Additional diagnoses in children with cleft lip and palate up to five years of age

Tilläggsdiagnoser hos barn med läpp-käk-gomspalt upp till fem års ålder

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Word count manuscript: 6643

Key Words: Cleft lip and palate, CL/P registry, Additional diagnoses

Abbreviations

BCLP	Bilateral cleft lip and palate
CL	Cleft lip
CLP	Cleft lip and palate
CL/P	Cleft lip and/or palate
CL/P registry	The Swedish national quality register for patients with cleft lip and/or palate
CP	Cleft palate
OFC	Orofacial clefts
UCLP	Unilateral cleft lip and palate

Abstract

Background: Cleft lip and/or palate (CL/P) is the most common congenital craniofacial malformation. It is known to be associated with additional diagnoses; however, the reported incidence varies. The Swedish national quality register for cleft care (CL/P registry) includes registrations of additional diagnoses.

Aim: To explore the cumulative five-years incidence of additional diagnoses and at what age children with CL/P received additional diagnoses up to five years of age. Further aims were to investigate the relationship between age of establishment of an additional diagnosis, type of cleft and type of additional diagnosis and to validate CL/P registry data on additional diagnoses.

Methods: Data from the CL/P registry regarding children with CL/P in the Southern Health Care Region were retrieved and based on the registry, participants were selected. A review of medical records of participants born 2006-2016 was performed and data regarding participant characteristics and additional diagnoses were collected.

Results: Of the 250 participants included in the review of medical records, 90 participants (36%) had an additional diagnosis. Of the total number of identified additional diagnoses (n=137), cardiovascular system (20.4%) and extremities and skeletal system (17.5%) were the most prevalent categories. Sixty-nine additional diagnoses were identified in direct connection with birth and 68 additional diagnoses were identified thereafter and up to five years of age. The comparison between medical records and the CL/P registry of all children showed a 14.4 percentage points higher incidence of additional diagnoses in the medical records.

Conclusion: Roughly every third child received an additional diagnosis and diagnoses related to the cardiovascular system were the most frequent. The number of additional diagnoses were almost doubled after birth up to the age of five years. This study also shows that additional diagnoses were under-reported in the CL/P registry. Future research is necessary to strengthen associations of additional diagnoses to CL/P.

Populärvetenskaplig sammanfattning

I Sverige föds ca 3% av alla barn med någon form av avvikelse från referenspopulationen. Läpp- käk- och/eller gomspalt (hädanefter ”LKG”) är de vanligaste förekommande ansiktsavvikelserna, och cirka 180 barn föds med någon form av LKG i Sverige varje år. Orsaken till LKG är inte helt klarlagd och ett flertal troliga förklaringar finns. Om spalten uppstår som en del av ett syndrom, det vill säga ett mönster av avvikelser med ett gemensamt ursprung, tros syndromets ursprung vara orsaken. Om spalten uppstår utan ett associerat syndrom är orsaken svårare att förklara, men det tros bero på en kombination av genetik och miljö. Kända riskfaktorer är alkoholkonsumtion, rökning och vissa läkemedel. Det finns flera typer av LKG och indelningen av de olika typerna av spalter beror på spaltens lokalisation och omfattning. Spalten kan vara både enkel- eller dubbelsidig och kan variera i svårighetsgrad. LKG kan potentiellt påverka utseende, bett, hörsel och tal.

Det är sedan tidigare känt att LKG är associerat med ytterligare diagnoser, så kallade tilläggsdiagnoser såsom till exempel medfödda hjärtavvikelser, Downs syndrom och Pierre Robin sekvens (en serie av händelser som leder till att gommen inte sluter sig korrekt). Idag är över 400 syndrom identifierade där olika typer av spalter kan förekomma. Det har gjorts många studier avseende barn med LKG som även har en eller fler tilläggsdiagnoser, men resultaten av studierna varierar kraftigt. Studier inom området möter svårigheter såsom den begränsade omfattningen av deltagare, olika kriterier för deltagarurval och varierande antal år efter födseln som det sker en uppföljning av barnet.

Huvudbehandlingen vid LKG består av kirurgi och uppföljning, och vid behov behandling av ett LKG-team, där bland annat plastikkirurg, öron-näsa-halsläkare, logoped, ortodontist, käkkirurg och kurator eller psykolog ingår. Uppföljning sker enligt ett standardiserat nationellt vårdprogram ungefär var tredje år fram till 19 års ålder. I Sverige finns ett nationellt

kvalitetsregister över barn med LKG (det så kallade LKG-registret) med syfte att säkerställa en jämlik vård med hög kvalitet över hela landet. Registret innehåller bland annat information om vilken typ av spalt barnen har, vilka tilläggsdiagnoser de har, deras talförmåga och bett. Över 90% av alla barn med LKG som är födda år 2009 eller senare omfattas av LKG-registret.

Syftet med denna studie var att ta reda på förekomsten av tilläggsdiagnoser och vid vilken ålder barn med LKG diagnosticerades med tilläggsdiagnoser upp till fem års ålder. Även att undersöka om det fanns någon koppling mellan ålder för diagnosticering av tilläggsdiagnoser, typ av spalt och typ av tilläggsdiagnos. Utöver detta var syftet att utvärdera om informationen i LKG-registret stämde.

Samtyckesblanketter för studien skickades till samtliga vårdnadshavare för barn i LKG-registret födda mellan åren 2006–2016, som hade behandlats för sin spalt vid Skånes universitetssjukhus i Malmö. De hade samtyckt till att deras barn skulle delta i LKG-registret vid tidigare besök på Plastiksektionen vid Skånes universitetssjukhus. En journalgranskning gjordes för de barn där samtycke till studien hade lämnats, avseende följande patientdata: kön, ålder, folkbokföringsort och om de hade flyttat till Region Skåne vid ett senare tillfälle än födseltillfället samt typ av spalt och eventuella tilläggsdiagnoser från födsel upp till fem års ålder. Data för barnen avseende förekomst av Pierre Robin sekvens, syndrom och andra avvikelser hämtades från LKG-registret, för jämförelse med resultaten från journalgranskningen.

Resultaten för de 250 deltagarna visade en förekomst av tilläggsdiagnoser hos 36% av deltagarna och 71 olika tilläggsdiagnoser kunde identifieras hos dessa. Majoriteten av barnen i studien var pojkar, och den spalttyp som förelåg hos flest antal deltagare var enkelsidig LKG. Flest antal identifierade tilläggsdiagnoser kunde återfinnas i kategorierna hjärt- och

kärlsjukdomar, arm- ben- och skelettavvikelser och mag-och tarmkanalen. Totalt 67 av de 250 deltagarna diagnosticerades med en enstaka tilläggsdiagnos och 13 deltagare diagnosticerades med tre eller fler tilläggsdiagnoser. Ungefär lika många diagnoser upptäcktes direkt i samband med födseln som efter och upp till fem års ålder, speciellt vid de mer omfattande spalttyperna enkelsidig LKG och dubbelsidig LKG. Inga syndromdiagnoser återfanns inom gruppen med enbart läppspalt. Några ytterligare slutsatser kring typ av tilläggsdiagnos och typ av spalt var svåra att dra. Data från journalgranskningen stämde inte helt överens med data registrerad i LKG-registret. Vid jämförelsen framkom det att kategorin syndrom var procentuellt lika stor både vid granskningen av deltagarnas journaler samt bland alla barn i registret medan kategorin andra avvikelser var 14,4 procentenheter större vid journalgranskningen.

Studien fann en förekomst av tilläggsdiagnoser hos 36% av deltagarna och resultaten indikerade att ett antal tilläggsdiagnoser hos barn med LKG kan vara kopplade till en viss ålder för diagnos och viss typ av spalt. Studien har gett ytterligare kunskap om tidpunkten för fastställandet av tilläggsdiagnoser och att dessa ofta ställs vid ett senare tillfälle än direkt vid födseln. Den uppmärksammade även behovet av validering av data avseende tilläggsdiagnoser i LKG-registret då antalet tilläggsdiagnoser uppmärksammats vara underrapporterade. Tilläggsdiagnoser hos barn med LKG är ett område som behöver bli föremål för ytterligare forskning. Med mer vetenskapligt belägg kan tydligare associationer mellan tilläggsdiagnos och LKG identifieras och verifieras.

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Introduction

Orofacial clefts

Orofacial clefts (OFC) is the most common congenital craniofacial malformations (1). Out of 1400 live births in Sweden, approximately two are born with this malformation every year. This estimates about 180 new patients per year in Sweden (2). There is a predominance for isolated cleft palate (CP) among females and unilateral cleft lip and palate (UCLP) among males (2). OFC may affect appearance, quality of life, social integration, and due to anatomic and/or functional alterations the malformation also affects the incidence of secretory otitis media, hearing deficiencies, and speech deviations (3-6).

