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# LONG-TERM FOLLOW-UP IN CHILDREN BORN WITH CONGENITAL DIAPHRAGMATIC HERNIA

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# Long-term follow-up in children born with congenital diaphragmatic hernia

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**Stockholm 2018**

*Till min familj*

“Not everything that counts can be counted, and not everything that can be counted counts.”

-Albert Einstein

# ABSTRACT

Congenital diaphragmatic hernia (CDH) is a developmental defect which occurs in approximately 1 per 3000 births. The incomplete development of the diaphragm early in gestation allows abdominal viscera to herniate into the thoracic cavity. The malformation differs in size and can occur on either one or both sides, but most commonly on the left. Normal lung development is impaired and the lungs become hypoplastic with an impaired lung structure, often causing acute respiratory distress shortly after birth. Children born with CDH, as well as their parents, very often experience a dramatic first period in life. There is also a large difference in the length of hospital stay and the initial care needed; where the size of the diaphragmatic defect seems to be crucial. The survival rate has increased over the last few decades and about 85% of all children born with CDH are discharged from hospital to their homes.

Children born with CDH who survive often suffer from morbidities related to pulmonary hypoplasia and associated anomalies, but also from the sequelae resulting from the intensive care they were exposed to.

The aim of this thesis was to study the long-term outcome of children and adolescents born with CDH in terms of perceived health, health-related quality of life (HRQoL) and psychosocial function. Further, the aim was to assess parental stress in parents of children born with CDH. All the studies were cross-sectional.

In *Study I*, all children born with CDH between 1990 and 2009 who had been treated at Sankt Görans and Astrid Lindgren Children's hospitals were asked to participate. Data from medical records were supplemented by a questionnaire consisting of questions regarding perceived physical function. Children born with CDH reported themselves as experiencing greater problems with asthma, developmental delay, seizure disorder, poor vision, and scoliosis compared with normal Swedish children. They also described a sense of having less strength and becoming breathless more often than their healthy friends. Symptoms of gastroesophageal reflux and abdominal pain were also reported. The symptoms increased with the severity of the malformation.

In *Study II*, parents of children born with CDH between 2005 and 2009 received *The Swedish Parenthood Stress Questionnaire (SPSQ)*, which was supplemented by data from

medical records. Parents of children born with CDH, who had been supported by ECMO or who had experienced a long hospital stay, showed a higher overall level of parental stress. Mothers scored an overall higher parental stress level compared with fathers. A prenatal diagnosis of CDH or lower parental educational level was followed with significantly higher parental stress on some of the factors.

In *Study III* the KIDSCREEN-52 questionnaire was used for measuring HRQoL in children born with CDH between 1993 and 2003 and, in addition, a detailed review of medical records was performed. Children born with CDH considered themselves to have an equally good HRQoL compared with a healthy population of Swedish children. There were only a few significant HRQoL differences within the group of children with CDH, although several median scores in ECMO-treated patients were somewhat lower. Correlations between child and parent scores on HRQoL were low.

In *Study IV* the Child Behavior Checklist or Adult Self-Report questionnaires were sent to children and adolescents born with CDH between 1990 and 2009 in order to assess psychosocial functioning. All the parents of children aged 1.5-5 years of age and 90% of parents of children aged 6-18 years of age reported a normal range on the syndrome scale. All young adults achieved a normal score on the syndrome scale. Eighty-five percent had normal school achievement, 79% had normal social scores and 40% had normal activity levels. Significantly fewer boys (23%) were in the normal activity range compared with 67% of girls.

In conclusion, the long-term outcome in children and adolescents born with CDH is, in general, good. There seem, however, to be differences within the group, and children who are more affected and have a more severe form of CDH, as well as their families, need extensive follow-up and support.

# POPULÄRVETENSKAPLIG SAMMANFATTNING

Varje år föds ca 25 barn i Sverige med medfött diafragmabråck (CDH). Diafragmamuskeln skiljer lungorna från buken och bildas redan under graviditetsvecka 7-9. Vid diafragmabråck har muskeln slutits ofullständigt, vilket medför att bukens organ kan glida upp i bröstkorgen, på den plats där lungorna hos det lilla fostret ska bildas. Detta får till följd att lungorna blir mindre och får en sämre funktion. Barnen mår bra så länge de ligger i mammans mage men när de föds och ska dra sitt första andetag märks oftast att något är fel. Barnen kan vanligen inte andas ordentligt och läggs då omedelbart i respirator. Idag upptäcks drygt hälften av alla barn med diafragmabråck före födseln, vid det riktade ultraljudet i vecka 17-19 på mödravården. Upptäckten av bråcket gör det möjligt att planera för barnets födsel så att man kan optimera omhändertagandet. Hur länge barnet behöver vårdas på sjukhus är oftast beroende av hur sjuka lungorna är och variationen är stor, alltifrån några veckor till månader. Tack vare många års forskning och utveckling av intensivvården har överlevnaden ökat till idag 85 %. Många av de barn som fötts med diafragmabråck får under uppväxten besvär relaterade till nedsatt lungfunktion men också andra symptom till följd av sitt diafragmabråck.

Denna avhandling syftade till att undersöka hur det går senare i livet för barn och ungdomar födda med diafragmabråck, hur det har påverkat dem och deras föräldrar i olika avseenden. Studierna har genomförts på barn som fötts med diafragmabråck och vårdats på Sankt Görans barnsjukhus och Astrid Lindgrens barnsjukhus under åren 1990 till 2009. Olika typer av enkäter har använts för att studera upplevd fysisk hälsa, föräldrastress, hälsorelaterad livskvalitet samt psykosocial funktion. En noggrann genomgång av barnens journaler har även utförts.

I *studie I* studerades upplevd fysisk funktion genom ett studiespecifikt formulär. Barn födda med diafragmabråck mellan år 1990 och 2009 rapporterade att de i högre grad än friska svenska barn hade problem med astma, utvecklingsförsening, krampsjukdom, nedsatt syn och skolios. De upplevde också att de hade mindre ork och lättare blev trötta än sina friska jämnåriga kompisar när de ansträngde sig. Symptom på halsbränna och ont i magen beskrevs också. Ju svårare form av diafragmabråck man var född med, desto mer besvär hade också barnen vid uppföljningen.

I *studie II* deltog föräldrar till barn födda med CDH mellan 2005 och 2009. Föräldrastress mättes med *The Swedish Parenthood Stress Questionnaire (SPSQ)*. Föräldrar till barn födda med CDH som hade vårdats i ECMO eller haft en lång sjukhusvistelse visade en högre föräldrastress. Mammor skattade en högre föräldrastress än vad pappor gjorde. Låg utbildningsnivå hos föräldrar medförde en högre föräldrastress inom vissa avseenden, detsamma sågs hos föräldrar som före födseln fick besked att barnet hade CDH.

I *studie III* användes frågeformuläret KIDSCREEN-52 för att mäta hälsorelaterad livskvalitet hos barn födda med CDH år 1993 till 2003. Barnen födda med CDH skattade generellt en god hälsorelaterad livskvalitet (HRQoL), lika bra som en svensk barn-normalbefolkning. Barn som hade behövt ECMO vård skattade oftare en sämre hälsorelaterad livskvalitet än barn som inte hade behövt ECMO. Föräldrar och barn skattade barnens livskvalitet helt olika.

I den sista studien, *studie IV*, studerade vi psykosocial funktion genom frågeformuläret Child Behavior Check-List (CBCL). Enkäten skickades till barn och ungdomar födda 1990 till 2009 med CDH. Föräldrar till barn som var 1.5-5 år gamla svarade att deras barn hade ett normalt socialt beteende. Nittio procent av föräldrarna till barn i åldrarna 6-18 år uppgav att deras barn hade ett normalt beteende medan övriga tio procent uppgav att deras barn hade ett socialt beteende som var mellan normalt och problematiskt. Fem föräldrar uppgav också att deras barn hade ett problematiskt introvert beteende. Inget barn uppgavs vara utåtagerande på ett problematiskt vis. Unga vuxna uppgav att de hade ett normalt känslomässigt beteende, en uppgav sig vara introvert. Åttiofem procent av alla barn i åldrarna 6-18 år hade normala skolprestationer, 79 % uppgav att deras barn hade ett normalt socialt liv och 40 % av föräldrarna upplevde att deras barn hade en normal fysisk aktivitetsnivå. Det var betydligt fler pojkar som inte hade en normal aktivitetsnivå i jämförelse med flickor.

Sammanfattningsvis visar de fyra delstudierna att de flesta barn och ungdomar födda med CDH har en god upplevd fysisk hälsa, en bra hälsorelaterad livskvalitet och att de fungerar normalt i skola och på fritiden, med undantag för fysisk aktivitet. Däremot finns det skillnader inom gruppen av barn födda med CDH där barn som är allvarligare sjuka och mer påverkade av sitt diafragmabråck behöver noggrann uppföljning och stöttning. Motsvarande gäller för deras föräldrar.

