinary teams at the university hospitals of each of the six Swedish health care regions (HC regions). Each team is responsible for the treatment and follow-up of children in its own HC region. Although exact follow-up routines can somewhat differ between centers, protocols are relatively standardized and include regular follow-up visits every 2–3 years until approximately age 19. However, treatment protocols differ, for example regarding the technique and timing used for palate repair. At two Swedish centers, one-stage palatoplasty is performed, whereas staged procedures dominate at the other four. The fact that a relatively small country like Sweden shows internal variation in the treatment of CL/P has generated discussions. The Swedish CL/P Registry enables quality assurance and comparisons between centers, to ensure that all Swedish children born with CL/P get adequate treatment and outcomes irrespective of which HC region they were born in.

The Swedish CL/P Registry

The Swedish CL/P Registry was founded in 1999. In 2009, it was designated a national quality registry by the Swedish National Board of Health and Welfare (SoS). Since then, all children born with CL/P in Sweden are invited to voluntarily participate in the registry, and all six Swedish CL/P centers contribute to it (194). The average degree of coverage for children born after 2009 is above 90% (194, 195). The overall aims of the registry are to contribute to the Swedish and international CL/P care through regular assessments of occlusion, speech, and appearance, to ascertain that Swedish CL/P care is equal, to facilitate national collaboration, and to improve methods used for treatment (194). Registration is done soon after birth (baseline) and then at regular time-points until 19 years of age (occlusion and speech). All surgical interventions are registered continuously (194). Although research is not the primary aim of the registry, it has nonetheless provided valuable data for several scientific studies (196).

Artificial Intelligence

AI is a broad field within computer science and engineering. The exact definition of AI varies, but the Merriam Webster Dictionary defines it as “the capability of computer systems or algorithms to imitate intelligent human behavior” and “a branch of computer science dealing with the simulation of intelligent human behavior by computers” (197). The concept of AI is broad and complex, but this

section will introduce some key concepts relevant to the AI related study included in this thesis, Paper V.

Machine learning (ML) is a subfield of AI where mathematical algorithms are trained on large datasets to identify patterns and make predictions. Unlike traditional statistical models, which generally rely on pre-defined assumptions about the input data, ML models are flexible and can adapt their functions to the data (198). ML models can handle and analyze vast amounts of information and discover associations that might not be clear for a human observer, including complex interactions and non-linear relationships (199). The ability of ML models to adapt to the input data allows the algorithm to change and "learn" from experience. This ability to improve automatically without explicit programming or human interference is a defining characteristic of ML (200). The concept was mentioned by AI pioneer Arthur L. Samuel in 1959 when he stated in an article regarding machine learning that "Enough work has been done to verify the fact that a computer can be programmed so that it will learn to play a better game of checkers than can be played by the person who wrote the program" (201). Deep learning (DL) refers to a subfield of machine learning that focuses on networks of algorithms consisting of many different "layers", so-called artificial neural networks (ANNs) (199). ANNs are loosely inspired by the structure of the human brain, with its interconnected nodes representing simplified neurons. However, ANNs function through mathematical rather than biological principles. This layered, intricate system enables the network to process input, identify patterns, and draw conclusions (202). The development and training of ANNs can be approached using different techniques. The network can be built from scratch, but it is also possible to use pre-existing networks and adapt them to new tasks, a method known as transfer learning (203). An example of transfer learning is using a network that has been trained to differentiate between cats and dogs as the basis for a new network that should instead distinguish cars from buses. The advantage of transfer learning is that the network has already been trained on large amounts of data, and "knows" the general features needed for the task. New, untrained layers can then be added and trained so that the network can perform new tasks with significantly less data than would be required if it were built from scratch (203).

Several different types of ANNs exist, one of them being convolutional neural networks (CNNs) (204). A CNN is built from interconnected layers, where the output from one layer is propagated to the next (205). What differentiates CNNs from other ANNs is that CNNs use convolutional layers that apply filters to the input data to automatically detect important features, such as edges, textures, or shapes (204, 205). This creates a so-called feature map, which enables the network to identify certain features in the input (206). During the training process, the filters adjust their internal weights based on patterns in the data. Hence, the network learns which features are most important at each layer and updates the filter weights accordingly (206). CNNs are effective for assessing 2D data such as images (205).

In this thesis, CNNs were used on audio data. Although the CNN architecture can be designed to operate directly on raw audio waveforms (207), it is common to transform the audio into a 2D representation to better exploit the strengths of the CNN. An example of such a conversion is to create Mel spectrograms, where the sound represented as the intensity of different frequency bands over time. Figure 1 shows examples of Mel spectrograms. The Mel spectrograms represent a female SLP and a 5-year-old child uttering the sentence “Kicki kokar korv”.

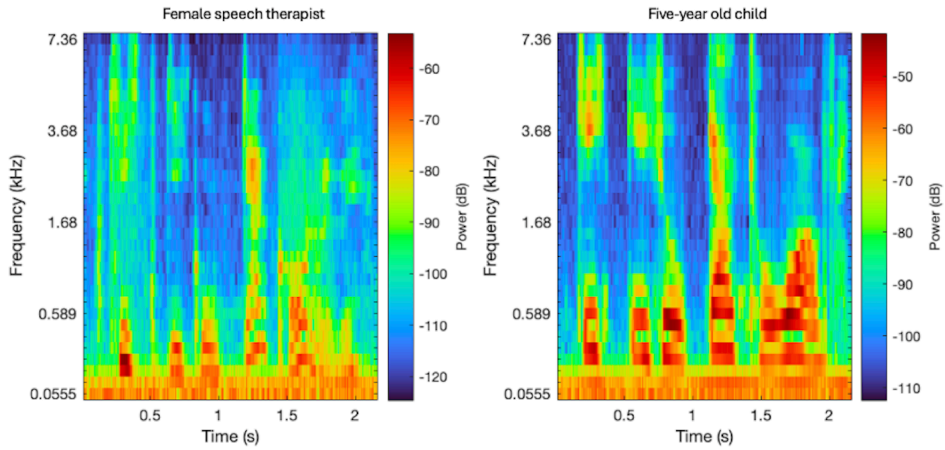


Figure 1 – Mel spectrograms.
Mel spectrograms representing a speech-language pathologist and a 5 year old child uttering the sentence “Kicki kokar korv”.

Artificial Intelligence in Medicine and Cleft Lip and/or Palate Care

In medicine, radiology is probably the discipline where AI has been implemented most extensively (208). Applications of AI in radiology include, for example, automated diagnostics (209) and detection of conditions that require rapid intervention (210), and research regarding uses of AI in interventional radiology is ongoing (211, 212). In the surgical field, AI has been evaluated for different tasks (213), such as simulation training (214), evaluation of surgical skills (215), and preoperative risk assessments (216, 217). Intraoperative potential applications of AI include tissue recognition and camera stabilization in robotic surgery (218, 219) and improvement of visualization in arthroscopic surgery (220), to mention a few. Although AI shows significant potential for use in surgery, both pre-, peri-, and postoperatively, further research is required. A recent review from 2024 found only six published RCTs within the surgical field, none of them focusing on intraoperative use of AI to facilitate the surgical procedure itself (221).

In plastic surgery, the potential uses of AI are being studied as well. A systematic review published in 2024 identified 96 studies regarding AI in plastic surgery (222). Among these 96 studies, the majority examined AI in surgical planning, diagnostics and assessments, administration and documentation, or preoperative consultations. Notably, only two of them involved CL/P surgery. One studied a type of CNN which managed to correctly identify anatomical structures relevant in cleft lip surgery using photographs(223). The other used DL models for identification of VPI using videofluoroscopy, with good results (224). Other studies regarding the use of AI in assessment of cleft palate speech, some of which have shown promising results, mostly focus on the detection of hypernasality (225-228). At our department, technological innovations in CL/P care have been introduced before, such as digital photographic morphometry for facial morphology in 1998 (229). In Paper V, we aimed to introduce AI as a tool for speech assessments in CP±L.

Perspectives on Cleft Lip and/or Palate Care

Comprehensive care for children with CL/P requires knowledge spanning from epidemiology to surgical treatment and long-term outcomes. Therefore, this thesis aims to explore several aspects of CL/P care. The epidemiology of CL/P in Sweden, where children with CL/P are treated at several different centers despite the country being relatively small, was in focus in Papers I and II. As presented above, the etiology of CL/P is not entirely known. Epidemiological studies of CL/P birth prevalence, including temporal trends and geographical differences, contribute not only to health care planning but also the understanding of possible contributing etiological factors. Additional diagnoses have been shown to occur relatively frequently in children with CL/P. Paper III investigated these additional diagnoses, thereby adding to general knowledge about the condition, facilitating information to patients and parents, highlighting potential risks that these diagnoses might entail, and aiding in the planning of CL/P care. Surgery is a cornerstone in the multidisciplinary treatment of CL/P, yet strategies and techniques differ between centers and surgeons. Paper IV addressed one of the long-standing questions in cleft surgery; whether one- or two-stage palatoplasty yields superior outcomes. Lastly, reliable and effective evaluation of CL/P outcomes can guide treatment and help ensure high-quality care. In Sweden, evaluation and follow-up are multidisciplinary and follow standardized protocols. A key outcome of CL/P care is satisfactory speech. Perceptual speech assessments by specialized SLPs are important in follow-up, but they may be supplemented by objective, automated methods. In Paper V, modern technology in the form of AI was tested for assessment of VPC in children with CP±L. Together, these studies provide new insights into the prevalence, comorbidities, treatment, and evaluation of CL/P, thereby contributing to the continuous improvement of care for affected children.

Aims

The overall aims of this thesis are to contribute to the understanding of the epidemiology of CL/P and the additional diagnoses associated with the condition, to advance treatment strategies for CP±L by addressing the long-standing debate on one- versus two-stage palatoplasty, and to introduce modern technology into the evaluation of treatment outcomes.

Paper I

To determine the birth prevalence of CL/P and certain cleft subtypes in Sweden between 2000 and 2020.

To assess temporal trends in the birth prevalence of CL/P and certain subtypes in Sweden between 2000 and 2020.

To determine whether the birth prevalence of CL/P and its subtypes differed depending on sex in Sweden between 2000 and 2020.

Paper II

To examine geographical variations in the birth prevalence of CL/P and certain cleft subtypes in Sweden between 2000 and 2020, including differences between the six Swedish HC regions.

To assess temporal trends in the birth prevalence of CL/P and certain subtypes in the six Swedish HC regions between 2000 and 2020.

Paper III

To determine the 5-year cumulative incidence of additional diagnoses in children born with CL/P.

To investigate the relationship between cleft subtype and specific additional diagnoses.

To validate data on additional diagnoses in the Swedish CL/P Registry.

Paper IV

To evaluate whether one- or two-stage cleft palate repair provides overall advantages in outcome compared with the other method.

Paper V

To develop an artificial neural network capable of reliably and automatically assessing VPC in children with CP±L using audio recordings.

Materials and Methods

The thesis consists of five methodologically different studies. Papers I and II were large registry-based studies using a dataset including all children born in Sweden between 2000 and 2020 who were registered in the Swedish National Medical Birth Register (MFR) managed by SoS. Paper III was a retrospective cohort study on additional diagnoses in children with CL/P, using data from the Swedish CL/P Registry and patient records. Paper IV was a systematic review of the available scientific literature on the subject of one- versus two-stage cleft palate repair. Lastly, Paper V was a methodological study where existing audio recordings and perceptual speech assessments from follow-up visits and previous studies were used to develop an AI tool for automated assessment of speech outcomes in children with CP±L. The methodology used in each of the five studies is described below, whilst methodological considerations will be elaborated on in the *Discussion* section.

Paper I

The study was a registry-based study, where data from the MFR and a subregistry, the National Register of Congenital Anomalies (FOK), was used to determine the birth prevalence of CL/P and certain cleft subtypes in Sweden between 2000 and 2020. The dataset was received from SoS. All children in the registry who had been born in Sweden between 2000 and 2020 were included, amounting to 2,230,771 children in total. The dataset was modified to only include variables relevant to Paper I; an anonymized ID-number for each child, year of birth, CL/P diagnosis, cleft subtype diagnoses (CP, CL±P, bilateral cleft lip with/without cleft palate (BCL±P), UCLP, and BCLP), maternal smoking, and sex. All analyses were performed for the CL/P group as a whole and for each cleft subtype group separately. Yearly and overall birth prevalence for the 21-year period were calculated, including 95% confidence intervals. Modified Poisson regression was used to model the temporal trends in birth prevalence during the study period. The models were then adjusted for sex and maternal smoking in order to examine the effects of these factors on birth prevalence. Lastly, the CL/P birth prevalence for boys and girls, respectively, was compared using the Chi2-test.