Embryology

The development of the lip and palate is a complex process. It occurs at gestational week four to twelve, and the process is controlled by regulation of signals between different types of cells (7). The neural crest cells migrate through mesenchymal tissue to the facial region. During fetal week four, the primary palate eventually is shaped by forming of the maxillary processes of which the medial and lateral processes fuse. The primary palate includes the upper lip, the alveolar crest, and the most anterior part of the hard palate. The remaining part of the hard and the soft palate is developed from the palatal shelves and forms the secondary palate. The primary and secondary palate is separated by the incisive foramina. The most critical time for palate development is gestational week six to nine (8). In gestational week twelve, these fusion processes are completed, and when the processes do not merge, different types of clefts appear (9).

Classification of clefts

OFC includes the most common clefts clinically; cleft lip (CL), cleft palate (CP), and cleft lip and palate (CLP) (Figure 1). CL only includes the primary palate and occurs when parts of the lip do not join completely. The cleft can be small and isolated to the lip or involve deformation of the nose. Complete CL involves a defect in the alveolar ridge (Figure 1A). CLP is defined as a cleft of the lip, the alveolus, and the palate (Figure 1 D, E) (10). Isolated CP occurs when only the secondary palate is involved and it can affect the hard and/or soft palate (Figure 1B) (11). Depending on the severity of the cleft, it can be either unilateral or bilateral and the clefts are as well distinguished as complete or incomplete. In this essay CL, CP and CLP will be included when reference is made to the term cleft lip and/or palate (CL/P).

There is a substantial diversity of phenotypes and combinations of cleft of the lip, alveolus, and palate, which makes classification difficult. In addition to the classifications mentioned above, there is also non-syndromic CL/P and syndromic CL/P (CL/P with a known genetic etiology) (12).

Etiology

Due to the complexity and heterogeneity of CL/P, there are several potential explanations for the emergence, and the cause is not fully clarified. Isolated CL, CLP, or CP seem to have different origins. If the cleft occurs as a part of a syndrome there is a causation between the syndrome and the emergence of the cleft (13). It has been managed to identify the loci of various mutations and functions of genes that are responsible for different syndromes, for example the Van der Woude syndrome, which can cause CL/P (14). When there is no associated syndrome, the origin is more difficult to establish. It seems to be subject to multifactorial factors; a combination of genetics, environment, and lifestyle of the parents (15, 16). The risk of isolated CL/P in a child increases with 3% to 5% if a parent is affected, and when one child is affected

the risk is 40% for the parents to receive another child with CL/P (17). It has been revealed that several different genes can alone or in combination be responsible for the occurrence of CL/P and multiple genes are responsible in different parts of the facial development, for example Tgfb2, Pax9 and Gli2 (14). The most sensitive period for the development of the embryo is one month before and two months after conception, especially during the first trimester (18). Profoundly, maternal factors such as lifestyle (including e.g. consumption of alcohol and cigarettes), medication, health status, and use of teratogenic antiepileptic, can affect the intrauterine environment (18, 19).

CL/P treatment in Sweden

Depending on the extent of the cleft it can affect structures such as the lip, palate, and alveolus. It in turn affects appearance and functions such as hearing, speech, occlusion, and dental growth (4, 6). The main treatment for CL/P is surgical intervention in combination with follow-up and treatment by one of six regional CL/P treatment teams. The teams are multidisciplinary, consisting of a reconstructive plastic surgeon, an otorhinolaryngologist, a speech-language pathologist, an orthodontist, an oral surgeon, a CLP coordinator and a counselor and/or psychologist (20). The child is followed by the CL/P team approximately every third year to the age of 19 (20).

The operation techniques for closing a cleft varies nationally and depends on the type of cleft. The primary surgery of the palate is performed in one stage at the age of nine to 15 months, or in two stages, with soft palate closure at about six months and hard palate closure at about 24 months of age (21). The surgery of the lip is performed at the age of three to five months. The closure of the cleft in the alveolar ridge is performed at seven to eleven years of age in general in Sweden, due to mixed dentation (21).

Before the operation of the alveolar ridge, the children usually undergo orthodontics. This may also be needed after the surgery (20). The cleft palate leads to an increased risk for media otitis, acute or secretory, and can cause a temporary hearing impairment that often requires multiple ventilation tubes placements, and, in some cases, hearing aid may be necessary (22, 23).

According to an international literary review, about 50% of the children with a cleft that involves the palate have age appropriate speech at three years of age (6). Some children may need speech therapy. A few syndromes and skeletal deformations can affect the anatomical structures in the pharynx, which can lead to deficiencies of the velopharynx, the area at the back in the pharynx towards the nose, and thereby affect the speech (6, 24).

In some cases, secondary operations may be necessary. This can for example be speech improving surgery, closure of a fistula or operations to correct the relation of the jaws or appearance (20).

Incidence of malformations, associated syndromes, and/or other diagnoses

Malformations occur during the fetal stage and depending on the timing and the specific event different malformations occur, often due to a mutation in one or several genes (7). When a fetus has a less severe malformation, it has usually no significance for the individual. If it has a more severe malformation or two or more malformations a common genetic change can be suspected (7). In Sweden, approximately 3% of all born children have some form of malformation or birth defect (25).

It is known that CL/P often is associated with additional diagnoses such as congenital heart defects, hand-and feet anomalies, hypospadias, 22q11-syndrome, Downs syndrome and van der Woude syndrome (24, 26, 27). A known associated sequence is Pierre Robin sequence that consists of a series of events; micrognathia (small jaw with a receding chin) that leads to

glossoptosis (downward retraction of the tongue), which hamper the palatal shelves from fusing during the fetal stage (28, 29). Today there are over 400 identified syndromes where different types of clefts can occur (30).

Plenty of research regarding the incidence of associated diagnoses to CL/P have been published the latest decades. One of the earliest publications is a report from 1924 that mostly included special cases (31). Thereafter multiple articles have presented significantly different results. In 1985, a retrospective study including 1000 participants showed an incidence of associated malformations of 63.4% among children with CL/P (24), compared with a prospective Swedish study from 1997 including 616 participants that showed an incidence of 21% of associated malformations (30). A larger study was the European registry study including 5449 children with CL/P. It was published 2007 and based on the EUROCAT network including 14 European countries and 23 registers and estimated that 1589 (29.2%) children had an associated defect (32).

Despite multiple studies no definite number of associated diagnoses among children with CL/P can be determined. Research in the field generally meets difficulties regarding selection of participants, sample size, inclusion/exclusion criteria for associated diagnoses and length of time after birth that diagnoses are studied (33). One study included 616 live born infants (30), whereas another study included 5449 participants: live births, stillbirths and induced abortions (32). Other complicating factors for this type of studies are the use of terms that have evolved over the years (33). To develop consensus regarding terms used to describe human morphology, an international group of clinicians has summarized definitions that this report will follow (34).

Malformation – is a non-progressive congenital anomaly of a solitary organ. Anomal*y* – is an anatomic phenotype that separates from its reference population. Variant – is a mild anomaly and represents a small departure from the reference population.

Syndrome – includes a pattern of anomalies, which origin from a common cause. Sequence – is one or more secondary morphologic anomalies originating from a single malformation, disruption, dysplasia, or deformation.
Association – is a pattern of anomalies, that is more likely to occur together than by chance (34).

There is occasionally a delay in some additional diagnoses as symptoms can be very subtle and this leads to that the diagnosis is not identified until later in life (35). It has been recognized that it is more common to have a single additional diagnosis than several diagnoses additional to CL/P, a more severe cleft is more likely to be associated with additional diagnoses and the association is more common in CP than CL/P (30, 36, 37). Moreover, the existence of additional diagnoses to CL/P can be established (38). For supplementary support of which diagnoses that are associated to CL/P and to enhance the care for children with CL/P by being able to connect a certain time for diagnose, a certain type of cleft and a certain type of additional diagnosis more research is necessary. Previous literature has mainly focused on associated diagnoses that are received in direct connection with birth (24, 30, 32, 36, 37).

The Swedish national quality register (CL/P registry)

Since 2009 all children with CL/P have been offered to participate in a national quality registry, the CL/P registry, which was created on an ideal basis 1999 and was certified as a national quality registry during 2016 by the National Board of Health and Welfare (*Sw. Socialstyrelsen*) and the Swedish association of Local Authorities and Regions (*Sw. Sveriges Kommuner och Regioner*) (21). The aim is to provide data for evaluation of the treatment of children born with CL/P, to ensure an equal care for all children with CL/P in Sweden, to improve the treatment methods and to expand the cooperation between the different CLP centers nationally. Included in the registry is data from CL/P centers regarding type of cleft and prevalence of Pierre Robin

sequence, syndromes and other deformities. Besides this it also includes data regarding performed surgeries, and results of speech and occlusion and teeth. The coverage for individuals with CL/P born 2009 or later rate above 90% (21, 39). Registry data on additional diagnoses needs to continuously be updated and to ensure this, a validation of the registry is of great importance.

Study aim

The primary aim of this study was to explore the cumulative five-years incidence of additional diagnoses and at what age children born with CL/P usually were detected with additional diagnoses up to five years of age. Further aims were to investigate the relationship between age of establishment with an additional diagnosis, type of cleft and type of additional diagnosis and to validate CL/P registry data on additional diagnoses.