# FÖRORD

För många år sedan träffade jag ett barn i åtta års ålder, tillsammans med sina föräldrar, vid en läkarundersökning i mitt arbete på barnkirurgmottagningen. Barnet var fött med diafragmabråck och hade haft en tuff start i livet. Nu skuttade barnet fram genom den välkända mottagningskorridoren och hälsade glatt på barnkirurgen. Efter att ha lyssnat på hjärta och lungor ställdes frågor om fysisk aktivitet och när kirurgen frågade om deltagande i skolgymnastiken blev svaret genast ja, föräldrarna nickade instämmande. Sedan kom frågan om simning och även då blev svaret ja från barnet, men denna gång började föräldrarna försiktigt skaka på huvudet. Till sist kom frågan om barnet orkade simma lika fort och långt som de andra i gruppen och då tittade barnet på oss med undrande ögon och svarade nej. Föräldrarna bekräftade. Efter besöket tänkte jag mycket på händelsen och insåg att vid mötet satt vi med åtminstone tre olika infallsvinklar. Kirurgen och jag hade sett testresultaten och visste att lungkapaciteten var nedsatt. Föräldrarna hade troligtvis sin syn på sitt barns ork, med allt som det kanske innebar. Minnen från första tiden, glädjen över att komma hem med ett barn och få se det växa upp. Kanske oron för att barnet inte orkar som de andra kompisarna eller syskonen. Barnet själv hade ett tredje perspektiv och som jag uppfattade det, i den åldern där barnet befann sig, var det tydligt att barnet var delaktigt, och med på allt. Frågan om att orka som sina jämnåriga var märklig, för det hade barnet nog aldrig gjort. Jag insåg också att vi i det rummet skulle ha svarat mycket olika på samma fråga gällande barnets hälsa och för att få en helhetsbedömning så måste våra olika svar vävas samman. Ett testresultat speglar en faktisk situation men upplevelsen av själva situationen kan variera.

Genom denna avhandling har jag haft förmånen att få ställa många frågor till barn, ungdomar och deras föräldrar samt unga vuxna födda med diafragmabråck. Jag är otroligt tacksam över allt ni delat med er av och jag hoppas att svaren kommer komma patientgruppen till gagn.

Astrid Lindgrens barnsjukhus
Januari 2018

Elin Öst

# LIST OF SCIENTIFIC PAPERS

This thesis is based on the following four papers, which will be referred to in the text by their Roman numerals (I-IV).

I. **Öst E,** Öjmyr Joelsson M, Mesas Burgos C, Frenckner B.
Self-assessed physical health among children with congenital diaphragmatic hernia.
*Pediatric Surgery International*, 2016, Vol.32(5), pp.493-503

II. **Öst E,** Nisell M, Frenckner B, Mesas Burgos C, Öjmyr Joelsson M.
Parenting stress among parents of children with congenital diaphragmatic hernia.
*Pediatric Surgery International*, 2017, Vol.33(7), pp.761-769

III. **Öst E,** Frenckner B, Nisell M, Mesas Burgos C, Öjmyr Joelsson M.
Health-related quality of life in children born with congenital diaphragmatic hernia.
*Pediatric Surgery International,* 2018, Vol.34(4), pp. 405-414

IV. **Öst E,** Nisell M, Mesas Burgos C, Frenckner B, Öjmyr Joelsson M.
Behavioral, emotional and social functioning in children born with congenital diaphragmatic hernia.
*Manuscript submitted.*

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ASR | Adult Self-Report |
| BMI | Body Mass Index |
| CBCL | Child Behavior Checklist |
| CDH | Congenital Diaphragmatic Hernia |
| ECMO | Extra Corporeal Membrane Oxygenation |
| FLV | Fetal Lung Volume |
| GER | Gastro Esophageal Reflux |
| HRQoL | Health-Related Quality of Life |
| ICC | Intraclass Correlation |
| LHR | Lung-to-Head Ratio |
| LOS | Length of hospital Stay |
| MRI | Magnetic Resonance Imaging |
| O/E LHR | Observed/Expected Lung-to-Head Ratio |
| PIN | Personal Identification Number |
| PSI | Parental Stress Index |
| QoL | Quality of Life |
| SD | Standard Deviation |
| SPSQ | Swedish Parenthood Questionnaire |
| UNCRC | United Nations Convention on the Rights of the Child |
| WHO | World Health Organisation |

# LIST OF DEFINITIONS

**Health**

The ability to adapt to one's environment, where health is not a fixed entity and varies for every individual depending on his or her circumstances.

**Health-related quality of life**

A multidimensional construct covering physical, emotional, mental, social and behavioral components of well-being and function as perceived by patients and/or other observers.

**Parental stress**

A notion of conflict between parental resources and the demands connected to the parental role.

**Quality of life**

How individuals' perceive their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns.

# 1 INTRODUCTION

## 1.1 EMBRYOLOGY AND PATHOPHYSIOLOGY

Congenital diaphragmatic hernia (CDH) is a rare anomaly with an incidence of approximately 1 per 3000 births [1]. The incomplete development of the diaphragm early in gestation allows abdominal viscera to herniate into the thoracic cavity (Figure 1). The malformation differs in size and can occur on the left, right or both sides. Left-sided defects are most common and occur in 85-90% of cases. Bilateral and right-sided defects generally have a worse outcome than left-sided cases [2,3]. The normal lung development is impaired and the lungs become hypoplastic with an impaired lung structure consisting of a reduced number of bronchial generations, a reduced number of alveoli, and structural abnormalities of the pulmonary vascular bed [4]. Whether this is a result of the defective diaphragm or vice versa is debated. The etiology of CDH is still unknown [5]. Congenital diaphragmatic hernia is most often an isolated anomaly, but there are associated anomalies in 33-50% of cases, such as cardiac and chromosomal anomalies and intestinal atresia. Children with isolated CDH have a better outcome than children with CDH and an associated anomaly [6].

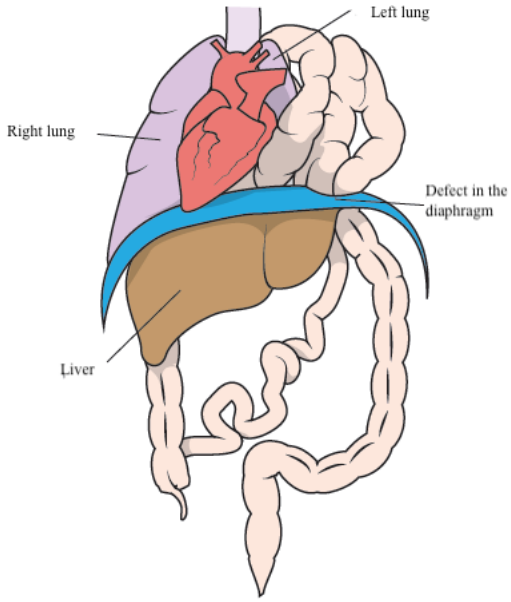



**Figure 1**. Schematic view of a left-sided diaphragmatic defect. Reproduced with kind permission from Frenckner et al: *Kompendium i Barnkirurgi och Barnortopedi*.

## 1.2 PRENATAL DIAGNOSIS

Due to the development of the ultrasound technique, prenatal detection of CDH is possible in more than 60% of all cases. Whether or not the malformation is detected is dependent upon several factors including the timing of the examination and the number of ultrasound scans. With the knowledge of a CDH malformation, new opportunities, but also questions, arise. Prenatal predictors for postnatal outcomes are desirable, but nevertheless hard to define. One predictor is lung-to-head ratio (LHR), where the contralateral lung area is divided by the fetal head circumference. LHR results change with gestational age but by comparing the observed ratio with the expected ratio (O/E LHR) the effect of gestational age at assessment can be eliminated [7]. Another predictor is the position of the liver, where a liver up in the thoracic cavity implies a larger size of the defect and a worse scenario. Using magnetic resonance imaging (MRI) the fetal lung volume (FLV) can be measured and a prognosis given by a comparison with the expected lung volume [8].

Prenatal detection enables parent counseling and planning of the postnatal management so that delivery can take place where the expertise is located. Even though there are obvious benefits with a prenatal awareness for the planning of the postnatal care, it often leads to difficult decisions for the expectant parents and increased psychological distress [9]. A prenatal diagnosis often indicates a more severe case of the malformation, with a higher mortality risk compared with a postnatal identification of the same condition [10].

## 1.3 MANAGEMENT OF THE NEWBORN CHILD WITH CDH

### 1.3.1 Symptoms

The vast majority of all patients with CDH are affected by acute respiratory distress shortly after birth, where the degree of the symptoms depends on the severity of the lung hypoplasia. Immediate intubation is often necessary [11]. Milder forms of CDH may show more subtle respiratory or gastrointestinal symptoms several months or even years after birth [12].

### 1.3.2 Postnatal care

Since 1940, when Ladd and Gross reported survival after laparotomy, surgery has been an accepted treatment for CDH [13]. In the beginning, CDH was considered as a surgical emergency but the understanding of the condition has evolved over the years and, since 1990, the strategy of therapy has included preoperative stabilization, gentle ventilation,

delayed surgery and, if necessary, preoperative extracorporeal membrane oxygenation (ECMO) [14,15]. With this new strategy survival rates have dramatically increased to 69-93% [16,17] and children, who earlier died of severe CDH, today most likely represent a new group of survivors.

ECMO is a modified lung-heart machine. Blood is drained from the patient and pumped through an artificial oxygenator and a heat exchanger back to the patient. This enables unstable patients with CDH to be stabilized, and further damage to the lungs due to high pressure from the ventilator can be avoided. Since ECMO is a complex and high-risk procedure this technically challenging treatment is only suitable at high volume ECMO centers with specifically trained staff [18]. Neonates with CDH and a need for ECMO treatment are the most severely ill, and in long-term follow-ups they have more late sequelae [19].