Paper II

In this study, the same dataset as in Paper I was used. The birth prevalence of CL/P and certain cleft subtypes in the six Swedish HC regions was studied. The modified dataset included the anonymized ID-number for each child, year of birth, the mother's municipality of residence at the time of delivery (hereafter referred to as "place of birth"), CL/P diagnosis, and cleft subtype diagnoses (CP, CL±P, BCL±P, UCLP, BCLP). The birth prevalence of CL/P and cleft subtypes was calculated for each HC region separately, with 95% confidence intervals. Modified Poisson regression models were used to examine the trends over time in each region, and to identify regional differences in birth prevalence by comparing each HC region to the rest of Sweden.

Paper III

Study participants were identified in the Swedish CL/P Registry. All 436 children in the registry who were born in the Southern HC region between 2006 and 2016 were eligible for inclusion. The guardians of 417 of the children were given information and asked to give written consent for their child's participation in the study. The remaining 19 children were deceased, had moved abroad, or had protected personal data in the population register. All children whose parents gave consent were included in the study, 250 in total. Patient records were examined, and included variables were age, sex, whether the participant lived in Skåne or had been born abroad, cleft subtype, and additional diagnoses at birth and up to age 5 years. The wide spectrum of included additional diagnoses was chosen based on previous research regarding diagnoses associated with CL/P. Certain diagnoses were excluded, namely those that are common in children both with or without CL/P (for example allergies, refractive errors, and transient infections) or those that are common and well-known consequences of the cleft (for example speech difficulties, malocclusion, and secretory media otitis). CL/P diagnoses were coded according to ICD-10 (230), and were then divided into four groups depending on the affected structures (CP, CL, UCLP, and BCLP). Data from the Swedish CL/P Registry was used for comparisons with the findings in the patient records. This included whether the participant had been diagnosed with PRS, syndromes, or other deformities. Statistical analyses were descriptive and included frequencies, medians, ranges, and percentages.

Paper IV

The study was a systematic review, conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (231, 232). The research question was: Does one-stage palatoplasty show overall advantages compared with two-stage palatoplasty? It was designed using the Patient, Intervention, Comparison and Outcome (PICO) format (233) and is specified in Table 2 together with other inclusion criteria. The outcomes of interest included facial growth, speech, hearing, presence of fistulae, other complications related to surgery, HRQoL, and health economics. Structured literature searches based on the research question were performed by two medical librarians in the medical databases Pubmed, Medline, and Cochrane Library. Duplicate records were removed, and the remaining studies were assessed by the medical librarians to remove obviously irrelevant ones based on the PICO. The titles and abstracts of the remaining studies were then screened in duplicate, half by one pair of members of the research group and the other half by a second pair. The senior investigator screened all records, and consensus decisions were used when abstracts were assessed differently. After screening of titles and abstracts, the remaining full-text manuscripts were assessed by the same two members of the project group, first with regard to relevance to the systematic review and fulfilment of the inclusion criteria, and then with regard to quality using risk of bias assessments according to the Swedish Agency for Health Technology Assessment and Assessment of Social Service's handbook (234). Only studies with low or moderate overall risk of bias (three-grade scale: low, moderate, high) were included. Findings from the included original studies were classified into showing advantages for one-stage palate repair, two-stage palate repair, or neither, for the specific outcomes assessed in the respective study. A narrative synthesis was conducted for each of the outcomes specified in the PICO model separately, through extensive consensus discussion within the project group. Conclusions were drawn for each of the studied outcomes and were then compared with the findings from previous systematic reviews. The certainty of evidence for each outcome was assessed using the Grading of Recommendations Assessment Development and Evaluation (GRADE) model (235).

Table 2 – Research question according to PICO model, and inclusion criteria.
Abbreviations: UCLP = unilateral cleft lip and palate. CP = cleft palate without cleft lip. BCLP = bilateral cleft lip and palate. RCT = Randomized controlled trial.

	Abbreviation	Meaning
Population (P)	P1a	UCLP, without comorbidities/syndromes
	P1b	UCLP, with comorbidities/syndromes
	P2a	CP, without comorbidities/syndromes
	P2b	CP, with comorbidities/syndromes
	P3a	BCLP, without comorbidities/syndromes
	P3b	BCLP, with comorbidities/syndromes
Intervention (I)	I	One-stage palatoplasty
Comparison (C)	C	Two-stage palatoplasty
Outcome (O)	O1	Facial growth
	O2	Speech
	O3	Hearing
	O4	Presence of fistulae
	O5	Other complications related to surgery
	O6	Health-related quality of life
	O7a	Usage of health care resources
	O7b	Usage of other supporting resources
Inclusion criteria		
Study design	RCTs, comparative cohort studies, systematic reviews. At most moderate overall risk of bias for all included studies	
Patient age	Surgical treatment of the cleft palate initiated before 2 years of age, staged repair completed (stage two) before 5 years of age	
Gender	No limitations	
Population size	≥25 children per arm (one- vs. two-stage palatoplasty)	
Follow-up time	Minimum 5 years of age follow-up time for O1–O4 and O7. No minimum follow-up time for O5–O6. If the same patient was included in several studies, the result used was taken from the study with the longest follow-up time	
Lost to follow-up	<30% of population lost to follow-up. Imputed data not allowed	
Date of publication	After 1970 for original studies, after 2005 for systematic reviews	
Language	English, French, German, Swedish, Danish, Norwegian, Icelandic, or Finnish for original studies. English, Swedish, Danish, Norwegian, Icelandic, or Finnish for systematic reviews	

Paper V

In the study, audio recordings of 5 and 10-year-olds with CP±L were used together with perceptual speech assessments made by SLPs. Based on the recordings and speech assessment data, two ANNs were designed, and their ability to make the same assessment of VPC as the SLPs was tested. The study was divided into two parts. In the first part, the recordings were of children treated at Skåne University Hospital in Malmö, Sweden, born between 2000 and 2010. Parents of 166 children were informed and given the opportunity to opt out of their child's participation. One hundred and sixty-two children were included. For further inclusion, the child had to have a speech recording from 5 or 10 years of age saved in the hospital records. Furthermore, the recording had to have a corresponding perceptual speech assessment of VPC on a three-grade scale, made by an SLP at the same time as the recording, registered in the Swedish CL/P Registry. In total, 141 audio recordings of sufficient quality with corresponding assessments of VPC were used in the first part of the study.

The recordings were pre-processed and harmonized, for example by removing adult speech to avoid confounding input and by resampling to a 16 kHz sample rate. The parts of the recording where voiced (tonal) speech was present were extracted and used as tonal speech is more sensitive to hypernasality (133), and the recordings were divided into shorter overlapping time frames to increase the number of frames. Two different ANNs were designed, using the CNN architecture. The first network (CNN) was built from scratch, whilst the second (VGGish (236)) is a pretrained CNN that is open source. The networks were trained and tested using the audio recordings and speech assessments. The "true" value for the speech assessment of VPC was that made by the SLP, and the accuracies with which the two ANNs made the same assessment as the SLP were measured and presented in confusion plots. Network architectures and training options were adjusted in an iterative, trial-and-error fashion to improve performance. Changes to the network architectures and training options that improved the performance were retained. Seventy percent of the recordings were used for training and the other 30% were used for testing after the training was completed. Ten-fold cross-validation was used.

The second stage of the study started with an attempt to reproduce the findings from the first stage. An error in the coding of the ANNs was discovered and corrected. Both ANNs were then modified and tested on another dataset consisting of 308 recordings and speech assessments from two previously published studies (237, 238). Changes were made to the audio preprocessing, the network architectures, and the training options in order to improve the performance of the networks. The networks' performances were then tested using the new dataset in a similar fashion as in the first stage.

Results

Paper I

Among the 2,230,771 children born in Sweden between 2000 and 2020, registered in MFR, 3,386 were born with CL/P. This corresponds to a birth prevalence of 1.52 per 1,000 births (95% CI 1.47–1.57). The birth prevalence of CL/P, CP, CL±P, BCL±P, UCLP, and BCLP during the 21-year period is shown in Table 3.

Table 3 – Birth prevalence of cleft lip and/or palate, and certain subtypes, Sweden 2000–2020.
Abbreviations: CL/P = cleft lip and/or palate. CP = cleft palate without cleft lip. CL±P = cleft lip with/without cleft palate. BCL±P = bilateral cleft lip with/without cleft palate. UCLP = unilateral cleft lip and palate. BCLP = bilateral cleft lip and palate. CI = confidence interval.

	CL/P	CP	CL±P	BCL±P	UCLP	BCLP
Birth prevalence / 1,000 (95% CI)	1.52 (1.47–1.57)	0.61 (0.58–0.65)	0.92 (0.88–0.96)	0.20 (0.18–0.22)	0.36 (0.33–0.38)	0.16 (0.14–0.18)

The birth prevalence of CL/P and all the included cleft subtypes, except CP, showed a significant decrease between 2000 and 2020. The CP birth prevalence remained stable. The risk ratio per year for CL/P was 0.989, indicating a 1.1% decrease in risk for each successive year of birth. The subtype risk ratios per year were as follows: CP: 1.001; CL±P: 0.981; BCL±P: 0.967; UCLP: 0.987; and BCLP: 0.966. All trends remained statistically significant after adjustment for sex, and all except that of UCLP remained significant after adjustment for maternal smoking, as reported in Paper I. The modified Poisson regression model for CL/P is illustrated in Figure 2, together with yearly point estimates of the birth prevalence and confidence intervals.

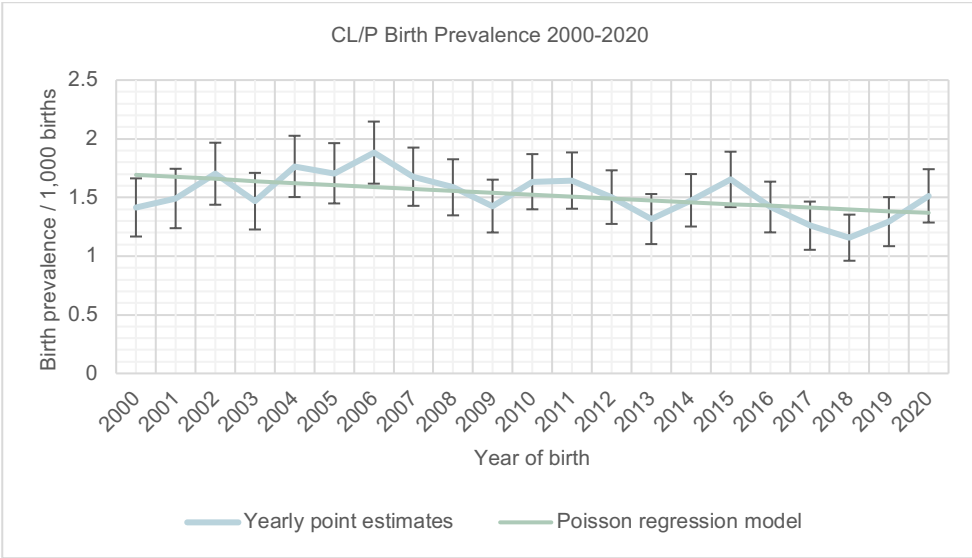


Figure 2 – Cleft lip and/or palate birth prevalence, Sweden 2000-2020.
Error bars represent 95% confidence intervals. Abbreviations: CL/P = Cleft lip and/or palate.

CL/P and all the studied subtypes except CP occurred significantly more often in boys than in girls. CP, however, was more common in girls. The birth prevalence for boys and girls, respectively, is shown in Table 4 together with results from Chi^2–tests.

Table 4 – Birth prevalence of cleft lip and/or palate and certain subtypes, for boys and girls, Sweden 2000–2020.
Abbreviations: CL/P = cleft lip and/or palate. CP = cleft palate without cleft lip. CL±P = cleft lip with/without cleft palate. BCL±P = bilateral cleft lip with/without cleft palate. UCLP = unilateral cleft lip and palate. BCLP = bilateral cleft lip and palate. CI = confidence interval.