Research questions

- What is the cumulative five-years incidence of additional diagnoses among children with CL/P born in the Southern Health Care Region during the years 2006-2016, and which categories of additional diagnoses can be identified?
- Which characteristics do children with CL/P have regarding establishment of additional diagnosis, type of cleft diagnosis and type of additional diagnoses, and is it possible to find a relationship between these?
- To what extent are data from the CL/P registry regarding Pierre Robins sequence, syndromes, and other deformities equivalent with data from the review of medical records?

Material and Methods

Study design

The participants in this retrospective study were collected from the CL/P registry. Data regarding the chosen variables were retrieved from medical records. Further, data from the CL/P registry were collected for all children from the Southern Health Care Region for comparison with the data retrieved from medical records.

Selection of participants

The participants were born 2006 to 2016. The guardians of the children had approved to the registration of their children in the CL/P registry at previous visits at the Plastic Surgery Clinic in Malmö at Skåne University Hospital. All guardians to children in the CL/P registry who were born in the Southern Health Care Region (Blekinge, southern Halland, Kronoberg and Skåne), with CL/P during that period were asked to provide consent for the participation in the study, and only the children with consent were included for the review of medical records (hereinafter referred to as participants).

Selection of variables

The selection of variables aimed to include clinically relevant diagnoses associated to CL/P (24, 30, 32, 36, 37). Only diagnoses coded according to the Swedish National Board of Health and Welfare's classification of health intervention or confirmed malformations were included (40). It was not considered sufficient to suspect and include a syndrome based on that a child had multiple malformations. Excluded diagnoses were transient infections, allergies, refractive errors, childbirth complications, physiological heart wheezing, hypertrophy of tonsils and adenoids. This was due to previous experience and research and that the frequency of these common diagnosis in the pediatric population was hard to evaluate without the knowledge about the prevalence within the population in general (24, 30, 32, 36, 37). Additional excluded

variables were secretory media otitis and speech deficiencies since these parameters are common among children with CL/P and is well-known associated diagnoses (5, 23). As well as dental anomalies and occlusions since they are closely related to the cleft and not included as separate events in many other studies (5, 23, 30).

The selection of clefts was based on diagnosis codes according to ICD-10 (41). The cleft diagnoses were thereafter gathered into four bigger groups depending on affected structure. Diagnosis code Q35.5 Cleft of the hard and soft palate and Q35.3 Cleft of the soft palate were grouped together, as well as Q36.9 Unilateral cleft lip and Q36.0 Bilateral cleft lip. The groups Q37.5 Unilateral cleft lip and palate and Q37.4 Bilateral cleft lip and palate were two separate groups.

The age when a child received an additional diagnosis or when an additional diagnosis was withdrawn was noted as whole years.

Variable description

The CL/P registry includes children from all Swedish Health Care Regions, and among them the Southern Health Care region, which includes the Health Care Region of Skåne, southern Halland, Kronoberg and Blekinge. The later three all have other system for medical records than Health Care Region of Skåne. This led to that for participants living outside of Skåne, only medical records performed in conjunction with visits to the CL/P team could be reviewed. Other reasons for not being able to continuously follow the participants for five years was if they had moved to Skåne after birth, due to for example adoption from abroad.

The classification of at what age a participant received its diagnosis or at what age the diagnosis was withdrawn was either at birth or at later age described in whole years; from birth to one

year, from one to two years, from two to three years, from three to four years or from four to five years.

A diagnosis was categorized according to a related theme with an overall title of category and thereafter into subdivisions based on more specific structures or systems. The categories that did not contain a subgroup were diagnoses related to sequence, cardiovascular system, central nervous system, eye, urogenital system, ears, nose or throat, endocrine system, respiratory system, and dermatology. The category syndromes was subdivided into the groups: chromosomal syndromes and recognized non-chromosomal syndromes. The category extremities and skeletal system was subdivided into the groups: head and neck, upper limb, hip and back, and the category gastrointestinal tract was subdivided into the groups: upper intestinal tract and lower intestinal tract.

CL/P registry and review of medical records

Data regarding occurrence of Pierre Robin sequence, syndromes and other deformities were retrieved from the CL/P registry for all registered children in the Southern Health Care Region and were compared with the results from the review of medical records of those who had given consent for the study. Medical records of the participants were reviewed for the chosen variables. The variables for general background characteristics were sex, age, if they lived in Skåne and if they were born abroad. The variables describing participant history were cleft diagnosis and additional diagnoses received at birth and until the child reached the age of five. Information was collected from medical records during visits to clinics in the Health Care Region of Skåne. All additional diagnoses from all categories were summed up except for the categories syndromes and sequence. In the report, all participants with a syndrome or sequence were only included once. A deformity that was significant for a specific syndrome or sequence

was included under the term syndrome or sequence and did not get noted as a deformity. In that case these deformities would have been noted doubled.

Calculations and statistics

Data was transmitted to IBM SPSS Statistics Version 28.0.0.0 where all statistics were performed. The results were presented with descriptive statistics, using frequencies, median, range, and percentage. Tables and figures were configurated based on the established statistics.

Ethical consideration

The study was approved by the Ethics Review Authority in Sweden (reference no. 2021-05893-01). To review the participants medical records, approval from the Consultation group for quality registries, care databases and preparation in Region Skåne (KVB), was obtained. The participants' guardians received written information by mail regarding the purpose of the study, voluntariness, management of sensitive personal data, GDPR and future profit.

The study included sensitive information from medical records regarding the participants health. Since the study included children below 15 years of age, their guardians decided whether the child should participate or not. This reduced the child's autonomy and affected its integrity. The information of each child was pseudonymized by giving them a personal id-number. The code-key was stored at a USB with password that was kept safely in a locked room. Only the research group had access to the USB.

The main critical ethical dilemma with the study was that questions regarding if the child had any additional diagnoses or if it was possible that the child should have been diagnosed earlier would create concern among the guardians. The research team included a patient coordinator

and a counselor that both are specialized on CL/P, and they could give active support if it was necessary.

Increased knowledge in the field will enable a developed caregiving and a strengthened substrate when information and support is given to patients with CL/P and their relatives in the future. Previous research in the field has mainly been focused on syndromes and/or other associated diagnoses that has been diagnosed at birth and it is known that many additional diagnoses are added the years after birth (42). Children with additional diagnoses are often excluded from studies, which have led to that these children do not get relevant care, treatment or support (43). Based on the argument that this study will provide a better care for the patients with CL/P in the future, the ethical reasons for not doing the study are outweighed.

Results

A total of 436 children with CL/P were born in the Southern Health Care Region of Sweden during the period 2006-2016 and registered in the CL/P registry. Informed consents were received for 250 children, and they were included in the study (Figure 2).

Participant characteristics

Out of 250 participants included in the study, 164 (65.6%) were males, 86 (34.4%) were females, 42 (16.8%) were born abroad and 191 (76.4%) lived in Skåne (Table 1). The number of participants within the cleft groups CL, CP and UCLP was similar. The group with bilateral cleft lip and palate (BCLP) was smaller. All groups included a majority of males, and the biggest difference between number of males and females was found within the groups BCLP and UCLP (Table 1). A comparison between the participant characteristics of our study group and the participant characteristics of all children in the CL/P registry showed that our participant selection was a well-represented cohort of all children with CL/P in the CL/P registry in the Southern Health Care Region (Table 1). No group of the participant characteristics had a

discrepancy of more than five percentage points besides the proportion of males and females within each cleft group, when the 250 participants in our study group were compared with all 436 children in the CL/P registry born in the Southern Health Care Region. The participant characteristic if a child lived in Skåne could only be obtained from the medical records and this data could therefore not be included in the comparison (Table 1).

Additional diagnoses

Based on the review of the medical records a total of 67 (28.8%) participants were diagnosed with one single additional diagnosis and 13 (5.2%) participants were diagnosed with three or more additional diagnoses (Figure 3). Among the 250 included participants, 71 different additional diagnoses were identified, (Table 2), and a total of 137 additional diagnoses, since one type of additional diagnosis can appear multiple times (Figure 4). The highest number of additional diagnoses, 28 (11.2%), was found within the category cardiovascular system, followed by 24 (9.6%) in the category extremities and skeletal system, and 14 (5.6%) in the gastrointestinal tract (Figure 4). Of the 137 additional diagnoses the share of cardiovascular system and extremities and skeletal system were 20.4% respectively 17.5% (Figure 5).

Age when an additional diagnosis was established

Of the 137 additional diagnoses, 69 diagnoses were received in direct connection with birth and seven of these diagnoses were withdrawn before the participant turned five. A total of 68 additional diagnoses were diagnosed after birth and up to the age of five (Table 3). The most common additional diagnoses that were removed were diagnoses related to the cardiovascular system due to corrected heart defects (Table 2).