Surgery is always necessary, and if the defect in the diaphragm is too large for primary closure a patch is used. There are different patch materials but Gore-Tex is the most commonly used. A large defect that requires a patch indicates a more severe malformation and is associated with an increased risk of mortality and morbidity compared with patients with a primary repair [20]. There is a standardized tool for reporting defect size ranging from A to D, where A is the smallest and D the largest size of defect [21]. A recurrence of the hernia occurs in approximately 15% of patients with a primary repair and up to 50% after patch repair [22,23]. Recurrences can occur asymptomatically several years after surgery and are detected by chest radiography.

## 1.4 OUTCOMES

### 1.4.1 Survival and morbidity

Children with CDH who survive often suffer from morbidities related to pulmonary hypoplasia and associated anomalies, but also from the intensive care they were exposed to as critically ill CDH neonates. Approximately 90% of CDH survivors have long lasting associated morbidity [24]. Many centers have initiated standardized follow-up programs to ensure that all morbidity areas are covered [25,26]. These areas are pulmonary-, gastrointestinal-, neurodevelopmental- and musculoskeletal-related outcomes [27,25]. Surgical complications in CDH survivors are common and can occur asymptomatically

many years after the repair [28,29]. The early recognition of symptoms may increase survival and prevent secondary morbidity [5].

Survival rates have dramatically increased over the last few decades and many centers are reporting a 90% survival rate to discharge from hospital [30]. However, survival rates vary widely between different centers and, in total, two thirds of all children born with CDH survive [31].

### 1.4.2 Pulmonary sequelae

Even though new therapy strategies aim to minimize pulmonary sequelae induced by barotrauma, pulmonary morbidities exist [32,33], with asthmatic symptoms, recurrent respiratory tract infections and impaired pulmonary function. Children treated with, and without, ECMO often need bronchodilators and inhalable steroids far beyond their initial hospitalization [34].

In long-term follow-up investigations of adult CDH survivors nearly 50% showed an impaired pulmonary function [35]. It should, however, be noted that those adults were born in a time prior to the introduction of gentle ventilation but, nevertheless, survivors from this era most likely represent a less severely ill group than those of today.

In a study where CDH survivors reviewed their personal fitness, a feeling of being less fit than their healthy peers and having a negative attitude towards exercise was described [36]. This is one of only a few studies where the children's own perceptions of their physical fitness have been described. Physical training has a lot of positive effects and children with CDH in a good clinical condition are encouraged to increase their physical function by training. A higher level of performance leads to a reduced perception of dyspnea and effort [37].

### 1.4.3 Gastrointestinal sequelae

Gastroesophageal reflux (GER) is a common consequence of CDH. Its prevalence is around 20-84% during the first year of life in different studies [38]. In adults with CDH, approximately 50% showed endoscopic or histological GER [39]. The cause of GER has not been completely clarified, but it seems that higher intra-abdominal pressure in combination with an abnormal hiatal anatomy is a contributory factor [4]. Gastroesophageal reflux can cause comorbidities such as failure to thrive (poor weight gain), oral aversion, pain, and worsened pulmonary morbidity. The duration of ventilation and the use of a patch

repair have been described as independent variables predictive of a failure to thrive [40]. Symptoms for the detection of esophagitis have been described as poor and many patients have been completely asymptomatic, while others have had heartburn or regurgitation [39].

A failure to thrive has been described as a result of GER, but it can also be due to prolonged endotracheal intubation and an increased caloric requirement because of pulmonary morbidity [40]. Routine nutritional assessment including measurements of height, weight and head circumference should be standard practice during follow-up, with the intention for an early intervention by nutritional specialists [4,41].

### 1.4.4 Neurodevelopmental sequelae

Children with CDH more often suffer from neurodevelopmental and neuro-functional sequelae than the healthy population [42], probably as a consequence of perinatal and neonatal hypoxemia [4]. Gestational age has been identified as one isolated predictor for neurodevelopmental delay, where preterm, late-preterm and near-preterm children with CDH are at an increased risk [43]. Motor performance, especially, seems to be affected by gestational age [43,44].

Children with CDH achieve normal IQ scores when tested with the Wechsler Intelligence Scale for Children (WISC), but seem to be at risk of attention and concentration deficits [45,46]. However, children born with CDH and treated with ECMO have shown lower IQ scores than those without ECMO treatment [47]. The vast majority of all children with CDH attend normal schools but it would appear that as many as half of them are in need of extra support in school [47]. Since children with CDH may be at risk of behavioral problems, cognitive functioning should be reviewed at standardized follow-up [48]. The risk of impaired outcome does not, however, seem to be related to the severity of the malformation [45,46].

Sensorineural hearing loss has been described with a varied frequency (3-60%) among children with CDH [49,50]. The underlying factor is unknown and seems to be independent of ECMO treatment. Some children, who initially had normal hearing, develop hearing loss later in life.

### 1.4.5 Musculoskeletal sequelae

Chest wall deformities, often in the form of an asymmetric pectus excavatum or flat chest, are present in about 50% of all children with CDH [23,51]. It is more common in children

who had a patch repair, and is probably dependent on the size of the defect. Scoliosis is present in around 10% of all children with CDH and, likewise, correlates with large defects. In adult survivors with CDH one third have scoliosis [51].

### 1.4.6 Health

There are a wide variety of definitions and meanings encompassing the concept of health, which is often divided into three domains; physical, mental and social. The WHO definition of health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" has been strongly criticized and implies an impossibility for people with a chronic disease to experience good health [52]. The view of health as "the ability to adapt to one's environment, where health is not a fixed entity and varies for every individual depending on his or her circumstances", is probably a truer and fairer definition [52]. An instrument for measuring health should relate to health as the ability to adapt and to self-manage [52].

### 1.4.7 Quality of Life and Health-Related Quality of Life

Even though the concept of quality of life has its origins in 1960s medical literature, until recently, the quality of children's lives was measured by survival rates, morbidity and the social problems affecting them [53]. Later it was stated in the United Nations Convention on the Rights of the Child (UNCRC) that "children have a right to have their views taken into account in matters that affect them" [54].

There are many definitions of quality of life (QoL) and health-related quality of life (HRQoL) is one approach for measuring QoL. One definition of HRQoL is "a multidimensional construct covering physical, emotional, mental, social and behavioral components of well-being and function as perceived by patients and/or other observers" [55]. Instruments for measuring HRQoL can be either generic or disease-specific. A generic instrument can be used across various patient groups and in the general public, which makes it possible to compare different groups with each other. A disease-specific instrument provides information about specific health problems, symptoms and treatment options for a given disease [53].

A central aspect to the definition of HRQoL is that it is subjective and should be assessed from the individual's perspective whenever possible [53]. For small children, without the possibility to be able to speak for themselves, the parents must be considered as their spokesmen.

### 1.4.8 Parental Stress

Parental stress is defined as an "adverse psychological reaction to the demands of being a parent" [56]. Another definition of parental stress is "a notion of conflict between parental resources and the demands connected to the parental role" [57]. There are different factors that contribute to the level of parental stress such as general health, anxiety and psychological problems [58]. Social background, employment, educational level and being a mother have also been described as strongly associated contributing factors for a higher level of stress [59]. Even a normal pregnancy and the first year of motherhood negatively affect a woman's physical and emotional self-rated health. The health of fathers is also affected by the first year of parenthood [60], but for most parents childbirth does not trigger long-term psychological distress [61]. Even though mothers report higher levels of psychological responses compared with fathers, expectant fathers of children with a known malformation experience higher levels of distress than fathers of healthy babies. Both the parents of a sick child are in need of psychological support and this knowledge is important to reduce strain within the parental relationship [62].

### 1.4.9 Quality of Life and Health-Related Quality of Life, Psychosocial function and parental stress in CDH

There are only a few QoL studies in children with CDH and they report ambiguous results. In common for three of the studies was that the youngest children scored lower than the general population [45,63,64]. Indeed, parents often score lower QoL when answering on behalf of their children. One explanation for this could be that parents compare the children to their healthy siblings and friends and have the ability to consider future complications. Older children and adolescents might underestimate their physical complaints and not fully comprehend their limitations [45]. Michel et al. (2013) showed that CDH survivors had altered QoL when compared with healthy controls but a similar QoL to survivors of childhood leukemia. These authors could derive several independent predicting parameters for a lower QoL such as a prenatal diagnosis, gastroesophageal reflux, neuropsychological issues, respiratory sequelae and length of hospital stay in the intensive care unit [64]. A recently published study investigated the association between a prenatal diagnosis of CDH and HRQoL and found no differences between the CDH patients and the healthy children. Even in children who had received ECMO treatment, there were no differences in HRQoL [65].

Quality of life in parents of children with CDH has also been measured, with few differences from the general population except for a lower emotional dimension score [64].

Children with CDH are, as has previously been described, at a high risk of serious neurodevelopmental delay. Long-term psychosocial functioning and behavioral problems can be expected [45,48,47]. Increased levels of emotional and behavioral problems have also been found in other groups of children with serious congenital malformations [66]. Parents of children with CDH report more social difficulties and problematic behaviors, which might be related to a limited attention span [48]. This is, however, a rather unexplored field since less than one percent of papers published over the last 30 years regarding surgical congenital malformations touch upon this issue [67].

Since CDH is known as a life-threating condition in a newborn, expectant parents experience intense emotional distress [68]. This has been described as a single independent predictor of acute parental distress after birth when comparing with parents who received the diagnosis postnatally. Other understandable independent predictors of psychological distress are mortality and associated anomalies. Receiving a severe prenatal diagnosis is a long-lasting psychological stressor for many parents [9]. The healthy transition to parenthood is influenced by fetal and future child health and how information about this is given is of great importance for the relationship between parent and baby [69]. Gestational age at diagnosis, severity of the anomaly, and prognostic ambiguity are important factors and strong predictors of psychological distress [70].