	CL/P	CP	CL±P	BCL±P	UCLP	BCLP
Birth prevalence in boys / 1,000 (95% CI)	1.67 (1.60–1.75)	0.52 (0.48–0.56)	1.16 (1.10–1.22)	0.26 (0.23–0.29)	0.45 (0.41–0.49)	0.20 (0.18–0.23)
Birth prevalence in girls / 1,000 (95% CI)	1.36 (1.29–1.43)	0.71 (0.66–0.76)	0.66 (0.61–0.71)	0.14 (0.12–0.16)	0.25 (0.22–0.28)	0.11 (0.09–0.13)
Chi^2 test, boys versus girls	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$

Paper II

Regional differences in the birth prevalence of CL/P and the studied cleft subtypes within Sweden were found, as well as significant temporal trends. Table 5 shows the birth prevalence of each cleft subtype in all HC regions, with significant regional differences and temporal declines indicated.

Table 5 – Birth prevalence of CL/P and cleft subtypes per health care region.

* indicates a significant difference compared with the rest of Sweden. ↓ indicates a significantly decreasing birth prevalence. Abbreviations: CL/P = cleft lip and/or palate. CP = cleft palate without cleft lip. CL±P = cleft lip with/without cleft palate. BCL±P = bilateral cleft lip with/without cleft palate. UCLP = unilateral cleft lip and palate. BCLP = bilateral cleft lip and palate.

Health care region	CL/P Birth prevalence / 1,000 (95% CI)	CP Birth prevalence / 1,000 (95% CI)	CL±P Birth prevalence / 1,000 (95% CI)	BCL±P Birth prevalence / 1,000 (95% CI)	UCLP Birth prevalence / 1,000 (95% CI)	BCLP Birth prevalence / 1,000 (95% CI)
Northern	1.67↓ (1.49–1.86)	0.79* (0.66–0.91)	0.91↓ (0.77–1.04)	0.20↓ (0.14–0.27)	0.40↓ (0.31–0.49)	0.16 (0.10–0.21)
Central	1.49↓ (1.38–1.61)	0.62 (0.54–0.69)	0.89↓ (0.80–0.98)	0.19 (0.15–0.23)	0.35 (0.30–0.41)	0.15 (0.11–0.18)
Stockholm	1.41* (1.31–1.51)	0.61 (0.55–0.67)	0.80* (0.73–0.88)	0.15* (0.12–0.19)	0.30* (0.25–0.34)	0.13* (0.10–0.16)
Western	1.48 (1.36–1.59)	0.56 (0.49–0.63)	0.94 (0.84–1.03)	0.19↓ (0.15–0.23)	0.39 (0.33–0.45)	0.16↓ (0.12–0.20)
Southeastern	1.65 (1.48–1.81)	0.61 (0.51–0.71)	1.06* (0.92–1.19)	0.27* (0.20–0.34)	0.40 (0.31–0.48)	0.22* (0.16–0.28)
Southern	1.59↓ (1.47–1.71)	0.59 (0.51–0.66)	1.02*↓ (0.92–1.11)	0.25*↓ (0.20–0.30)	0.36↓ (0.30–0.41)	0.19↓ (0.15–0.23)

Overall, CL/P was less common in the Stockholm HC region compared with the rest of the country. Regarding cleft subtypes, all subtypes except CP were less common in the Stockholm HC region. CP was more common in the Northern HC region and clefts involving the lip (CL±P, BCL±P) were more common in the Southeastern and Southern HC regions. Lastly, BCLP was more common in the Southeastern HC region.

Temporal trends were observed. The birth prevalence of CL/P declined in three out of six HC regions between 2000 and 2020, whilst the birth prevalence of all cleft subtypes except CP decreased in at least two HC regions. The CP birth prevalence

did not change in any HC region. The Southern HC region showed the most decreasing trends, with declines in the birth prevalence of CL/P and all subtypes except CP.

Paper III

In total, 250 children were included in the study after parental consent. Boys (n=164) represented 65.6% of the study population. Of the included children, 67 (26.8%) had a CP, 67 (26.8%) a CL, 73 (29.2%) a UCLP, and 43 (17.2%) a BCLP.

Ninety children (36.0%) were given at least one additional diagnosis before 5 years of age. Among them, 67 (29.8%) were given one diagnosis whilst 23 (9.2%) were given two or more diagnoses. In total, 137 diagnoses were identified, with the most frequently occurring categories being diagnoses affecting the cardiovascular system (20.4%) and the extremities and skeletal system (17.5%). The distribution is shown in Figure 3. When analyzed by cleft subtype, cardiovascular diagnoses were most common in the CL and UCLP groups. Sequences, as well as diagnoses affecting the extremities and skeletal system occurred most frequently in the CP group. In the BCLP group, diagnoses affecting the extremities and skeletal system together with otorhinolaryngological diagnoses were most common.

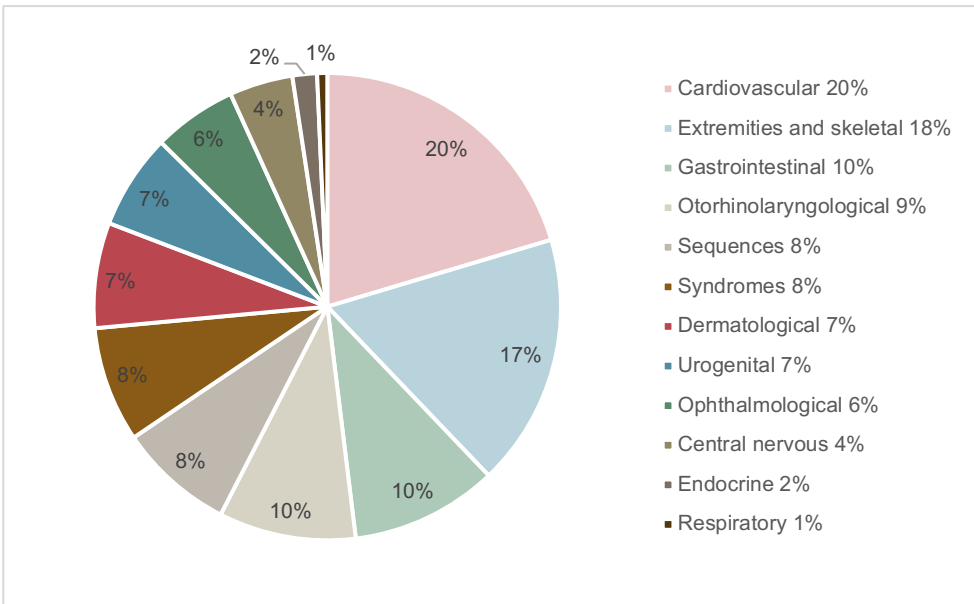


Figure 3 – Distribution of additional diagnoses by affected organ/system.
Proportions (percentages) of the total number of identified additional diagnoses per category.

When comparing the findings to data from the Swedish CL/P Registry, only 47 (18.8%) of the 250 study participants were given an additional diagnosis in the registry, as opposed to 90 (36.0%) in the medical records. In the registry data for all eligible children born in the Southern HC region, 93 of the 436 children (21.3%) were given an additional diagnosis.

Paper IV

The literature searches generated 3,540 unique records, of which 841 abstracts and 195 full-text manuscripts were assessed. In total, 14 original studies were included in the synthesis, and the findings from six systematic reviews were used for comparison. Figure 4 shows a flowchart illustrating the study selection process.

The findings from each of the included studies, categorized into showing an advantage for one-stage palate repair, two-stage palate repair, or neither, are shown in Table 6. Facial growth was assessed in six of the included original studies, speech in four, presence of fistulae in eight, and surgical complications in two. No studies regarding hearing, HRQoL, or health economics were included. No clear overall advantage of either one- or two-stage palate repair was found for any of the outcomes. Although other cleft subtypes were included in the study design, the majority of the studies focused on children with UCLP without comorbidities or syndromes. It should be noted that a few studies reported conflicting results depending on outcome measure and/or cleft subtype group, and hence occur more than once per outcome in Table 6.

After GRADE assessments (shown in Table 7), the conclusions that could be drawn were that for children with UCLP without comorbidities or syndromes, no differences in outcome could be found for presence of fistulae (moderate certainty of evidence), facial growth (low certainty of evidence), and speech (low certainty of evidence). The certainty of evidence for surgical complications was considered very low, and no conclusions could be drawn. For cleft subtype groups other than UCLP without comorbidities/syndromes, the available scientific evidence was too weak to allow for any conclusions. The relatively small sample sizes across outcomes, ranging from 269 (speech) to 637 (fistulae), further limit the strength of evidence. In summary, no clear differences between one- and two-stage palate repair could be established for the studied outcomes.

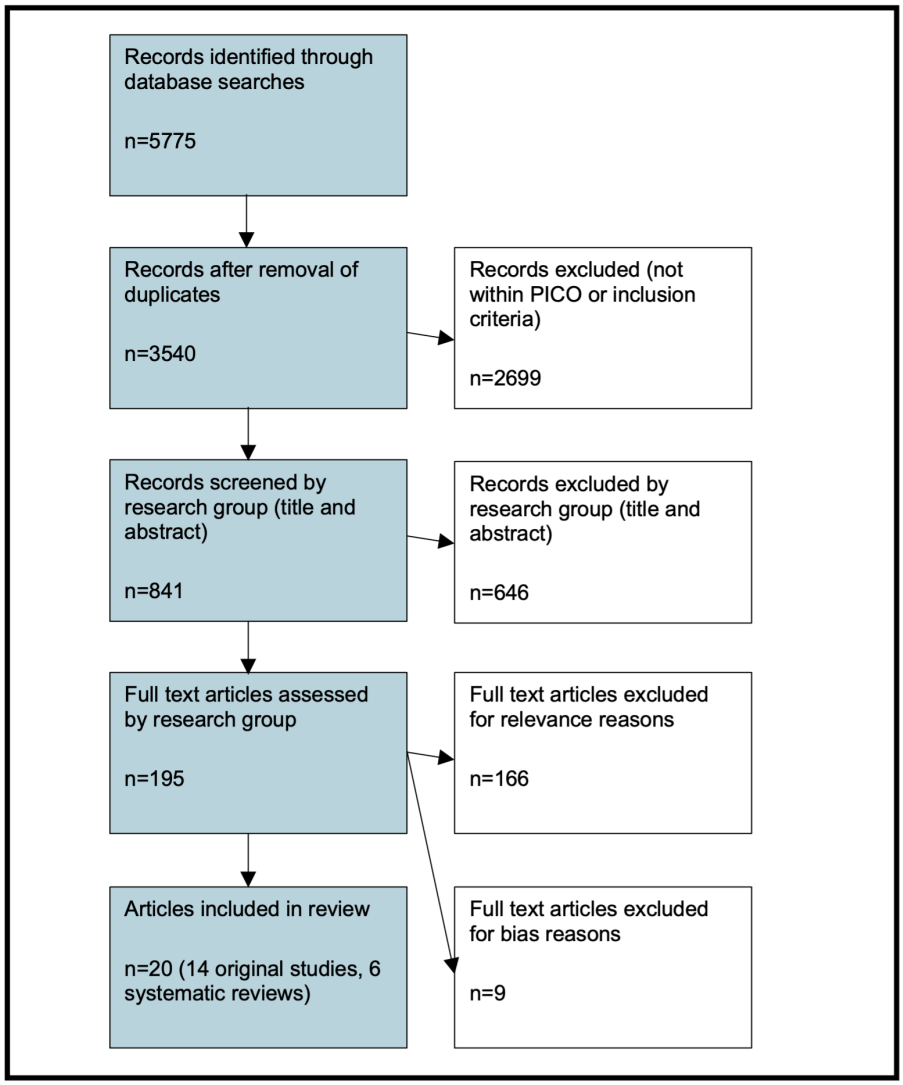


Figure 4 – Flowchart illustrating the study selection process in Paper IV.

Table 6 – Categorized results from original studies studies included in Paper IV.
Abbreviations: PCC = Percent consonants correct. VPC = Velopharyngeal competence. P1a = Unilateral cleft lip and palate without comorbidities/syndromes. P2a = Cleft palate without cleft lip without comorbidities/syndromes. P3a = Bilateral cleft lip and palate without comorbidities/syndromes.