Type of cleft and cumulative five-years incidence of additional diagnoses

In the groups BCLP and UCLP the additional diagnoses were generally diagnosed later than at birth (Figure 6c-d). In the group CP, the highest number of additional diagnoses were within the categories sequence and extremities and skeletal system, and the most common age for diagnose was in direct connection with birth. No participants received their diagnosis at two to five years of age (Figure 6a). Among the CL group, the highest number of additional diagnoses were found within the category cardiovascular system, and the most common age for diagnose was in direct connection with birth. Additional diagnoses were identified at all represented ages (Figure 6b). In the group BCLP the highest number of additional diagnoses were identified within the categories extremities and skeletal system, and ears, nose or throat and the most common age for diagnose was at one to two years of age. There were additional diagnoses identified at all represented ages, except for three to four years of age (Figure 6c). Among the UCLP group the additional diagnoses was evenly allocated from birth up to five years of age. The highest number of additional diagnoses were within the category cardiovascular system, and the most common age for diagnose was in direct connection with birth. Additional diagnoses were identified at all represented ages (Figure 6d).

Further, ten out of 11 participants that were diagnosed with a sequence received this additional diagnosis in direct connection with birth and all participants were in the group CP (Figure 6a). In the category syndromes, seven out of 11 participants did not receive their additional diagnosis in direct connection with birth. No participants in the CL group had a syndrome diagnosis and for the other cleft groups the allocation was even. A total of 12 participants who had a diagnosis within the category extremities and skeleton, received their additional diagnosis in direct connection with birth. Eight of these 12 additional diagnoses belonged to the group CP. In the category cardiovascular system, 18 of 28 participants received their diagnosis in direct connection with birth and eight of these 18 participants belonged to the group UCLP. In

the category gastrointestinal tract, six of 14 participants received their diagnosis from one year to three years of age. The allocation of additional diagnoses of this category was even between the different types of cleft diagnoses.

Comparison with data in the CL/P registry

Of all children in the CL/P registry (n=436), 14 participants (3.2%) were registered having Pierre Robin sequence, 19 participants (4.4%) were registered having a syndrome and 60 participants (13.8%) were registered having another deformity. Thus, a total of 93 participants (21.3%) had an additional diagnosis (Table 4). Data from the CL/P registry regarding the participants in the study (n=250) showed that seven participants (2.8%) were registered having Pierre Robin sequence, eight participants (3.2%) a syndrome and 32 participants (12.8%) a deformity, resulting in a total of 47 participants (18.8%) having an additional diagnosis (Table 4). From the review of medical records of the participants included in the study (n=250), 11 participants (4.4%) were identified with Pierre Robin sequence, 11 participants (4.4%) were identified with a syndrome and 68 participants (27.2%) were identified with another deformity. Thus, when reviewing the medical records, a total of 90 participants (36.0%) had an additional diagnosis (Table 4).

The comparison between the participants' data of additional diagnoses in the CL/P registry and data in the medical records showed that for four participants the Pierre Robin sequence diagnosis had not been registered in the CL/P registry. Two participants had a syndrome according to what was registered in the CL/P registry, but this was not confirmed during the review of medical records. Five participants were diagnosed with a syndrome according to the medical records, but this had not been registered in the CL/P registry. A total of 11 participants were diagnosed with another deformity according to the CL/P registry, but this had not been registered in the medical records. Furthermore, 44 participants who had not been registered

with another deformity in the CL/P registry, had been registered with another deformity in the medical records.

Discussion

The purpose of this study was to explore the cumulative five-years incidence of additional diagnoses among children with CL/P and in such cases at what age they received the additional diagnosis before they reached five years of age. Another purpose was to investigate potential relationships between time for establishment of additional diagnosis, type of additional diagnosis and type of cleft. Further the study functioned as a validation of data on additional diagnoses in the CL/P registry. The study showed that the highest number of additional diagnoses were identified within the categories cardiovascular system, and extremities and skeletal system when reviewing the medical records. Out of 137 additional diagnoses a total of 69 additional diagnoses were established in direct connection with birth and 68 additional diagnoses were received after birth and before the age of five. A majority of the participants were only diagnosed with one single additional diagnosis.

Previous published studies have mainly investigated the total incidence of associated malformations to CL/P as well as associated diagnoses to CL/P diagnosed in direct connection with birth (24, 30, 32, 36, 37). The results of total incidence in these studies were varying from 21 % to 63.4%. Our study presented a cumulative five-years incidence of additional diagnoses of 36%, which is similar results as in the registry studies by Beriaghi et al. (36), and Calzolari et al. (32), who published an incidence of 32.3% respectively 29.2%. The results in our study, showing a higher incidence of associated diagnoses, could partially be explained by the fact that we scrutinized the medical records and included diagnoses established later than at birth as well as a wide inclusion of diagnoses. Generally, there were inconsistencies in the design of previous studies, which could partly be explained by the difficulties of choosing inclusion and

exclusion criteria (24, 30, 32, 36, 37). According to two studies, an abnormality was noted as a congenital defect if follow up treatment was necessary (30, 44), and another study included all diagnoses based on diagnosis codes (32). Some studies included stillbirths whereas others did not, which could affect the results in the way that the severest associated diagnoses were not included if still births and abortions were excluded (30, 32, 33).

In this study, the main type of participants were males with UCLP, which implies a tendency towards a predominant share of males with the malformation CL/P (32). Diagnoses in the cardiovascular system, ear, nose or throat and skeletal system have been identified in the literature as the most occurrent associated diagnoses (24, 30, 36), which is similar to the results found in our study. We have not found any previous research regarding at what age additional diagnoses were established. In the review of medical records, the number of additional diagnoses were almost doubled after birth up to the age of five. This strengthens the substrate for frequent follow-ups and should be taken into consideration when planning for surgeries in the early days of life, and when providing information for parents regarding when additional diagnoses can be detected. For the more extensive clefts, the groups BCLP and UCLP, a higher rate of additional diagnoses were registered later than in direct connection with birth, whereas in the group CP the majority of all additional diagnoses were retrieved in direct connection with birth. Knowledge of when specific additional diagnoses are established can improve the detection of subtle signs and precure for a diagnosis at earlier age. The results regarding at what age additional diagnoses were withdrawn were inconsistent and further research would be necessary.

In this study the prevalence of Pierre Robin sequence was higher than what was registered in the CL/P registry. Overreporting in medical records is probably more common when a child has a small chin and isolated CP, due to the difficulties to distinguish between Pierre Robin

sequence and isolated CP (45). The high prevalence of Pierre Robin sequence within the group CP can be explained by its etiology. No syndromes were found within the CL group, which can confirm the thesis that a more extensive cleft seems to be associated with a higher risk of additional diagnoses (32). The result that seven out of 11 children received their syndrome diagnosis later than in direct connection with birth can possibly be explained by the time it takes for genetic analysis. Additional diagnoses in the category extremities and skeletal system were diagnosed in direct connection with birth because these conditions can be detected right away with the bare eye.

This study provides with knowledge of types of additional diagnoses in children with CL/P and the connection between age for establishment of additional diagnosis, type of additional diagnosis and type of cleft. The high cumulative five-years incidence of additional diagnoses of which some are severe has implications for the genetic counseling offered and the type of information that may be given to guardians. It also suggests that systematic and regular well-child exams of children with CL/P might be worthwhile. However, by the methods used in this retrospective study it was not possible to provide statistically verifiable results, and the results cannot be generalized to the whole population. In order to get a deepened understanding of the relationships, further research will be necessary. A prospective study which follows the children from birth until they are adults may be a way forward to achieve this. Optimally, the follow up would be done similarly for all children and with sharp inclusion and exclusion criteria from the beginning. This would optimize the basis for the collection of data regarding at what age additional diagnoses are diagnosed and withdrawn, which in this study could not be conclusively established. Another possible option would be to explore the co-occurrence between additional diagnoses and CL/P, as research like this has only been made to a small extent (38).

It was beneficial that the study also could function as a validation of the data in the CL/P registry, which not was the main purpose of the study from the beginning but was elaborated during the ongoing study. It is of high importance to validate the data in the CL/P registry, since the CL/P registry is the basis of improvement for the care for children with CL/P. There was a notably discrepancy between registrations of additional diagnoses in the CL/P registry of the included children and what was retrieved during the review of medical records of the same children. Some children were registered with an additional diagnosis in the registry, which could not be confirmed in the review of medical records and some children were diagnosed with an additional diagnosis in the medical records, which was not registered in the CL/P registry. A possible explanation for that a syndrome was registered in the CL/P registry but not in the medical records could be that the child received the diagnosis after five years of age, which our study did not include. Further possible reasons for the differences could be varying inclusion criteria of an additional diagnosis, since each registration of data in the CL/P registry is due to individual considerations by the health care personnel. This implies the importance of a well-structured guide for registration of data for the personnel that registers, as the registration in the CL/P registry also is dependent of that all health care personnel remembers and have the knowledge of how to perform the registration in the CL/P registry. It would have been preferable if all children in the registry would have participated in the study for us to be able to complete a full validation.

To be able to use large registries for open comparisons, research, and statistics, it is crucial that they are up to date and correctly filled in. Health care personnel should therefore update the CL/P registry continuously when they encounter a child with CL/P. To motivate to the clinical geneticist to perform genetic tests on children with CL/P a well-developed substrate is necessary. If there is an interest from the guardians, a diagnosis of a syndrome may help them to understand their child's needs and to be better prepared for potential future health care.