To reduce the levels of stress, healthcare staff can provide support by having a prenatal consulting team with the opportunity of repetitive follow-ups, since the ability to assimilate information when being under extreme emotional distress is affected [71]. Extra psychological attention and support for the parents may be needed [70].

Parents of chronically ill children, especially mothers, report higher levels of anxiety and depression than parents of healthy children, where problems in daily life and parenting stress are significant predictors. Attention on parental wellbeing during the follow-ups for children with CDH, for example by the use of screening-tools, could serve as a start of communication regarding the parents' needs [72].

# 2 AIMS OF THE THESIS

The overall aim was to increase knowledge in different aspects of how children born with CDH manage during childhood and adolescence. The specific aims were to investigate perceived physical function (Study I), health-related quality of life (Study III) and psychosocial function (Study IV) in children born with congenital diaphragmatic hernia. Furthermore, the aim was also to investigate experienced parental stress among the parents (Study II).

Specifically, the following questions were addressed:

- What is the long-term survival in this selection of children and adolescents with CDH? How do children with CDH view their own physical health? (Study I)
- Do parents of children born with CDH experience parental stress? (Study II)
- How is the health-related quality of life among children born with CDH? (Study III)
- How do children with CDH function psychosocially in school and during their leisure time? (Study IV)

# 3 PATIENTS AND METHODS

## 3.1 PATIENTS

Between 1990 and 2009 a total of 195 children were treated for CDH (Bochdalek type) at Sankt Görans and Astrid Lindgren Children's Hospitals in Stockholm, Sweden. Ten of those newborn children came for ECMO support from abroad and were excluded from the study since they did not have a Swedish personal identification number (PIN). Of the remaining 185 neonates, 157 children (85%) survived to discharge from the hospital. Due to the Swedish PIN, in late 2010 we were able to track all the children and 145 (78%) were alive at that point. All the long-term survivors were asked to participate in our studies and 109 families (75%) accepted, 8 families (6%) declined and 28 families (19%) were lost to follow-up (Figure 2).

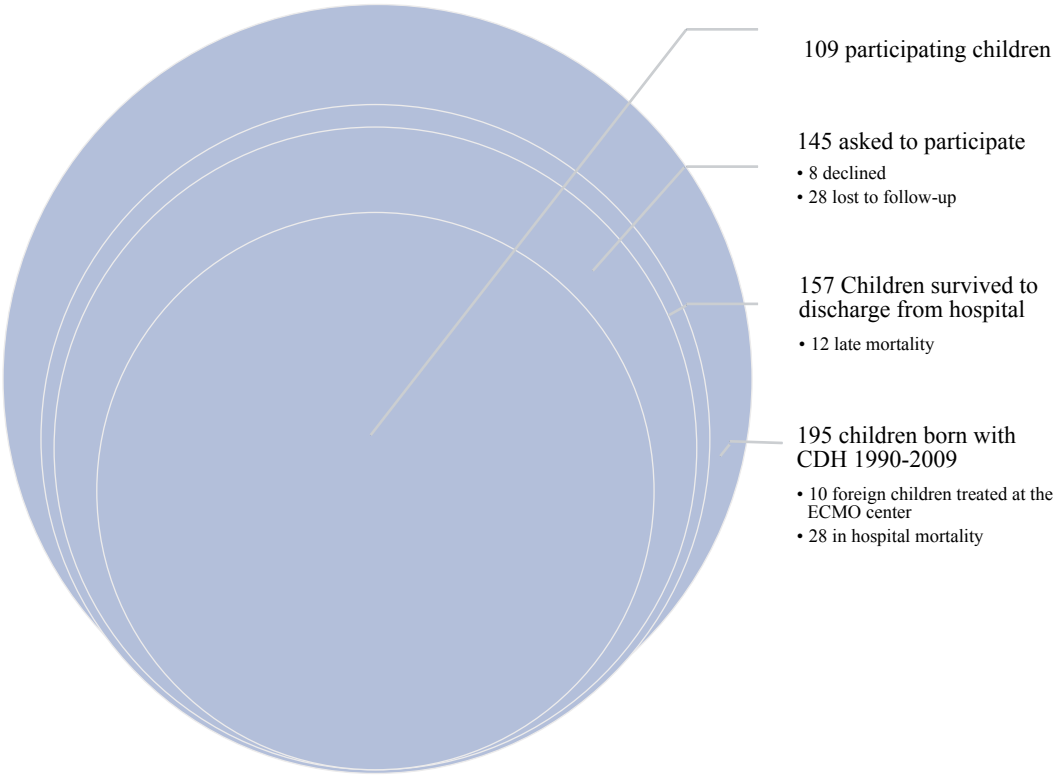



**Figure 2.** Patient cohort.

## 3.2 STUDY I

This was the first of the four long-term follow-up studies, where we made a thorough review of the medical records of all the 185 children who were initially treated at the

hospitals. We collected information on sex, prenatal diagnosis, birth weight, gestational age, side of lesion, method of surgical repair, age at surgery, time to intubation, history of ECMO support and type of discharge from hospital and length of hospital stay (LOS). After obtaining written informed consent from either the children's guardians or participants of majority age, a study-specific questionnaire was sent out. The questionnaire contained questions regarding self- or proxy-rated physical health status. It covered the most relevant systems, including cardio-respiratory, gastrointestinal, neurological and musculoskeletal (specifying weight and height, respiratory tract infections, asthma, physical condition, nutrition and nutritional status, symptoms of gastroesophageal reflux, abdominal pain, cognitive difficulties, seizure disorders, neurological diseases, vision and hearing disabilities, chest wall deformities and scoliosis). The questionnaire was filled out either by parents of children younger than 18 years of age, or by the adolescents themselves if they were 18 years or older. The complete questionnaire can be found as an appendix to Study I.

The patients were divided into different severity groups according to time to intubation and need for ECMO treatment, which resulted in three different groups and one subgroup. Group 1 included all patients who were not intubated within the first six hours of life. Group 2 consisted of children who were intubated within their first six hours of life but did not require ECMO. Group 3 comprised all children who needed ECMO support. Group $3^{b}$ was a break-out group from Group 3 and consisted of patients who received a second round of ECMO treatment.

### 3.3 STUDY II

In this study, parents of children born with CDH between 2005 and 2009 were sent the *Swedish Parenthood Stress Questionnaire* (SPSQ), which aims to measure stress levels related to parenting. During the years 2005 and 2009, 51 children with CDH were treated at Astrid Lindgren Children's hospital, however, of the 34 parents who had agreed to participate, 27 mothers or fathers completed the form. The Swedish Parenthood Stress Questionnaire is based on the American questionnaire *Parenting Stress Index* (PSI) by Abidin, 1990 [73], and was translated and adjusted to a Swedish population by Östberg et al. in 1997 [74]. Furthermore, they concluded that the SPSQ could be used as a reliable and valid instrument for measuring experienced parental stress [74]. The Swedish version contains 34 questions within five factors: *Incompetence regarding parenthood* (general experiences of caregiving, feelings of incompetence in the parental role and the difficulties of parenthood), *Restrictions of role* (parental responsibilities), *Social isolation* (social contacts outside the family), *Relationship with spouse* (social experiences within the

family) and *Parental health* (physical fitness, infections and fatigue). Answers are made through a 5-point Likert-type response scale on which the parents mark to what extent they agree or disagree with the statement presented. High values indicate a high level of stress.

A total score for all the study participants was calculated, and for identifying any potential risk factors for parental stress within the group, data was divided into subgroups and compared thus: parents with/without a prenatal diagnosis of CDH, parents of children treated with/without ECMO, parents with a higher/lower level of education, parents of children with a long/short hospital stay (divided by the median), parents of children with CDH born 2005-2006/2007-2009 (younger vs. older children at the time of filling out the questionnaire) and according to whom had answered the questionnaire (mothers/fathers).

A Swedish nationwide representative sample, which has earlier been described by Östberg et al., when developing the questionnaire, was used as a reference [74].

### 3.4 STUDY III

In the third study concerning HRQoL, children born with CDH between the years 1993 and 2003 were asked to participate, a total of 77 children/adolescents and their parents. Fifty-one families (67%) agreed to participate, five families disagreed and 21 families never answered, despite several invitations. Of the 51 families who were willing to participate, 35 completed the study (a 46% response rate) by returning the questionnaire KIDSCREEN-52, which is a generic questionnaire designed to assess HRQoL in healthy and chronically ill children and adolescents from 8 to 18 years of age [75]. A proxy version is available for parents. The questionnaire is designed to measure children's and adolescents' subjective health and well-being, which is the signification of HRQoL [55], and aims to provide a better understanding of perceived health in children and adolescents in order to identify populations at risk. The KIDSCREEN project is cross-cultural and was developed in 13 European countries, with Sweden as one of the participants. The instrument measures 10 domains on HRQoL distributed over 52 questions: physical well-being (five items); psychological well-being (six items); moods and emotions (seven items); self-perception (five items); autonomy (five items); parent relations and home life (six items); social support and peers (six items); school environment (six items); social acceptance (bullying) (three items); and financial resources (three items) [76]. The KIDSCREEN-52 is a valid and reliable questionnaire with Swedish and European normative data available [77]. Answers are given through a five-point scale ranging from never/not at all to always, and refer to the previous week. The questionnaire takes about 15-20 minutes to complete and a

lower score indicates a higher HRQoL. The proxy version has the same structure as the child and adolescent version, but asks the parent to answer how they think their child feels. The proxy version is a substitute for when a child's self-report of their HRQoL is not available.