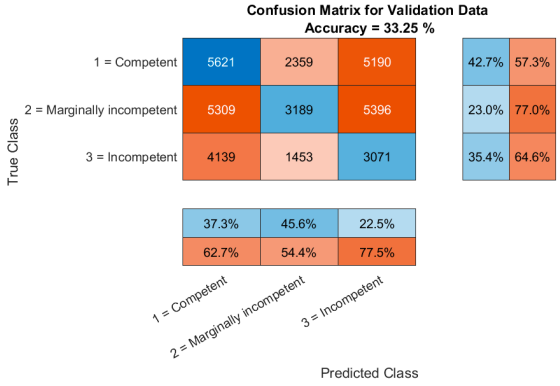
Outcome	Study	Advantage one-stage	No significant difference	Advantage two-stage	Comments
O1: Facial growth	Heliövaara et al. 2017		X		
	Karsten et al. 2020		X		
	Küseler et al. 2020		X		
	Pereira et al. 2018			X	
	Mikoya et al. 2015			X	Transversal growth
	Mikoya et al. 2015		X		Sagittal growth
	Otsuki et al. 2022			X	
O2: Speech	Lohmander et al. 2017		X		
	Lundeborg-Hammarström et. al 2020		X		
	Reddy et al. 2018		X		
	Willadsen et al. 2022	X			PCC
	Willadsen et al. 2022			X	VPC
O4: Presence of fistulae	Willadsen et al. 2017		X		
	Lohmander et al. 2017		X		
	Rautio et al. 2017		X		
	Lundeborg-Hammarström et. al 2020		X		
	Pereira et al. 2018		X		
	Reddy et al. 2018		X		
	Jakobsson & Pontén 1990		X		
	Vedung et al. 1995		X		For P1a
	Vedung et al. 1995	X			For P2a
	Vedung et al. 1995			X	For P3a
O5: Other complications related to surgery	Rautio et al. 2017	X			Airway complications
	Rautio et al. 2017		X		Bleeding, infection
	Jakobsson & Pontén 1990		X		

Table 7 – GRADE assessments.
Assessment of certainty of evidence for conclusions drawn for UCLP without comorbidities/syndromes.

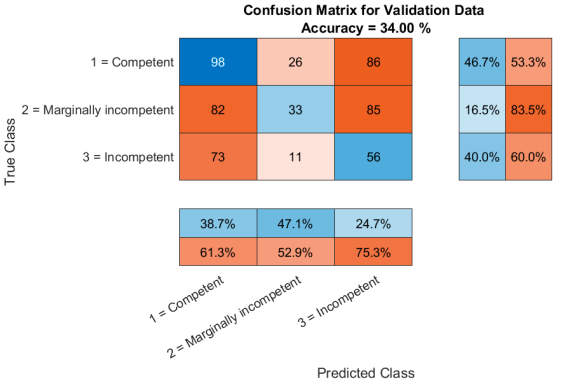
Outcome	Number of studies	Number of unique patients	GRADE score	Overall difference between groups
O4: Presence of fistulae	8	637	Moderate ⊕⊕⊕◯	No
O1: Facial growth	6	365	Low ⊕⊕◯◯	No
O2: Speech	4	269	Low ⊕⊕◯◯	No
O5: Other complications related to surgery	2	265	Very low ⊕◯◯◯	No

Paper V

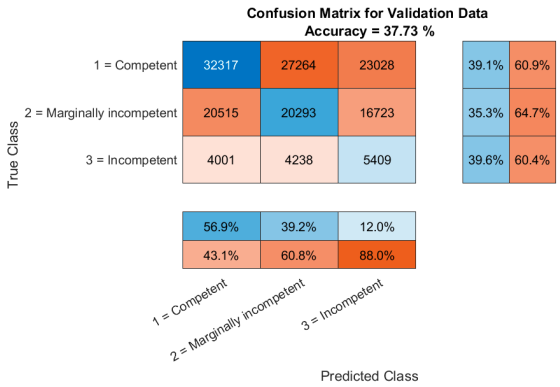
VGGish outperformed CNN both before and after modifications were made in the second stage of the study. Both networks performed better after the modifications, but neither exceeded an accuracy of 57.1%. Predictions were first generated frame-wise in 200 (first part) or 20 (second part) millisecond segments. File-wise predictions were then derived by aggregating the frame-wise outputs, using a majority decision rule. Confusion plots illustrating classification performance, including category-specific and overall accuracies, before and after modifications, are shown in Figure 5 for CNN and in Figure 6 for VGGish. The accuracies when assessing both shorter audio frames and whole audio recordings are shown.



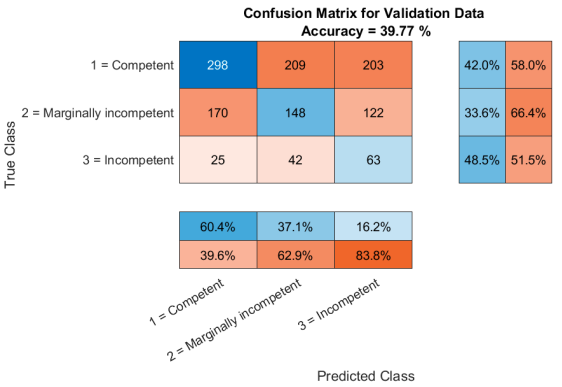
CNN – Frame-wise confusion plot before modifications



CNN – File-wise confusion plot before modifications

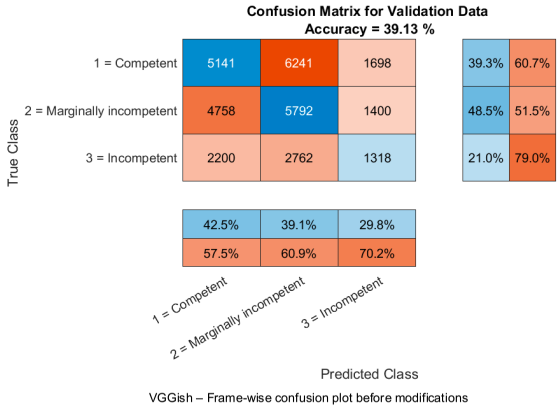


CNN – Frame-wise confusion plot after modifications

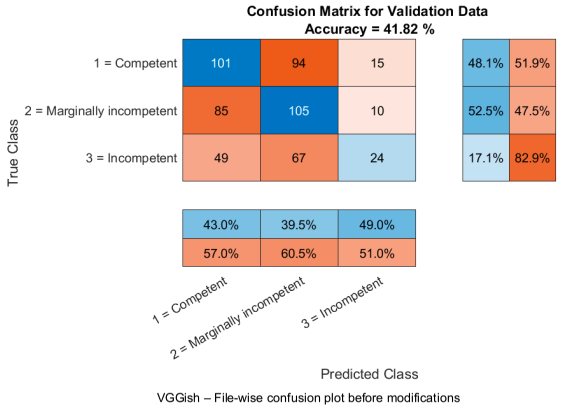


CNN – File-wise confusion plot after modifications

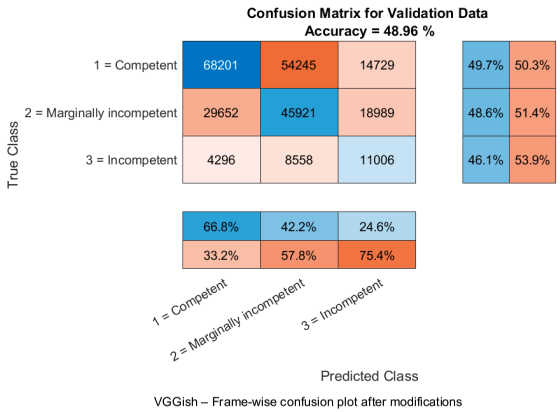
Figure 5 – Confusion plots for CNN.
Frame-wise and file-wise accuracies, before and after modifications.



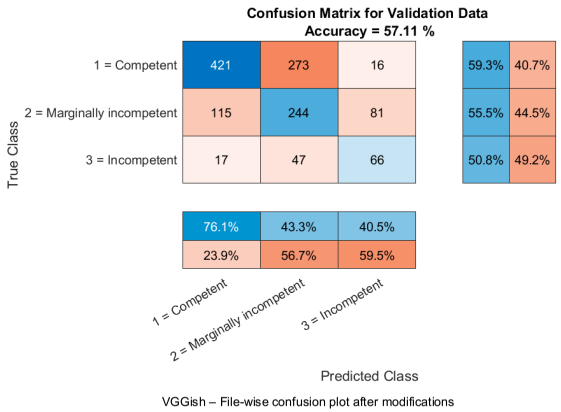
VGGish – Frame-wise confusion plot before modifications



VGGish – File-wise confusion plot before modifications



VGGish – Frame-wise confusion plot after modifications



VGGish – File-wise confusion plot after modifications

Figure 6 – Confusion plots for VGGish.
Frame-wise and file-wise accuracies, before and after modifications.

Discussion

The Birth Prevalence of Cleft Lip and/or Palate in Sweden

The birth prevalence of CL/P was 1.52 per 1,000 births between 2000 and 2020 in Sweden. This prevalence is somewhat lower than in previously reported studies where it ranged from approximately 1.7 to 2.0 per 1,000 births (78-80). The difference could be due to missing cleft diagnoses in MFR, however this seems quite unlikely as the risk of a cleft being overlooked must be considered low as a result of the standardized examinations of newborns in Sweden. It should be noted that the findings from Hagberg et al. (78) and Beckman and Myrberg (79) are based on the number of children treated at their cleft care centers, and as such they had a longer follow-up, and that Amini et al. used data from several registries (80). Both these facts decrease the risk of children with CL/P being missed in the previous studies. Another potential explanation for the lower prevalence found in Paper I is that a decreasing trend (discussed in detail below) started before 2000, and that the true birth prevalence of today is indeed lower than it was when the data from previous studies were collected.

From a global perspective, our findings confirm that the Swedish CL/P birth prevalence is relatively similar to that reported internationally (1, 70, 71). A recent registry-based Swiss study, which was similar to Paper I in its methodology, included more than 1,200,000 children born between 2007 and 2021 (239). In the study, 1,567 cases of CL/P (CP, CL, CLP) were identified, representing a birth prevalence of 1.25 / 1,000 births. Hence, the birth prevalence in Switzerland was lower than that observed in Sweden in Paper I. Findings pointing towards a higher birth prevalence in Northern Europe have been reported before, for example in the large EUROCAT register studies published by Calzolari et al (19, 24).

Differences in Birth Prevalence by Sex

Differences in the birth prevalence for boys and girls, respectively, were observed for CL/P as well as for all studied cleft subtypes. CL/P was more common in boys, as were all cleft subtypes with the exception of CP, which was more common in girls. These findings are consistent with previous reports and suggest that sex-

specific etiological factors may play a role, possibly reflecting differences in embryological development or genetic susceptibility (32-37, 239). The patterns highlight the importance of considering sex differences in future epidemiological and etiological research on CL/P, and they should be kept in mind when comparing results between populations.

National Trends

A decreasing trend in the birth prevalence of CL/P was seen between 2000 and 2020. When studying the included cleft subtypes separately, the analyses showed that there was no change in the prevalence of CP, but that the prevalence of all other cleft subtypes decreased. As clefts of only the palate are more difficult to diagnose with ultrasonography during pregnancy, compared with clefts affecting the lip (240-242), a potential explanation that quickly comes to mind is that pregnancies where a cleft has been diagnosed might be terminated more frequently. There are previous studies from other countries that suggest that this might be the case (243, 244). Evaluating this hypothesis in Sweden is difficult, since specific reasons for pregnancy termination do not need to be specified. The existing data on the subject, a report published by SoS in 2024, suggests that the number of pregnancies that are terminated because a cleft has been diagnosed is quite low, although it should be noted that it increased from 0.7% (22 / 3,160) years 1999–2017 to 3.2% (24 / 761) years 2018–2022 (245). Taken together, it does not seem like an increasing rate of pregnancy termination can fully explain the declining trend in CL/P birth prevalence in Sweden.

Another potential explanation is improved management of risk factors and better general public health. This hypothesis is supported by, for example, the fact that when the modified Poisson regression models in Paper I were adjusted for maternal smoking, a well-known risk factor for CL/P (40-42), maternal smoking came out as a significant covariate for all cleft subtypes. Still, the declining trends remained significant for all cleft subtypes except UCLP. This suggests that even though maternal smoking is likely decreasing, this decrease cannot entirely explain the declining birth prevalence of CL/P and its subtypes, with the exception of UCLP. Other risk factors were not investigated in detail in the studies included in this thesis, but there are several potential factors that can contribute to the declining trends, for example maternal body mass index (64, 65), parental level of education (60, 61), and socioeconomic factors (58, 59). Taking the trends observed in Paper I into consideration, two previous studies are of special interest. In a 2015 American study by Lupo et al., it was noted that the risk of having a child with CL±P, but not CP, was higher for mothers living in areas with socioeconomical challenges (59). Similar findings were presented in a Scottish study by Clark et al., where they saw that the risk of CL/P, but not CP, increased with socioeconomic deprivation (58).