This study, which was derived from medical records, has both limitations and strengths. The main strengths are the thorough review of medical records and the wide inclusion and exclusion criteria. Another strength is that even though not all children from the Southern Health Care Region in the CL/P registry participated, the participants in this study could be compared with the children in the CL/P registry, and it was then possible to get an overview of the representation. The CL/P registry have a very high coverage of the children with CL/P and gives an almost complete picture of the number of children with CL/P (21). The wide inclusion criteria regarding diagnoses in this study might contribute to increased knowledge regarding which additional diagnoses could be associated to CL/P.

This study was a retrospective study in the meaning that it was based on the existing material found in medical records. The documentation of the children's diagnoses varied both in quality and in quantity. Results in this study were dependent on correctly registered diagnosis codes and that the registrations of diagnoses were made at the correct time in the medical records. Some syndromes may not have been diagnosed, since genetic test are not provided to all children with CL/P and there are probably syndromes that not yet have been described in the literature.

Other factors that may have affected the results were that 16.8% of the children were born abroad and that 23.6% lived in other health care regions than Health Care Region of Skåne. It was therefore not possible to discover their additional diagnoses until they either moved to Skåne or revisited clinics in the Health Care Region of Skåne.

Additionally, there is another aspect to take into consideration. Since consents were needed for the study, and the participation was voluntary, it could potentially result in a skewed participant selection. Participant characteristics could be compared with the characteristics from the CL/P

registry, and they were stated to be a well representing cohort. However, it cannot be ruled out that guardians were reluctant to participation. For example, guardians to children with CL/P and additional diagnoses may have felt the study emotionally demanding. On the other hand, guardians to children with CL/P and additional diagnoses might also to a greater extent than guardians to children with CL/P without known additional diagnoses, have experienced the necessity of the study, and hence might have had a greater desire to participate. In further research, an explanation of the importance of the study, on a revisit at the clinic, could hopefully lead to a higher degree of consents, which could lessen the risk of participant selection bias.

Another limitation of the study was the set limit for the age of the children for the review of medical records. Many additional diagnoses could potentially be detected after five years of age, for example neuropsychiatric diagnoses which did not occur more than a few times in this study. Previous literature has shown a connection between CL/P and neuropsychiatric diagnoses, which could not be verified in this study (46).

Finally, the knowledge of the high percentage of additional diagnoses in children with CL/P, and especially the high percentage of additional diagnoses related to the cardiovascular system should be taken in consideration before planning the standard procedures, as numerous severe heart defects can affect the child's condition. If further research would show a connection between syndromes and CL/P, the high percentage of additional diagnoses should be taken in consideration when discussing genetic tests.

Conclusions

In this study a considerable number of additional diagnoses among children with CL/P were identified and roughly every third child with CL/P received an additional diagnosis up to the age of five. The majority of the participants were males, and the biggest group were males with UCLP. The highest number of additional diagnoses were established within the categories

cardiovascular system, and extremities and skeletal system. The number of identified additional diagnoses were almost doubled after birth up to five years. It was more common for an additional diagnosis to be established later than in direct connection with birth among the groups with more extensive clefts, UCLP and BCLP. No syndromes were found within the group CL, while other conclusions regarding the relationship between type of additional diagnosis and type of cleft were hard to establish. The high cumulative five-years incidence of additional diagnoses of which some are severe suggest that systematic and regular well-child exams of children with CL/P might be worthwhile. This study also gives a perspective on the use of registry data and the difficulties that arise when using them. The number of additional diagnoses registered in the CL/P registry were under-reported in the registry. Additional diagnoses among children with CL/P should be subject to further research, to strengthen the substrate of associations of additional diagnoses to CL/P.

Author contributions

When contact was established, the supervisors presented an idea of a project, thereafter, the author together with the supervisors compiled the research questions. When inclusion criterions were set, the author did the work with sending out the letters, compiling the consents and reviewing the medical records. Together with the supervisors the author decided what diagnoses to include and how to form the structure of the results. The author calculated all statistics and created tables and figures. The thesis was compiled by the author, with continuous help and feedback from the supervisors.

Acknowledgments

I would like to express my gratitude towards my supervisors Magnus Becker and Kristina Klintö for all support, valuable contributions and for inviting me to the Plastic Surgery Clinic

and this project. I am also grateful to CLP coordinator Annika Uvemark for all the help with the practicalities around the work.

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Figures and tables

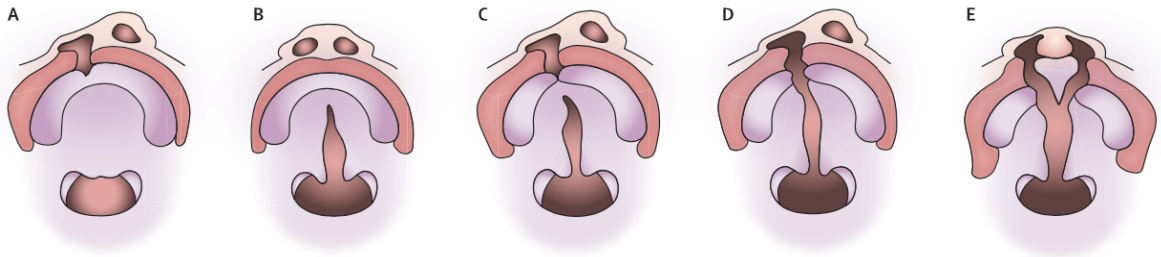


Figure 1. A. Cleft lip and alveolus (CL) B. Cleft palate (CP) C. Incomplete cleft lip and palate D. Unilateral cleft lip and palate (CLP) E. Complete bilateral cleft lip and palate (BCLP). Reprinted with permission from Bill Shaw.

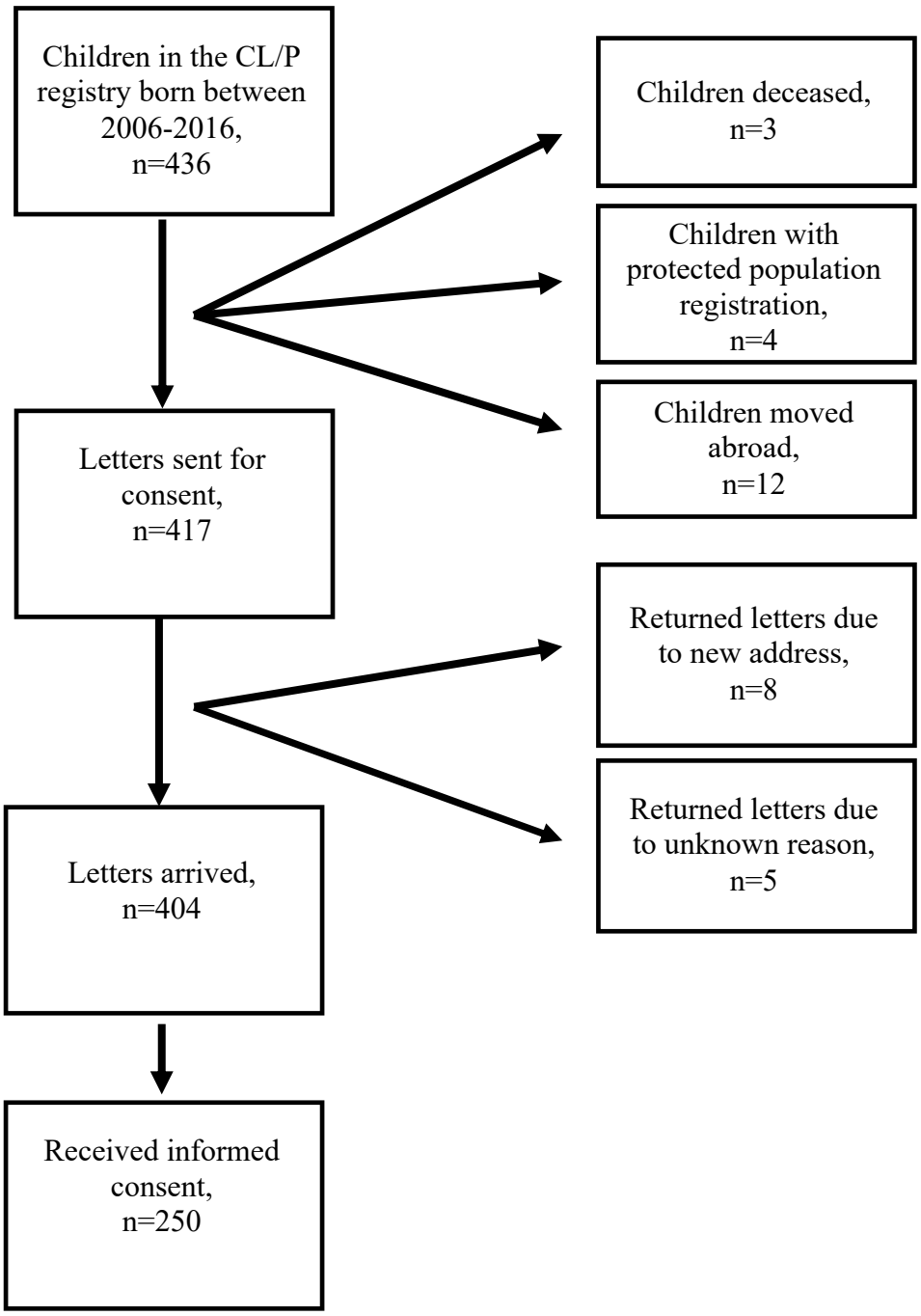


Figure 2. Flow chart of participant selection. Returned letters were letters that never arrived to the guardians of the child.