### 3.5 STUDY IV

In the last study which concerns psychosocial function, the entire study population (children born with CDH 1990-2009), which has previously been described, was invited to participate. The study participants received the Child Behavior Checklist (CBCL), which is a questionnaire designed to assess competence and behavioral and emotional problems in children and adolescents [78]. Seventy-four parents or adolescents of majority age returned a completed questionnaire (51% response rate). There are different versions of the questionnaire depending on the child's or adolescent's age and the respondent who is supposed to fill in the form. There is one CBCL version for children aged 1.5-5 years and another, CBCL 6-18 years, for older children. Both these versions are answered by parents or others who know the children in their normal home environments. For young adults >18 years the Adult Self-Report (ASR) was used, which is a continuation of the CBCL but adapted to a more adult way of life and answered by the individuals themselves. Common to the three questionnaires is the syndrome scale with 100-126 statements of behavioral, emotional and social problems, based on the previous two months in the youngest population and six months for children and adolescents older than six years. Responses are rated as 0= not true (as far as you know), 1= somewhat or sometimes true and 2= very true or often true. Answers from the syndrome scale generate a total value as well as internalizing or externalizing behavior. What is considered internalizing and externalizing behavior is age-adjusted.

Both the CBCL questionnaires end with three open-ended questions where the parent can describe the child's illnesses and disabilities, concerns about the child and the best things about the child, while on the ASR the young adult is asked if he or she has any illness, disability, or handicap, concerns or worries about family, work, education, or other things. Finally, the young adult is asked to describe the best things about him or herself.

For the CBCL 6-18, the competence scale was also used, divided into four aspects: activities, social relations, school and total competence [78].

**Table 1.** Questionnaires and responders.

| *Questionnaire* | *1990-1992* | *1993-2004* | *2005-2009* |
|---|---|---|---|
| *Physical function* | X | X | X |
| *SPSQ* | | | X |
| *KIDSCREEN-52* | | X | |
| *CBCL* | X | X | X |

### 3.6 STATISTICS

A p-value <0.05 was considered significant in all four studies.

#### 3.6.1 Study I

Frequencies are reported for categorical variables. A chi-square test was used to test differences among the groups and, for numerical variables, Fischer's exact test was used to make pairwise comparisons between groups.

#### 3.6.2 Study II

For numerical data, the Mann-Whitney U test for independent samples was used for comparing differences regarding parental stress between the subgroups. Fisher's exact test was used to compare differences between the groups. Data are presented as means ± SD, median, absolute values (n) and frequencies (%) for categorical variables.

#### 3.6.3 Study III

A sum score for each of the 10 domains was calculated after negatively formulated items were recoded according to standard scoring algorithms. The KIDSCREEN-52 instrument supplies a Rasch model to interpret the results on a standardized interval scale [75]. When transforming the data into the given model normal distributed T-values were available. Data are presented as means and SD, maximum and minimum. Pearson correlation coefficients were used to calculate the correlation between scores of the different domains and age. To measure the correlation between the children's and parents' T-values, a two-way random single measure intra-class correlation coefficient (ICC) was used.

#### 3.6.4 Study IV

A Chi-square test was used to analyze differences between study population, the entire group and non-participants. The three different questionnaires were analyzed separately according to the handbooks for the CBCL 1.5-5, CBCL 6-18 and ASR [78-80]. A total problem score, sub-scores and two broad-band groupings of behavioral, emotional and social problems (internalizing and externalizing) were calculated. The total problem,

internalizing and externalizing scores were then converted into T-scores according to profiles where normal and clinical range are given. Fisher's exact test was used to analyze categorical differences between subgroups according to sex, age at intubation, ECMO support and side of the hernia. Spearman's correlation test was applied in order to analyze the correlation between CBCL values and length of hospital stay.

The open-ended questions were analyzed with manifest content analysis inspired by Graneheim and Lundman [81]. All the answers were carefully read and written down. The text was then condensed into meaning units, consisting of words that were reminiscent of the original text. The next step was to code the condensed meaning units into sub-categories and categories.

### 3.7 ETHICS

All the studies were approved by the regional ethical committee in Stockholm, Dnr 2011/472-31/4. Written informed consent was obtained upon inclusion in the study from parents of underage children and adolescents of majority age.

Research on children is an ethical challenge, especially when the children are young and cannot understand what they are participating in, or what the research is aimed at. The decision to take part in a study rests entirely with the parents. Medical ethics is based on four guiding principles: autonomy, justice, beneficence and non-maleficence [82]. Considering this theory, the autonomy of the children is disregarded and the parents must act in their place. This, of course, is based on the thought and hope that all parents want what is best for their children. To respect autonomy and the ability to take a stand, it is important to explain the purpose of the research in an understandable way. As for the other three principles, the intention is to do good for the group of children born with CDH. The aim is to gain a greater knowledge of how life develops for them and what potential problems they face. The results can then be directly implemented in our healthcare system as support is easier to target when it is known where it is most needed. Several of the questions in the questionnaires that were used could be perceived as sensitive with a risk that they might raise unpleasant memories, perhaps primarily with the parents themselves who recall the shock of what it meant to be presented with a severally ill child. In young adults who reach majority age, the question of participation is, of course, only applicable to the individuals themselves. There might also be adolescents and young adults who necessarily don't know exactly what they experienced as neonates. An answer that promptly appeared when asking for participation was "I would like to participate in your

study but I do not have the disease that you are writing about". In this case, it was clear that the young adult did not know the history of their own illness and, of course, the risk is that the letter of participation raised some important questions. Hopefully, they received the answers they needed from a guardian. It is also important to note that even though the feeling exists that the children / young adults are entitled to know what they have undergone, this does not automatically mean that the healthcare professional / researcher has the right to inform them of it. As for the fourth principle of justice, the study cannot be done on any other group and, hopefully, the results will benefit them later.

# 4 RESULTS

## 4.1 STUDY I

Demographic details regarding all the children treated for CDH in Stockholm between 1990 and 2009 and the study participants in Study I are shown in Table 2 with an overview of the results in Figure 3.

**Table 2.** Demographic data of the 185 patients.

| Demographic details N (%) | | | | | |
|---|---|---|---|---|---|
| | Total n=185 | Group 1* n=50 | Group 2* n=81 | Group 3* n=54 | Group 3[B]* n=13 |
| Sex | | | | | |
| Male | 118(64) | 30(60) | 56(69) | 32(59) | 7(54) |
| Female | 67(36) | 20(40) | 25(31) | 22(41) | 6(46) |
| Prenatally known | 67(36) | 3(6) | 34(42) | 30(56) | 9(69) |
| Birth weight | 3.3±0.7 kg | 3.4±0.6 kg | 3.3±0.7 kg | 3.2±0.5 kg | 3.0±0.5 kg |
| Gestational week | 38.3±2.4 w | 39.1±2.3 w | 38.5±2.3 w | 38.5±2.3 w | 37.8±1.8 w |
| Side of lesion | | | | | |
| Left | 145(78) | 44(88) | 60(74) | 41(76) | 11(85) |
| Right | 22(12) | 4(8) | 9(11) | 9(17) | 1(8) |
| Bilateral | 1(0.5) | 0(0) | 1(1) | 0(0) | 0(0) |
| Repaired | | | | | |
| Primary | 98(53) | 44(88) | 48(59) | 6(11) | 1(8) |
| Patch | 65(35) | 3(6) | 19(23) | 43(80) | 12(92) |
| No repair | 6(3) | | | | |
| Unknown | 16(9) | 3(6) | 14(17) | 5(9) | |
| Age at surgery | | 96 hrs | 96 hrs | 144 hrs | |
| Intubated within 6 hrs from birth | 134(72) | | 81(100) | 53(98) | 13(100) |
| ECMO | 54(29) | | | 54(100) | 13(100) |
| ECMO>once | 13(7) | | | 13(24) | 13(100) |
| Discharged alive | 157(85) | 50(100) | 70(86) | 37(69) | 8(62) |
| Alive 2010 | 145(78) | 48(96) | 67(83) | 30(56) | 7(54) |
| Participating in present study | 109(75) | 40(83) | 45(67) | 24(80) | 7(100) |

**Group 1 late intubated >6 hours of life, Group 2 intubated <6 hours of life exl. ECMO, Group 3 ECMO, Group 3b ECMO >once.*

### 4.1.1 Pulmonary

In Group 1, 33% answered that they experienced some kind of respiratory symptom compared with 60% in Group 2, 71% in Group 3, and 86% in Group $3^b$. The differences in reported symptoms among the groups were highly significant between Groups 1 and 2 (p=0.007) and Groups 1 and 3 (p=0.007).

There were no significant differences among groups in the rate of reported frequency of respiratory tract infections (18%, 18% and 33%, respectively). Asthma was reported in 15% of the patients in Group 1 compared with 30% in Group 2 and 42% in Group 3, the differences were significant between Groups 1 and 3 (p=0.02).

In Group 1, 18% of the patients reported that they became breathless more easily than their age-matched friends, compared with 47% in Group 2 and 58% in Group 3. The differences among all three groups were highly significant (p=0.0005). The differences were found to be both between Groups 1 and 2 (p=0.003) and between Groups 1 and 3 (p=0.001).
In Group 1, 13% of the children reported that they had less strength when participating in physical activities compared with healthy friends of the same age, compared with 40% in Group 2 and 50% in Group 3 (p=0.0007). Significant differences were found between Groups 1 and 2 (p=0.003) and Groups 1 and 3 (p=0.001).