Lastly, the genetics of the Swedish population are changing with substantial immigration in later years (246). It has been shown that the risk for CL/P differs between ethnical groups (8, 70, 71, 77), and hence immigration can affect the birth prevalence of CL/P.

Findings from previous studies regarding trends in CL/P birth prevalence are somewhat conflicting. The aforementioned recent Swiss study reported a stable trend for CL/P between 2007 and 2021, but a decreasing trend for CLP specifically (239). In a Taiwanese study including over four million births, a decreasing trend in CL±P birth prevalence was observed between 1994 and 2013, whereas CP increased slightly (247). On a more global level, Tanaka et al. (2012) reported a decline in CL±P prevalence across 30 countries from 2002 to 2006, but trends in CP birth prevalence were not included (248). Overall, although trends may vary across populations and time periods, declining trends similar to those observed in Paper I have been reported before, and recent studies reporting an increasing birth prevalence of CL/P seem to be lacking.

Regional Differences Within Sweden – Birth Prevalence

When studying differences in CL/P birth prevalence between the Swedish HC regions (Paper II), several significant findings were identified. Specifically, the Northern, Stockholm, Southeastern, and Southern HC regions stood out when it came to the prevalence of certain cleft subtypes compared with the rest of the country.

In the Northern HC region, CP was significantly more common than in the rest of Sweden. This confirms the findings from a previous study from the 1970s, where a similar pattern was seen (79). The reason for this finding is likely the close connections between the Northern parts of Sweden, and Finland. In Finland, previous studies have shown an unusually high prevalence of CP compared with the rest of Europe, especially in the Northern parts (19, 74, 82). It has been suggested that this is the result of genetically relatively isolated populations in parts of Finland, which has led to for example a higher prevalence of a risk variant of the IRF6 gene, something that is associated with a higher risk for CP (83).

Secondly, the Stockholm HC region showed significantly lower birth prevalence for the CL/P group as a whole, as well as for all studied cleft subtypes except CP. As was the case for the whole country, it is possible that the fact that clefts involving the lip were less common than CP is a result of cleft pregnancies being terminated to a larger extent. Women in Stockholm might have better access to prenatal diagnostics as the region is the wealthiest and most densely populated in Sweden (249, 250). However, this hypothesis is challenged by the fact that no declining trends were seen in Stockholm between 2000 and 2020. An alternative explanation is that improvements in health care and public health may have reached Stockholm

earlier than the rest of the country. The role of migration and changing genetics in the Swedish population should be considered when it comes to regional differences as well. In fact, the Stockholm HC region has the highest proportion of foreign-born residents of the Swedish HC regions (246), something that might also contribute to the differences in cleft birth prevalence between Stockholm and the rest of the country.

In the Southeastern and Southern HC regions, clefts involving the lip (CL±P, BCL±P) were more common than in the rest of the country. In the Southeastern HC region, BCLP was more common as well. A higher birth prevalence for BCLP was seen in the Southern HC region too, but the difference compared to the rest of the country was not statistically significant. The explanations for these findings are still unclear, but it is a noteworthy finding that the regions that are geographically the furthest away from the Northern HC region, where CP is more common, have the highest prevalence of clefts involving the lip. Further studies are required to explore whether this is related to genetic clustering, environmental exposures, or stochastic variation.

The findings from the Central and Western HC regions did not differ significantly from the other regions. However, Chetpakdeechit et al. (2010) reported CP birth prevalence, 0.64 / 1,000 births, for children treated in Gothenburg (Western HC region) (81). These numbers can be compared to the CP birth prevalence in the Western HC region in Paper II, which was 0.56 / 1000 births and hence slightly lower.

Regional Differences Within Sweden – Temporal Trends

The temporal trends observed in Paper II varied between HC regions. CL/P birth prevalence decreased in three out of six HC regions (Northern, Central, and Southern). CP prevalence did not change in any region, whilst the prevalence of all other cleft subtypes decreased in two or three HC regions. The Southern and Northern HC regions were those where the highest number of cleft subtypes decreased in prevalence, with five and four decreasing prevalences, respectively (CL/P, CL±P, BCL±P, and BCLP in both; and UCLP in the Southern HC region). In the Western and Central HC regions, two and one cleft subtype(s), respectively, decreased in prevalence. In contrast, no changes in birth prevalence were observed in the Stockholm and Southeastern HC regions.

The findings confirm the national trends reported in Paper I, namely a declining birth prevalence of CL/P and all studied cleft subtypes except CP between 2000 and 2020, but Paper II demonstrates that such trends are not consistent across regions. The reasons remain unclear, and the Northern and Southern HC regions, where the trends were the most obvious, are in fact the two HC regions that are the furthest away from each other geographically. In the Stockholm HC region, trends might

have occurred earlier, while the relatively small population in the Southeastern HC region could limit statistical power. Nevertheless, significant trends were detected in the even smaller Northern HC region. The consistently stable CP birth prevalence across regions mirrors the findings in Paper I, and potential explanations are discussed in the *National Trends* section. From an international perspective, geographical variation within countries has been reported before, for instance in the U.S., Switzerland, and Finland (239, 248, 251).

Taken together, the results from Paper II illustrate that regional variations in CL/P occurrence may manifest both as differences in absolute birth prevalence and as differences in temporal trends. These two aspects do not always coincide. A region with relatively high prevalence may show pronounced declines over time, as was the case with CL±P and BCL±P in the Southern HC region. Conversely, a region may show comparatively low but stable prevalence over the study period, as observed in the Stockholm HC region. The patterns suggest that long-term genetic and environmental factors may contribute to the differences in absolute birth prevalence, whilst dynamic processes such as improvements in health care, differences in maternal exposures, or changes in prenatal diagnostics may be more clearly reflected in temporal trends. Both perspectives are therefore necessary to fully understand regional variation in CL/P birth prevalence.

Future Research

The dataset used in Papers I and II included more than two million children born in Sweden over a 21-year period, with data from registries of high coverage and reliability. Hence, the findings are likely representative of the epidemiology of CL/P in Sweden during the period. However, the explanations for the identified temporal trends and geographical differences require further investigation. A reasonable first step would be to include additional potential risk factors in the statistical models in order to assess their effects on the birth prevalence of CL/P and its subtypes. The dataset used already contains several unused variables, such as maternal diagnoses and medications, maternal body mass index, parental country or region of birth, and parental level of education. A potential pitfall in such analyses is the risk of confounding factors and interaction between risk factors. For example, maternal diagnoses and medications, or parental level of education and maternal smoking, may be interrelated.

Advances in medical genetics also provide opportunities to combine epidemiological registry data with data from genomic analyses such as genome-wide sequencing, which could offer deeper insight into the etiology of CL/P. Internationally, similar registry-based studies should be conducted in order to investigate the epidemiology of CL/P in other regions of the world. However, the reliability of medical registries might pose a problem particularly in low- and middle-income countries. Studies including participants from different ethnic

backgrounds but living in the same geographical area, such as that published by Croen et al. in 1998 (77), can also help disentangle genetic from environmental influences. With increasing globalization and migration, the feasibility and importance of such comparative studies are likely to grow in the future.

Additional Diagnoses in Cleft Lip and/or Palate

The 5-year cumulative incidence of additional diagnoses for children with CL/P in the Southern HC region was studied in Paper III, and found to be 36.0% (90/250 children). This is similar to the proportions reported in other relatively recent European studies (22, 142, 145), but lower percentages have also been reported (23, 148). Large registry studies were published by Calzolari et al. in 2004 and 2007, where data from 16 and 14 countries, respectively, was included as part of the EUROCAT network (19, 24). The findings from these large studies are not directly comparable to our data, as the proportions of additional diagnoses in CP (45.2%) and CL±P (29.2%) were reported separately, but were relatively similar to those observed in our study. Compared to previous Swedish studies, where additional diagnoses have been reported in around 20% of children with CL/P, our findings indicate a higher percentage (78, 146).

A potential explanation for the relatively high percentage observed in our study is the fact that we used a 5-year cumulative incidence, whilst other studies may have had shorter follow-up times. This hypothesis is speculative, though, as follow-up times were unknown or not reported in many previous studies (19, 22-24, 78, 142, 146, 148). The fact that only half of the diagnoses in the study (69/137) were found at birth, whilst the other half (68/137) were found at a later time-point before age 5, supports the hypothesis that follow-up time affects the findings.

Another factor that affects results is how additional diagnoses are defined. In Paper III, we used a wide definition, essentially including all diagnoses except those that either affect children both with and without CL/P (transient infections, allergies, refractive errors, complications related to childbirth, physiological heart wheezing, hypertrophy of tonsils/adenoid) or that are well-known consequences of the cleft (secretory media otitis, speech deviations, malocclusion, dental anomalies). In contrast, all the abovementioned studies included only congenital diagnoses/malformations/syndromes (19, 22-24, 78, 142, 145, 146, 148). Hence, the wider inclusion criteria used in our study likely contributed to the relatively high percentage of children with additional diagnoses.

In the 90 children who received additional diagnoses before age 5, a total of 137 diagnoses were found. Sixty-seven of the 90 children had only one additional diagnosis, ten children had two, eight children had three, and five children had more than three. The ratio of total number of diagnoses to the number of affected children

was 1.5, which supports the hypothesis that many children are affected by more than one additional diagnosis. This finding has also been reported in previous studies (23, 142, 145-147).

In Paper III, the identified additional diagnoses were grouped depending on the affected organ. The largest group was diagnoses affecting the cardiovascular system (28/137 diagnoses, 20.4%), followed by the extremities and skeletal system (24/137 diagnoses, 17.5%). Cardiovascular diagnoses were found in 11.2% of the included children (28/250 participants) whereas the extremities and skeletal system was affected in 9.6% of participants (24/250 participants). These two groups of diagnoses have been reported as common in several previous studies (23, 142, 145-148).

Eleven children (4.4%) were diagnosed with a syndrome before age 5. Among these 11, four were chromosomal whilst seven were non-chromosomal recognized syndromes. Notably, nine different syndromes were found in the 11 children, with CHARGE and Goldenhar's syndromes being the only ones affecting more than one child (two cases each). This illustrates the variance and broad spectrum of syndromes that can be associated with CL/P. The overall syndromic prevalence of 4.4% was relatively low compared with other studies, but as mentioned in the introduction the findings differ markedly between studies (22, 23, 145). A potential explanation for the low prevalence of syndromes in Paper III is that the criteria were strict. Syndromes had to be confirmed through either genetic testing or a clear clinical picture; mere suspicion was not sufficient. These stringent criteria may have led to an underrepresentation of syndromic cases in our study, as children with syndromes that had not yet been confirmed were missed. In contrast, the use of less strict criteria in previous studies may have contributed to higher reported numbers, and in some cases potentially to an overestimation of the occurrence of syndromes. However, when reviewing the methodology sections of previous studies reporting higher proportions, it is not entirely clear that their criteria differed substantially from ours (22, 145).

The most common additional diagnoses differed by cleft subtype, although these differences were not tested for statistical significance. Although the proportions varied between the cleft subtype groups, the categories that occurred most frequently (CL and UCLP: cardiovascular; CP: sequences, extremities and skeletal; BCLP: extremities and skeletal, otorhinolaryngological) were also common in the CL/P group as a whole.

Reliability of Swedish CL/P Registry Data on Additional Diagnoses

Paper III compared the 5-year cumulative incidence of additional diagnoses among the 250 children whose medical records were reviewed with corresponding data from the Swedish CL/P Registry (194). The proportion of children with additional diagnoses was markedly lower in the registry (18.8%) compared with the medical records (36.0%). As the data in the medical records included information from a broader range of health care visits, not only those related to the cleft, they likely provided a more complete picture. This suggests that additional diagnoses are underreported in the Swedish CL/P Registry – an important finding directly addressing the aim of validating registry data. These results highlight the need to improve registration routines, for example by ensuring that the child's general medical condition is also addressed at cleft-related follow-up visits.

Future Research

Future studies regarding additional diagnoses in CL/P should try to include larger study populations, preferably in a prospective manner. However, such studies can be challenging as follow-up times should be long in order to detect diagnoses that might not be apparent at birth and in infancy. For example, neurodevelopmental disorders have been shown to occur more frequently in children with CL/P (252). The prevalence of these diagnoses increases with age all through childhood, suggesting that long term follow-up is necessary in order to identify all cases (253). To increase comparability between studies, it is essential that the inclusion and exclusion criteria for diagnoses are clearly stated, as well as follow-up times and categorization of diagnoses. Harmonization in defining and categorizing additional diagnoses would facilitate international collaborations and comparisons.