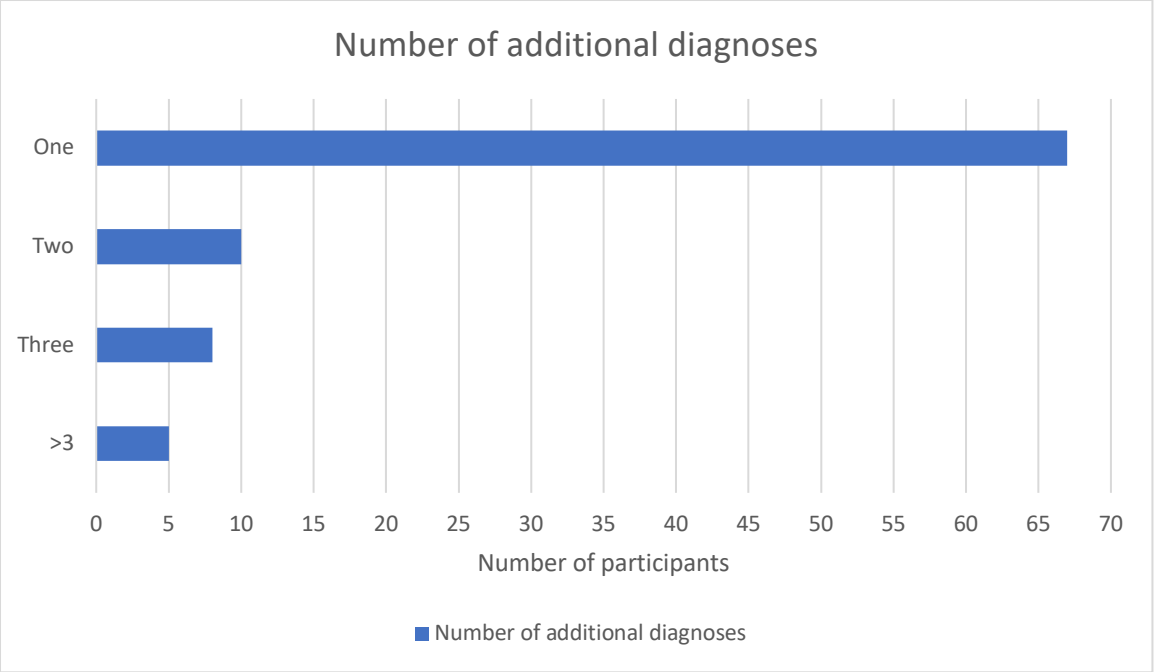


Figure 3. Number of additional diagnoses in individual participants among the 250 participants, when diagnoses related to syndromes and sequences excluded.

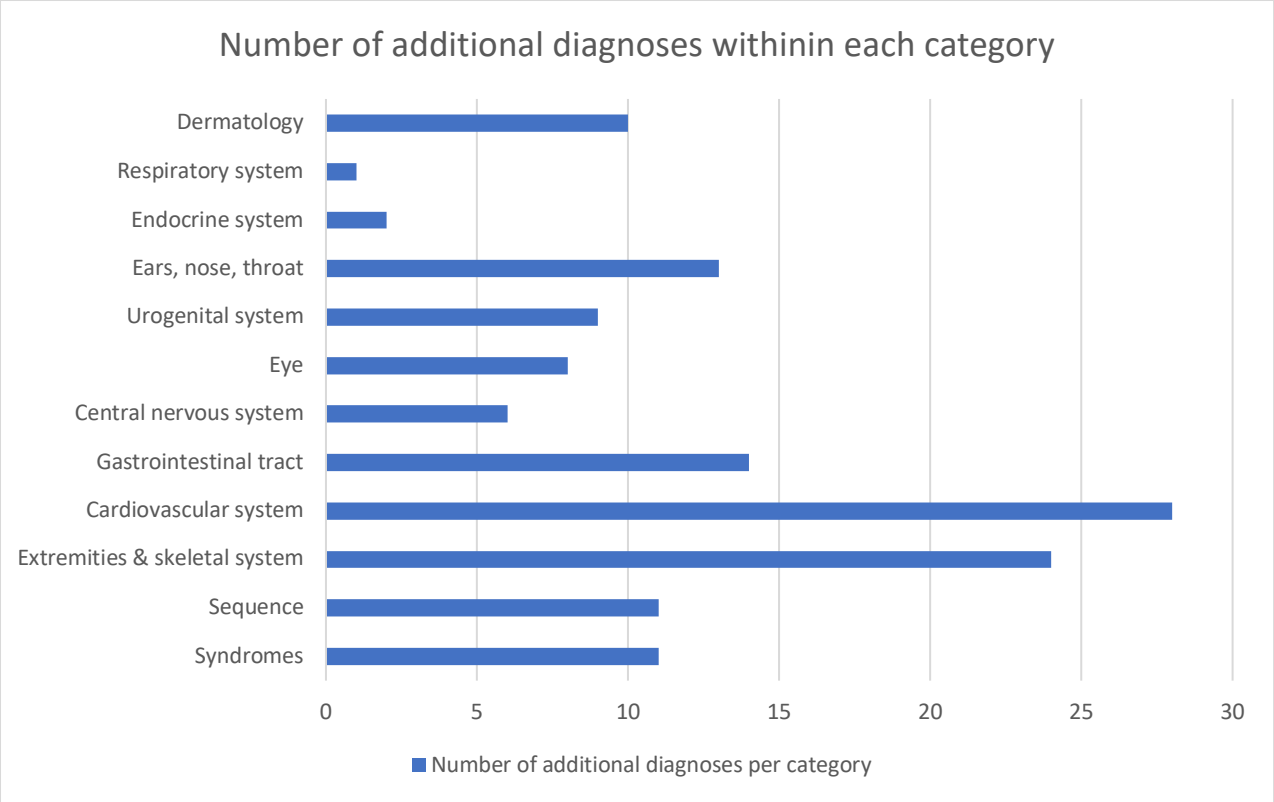


Figure 4. Total number of additional diagnoses within each category in the review of medical records.