### 4.1.2 Gastrointestinal

The proportion of responders who reported any GI symptoms varied from 15% in Group 1, 49% in Group 2, 71% in Group 3, and 57% in Subgroup 3b. Patients in Group 1 had significantly less GI symptoms when compared with Groups 2 (p=0.001) and 3 (p=0.0009). The majority of children in all the groups ate normal food and did not have any special food requirements, but there were differences among groups in the reported time to eat. Of the children in Group 1, 5% answered that it took a longer time for them to eat than for other healthy children, compared with 27% in Group 2 and 50% in Group 3. Significantly more children in Groups 2 (p=0.006) and 3 (p<0.0001) reported that it took them a longer time to eat compared with the children in Group 1.

Symptoms of gastroesophageal reflux, GER, were experienced by 3% of the children in Group 1, 22% in Group 2 and 25% in Group 3.GER was more commonly experienced among children in Group 2 (p=0.006) and Group 3 (p=0.009), compared with Group 1. Abdominal pain was reported by one third (33%) of the children in Group 2, which was a significantly higher number (p=0.02) than in Group 1(13%). In Group 3, 21% reported symptoms of abdominal pain.

### 4.1.3 Weight, Height and Body Mass Index

All the children in Group 1 reported normal weight, within the range of the average ± 2 standard deviations (SD). In Group 2, 18% had a weight of <-2SD while 83% reported normal weight. In Group 3, 65% reported normal weight, and 35% <-2SD. In Subgroup $3^b$, 86% reported normal weight and 14% had a weight below <-2SD. The proportion of children reporting underweight (< 2SD below average) differed significantly among the groups (p=0.03). The differences were found between Groups 1 and 3 (p=0.007) and 2 and 3 (p=0.02). In Group 1, 87% of the children had a normal BMI, while 7% were classified as overweight and 7% underweight. In Group 2, the proportion of children classified with a

normal BMI was 74%, overweight 11% and underweight 13%, while 3% were severely underweight. Overweight was present in 9% of the patients in Group 3, 78% had a normal weight, 9% were classified as underweight, and 4% as severely underweight. In Group $3^b$ 86% had a normal BMI, while none were overweight and 14% were classified as underweight according to the WHO's Child Growth Standards. The differences between the groups were not significant.

### 4.1.4 Neurology

The proportion of respondents who reported any neurological symptoms among the groups varied from 20% in Group 1, 36% in Group 2, 41% in Group 3 and 43% in Subgroup $3^b$. The differences between the groups were not significant.

There were no significant differences among the groups in the reported rate of seizure disorders, hearing impairment, or vision deficiency. In Group 3, 29% reported that they had some kind of developmental delay, which made a significant difference (p=0.04) compared with the children in Group 1 (10%). In Group 2 the number was 22%. No one in Group 1 reported any neurological disease in an extremity compared with 2% in Group 2 and 13% in Group 3 (p=0.05).

### 4.1.5 Musculoskeletal

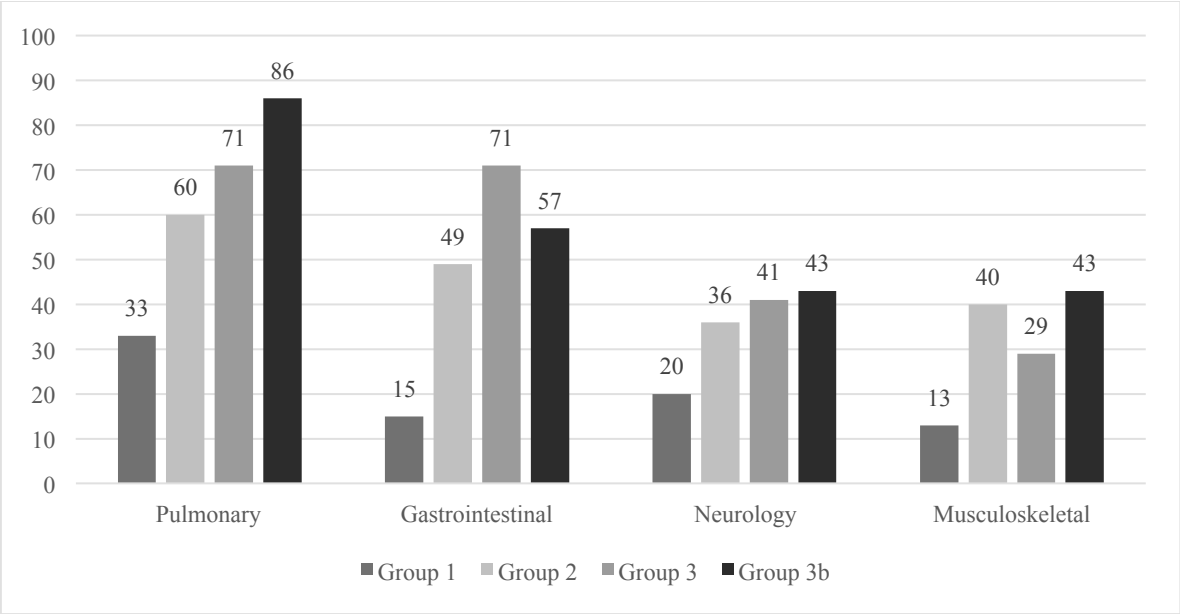
The amount of responders who reported any musculoskeletal sequelae among groups was 13%, 40%, 29% and 43%, respectively. The overall difference was significant between Groups 1 and 2 (p=0.003).

Chest wall deformities were reported among 13% of the patients in Group 1, compared with 33% (p=0.02) in Group 2 and 33% (p=0.04) in Group 3. None of the patients in Group 1 had been treated or followed-up for scoliosis, but 20% of the children in Group 2 and 8% in Group 3 did report scoliosis. We found a significant difference between Groups 1 and 2 (p=0.002), but none when compared with the group treated with ECMO.

In children with a primary repair of the diaphragm, 8% reported chest wall deformities and 19% scoliosis, in comparison with the group of children with a patch repair where 14% reported chest wall deformities and 40% scoliosis. This difference was not significant.

When comparing children treated with ECMO once and twice (Group $3^b$) there were no significant differences on any of the domains.

**Figure 3.** Number of patients with symptoms within domains.




**Group 1 late intubated >6 hours of life, Group 2 intubated <6 hours of life exl. ECMO, Group 3 ECMO, Group 3b ECMO >once.*

## 4.2 STUDY II

A total of 34 parents (83%) participated in the study, while seven declined actively or passively. Out of the 34 who were willing to participate, six never completed the questionnaire and one returned the questionnaire incomplete, and was thus excluded. The final number of participants was 27 parents (66%); 21 mothers and 6 fathers. There were no significant differences among the children of the study participants and non-participants who had declined to participate or had been excluded from the study regarding sex, prenatal diagnosis, birth weight, gestational age, side of lesion, method of surgical repair, age at surgery, time to intubation, history of ECMO support or type of discharge from hospital. However, among the non-participants there were differences between those whose children had died and those who declined to participate. The deceased children had undergone a patch repair, were intubated immediately after birth, and needed ECMO support more frequently than the children of the study participants and the other non-participants. Eight families in the group of non-participants, compared with six in the study group, had been referred to another hospital and did not attend our long-term follow-up program.

### 4.2.1 Parental stress

The total score of all five subscales in the questionnaire for all parents resulted in M=2.26 (SD 0.58); Incompetence regarding Parenthood M=1.91 (SD 0.63), Restrictions of Role M=3.16 (SD 0.81), Social Isolation M=1.92 (SD 0.78), Relationship with Spouse M=2.12

(SD 0.95), and Parental Health M=2.44 (SD 0.84). Parents whose children had required ECMO support reported a total mean of 2.51 and a mean of 3.49 regarding Restrictions of Role. Parents of children with CDH who required versus not required ECMO treatment had a significantly higher level (p=0.03) of parental stress in general, and within the Parental Health factor in particular (p=0.05) when compared with the former group.

Being a mother of a child with CDH was a single significant predictor of a higher level of total parental stress (p=0.04). The distinguishing factors were Incompetence regarding Parenthood (p=0.005) and Restrictions of Role (p=0.007), where mothers had a strongly significant higher parental stress compared with fathers. There were no significant differences in background parameters between mothers or fathers.

Parents of children with a long hospital stay (mean of 88 days compared with a mean of 25 days) showed a significantly higher total level of parental stress (p=0.04) with significantly higher levels within the Parental Health factor (p=0.03). Having a history of a prenatal diagnosis of CDH, compared with parents of children with a postnatal diagnosis of the malformation, resulted in a significantly higher experience of parental stress within the Parental Health factor (p=0.01). There was no significant difference in parental stress between parents with younger (2-5 years) versus older (6-8 years) children at the time of filling out the questionnaire. Parents with a lower educational degree showed a significantly higher level of parental stress within the factors Social Isolation (p=0.03) and Relationship with Spouse (p=0.01) (Table 3).