Further research on additional diagnoses could contribute to the knowledge about the etiology of CL/P, and vice versa. It seems likely that both environmental and genetic factors contributing to CL/P could also increase the risk of other diagnoses occurring. As the field of medical genetics advances, it is also likely that additional syndromes involving CL/P will be identified. This needs to be kept in mind when studying the proportion of syndromic CL/P cases.

Surgical Approach for Palate Repair

Whether one- or two-stage palatoplasty should be preferred has been discussed for a long time. Unfortunately, the systematic review included in this thesis (Paper IV) did not find the answer. Several different outcomes were included to identify any potential advantage for either method.

Fistula formation, speech, and facial growth were the outcomes for which conclusions could be drawn, but no overall advantages for either surgical approach were found. There was a lack of scientific evidence across outcomes. Even for presence of fistulae, where evidence was strongest, the certainty of evidence was only moderate. For facial growth and speech, the certainty was low, making conclusions uncertain. For the other outcomes, the certainty was very low (complications related to surgery), or studies were lacking (hearing, HRQoL, health economics). Furthermore, most of the studies only included children with UCLP without comorbidities or syndromes. Overall, the conclusions that could be drawn were of limited reliability, and original studies including more outcomes and patient groups are required for a complete picture.

A comparison with previous systematic reviews was included in Paper IV. As in our study, conclusions could only be drawn for facial growth (187, 254), speech (255) and fistulae (256-258). The findings correlate with those presented in Paper IV – all except one showed no overall advantage for either surgical approach. The exception was Stein et al. which reported fewer fistulae in the one-stage group (258). Since the publication of Paper IV, a recent systematic review and meta-analysis has compared one- and two-stage palatoplasty with regard to facial growth, speech, postoperative complications including fistulae, and hearing (259). As in most previous studies, only UCLP was investigated. A major difference from Paper IV is that it included studies of either surgical method whilst ours only included comparative studies. This increased the number of eligible studies and made a meta-analysis possible but may have increased the risk of bias due to heterogeneity between studies. Overall, although the fistula rates were lower in the one-stage group, the certainty of evidence was deemed very low.

If no significant medical advantages can be observed for either surgical approach, which was the case Paper IV, other factors need to be considered. One argument is that surgeons should use the technique that they are more comfortable with, as changing technique involves a learning curve (260). However, an argument could also be made in favor of the one-stage approach because of the risks associated with anesthesia. A staged approach means two procedures under anesthesia and likely a longer total time under anesthesia. Both a higher number of procedures under general anesthesia and longer duration have been suggested to have negative neurocognitive effects on children (261). Lastly, ethical considerations should be considered. According to the principle of autonomy, individuals should be allowed

to make decisions regarding their own health (262). In young children, this may not be possible, but it seems reasonable to minimize surgical procedures before the child is old enough to speak for him-/herself. This is especially true if there are risks associated with the procedures, which reflects the principles of beneficence (to do good) and non-maleficence (to avoid harm) (262). Ethical considerations also play a role in health economy. No studies assessed health economics, but a two-stage approach is plausibly more costly due to additional procedures and longer total hospital stays. Minimizing health care resource use, when medical outcomes are identical, allows resources to be allocated to other patients, which is consistent with the principle of justice (262).

Future Research

The time span of included studies (1970–2023) was long, and the search strategies were thoroughly designed in collaboration with medical librarians. Therefore, it is unlikely that new systematic reviews will contribute significantly towards answering the research question in the near future. Hence, there is a need for new original studies. One obstacle in the systematic review was the heterogeneity of outcome measures used in the included studies. For example, facial growth can be measured on photos, radiographs, or models, and several different indices exist. A homogenization and standardization of outcome measures would greatly facilitate comparisons and meta-analyses, something that is of utmost importance when the diagnosis is relatively uncommon, and study populations are small. One alternative in order to achieve this could be to follow the standard outcome set suggested by the ICHOM working group in future studies (84). Another obstacle is the heterogeneity in surgical techniques – grouping into one- and two-stage techniques facilitates comparison, but several different methods exist within each group.

Future studies should be preferably prospective and include standardized outcome measures. International collaborations may be challenging but can increase sample sizes substantially. One such ambitious prospective study was the Scandcleft project, from which many of the reviewed studies originated (263). Even there, no clear conclusions could be drawn, highlighting the difficulties in this field. A particular challenge in CL/P research is the long follow-up required to reliably evaluate final outcomes, another obstacle for such studies. An alternative to prospective randomized studies could be large registry-based studies, which can be less time consuming and generate large study populations. However, they require reliable registries with high coverage and relevant outcomes. Such registries tend to exist mostly in high-income countries. Furthermore, future research needs to include a wider range of cleft subtypes, not only UCLP. Similarly, important outcomes such as hearing, health economics, HRQoL, and PROMs need to be assessed further.

Artificial Intelligence for Assessment of Speech in Cleft Palate with/without Cleft Lip

Paper V was an innovative, methodological study where we explored AI as a tool for speech evaluation in children with CP±L. The study is to be seen as a foundation for further research, and although it did not produce an ANN with sufficient performance for clinical use, it showed that two ANNs could be developed with less than 500 audio recordings, and that modest modifications in the network architectures and training options could substantially improve performance.

The study also highlighted some key challenges in this field of research. Firstly, an error in the code falsely inflated the accuracy of the ANNs in the first part of the study. It was discovered and corrected in the second part of the study when the results from the first part were reproduced. This underscores the importance of transparence and reproducibility, particularly in technically complex AI studies where small programming inaccuracies can be difficult to detect.

Another key challenge was the pre-processing and quality of the audio recordings. Many recordings included adult speech. For the human listener, it is easy to hear and ignore the adults, but for the AI tool, these parts needed to be removed, a process that had to be checked manually for reliability. Even though the recordings were made using high-tech equipment in a hospital setting, the quality of some of them was too low to allow use in the ANNs. The recordings that were usable were often of suboptimal quality, for example because the child was sitting far away from the microphone. The 308 recordings used in the second part of the study were substantially different from those in the first phase, as they were shorter and more heavily cut. This may be useful for SLP assessments in cross-linguistic research (which was the original use of the recordings in the previously published studies using the recordings) but may not be optimal in the AI setting. Variance in the recordings — in terms of content, length, and language — is valuable to avoid overfitting. Overfitting means that the networks can achieve excellent results using the same or a similar dataset, but fail to maintain their performance on new datasets (264). However, for training and testing the ANNs, more homogeneous recordings with more speech data would likely have been more suitable. Hence, the heterogeneity may have reduced learning and, consequently, performance.

Direct comparisons with previous studies using AI to assess CL/P speech are difficult, mainly because Paper V is one of the first studies that has focused on VPC assessments. One other VPC-focused study was published by Zhang et al. in 2023, where a support vector machine model was combined with DL. Very high internal cross-validated accuracy when identifying VPI (265) was reported. However, there were some key differences compared to Paper V, beyond the AI model itself. VPI was classified dichotomously (VPI or no-VPI), and participants ranged from

children to adults and were not necessarily individuals with CP. Furthermore, the model was only tested on their own internal dataset.

Three reviews, two of them systematic and one scoping, found between eight and 12 studies regarding the use of AI for speech assessments in CP±L care (266-268). However, the wide definition of AI poses another problem when comparing the findings to those presented in Paper V, namely that many previous studies do not explore DL specifically but rather older "classical" approaches to AI. Combining the findings in the three reviews, only four unique studies that investigated DL algorithms for speech assessment in CP±L were identified, all focusing on evaluation of hypernasality (226-228, 269). All four studies produced better performing AI tools than did Paper V, even though the number of included research subjects was smaller, but detailed comparisons are hindered by the fact that the studied speech outcomes differed. The markedly higher performance reported in those studies may partly reflect overfitting to small, homogeneous datasets and the use of narrowly defined speech tasks, whereas the more variable and clinically realistic recordings used in Paper V may provide a stronger basis for future model generalization.

A strength of our study was the systematic comparison between different network architectures. The CNN and the pre-trained VGGish were used in the entire process, and a bilateral long-short term memory layer (BiLSTM) network (270) was tested in the earlier stages. However, the BiLSTM network performed worse than the CNN and VGGish, and was discarded at an early stage, which is why it was not mentioned in Paper V.

In summary, Paper V represents an important step towards the use AI in CP±L speech assessment. While substantial refinement is needed before clinical implementation, the study provides valuable methodological insights and a foundation for future research.

Future Research

Paper V showed somewhat promising results, and future studies should focus on developing the ANNs further using new speech material. Datasets need to be larger and of higher quality. Ideally, the recordings should include only the children's speech. In future studies, this could be handled for example through pausing of the recording when the SLP or parent is speaking. Another alternative is to record older children, who may require less oral prompting. However, older children are likely to have a better speech, leading to an imbalanced dataset where children with VPI are lacking. This was already an issue in our study, where the worst VPC category was the smallest (as presented in Paper V).

Furthermore, greater variability of VPC within datasets would be valuable, including more recordings of children with very good or poor velopharyngeal

function. The ANNs should ideally be trained and tested on recordings that are representative of a specific VPC category. It is reasonable to assume that the ANN, like the SLPs, may find it more difficult to correctly assess speech samples that fall on the borderline between two categories. One way to address this would be to use multiple SLP assessments to determine the VPC category, as was done in the second phase, and to include only those recordings for which the SLPs were in agreement when training the ANNs. This approach, however, would require even larger datasets. Future studies should also include external validation on an independent cohort to assess generalizability.

Creating purpose-made recordings where only the child is speaking, perhaps with a modified content, could prove worthwhile. Another method, which was used in one of the studies regarding assessment of hypernasality, is training the network on normal speech samples (226). This approach uses transfer learning in a similar manner to the VGGish network that was included in Paper V.

There are also other network architectures that could be tested. Transformer-based models, in particular, have shown promise in speech tasks and could be valuable to evaluate in future studies (271). Moreover, velopharyngeal competence is not the only speech outcome that could be evaluated with AI. In fact, VPC is a combined variable, consisting of an assessment of the overall impression of hypernasality, weak pressurized consonants, and nasal air emission. As such, it might be complicated for the ANN to evaluate. Developing a tool for assessing hypernasality could prove more feasible, and clinically relevant as it is one of the speech variables that are most difficult for SLPs to assess perceptually (272). It must also be acknowledged that, as long as the SLPs' assessments are used as the true values in studies, the performance of the ANNs cannot surpass the reliability of their assessments. This becomes particularly relevant if focus is shifted to for example hypernasality, where inter-rater agreement among SLPs could be limited.

Methodological Considerations

This section elaborates on the methodological considerations and choices made in the design of the five included studies.

Paper I

The methodology in Paper I can be viewed from two different perspectives: the dataset and the statistical analyses. MFR has a high degree of coverage, approximately 97–99% (273), making it suitable for epidemiological studies, although some underreporting or misclassification cannot be excluded. As the dataset was anonymized, comparison with other data sources such as the Swedish

CL/P Registry was not possible. However, data from the Swedish National Patient Register, another registry managed by SoS, could have been used to identify patients with clefts discovered at a later age. Nonetheless, the standardized examination of newborns in Sweden, which includes examination of the palate, means that the underreporting is likely to be small.

Regarding cleft subtypes, we chose to analyze CP, CL±P, BCL±P, UCLP, and BCLP separately. CP was chosen as it is a distinct group with different pathophysiology compared with clefts involving the lip. CL±P includes all clefts involving the lip, which are more likely to be diagnosed prenatally using ultrasonography (240-242). Just like CP, UCLP is a clinically distinct group that is often seen as a separate group both in clinical practice and in research. Bilateral cases were studied separately as we had noticed that they seemed to have become less common in our clinical practice. Although the choice of subtypes added depth to the analyses, some of the groups were overlapping which can make the results more challenging to interpret.

For the statistical analyses, modified Poisson regression models were used to assess temporal trends, with and without adjustment for sex and maternal smoking. Chi2-tests were used for comparisons between boys and girls. Poisson regression is suitable for studying count data and how certain factors affect the frequency of the "event" (in this case a child being born with a cleft). Modified Poisson regression models provide risk ratios, which can be easier to interpret than for example odds ratios. Model assumptions for Poisson regression include independent observations, a count outcome, equality of variance and mean, a log-linear association between predictors and the expected outcome, and identifiability of parameters (i.e., no severe collinearity among covariates**)** (274). The assumptions were deemed acceptable. It should be noted that observations were not always fully independent, for example in familial cases. However, the vast majority of CL/P cases in this large dataset were independent. Robust standard errors were used to account for possible overdispersion (i.e. when the variance exceeds the mean). Log-linear associations were not formally tested, which is a limitation of the study design. The only covariates used were maternal smoking and sex of the child, two variables not strongly associated with each other.