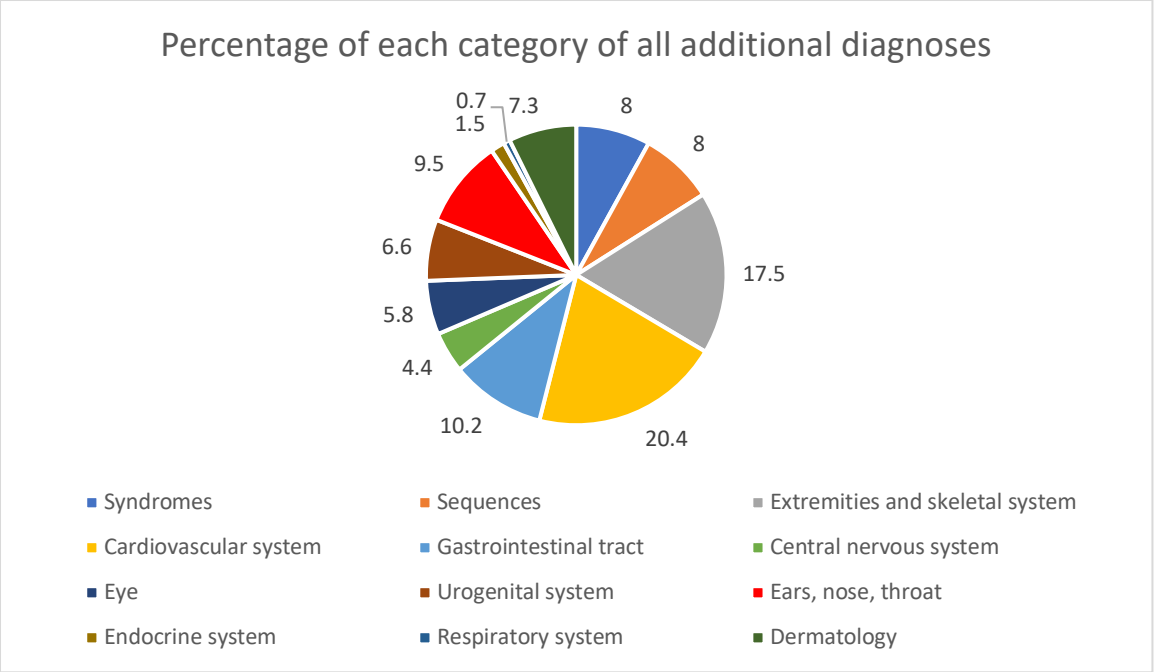
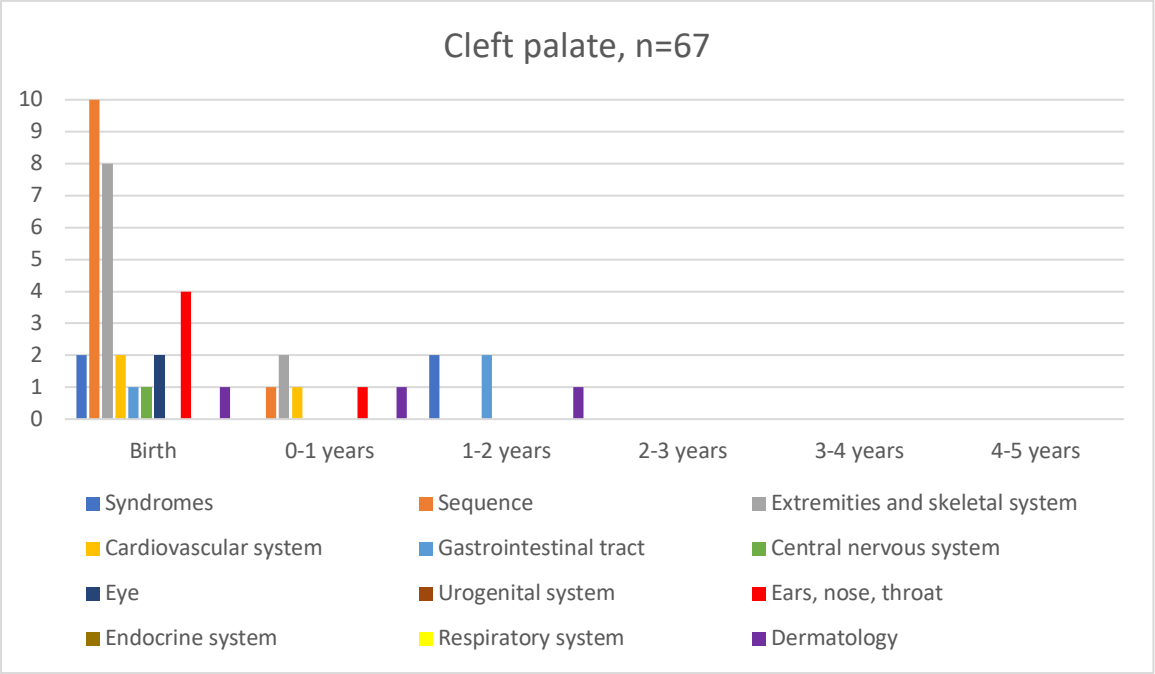
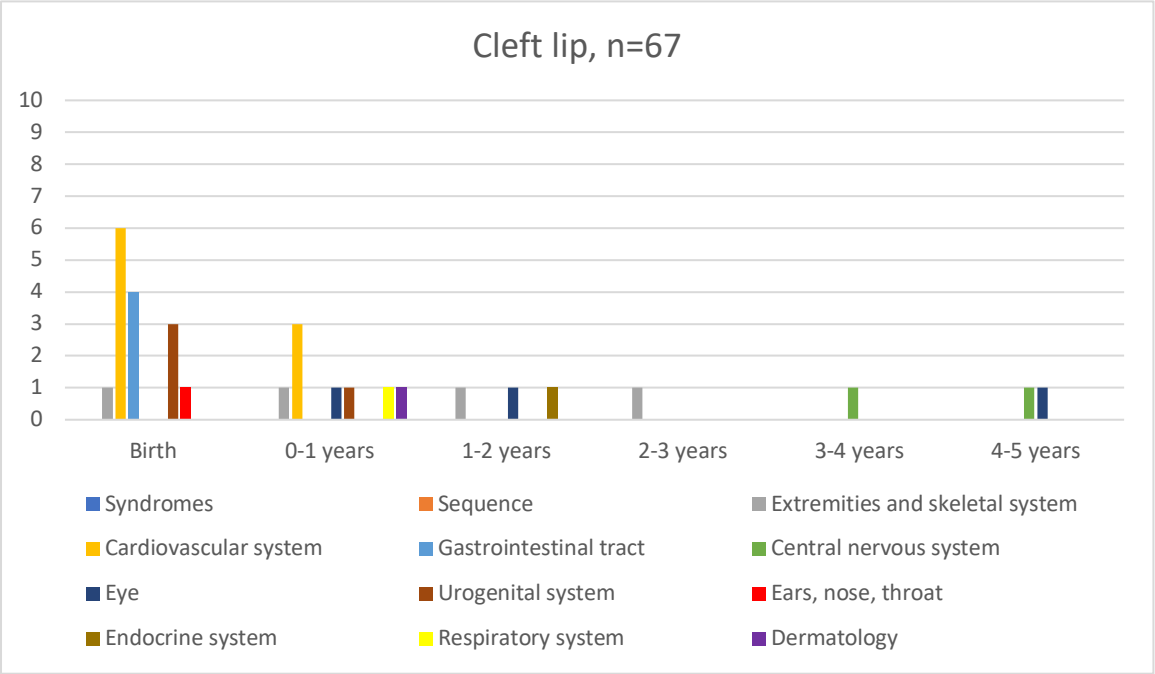


Figure 5. Percentage of each category out of all identified additional diagnoses (n=137) in the review of medical records.

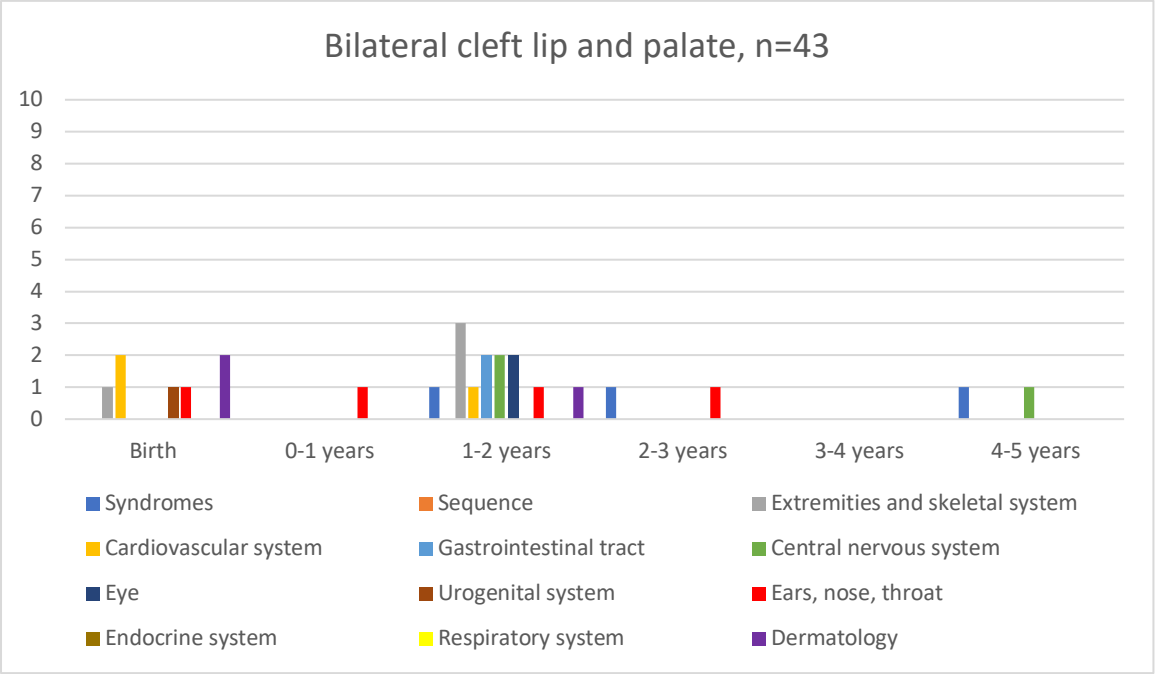
a


Cleft palate, n=67
10
9
8
7
6
5
4
3
2
1
0
Birth
0-1 years
1-2 years
2-3 years
3-4 years
4-5 years
Syndromes
Sequence
Extremities and skeletal system
Cardiovascular system
Gastrointestinal tract
Central nervous system
Eye
Urogenital system
Ears, nose, throat
Endocrine system
Respiratory system
Dermatology

b


Cleft lip, n=67
10
9
8
7
6
5
4
3
2
1
0
Birth
0-1 years
1-2 years
2-3 years
3-4 years
4-5 years
Syndromes
Sequence
Extremities and skeletal system
Cardiovascular system
Gastrointestinal tract
Central nervous system
Eye
Urogenital system
Ears, nose, throat
Endocrine system
Respiratory system
Dermatology