**Table 3.** Comparison of responses to parental stress among parents of children born with CDH

| Comparative groups | Treated with vs. without ECMO n=12/n=15 | Prenatal vs Postnatal diagnosis n=15/n=12 | Higher vs. Lower educational level n=13/n=14 | Mothers vs. Fathers n=21/n=6 | Long vs. Short LOS n=13/n=14 |
|---|---|---|---|---|---|
| Total SPSQ score | 2.51/2.06* | 2.32/2.19 | 2.05/2.46 | 2.37/1.89* | 2.49/2.05* |
| Incompetence | 2.08/1.76 | 1.87/1.95 | 1.71/2.08 | 2.04/1.44* | 2.08/1.75 |
| Role restriction | 3.49/2.90 | 3.35/2.93 | 3.14/3.18 | 3.37/2.43* | 3.46/2.89 |
| Social isolation | 3.18/1.71 | 2.00/1.82 | 1.63/2.19* | 1.93/1.88 | 2.11/1.74 |
| Spouse relationship | 2.40/1.89 | 2.01/2.25 | 1.66/2.54* | 2.12/2.10 | 2.35/1.90 |
| Health problems | 2.71/2.23* | 2.72/2.10* | 2.27/2.61 | 2.58/1.96 | 2.75/2.16* |

** Significant difference based on comparisons of the groups using the Mann-Whitney test.*

### 4.3 STUDY III

The participants did not differ from the entire cohort regarding prenatal diagnosis, sex, side of lesion, method of surgical repair, time to intubation, need for ECMO support or type of hospital discharge. For natural causes, however, there was a difference in survival rates.

Among the non-participants there was no significant difference between the study participants and those who declined or never answered the questionnaire. However, between the group of deceased children and the study's participants there were several significant differences. The group of deceased children had a prenatal diagnosis, were intubated within their first six hours of life and needed ECMO support more often.

### 4.3.1 Health-related quality of life

Children born with CDH aged 8-18 years scored a higher health-related quality of life compared with European normative data for children of the same age on all domains. Significantly higher scores were found in the study group within the domains self-perception, autonomy, parent relations and home life, financial resources and school environment. When comparing HRQoL in children born with CDH aged 12-18 years and Swedish normative data, similar sum scores were found, except for parent relations and home life scoring significantly higher within the study group. There were no correlations between the different domains and a child's age.

Group level scores from parents as a proxy for their children's HRQoL were similar to the children's own scores, however, when matching child and parent reports on a pair level, the correlations between scores were low.

When dividing study participants into subgroups according to the time to intubation, need for ECMO support, side of lesion and prenatal diagnosis no significant differences were found except for social support and peers being negatively affected in the ECMO group. Nevertheless, the median score was lower in children who were in need of ECMO support compared with the others on 8 of the 10 domains.

## 4.4 STUDY IV

Fifteen (65%) parents answered the CBCL 1.5-5, 48 (50%) parents answered the CBCL 6-18, and 11 (42%) young adults answered the ASR. The participants did not differ from the entire cohort nor the non-participants who had declined to participate or who had been excluded from the study regarding prenatal diagnosis, sex, side of lesion, method of surgical repair, time to intubation, need for ECMO support or type of hospital discharge. However, there were several significant differences between participants and children who had died, since the latter group represents the most severely affected children. Furthermore, prenatal diagnosis, immediate intubation and need for ECMO support were more frequent in the group of deceased children and primary closure and left hernias were more frequent

in the group of participants. Length of hospital stay (LOS) was measured within the group of participants in order to see possible correlations with the CBCL results, with a mean of 44 days, ranging from 5 to 304 days.

### 4.4.1 Behavioral and emotional problems

All the parents of children aged 1.5-5 years returned a normal score on the syndrome scale. One parent reported sleeping problems. Six of the parents of the youngest children answered that their child had a disease or some kind of remaining handicap, where impaired lung function was mentioned three times and other associated impairments three times.

Forty-three parents (90%) in the group of children 6-18 years of age scored within a normal range on the syndrome scale, while five parents scored within a borderline range. A total of five indicated internalizing behavior, whereas three were considered as borderline and two clinical. None were in the externalizing range. Parents reported somatic complaints in four children. Significantly more children who had received ECMO support had an internalizing behavior. There were no differences within the syndrome scale regarding sex, side of hernia or time to intubation. Of the parents to children aged 6 to 18 years, 12 (25%) mentioned a disease or some kind of handicap, where impaired lung function and asthma occurred seven times, developmental delay three times, neuropsychiatric disorder once and another syndrome once.

In the group of young adults, everyone scored within a normal range on the syndrome scale. One person had an internalizing borderline behavior, while no one in this group had an externalizing behavior. Of the young adults, 27% had a remaining disease or handicap in terms of asthma, mild developmental delay or difficulty with gaining weight.

### 4.4.2 Psychosocial competence

Regarding the competence scale, children 6-18 years of age who had not yet started school (n=14) were excluded from the school-related questions in addition to the total scores on the competence scales since school achievements are included. Twenty-two (65%) parents registered a normal score on the total competence scale, while four were in the clinical range and eight borderline. Forty percent ended up within a normal activity level, while 27% had below the clinical activity range and the remaining 33% in-between. Seventy-nine percent had a normal social score, while 13% ended up below the clinical range and the remaining 8% were borderline. Normal school scores were achieved in 85% of the children, while 9% were clinical and 6% borderline. There was a significantly lower number of boys

(p=0.003) with a normal activity score compared with girls, and furthermore a significantly larger number (p=0.008) of boys scored within the clinical range. None of the children with a right-sided diaphragmatic hernia achieved normal total scores (p=0.05). The total score on the competence scale was significantly lower in children who had been intubated within their first six hours of life. Fewer children who had received ECMO support had normal social scores (p=0.01).

### 4.4.3 Qualitative results

The qualitative result from Study IV resulted in sub-categories and categories shown below.

**Table 4.** Qualitative content analysis open-ended questions.

| n=Number of participants (%) | Sub-category | Category |
|---|---|---|
| Concerns about child 1.5-5 y n=12 (80%) | Lung function | Sequelae |
| | Respiratory tract infections | Sequelae |
| | Eating problems | Sequelae |
| | Being outside | Social issues |
| | Interaction with others | Social issues |
| | Something might happen | General concern |
| Best thing about child 1.5-5 y n=15 (100%) | Empathetic | Social skills |
| | Social | Social skills |
| | Intelligent | Competent |
| | Strong individual | Fighter |
| | Strong vitality | Fighter |
| Concerns about child 6-18 y n=28 (58%) | Meet requirements | Future options |
| | Effects of poor lung function | Future options |
| | Poor growth | Future options |
| | Scars | Self-esteem |
| | Chest wall deformities | Self-esteem |
| Best thing about child 6-18 y n= 45 (94%) | Empathetic | Social skills |
| | Social | Social skills |
| | Kind | Social skills |
| | Reliable | Social skills |
| | Creative | Competent |
| | Curious | Competent |
| | Alert | Competent |
| | Intelligent | Competent |
| Concerns about oneself >18 y n=4 (36%) | Economy | General concern |
| | School achievements | General concern |
| | Family | General concern |
| Best thing about oneself >18 y n=11 (100%) | Good friend | Social skills |
| | Thoughtful | Social skills |
| | Social | Social skills |
| | Ambitious | Competent |

# 5 DISCUSSION

## 5.1 HEALTH

In Study I we intended to explore physical health within a congenital diaphragmatic hernia child population. As previously described, there are a variety of known symptoms that these children may suffer from, and pulmonary function is often described as one of the determining parts of the postoperative condition and wellbeing among children born with CDH. In Study I, the patients who managed to breathe spontaneously for at least six hours (Group 1) were assumed to be the least affected by the pulmonary hypoplasia, whereas the patients who had been in need of ECMO support (Group 3) were assumed to be the most severely affected. Group $3^b$ was a subgroup of Group 3 and consisted of patients who had had a second ECMO after decannulation. They do not necessarily represent a more severe malformation compared with other ECMO patients as they may have been decannulated too early, and therefore did not constitute a group of their own.

The core findings in Study I were that rates of reported symptoms increased with the degree of severity of the malformation. Higher reported rates of cardio-respiratory, gastrointestinal, neurological, and musculoskeletal symptoms were seen in patients who were intubated within the first six hours of life or required ECMO treatment, compared with those who were intubated later. Children who required ECMO treatment were not generally more affected than those who were intubated early in life, and no difference in reported symptoms was found in the subgroup of children who underwent ECMO treatment twice, in comparison with the ECMO group.

Regarding pulmonary function, there were significant differences between the groups in easily becoming breathless and having less strength during physical activity, and the symptoms increased with the severity of the malformation. Furthermore, a considerably higher proportion of children with asthmatic symptoms were reported within the study population in comparison with the Swedish prevalence of 8-10% [83].

Even though it might be difficult for children who could have experienced reflux since early childhood to make a comparison with not having these symptoms, and an underreporting of symptoms probably exists, symptoms of gastroesophageal reflux were 10 times as common in children treated with ECMO compared with children intubated later.

Comprehensive measurements of gastroesophageal reflux are probably necessary to obtain a more accurate picture.

The previously described frequency of hearing deficiency in children born with CDH shows a great variation; from 3% to 11% [49,25]. In our entire study group, 2% of children reported any kind of hearing deficiency. The overall prevalence of congenital hearing loss among Swedish children is 2/1000 [84].

The prevalence rate concerning seizure disorder for Swedish children is 3.4/1000 with a peak in the 8-11 years age group [85]. Children in Study I reported seizure disorders ranging from none in Group 1 to 2% in Group 2 and 8% in Group 3. The differences were ,however, not statistically significant. Furthermore, developmental disorders have been described as relatively common sequelae of diaphragmatic hernia patients [86,4]. In the group of children intubated later, 10% reported some kind of developmental disorder, whereas the incidence was three times higher in the group treated with ECMO. It is important to clarify that the question about developmental disorders is crudely framed and can include a variety of diagnoses of different magnitudes. In the Swedish population, 5% of preschool children and 10% of school-age children have been reported to have any neurodevelopmental disabilities that have a significant impact on their lives [87].