Adjusting for maternal smoking and sex was used to account for potential confounding, since both maternal smoking (40-42) and sex (32-37) affect CL/P birth prevalence. To further examine the reasons behind the temporal trends, the models could have been adjusted for other potential risk factors as well. However, this was considered outside the scope of the study.

Chi2-tests were used to compare the birth prevalence of CL/P between boys and girls. The test is appropriate for testing differences between two independent groups on binary outcomes (sex: boy/girl; CL/P diagnosis: yes/no)(275). A disadvantage of the Chi2-test is that it only determines whether a statistically significant difference

between the groups exists, not its magnitude. However, this could be determined by comparing the absolute birth prevalence in the respective groups directly.

Paper II

The methodological considerations in this paper were largely similar to those in Paper I. In Paper II, modified Poisson regression models were used not only to examine temporal trends, but also to compare the birth prevalence in each HC region compared with the rest of the country. In this case, the independent variable was binary (born in the region: yes/no), but the dependent variable was still count data (CL/P: yes/no) and therefore modified Poisson regression models were deemed appropriate.

Potential confounding factors should be considered, as regional differences in CL/P birth prevalence can reflect differences in exposure to underlying risk factors, both genetic and environmental. The aim of Paper II was to identify and describe geographical variation, not to determine its causes. Hence, adjusting for potential risk factors was outside the scope of the study, and would risk obscuring the regional differences that the study aimed to highlight. Instead, identifying these differences provides a basis for future studies on the underlying factors, as stated in the *Future Research* section. It should be addressed that the variable used to determine where the child "was born" was in fact the municipality where the mother had her registered address at childbirth. This introduces a risk of misclassification, since the child may actually have been delivered in another HC region. However, for this study, the mother's place of residence is likely to be a more relevant indicator than the physical place of birth, as geographical differences in CL/P birth prevalence presumably rely on environmental and genetic factors in the area and population where the family lives, rather than the hospital/clinic at which the child was delivered.

Of the 2,230,771 included children, 1,877 (0.1%) were missing data on place of birth, including six with CL/P. The most likely explanation is that the mother had no registered Swedish address at the time of delivery, due to for example recent arrival or temporary stay in Sweden. Since the proportion of recently arrived or temporarily staying mothers may differ between HC regions, the missing data were not regarded as "missing completely at random" (MCAR) (276, 277). However, as possible relevant covariates such as maternal country of birth and education were available in the raw data, the missing data were considered "missing at random" (MAR) (276, 277). While "missing not at random" (MNAR) could not be completely excluded, as the reasons for lacking a registered address cannot be established with certainty, it was deemed unlikely (276, 277).

One method of handling missing data is complete-case-analysis (CCA, or listwise deletion), which excludes cases with missing data (278). Although CCA is usually

avoided when the missing data are considered MAR due to the risk of biased results (278), it can be justified when the proportion of cases missing data is very small (278-280). As the proportion in our dataset was below 0.1%, CCA was considered appropriate. Had the proportion been larger, multiple imputation could have been a valid method to use to avoid biased estimations (277).

Paper III

The Swedish CL/P Registry has a high degree of coverage, on average 94.6% for children born between 2009 and 2022 when comparing it to the Swedish National Patient Register (195). This implies that a vast majority of children born with CL/P in the Southern HC region were identified and available for inclusion in the study. Letters asking for consent to participate in the study reached the guardians of more than 90% of the identified children (404/436). However, only 250 children (57%) were included after the guardians' consent. This introduced a potential selection bias, which could mean that the study population differed systematically from those not included (281). Comparisons of sex and cleft subtype distributions between included and eligible groups revealed no major differences, but formal statistical tests were not performed, as they are primarily intended for hypothesis testing and could have overstated minor differences of limited clinical relevance.

The review of medical records was thorough and based on structured diagnosis classification systems such as ICD-10 (230). Still, some diagnoses may have been missed or misclassified, which may have introduced information bias (281). The follow-up in the study was until age 5, which allowed for identification of additional diagnoses that are not found at birth, but an even longer follow-up would likely reveal more additional diagnoses in the study population. Particularly, diagnoses that are likely to be found at an older age, such as neurodevelopmental disorders (see the *Additional Diagnoses in Cleft Lip and/or Palate* discussion section), were at risk of being missed in Paper III.

External validity was limited as only children from the Southern HC region were included. Including other regions or countries would improve generalizability and enable comparisons. However, including more regions could also increase the risk of information bias due to differences in registration routines. Indeed, even within Sweden, the 2024 Swedish CL/P Registry report showed that one HC region reported only one-fourth as many additional diagnoses as the national average, suggesting registration differences rather than true variation (195).

The study was descriptive and retrospective in design, and only descriptive statistics were used. Statistical comparisons could have made the findings more robust and easier to interpret. For example, the observed differences between cleft type subgroups could have been formally assessed. Furthermore, comparison with a non-

CL/P control population could have provided further insight into the prevalence of these diagnoses in the CL/P group.

Paper IV

Paper IV was designed to provide a systematic and reliable review of the available scientific evidence regarding outcomes of one- versus two-stage palatoplasty, and it had a few key strengths. The literature searches were performed by experienced medical librarians, based on a structured research question in the established PICO format. Relevance was assessed blindly, and evaluations of relevance, quality, and risk of bias were performed independently by at least two researchers according to established guidelines. GRADE assessments of the certainty of evidence were done according to established guidelines after extensive group discussions.

The study faced two main obstacles. Firstly, only 14 original studies met the inclusion criteria. This number could have been increased by widening the criteria or by lowering quality demands. The quality threshold was set at moderate risk of bias, since including studies with high risk would increase the chance of erroneous conclusions. However, more generous inclusion criteria could have been considered, for example regarding minimum sample size, time of publication, or inclusion of non-comparative cohort studies. Secondly, the analysis was performed as a narrative synthesis. The alternative, a meta-analysis, pools data from the included studies, increasing statistical power and resulting in more precise estimates (282-284). This is turn can strengthen the conclusions drawn (282). A meta-analysis was planned, but not feasible due to heterogeneity of outcome measures across studies – a known obstacle when attempting to perform meta-analyses (283).

An attempt to illustrate the results in a quantitative manner was made through presenting the findings of each study in a category indicating an advantage for one-stage palatoplasty, an advantage for two-stage palatoplasty, or no difference. Had a meta-analysis been possible, the outcomes could have been assessed quantitatively rather than descriptively, strengthening the conclusions from the study.

Paper V

A key limitation in Paper V was the quality and content of the audio recordings. Although high-quality recording equipment was used, background noise and overlapping speech from adults reduced usability. Automated removal of adult speech using a toolbox called PyAnnote was tested (285), primarily using the pitch as the defining factor (higher pitch for the children, lower pitch for adults). However, this method proved suboptimal, and manual verification was required. The dataset in the second phase was particularly problematic, as recordings were clipped tightly, contained too little actual speech data, and differed substantially

from the material from regular follow-up visits used in the first phase. This likely impaired model learning. Overall, a larger number of high-quality and standardized recordings are essential for further development of our ANNs. However, the heterogeneity in the recordings used – and the fact that those in the first part of the study were collected in a clinical setting and unclipped – could also prove to be a strength if the networks were applied clinically. This is because training and testing the ANNs on overly homogenous datasets introduces a risk of overfitting (264).

Network architecture and programming choices also require consideration. In the early stages of the study, a BiLSTM network was developed but later discarded due to poor performance. This was likely related to a combination of limited training data, heterogeneous recordings, and frame-wise labelling that diluted clinically relevant speech segments, preventing the network from identifying which segments were indicative of VPC (286). In contrast, the CNN and pre-trained VGGish networks were more robust to these issues, as they could extract local time-frequency patterns from spectrograms and leverage large scale pre-training (transfer learning), making them better suited for the available data (236).

When the data available for training the networks is limited, transfer learning can be leveraged to improve performance. This concept was used in the pre-trained network (VGGish), but the study also included one network built from scratch specifically designed for the task of evaluating VPC in cleft palate speech. Overall, both data quality and network design are critical factors influencing the performance of the ANNs, and improvements are essential in order to advance automated speech assessment in children with CP±L.

Ethical Considerations

Ethics are always of utmost importance when conducting research, perhaps even more so when it comes to pediatric fields such as CL/P care. In this thesis, the ethical considerations involve the methodology of the studies as well as the interpretation and implications of the findings. Paper IV was a systematic review and included no research subjects or new original data. It was therefore methodologically relatively unproblematic from an ethical standpoint.

Papers I and II were both large registry-based studies, where the data was anonymized at receival. The risk of a specific child being identifiable in such a dataset must be considered low, although combining the many variables could theoretically reveal individuals with rare values. The dataset also included sensitive variables such as child and maternal diagnoses, malformation diagnoses, and smoking during pregnancy. Therefore, even though it was anonymized, it required strict data security, e.g. analyses performed only on a local computer. Importantly, all results were presented on a national or regional level only.

In Paper III, patients were identified in the Swedish CL/P Registry. Guardians of eligible participants were contacted and given written information about the study, as well as the option to give consent for participation. This was a thorough consent process. The medical records of the participants were reviewed, which can be seen as a breach of integrity for the participants, highlighting the importance of consent. As in Papers I and II, sensitive information was collected, but all data were anonymized, and all results were presented only at a group level. The occurrence of additional diagnoses in the study population was compared to that of the patients in the registry who had not given consent for participation. This, however, was not a detailed analysis, as only diagnoses registered in the Swedish CL/P Registry were evaluated and no review of medical records was conducted. Also, it should be noted that all guardians are informed and asked for consent before their child is included in the Swedish CL/P Registry.

Paper V used audio recordings, which are inherently identifiable if the voice is recognized. The recordings had to be paired with the corresponding perceptual speech assessment using the child's personal identification number, but as soon as this was done it was changed to a random number, and no key was kept. In the future, research involving AI based tools need to keep considering data security and the risks of secondary use and privacy breaches if recordings or trained models are shared.

Papers I, II, III, and V all required approval from the ethical board. The first two were approved without requiring parental consent, which would have been very problematic in such large studies. Paper III used an opt-in approach for consent. This is perhaps the safest strategy, but it is work-intensive and comes with the risk of smaller study populations if researchers are unable to reach guardians or patients. An alternative was used in the first step of Paper V, where an opt-out approach was used. The parents were given information via post, including an opt-out form which they could fill in and resend in order to decline participation. Although this is a much more time effective and convenient approach than opt-in, one could consider it more ethically challenging as it is not certain that the information reaches the parents via post, or that they will be able to interpret it. Both opt-in and opt-out strategies risk introducing a selection bias, as studies have shown that families with higher socioeconomic status are more likely to partake in clinical trials as well as surveys (287-289).

When it comes to the interpretations and implications of the findings in the studies, several reflections can be made. The findings in Papers I and II regarding birth prevalence and temporal trends raise sensitive issues. For example, clefts involving the lip are more often diagnosed prenatally, and a possible explanation for the decreasing prevalence of these types of clefts is that cleft pregnancies are terminated more often. This is ethically complex if true, as most children who are born with a cleft grow up to be healthy adults with a quality of life that is comparable to general population (101, 102). Secondly, one should be careful not to jump the conclusion

that “parents do not want a child with a cleft”, as there are many other potential explanations for the decreasing birth prevalence. The studies in no way prove that abortion is a significant explanation for the trends, and further research is needed before this hypothesis can be confirmed or discarded. Other ethically interesting subjects include, for example, the potentially sensitive concept of ethnicity. The birth prevalence of CL/P has been shown to differ between ethnic groups before, but to say that the differences are due to genetic differences could cause fragmentation and people feeling that they are being “pointed out”.

Similar arguments can be made regarding the findings in Paper III, where it was shown that around one in three children with CL/P also has additional diagnoses. This is an important finding that can be valuable in consultations with guardians and patients, but it is important to acknowledge that most studies have found that the majority of CL/P cases occur in isolation. Knowledge of the higher risk of additional diagnoses can also cause worry for patients and guardians – a group already more engaged with the health care system than the general population.