c



d

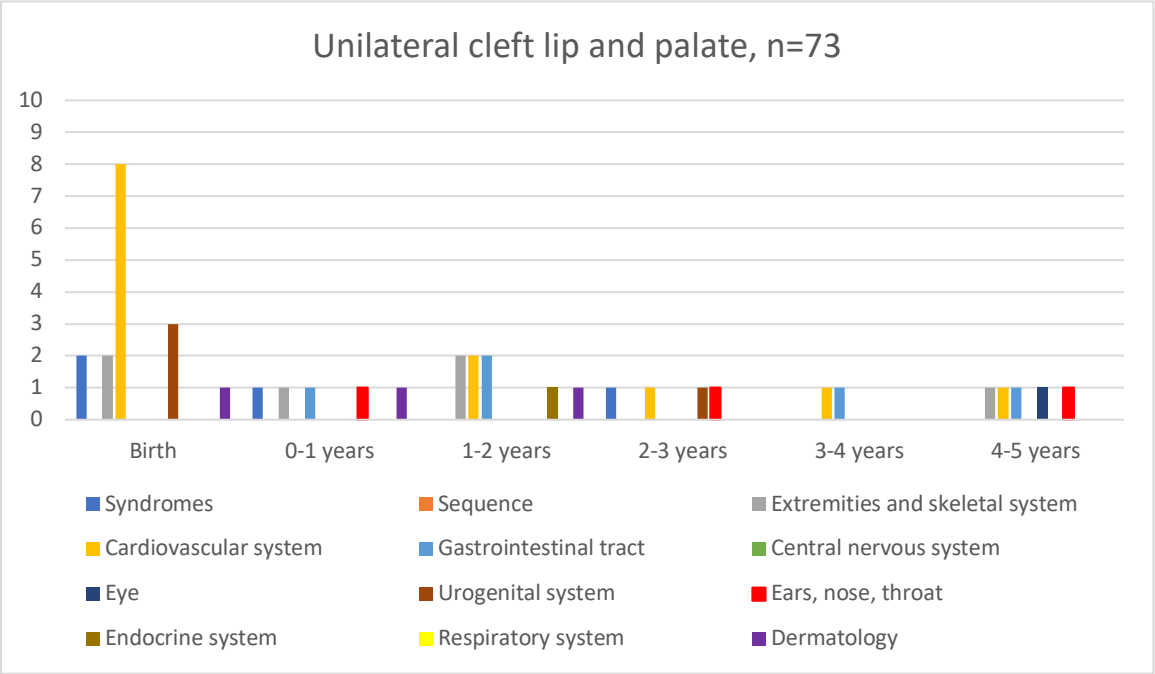


Figure 6. Number of additional diagnoses within each category at the different age intervals among the participants with cleft palate (a), cleft lip (b), bilateral cleft lip and palate (c) and unilateral cleft lip and palate (d) shown as frequency.

Variables of participant characteristics, n (%)	**Participants in the study, n= 250**	**Children in the CLP registry, n=436**
Male, n (%)	164 (65.6)	280 (64.2)
Female, n (%)	86 (34.4)	156 (35.8)
Born abroad, n (%)	42 (16.8)	62 (14.2)
Lived in Skåne, (%)	191 (76.4)	
Type of cleft, n (%)		
Cleft palate	**67 (26.8)**	**136 (31.2)**
Male	39 (58.2)	67 (49.3)
Female	28 (41.8)	69 (50.7)
Cleft lip	**67 (26.8)**	**126 (28.9)**
Male	44 (65.6)	85 (67.5)
Female	23 (34.3)	41 (32.5)
Bilateral cleft lip and palate	**43 (17.2)**	**65 (14.9)**
Male	31 (72.1)	42 (64.6)
Female	12 (27.9)	23 (35.4)
Unilateral cleft lip and palate	**73 (29.2)**	**109 (25.0)**
Male	52 (71.2)	80 (73.4)
Female	21 (28.8)	29 (26.6)

Table 1. Characteristics of participants in the study and children in the CLP registry, with data presented as frequency and percentage. The participant characteristic if a child lived in Skåne could only be obtained from the medical records.

Clinical variables, categories, n (%)	Descriptive statistic	Age in years at diagnosis, Median (Range)	Age in years at withdrawn diagnosis, Median (Range)
Syndromes	**11 (4.4)**	1 (4)	
Chromosomal, n (%)			
Trisomy 18	1 (0.4)		
Trisomy 21	1 (0.4)		
Deletion chromosome 16	1 (0.4)		
Deletion chromosome 1	1 (0.4)		
Recognized non-chromosomal, n (%)			
Charge syndrome	2 (0.8)		
Goldenhars syndrome	2 (0.8)		
Treacher Collins syndrome	1 (0.4)		
Stickler syndrome	1 (0.4)		
Klinefelter syndrome	1 (0.4)		
Sequence, n (%)	**11 (4.4)**	0 (1)	
Pierre Robin sequence	11 (4.4)		
Extremities and skeletal system	**24 (9.6)**	0 (4)	0 (0)
Head and Neck, n (%)			
Plagiocephaly	3 (1.2)		
Bifid uvula	4 (1.6)		
Misses' uvula	2 (0.8)		
Torticollis	2 (0.8)		
Ankyglossia	2 (0.8)		
Craniosynostos	1 (0.4)		
Head asymmetry	1 (0.4)		
Upper limb, n (%)			
Digits	2 (0.8)		
Congenital stenosis digit	1 (0.4)		
Abbreviated right arm	1 (0.4)		
Hip, n (%)			
Hip dislocation	1 (0.4)		
Unstable hip joint	1 (0.4)		
Back, n (%)			
Scoliosis	1 (0.4)		
Feet, (%)			
Supinated feet	1 (0.4)		
PEVA	1 (0.4)		
Cardiovascular system, n (%)	**28 (11.2)**	0 (4)	0 (4)
Aortic stenosis	3 (1.2)		
Atrial septal defect	4 (1.6)		
Ventricular septal defect	7 (2.4)		
Patent foramen ovale	4 (1.2)		
Patent ductus arteriosus	4 (1.6)		
Peripheral pulmoarterial stenosis	3 (1.2)		
Single atrium	1 (0.4)		
Single ventricle	1 (0.4)		
Atresia of the mitralis valve	1 (0.4)		
Right aortic arch	1 (0.4)		
Gastrointestinal tract, n (%)	**14 (5.6)**	1 (4)	
Upper intestinal tract, n (%)			

Kidney agenesia	1 (0.4)	
Umbilical hernia	2 (0.4)	
Asplenia	1 (0.4)	
Lower intestinal tract, n (%)		
Inguinal hernia	5 (2.0)	
Perianal fistula	1 (0.4)	
Anal fistula	2 (0.8)	
Anal atresia	1 (0.4)	
Hemorrhoids	1 (0.4)	
Central nervous system, n (%)	**6 (2.4)**	1 (4)
Development delay	3 (1.2)	
Epilepsy	1 (0.4)	
Autism	1 (0.4)	
Facial nerve palsy	1 (0.4)	
Eye, n (%)	**8 (3.2)**	1 (4)
Ptosis	1 (0.4)	
Nystagmus	1 (0.4)	
Hypertelorism	2 (0.8)	
Abducens paresis	2 (0.8)	
Epicantus fold	1 (0.4)	
Coloboma	1 (0.4)	
Urogenital system, n (%)	**9 (3.6)**	0 (2)
Hydronefrosis	2 (0.8)	
Hydroureter	2 (0.8)	
Micropenis	1 (0.4)	
Bilateral retention testis	1 (0.4)	
Fimosis	1 (0.4)	
Hydrocele	1 (0.4)	
Hypospadia	1 (0.4)	
Ears, nose, throat, n (%)	**13 (5.2)**	0.5 (4)
Preaurical skin tag	3 (1.2)	
Auricular malformation	3 (1.2)	
Sensorineural hearing loss	3 (1.2)	
Swallowing difficulties	2 (0.8)	
Low set ears	1 (0.4)	
Laryngomalacia	1 (0.4)	
Endocrine system, n (%)	**2 (0.8)**	1 (0)
Diabetes insipidus	1 (0.4)	
Hypopituitarism	1 (0.4)	
Respiratory system, n (%)	**1 (0.4)**	0 (0)
Cystic fibrosis	1 (0.4)	
Dermatology, n (%)	**10 (4.0)**	0 (1)
Salmon patch	4 (1.6)	
Hemangioma	5 (2.0)	
Dermatofibroma	1 (0.4)	

Table 2. Identified syndromes, sequences, and other additional diagnoses in the medical records among the 250 participants, with separate diagnoses included in a syndrome or sequence excluded.

Age	Number of additional diagnoses for each age
At birth	69
0-1 years	20
1-2 years	29
2-3 years	7
3-4 years	3
4-5 years	9

Table 3. Number of additional diagnoses that were diagnosed at birth, after birth up to one year, from one year to two years, from two years to three years, from three years to four years and from four years to five years in the review of medical records.

Categories, n (%)	Data for all children in the CLP registry, n=436	Data for study participants, n=250, from the CLP registry	Data for study participants, n=250, from medical records,
Pierre Robin	14 (3.2)	7 (2.8)	11 (4.4)
Syndrome	19 (4.4)	8 (3.2)	11 (4.4)
Other deformity	60 (13.8)	32 (12.8)	68 (27.2)
Total	*93 (21.3)*	*47 (18.8)*	*90 (36.0)*

Table 4. Cases of Pierre Robin sequence, syndrome and other deformities in the CLP registry and from the review of medical records of the 250 participants, presented as frequency and percentage. All separate diagnoses for each participant with a syndrome were excluded.