The conclusions of Paper IV also led to ethical discussions. According to the principle of autonomy, individuals should be allowed to make their own decisions regarding for example their health (262). In the case of surgery, it seems reasonable that a person should be allowed to decide him-/herself whether or not to undergo a procedure. However, for young children this is not always the case. Most would probably agree that it would be unethical not to perform necessary surgery on a child, and therefore we leave it to the patients to decide. However, an argument can be made that we should not put children through more treatments than necessary before they can decide for themselves. This could favor a one-stage palate repair. On the other hand, the principle of beneficence holds that we should act in the best interest of the child (262). If a two-stage approach were believed to lead to better outcomes, it might be ethically justified despite the additional procedures.

Conclusions

Together, the five studies in this thesis provide updated and comprehensive epidemiological data on CL/P in Sweden, insights into additional diagnoses in CL/P, evidence regarding surgical techniques for primary palate repair, and methodological innovation. The thesis contributes new knowledge that may influence health care planning, guide clinical decision-making, and inspire further research on the causes, treatment, and evaluation of CL/P care. The conclusions from each respective study are presented below.

Paper I

The birth prevalence of CL/P in Sweden between 2000 and 2020 was 1.52 per 1,000 births.

The birth prevalence for specific cleft subtypes (per 1,000 births) was 0.61 for CP, 0.92 for CL±P, 0.20 for BCL±P, 0.36 for UCLP, and 0.16 for BCLP.

The birth prevalence of CL/P in Sweden decreased significantly between 2000 and 2020.

Declining trends were seen for CL±P, BCL±P, UCLP, and BCLP, whilst CP birth prevalence remained stable.

CL/P, CL±P, BCL±P, UCLP, and BCLP were common in boys than girls, whilst CP occurred more frequently in girls.

The decreasing birth prevalence of CL/P may have implications for future health care planning and provides a foundation for further research into underlying risk factors.

Paper II

Significant regional variations in the birth prevalence of CL/P were observed in Sweden between 2000 and 2020.

CL/P, CL±P, BCL±P, UCLP, and BCLP were less common in the Stockholm HC region. CP was more common in the Northern HC region; CL±P, BCL±P, and BCLP in the Southeastern HC region; and CL±P and BCL±P in the Southern HC region.

Decreasing birth prevalence for CL/P and all studied cleft subtypes except CP was observed, but varied between HC regions. CL/P prevalence decreased in three HC regions. All subtypes except CP decreased in two or three HC regions.

The observed regional differences highlight the need for further research into explanatory factors, and declining birth prevalence may have implications for future health care planning.

Paper III

The cumulative 5-year incidence of additional diagnoses in children with CL/P was 36.0%, with more than one diagnosis in 9.2% of participants.

Additional diagnoses most often affected the extremities/skeletal system or cardiovascular system.

The most common categories of additional diagnoses differed depending on cleft subtype.

The Swedish CL/P Registry reported fewer additional diagnoses in the study population (18.8%) than were found in medical records (36.0%).

The risk of additional diagnoses must be considered in patient information and treatment planning, for example prior to surgical procedures.

Paper IV

Neither one- nor two-stage palate repair showed overall advantages in outcome.

For children with UCLP without comorbidities/syndromes, conclusions could be drawn regarding facial growth, speech, and fistula rates.

No conclusions could be drawn for other cleft subtypes or outcomes.

When differences in medical outcome are small, ethics, health economics, and local traditions may be of greater importance.

Paper V

Two ANNs were developed for automated assessment of VPC in children with CP±L.

Both models had an accuracy below 60% compared with perceptual speech assessments by SLPs, with the best ANN (VGGish) reaching 57.1% accuracy.

Future research on AI for speech assessments in CL/P will require larger, high-quality, preferably purpose-built datasets.

Populärvetenskaplig sammanfattning

Läpp-käk-gomspalt (LKG) är den vanligast förekommande ansiktsvariationen hos barn i världen. Förekomsten varierar mellan studier, men brukar anges till mellan 1 och 2 fall per 1 000 födda barn. Det finns tydliga geografiska variationer i förekomst, där man sett att LKG förekommer mer i vissa asiatiska populationer och hos den amerikanska ursprungsbefolkningen, och mindre i exempelvis Afrika. Förekomsten i Sverige brukar uppges till cirka 2 per 1 000 födda, siffror som i huvudsak är baserade på studier som är mer än 20 år gamla och bara har inkluderat barn från vissa delar av landet.

Varför en spalt uppstår är inte helt klarlagt, och orsakerna bakom tillståndet anses vara både genetiska och miljörelaterade. Talande för genetiska orsaker är exempelvis att det finns familjer och släkter med ökad förekomst av LKG och att man har kunnat identifiera ett stort antal genetiska syndrom som är relaterade till LKG. Kända miljöfaktorer som ökar risken för LKG inkluderar rökning under graviditet, men även exempelvis intag av vissa läkemedel.

Spalten kan påverka överläpp, överkäke och gom i olika kombinationer, och den kan vara enkel- eller dubbelsidig. Vilka strukturer som är påverkade styr till stor grad symtomen. Spalter som omfattar läppen ger generellt problem relaterade till utseende. Tandutvecklingen kan påverkas av de flesta typer av spalter. Ansiktstillväxten och talet påverkas i regel främst av spalter som omfattar gommen. Utöver detta kan spalten ge sekundära problem såsom hörselpåverkan och psykosocialt illabefinnande.

Vid LKG förekommer också andra diagnoser. Studier har visat olika resultat kring hur stor andel av barnen med LKG som drabbas av tilläggsdiagnoser, ofta kring 20–30%. Vanligt förekommande är påverkan på muskler och skelett, extremiteter, hjärta och kärl samt centrala nervsystemet.

Kirurgi kan ses som den huvudsakliga behandlingen vid LKG. Operationerna syftar till att reparera spalten och ge både bästa möjliga estetik och förutsättningar för tand- och talutveckling. Ett stort antal kirurgiska tekniker finns och används. Vilken teknik som används kan bero på hur spalten ser ut, men även på lokala traditioner och vilken teknik som kirurgen i fråga är mest van vid. En omdiskuterad fråga är om gommen bör opereras i ett eller två steg – båda metoderna används i Sverige, men hittills har ingen visats vara överlägsen den andra. Utöver kirurgi är logopedisk behandling, tandreglering, psykosocialt stöd och ofta även öron-näsa-halsrelaterade

behandlingar viktiga. Ett välfungerande samarbete mellan olika medicinska specialiteter och yrkesgrupper är därför en förutsättning för en bra vård av barn med LKG. I Sverige följs alla barn regelbundet upp till cirka 19 års ålder av ett multidisciplinärt team.

Påverkan på talet vid LKG beror till stor del på att en spalt i gommen försvårar stängning mellan mun- och näshåla, något som är nödvändigt för ett bra tal. Dessa svårigheter kan kvarstå även efter operation, om gommen exempelvis blir för kort eller stel för att kunna sluta tätt mot bakre svalgväggen. Därför är logopedisk bedömning av talet en viktig pusselbit i uppföljningen. Dessa bedömningar görs av logopeder tränade på att bedöma tal vid LKG, som lyssnar på talet och bedömer ett antal olika parametrar. En sådan parameter är perceptuellt uppfattad velofarynxfunktion som är ett mått på hur väl barnet kan sluta tätt mellan mun- och näshåla. Bedömningarna kräver träning och är tidskrävande. Dessutom är de i sig själva subjektiva, eftersom de baseras på att en person lyssnar och därefter bedömer talet. En objektiv, automatiserad bedömning av olika parametrar i talet, exempelvis velofarynxfunktion, skulle därför vara av värde i uppföljningen av barn med LKG.

Studierna i denna avhandling berör flera av de frågeställningar och kunskapsluckor som presenterats ovan. Avhandlingsprojektet består av fem studier med olika metodik. Studie I och II var registerstudier som baserade på Socialstyrelsens register Medicinska födelseregistret. I Studie III undersöktes förekomsten av tilläggsdiagnoser hos barn med LKG i södra Sverige genom journalgranskning. Studie IV var en så kallad systematisk översikt, där den tillgängliga vetenskapliga litteraturen strukturerat analyserades för att avgöra om gomplastik i ett eller två steg ger fördelar i utfall. Den avslutande studien, Studie V, var en metodologisk studie där artificiell intelligens (AI) användes för att bedöma tal hos barn med gomspalt (med eller utan läpp-käkspalt).

I Studie I och II ingick alla barn födda i Sverige mellan 2000 och 2020 som fanns med i Medicinska födelseregistret, totalt drygt 2,2 miljoner barn. Förekomsten av LKG och ett antal av dess undergrupper under perioden 2000 till 2020 undersöktes i Studie I. I Studie II undersöktes förekomsten av LKG och dess undergrupper i de sex svenska sjukvårdsregionerna under samma period. Statistiska metoder användes för att studera trender i förekomsten under 21-årsperioden och skillnader mellan regionerna. Den totala förekomsten av LKG i Sverige under perioden var 1,52 per 1 000 födda, och minskade under perioden. Ett intressant fynd var att förekomsten minskade för alla studerade undergrupper av LKG, förutom gomspalt (endast gomspalt utan spalt i läpp eller käke). Liknande trender sågs i Studie II, där förekomsten av LKG och samtliga undergrupper förutom gomspalt minskade i åtminstone två regioner för varje undergrupp. Vissa geografiska skillnader mellan enskilda regioner och resten av landet noterades; förekomsten av LKG och alla undergrupper förutom gomspalt var lägre i Sjukvårdsregion Stockholm-Gotland, förekomsten av spalter som inkluderade läppen (dvs. med eller utan spalt i gom eller

käke) var högre i Sydöstra och Södra sjukvårdsregionerna, och gomspalt var vanligare i Norra sjukvårdsregionen.

Studie III inkluderade 250 barn från Södra sjukvårdsregionen med LKG. I studien såg man att drygt en tredjedel av barnen fick någon ytterligare diagnos registrerad i sina journaler innan fem års ålder. De vanligaste typerna av tilläggsdiagnoser var sådana som påverkar skelett och extremiteter samt hjärta och kärl.

Den systematiska litteratursökningen i Studie IV genererade 14 vetenskapliga studier som undersökte huruvida gomplastik i ett eller två steg ger fördelar i utfall. På det stora hela sågs inga klara fördelar för endera metoden. För många aspekter av utfallet av LKG-behandling fanns för få studier för att det skulle vara möjligt att dra några starka slutsatser, men för förekomst av oönskade hål i gommen (fistlar), ansiktstillväxt och tal var underlaget tillräckligt starkt för att man med åtminstone viss säkerhet kunde dra slutsatsen att inga skillnader föreligger mellan metoderna. Det noterades också att en majoritet av studierna inkluderade barn med enkelsidig LKG utan tilläggsdiagnoser, vilket försvårar uttalanden om barn med annan typ av spalt.

I Studie V utvecklades två AI-nätverk med syftet att bedöma velofarynxfunktion hos barn med LKG. Fler än 400 ljudinspelningar av fem- och tioåringar med gomspalt användes. Till varje ljudinspelning fanns en logopedbedömning av velofarynxfunktionen, och nätverken testades i hur ofta de klarade att göra samma bedömning som logopeden. På så sätt blev utfallet en procentsats; på hur stor andel av inspelningarna satte nätverken samma siffra som logopeden? Två olika AI-nätverk tränades och testades på ljudinspelningarna. Det bäst presterande nätverket nådde knappt 60% överensstämmelse med logopedernas bedömningar.

Sammantaget bidrar avhandlingen med nya, tillförlitliga siffror kring förekomsten av LKG i Sverige, och visar på skillnader över tid och mellan regioner. Orsakerna bakom den minskande förekomsten är ännu inte klarlagda, men studierna ger en utgångspunkt för framtida forskning och har betydelse för planeringen av framtidens LKG-vård. Avhandlingen visar också att en betydande andel av barnen får andra diagnoser tidigt i livet. Dessa fynd är viktiga för information till patienter och anhöriga, samt understryker vikten av uppföljning och hänsyn till eventuella tilläggsdiagnoser vid behandling. Frågan om en- eller tvåstegsoperation av gommen är att föredra kunde inte besvaras entydigt, men fynden belyser att andra faktorer såsom etik, hälsoekonomi och lokala traditioner blir viktiga när medicinska skillnader är små. Slutligen presenteras ett första steg mot att använda AI som komplement vid talbedömning. Även om träffsäkerheten i dagsläget inte är tillräcklig för klinisk användning, kan större datamaterial och vidareutvecklade modeller på sikt ge verktyg som underlättar logopedernas arbete och bidrar till en mer jämlik uppföljning. Tillsammans ger avhandlingens fem studier en bred bild av dagens utmaningar och framtida möjligheter inom vården av barn med LKG.

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