Scoliosis is tested for in all Swedish school children from the 4$^{th}$ grade in primary school by the school health care system. Of the normal Swedish population, 10% have scoliosis when including all forms of the condition, whereas only 3/1000 need correction [88]. In Study I there was a non-significant trend of an increased proportion of scoliosis and chest wall deformities in patients who had had a patch repair, compared with patients with a primary repair. It is unclear to what extent the patch repair per se may contribute to chest wall deformities and scoliosis as there is a strong correlation between severity of the malformation and size of the defect [89,31].

Impaired growth due to multifactorial causes has been reported in children born with CDH and might, for instance, negatively impact neurodevelopmental outcome [90]. In Study I we concluded that all the children in Group 1 had a normal weight, while 18% in Group 2, and almost twice as many in Group 3, reported being underweight ($p=0.03$).

## 5.2 PARENTAL STRESS

Parental stress has earlier been defined as “an adverse psychological reaction to the demands of being a parent” [56] or “a notion of conflict between parental resources and the demands connected to the parental role” [57]. There are many factors that contribute to parental stress, which has been described earlier in this thesis. In Study II, however, we wanted to assess the presence of parental stress within the group of parents of children born with CDH. The core findings of Study II were that the parents of children born with CDH who required ECMO support and/or had a long hospital stay showed a high level of parental stress. Children who required ECMO support and had a long hospital stay represented a more severely ill group of children, which indicates a correlation between the severity of the child’s malformation and the level of parental stress. Additionally, mothers and fathers scored differently, with the mothers scoring higher parental stress than the fathers. We also found an association between parental stress and receiving a prenatal diagnosis of CDH. A parent’s low educational level was associated with parental stress in some of the factors.

According to a Swedish nationwide representative sample, a total score of all the five scale scores was calculated; mean 2.52 (SD 0.56). The mean for Role of Restriction was 3.42 (SD 0.82), while all the other scales had a mean below 3, ranging between 2.05 and 2.61 (SD range between 0.68 and 0.94) [74]. An interesting result is that the study population in general, and most of the examined subgroups, reported a total lower parental stress level than the Swedish nationwide representative sample, with the exception of parents of children who required ECMO support. Even though becoming a parent to a critically ill child is a severely challenging life event, there are many other regulating stressors that influence parental stress such as social support, single parenting, domestic work load, parity, care-taking issues, the mother´s age and educational level [91,92]. Becoming a parent to a child with CDH could not be stated as a single isolated down-regulating stressor of parental stress according to the findings in this study. We did, however, find risk factors for parental stress within our study group.

More than half of the children with CDH in Study II were detected prenatally, which seemed to influence negatively on parental stress within the Parental Health factor. It is commonly known that CDH is a life-threatening condition that often leads to an intensive, uncertain start in life, and the assumption that foreknowledge of a congenital malformation is beneficial for parents-to-be is questioned. Skari et al. found that a prenatal diagnosis of a

congenital malformation is a single independent predictor of acute parental psychological distress after birth when compared with parents who received a postnatal diagnosis [9]. Moreover, children with a prenatal diagnosis of the malformation seem to have a more severe condition compared with infants diagnosed after birth [10]. Furthermore, Kaasen et al. showed that maternal psychological distress shortly after the detection of a fetal malformation is related to the severity of the anomaly, diagnostic and prognostic ambiguity, and gestational age [70]. Severity of the malformation, including ambiguity, has similarly been described to inflect the paternal response [62]. Aite et al. studied couples undergoing prenatal consultations due to a surgically correctable congenital malformation and found no linear correlation between the severity of a malformation and the extent of parental anxiety. However, the number of antenatal consultations could reduce the level of parental anxiety [93]. Subsequently, they studied parents' emotional and cognitive reactions and stated that antenatal information, both written and visual, should be given several times during an ongoing pregnancy because of the intense emotional distress that parents-to-be experience at diagnosis and how their ability to assimilate information is affected [71]. In our clinic, parents are offered several consultations during pregnancy with a multidisciplinary team which includes a pediatric surgeon and specialist nurse, an obstetrician, a midwife and, if requested, a psychologist. What additional information parents are influenced by is, however, impossible to know because of the magnitude of information available today. In a study of parents to children born with a congenital heart defect, parents experienced the amount of reachable information as overwhelming and asked for easily accessible and reliable information sources via the Internet [94]. Fonseca et al. stated that it is important to assess parental prior knowledge in order to rectify any potentially incorrect information [95].

Over the last few decades, medical care has rapidly developed for infants born with CDH with increasing survival rates up to 80-90%, and a further late mortality rate after the first year of life of less than 5% [96]. Long-term sequelae is often related to the severity of the malformation, whereas children who require ECMO treatment are more affected than others [19]. Even in this study, the group of children who required ECMO treatment represented a more severely ill group, compared with those without the need of ECMO treatment. This is shown in the higher rates of prenatal diagnosis, patch repair, and the longer LOS. Since parental stress was high within this group of parents, there might be an association between parental stress and the severity of the child's condition. Lewis et al.

investigated post-traumatic stress disorder in parents of children supported with ECMO and found a substantial number of parents who were affected by it [97].

Even though there are several prenatal measurements for predicting postnatal outcome, there are no guaranties for the future. Skari et al. found that mortality and the presence of associated anomalies were consistent with psychological distress at follow-up [9]. We could not confirm any differences in parental stress over time when comparing parents with younger versus parents with older children, bearing in mind that this was a cross-sectional study. However, it would have been interesting to adjust for factors such as prenatal diagnosis, associated anomalies, and ECMO treatment to be able to specify any differences in parental stress over time.

The scoring of fathers' parental stress in this study is consistent with previous findings, where fathers reported significantly lower scores compared with mothers [62,59]. Widarsson et al. showed in a study of 320 mothers and 315 fathers of healthy children that mothers with a low educational level, without a role model, and with a poor sense of coherence, had a higher level of perceived parental stress [98]. Even though fathers report lower total parental stress than mothers, Skreden et al. found that they report significantly more social isolation [59]. According to a study by Fonseca et al. mothers and fathers benefitted from different kinds of social support in order to reduce parental stress, but there was diffusion between both parents' adjustments, suggesting that parents affect each other and greatly impact their partner's level of parental stress [99]. It is well known that mothers who experience a negative childbirth subsequently have fewer children and a longer interval to their second birth [100]. Additionally, a previous history of traumatic birth indicates a significantly higher risk of developing clinically important psychological distress [61].

## 5.3 HEALTH-RELATED QUALITY OF LIFE

Keeping in mind the definition of HRQoL as "a multidimensional construct covering physical, emotional, mental, social and behavioral components of well-being and function as perceived by patients and/or other observers", the most important result in Study III is that children born with CDH express, overall, a high HRQoL. Even though the group of children who needed ECMO support scored lower HRQoL on 8 of the 10 domains compared with children without ECMO support, the only significant difference was on the social support and peers domain.

Extracorporeal membrane oxygenation can be a support for children with CDH in order to avoid ventilator-induced injury, mainly during the neonatal period when many children with CDH suffer from pulmonary hypertension. On the other hand, ECMO is an invasive and technically challenging treatment associated with serious complications such as bleeding and thrombosis [18]. The role of ECMO support in CDH remains controversial, even though it is clear that centers that have access to it report the highest survival rates [101]. Nevertheless, the criteria for ECMO treatment are narrow. There has to be an estimated risk of mortality >80% when conventional intensive care is applied [18]. In our center, 28% of the neonates with CDH between 1993 and 2003 met these criteria. The long-term survival rate within this group was low, 41%, and previously published results from our group indicate an increased morbidity within this group of children [102]. We expected HRQoL to be negatively affected in this subgroup of patients treated with ECMO, but despite the visually lower HRQoL scores there was no significant difference except for the social support and peers domain. The results from Study III are in line with F. Sheikh et al. where parents of children with CDH as a proxy reported QoL scores similar to parents of healthy children [65]. It should, though, be mentioned that there is a distinction between the terms QoL and HRQoL, where QoL in general measures subjective well-being and HRQoL is the way that health affects QoL [103]. Further, F. Sheikh et al. concluded that the parents of children with CDH who had a prenatal diagnosis of the malformation scored good QoL on behalf of their children. Having a prenatal diagnosis of CDH is a predictor of a severe form of the malformation with accompanying higher mortality rates [104]. Similarly, Peetsold et al. demonstrated no correlation between HRQoL and severity of the malformation, with the conclusion that the perception of general health within children with CDH was reduced [45]. This indicates that HRQoL might not be strongly affected by the severity of CDH or by morbidity, but rather by individual factors.

In contrast, F. Michel et al. studied children with CDH born during the same era with preoperative stabilization, gentle ventilation, and access to ECMO with the opposite results. They used KIDSCREEN-27, a shorter form of the KIDSCREEN-52, but still with great reliability and found lower HRQoL scores on all the scales compared with norms [64]. Further, they observed an association between low HRQoL, prenatal diagnosis, and length of hospital stay. One possible explanation for this could be that the patient cohorts were not comparable since the survival rates differ highly between the 58% in their study and the 82% in our study, and that the rates of ECMO were much lower in their study.

In a report by Koivusalo et al., HRQoL was studied in adults born with congenital diaphragmatic defects, diaphragmatic hernia and diaphragmatic eventration [105]. These patients were born in the older era when CDH was considered to be an emergency surgical condition and before the introduction of the new successful therapeutical strategies previously stated, including ECMO. Additionally, only one patient had a patch-repair, representing a less severely affected study population. Further, they reported that most patients had good or satisfactory HRQoL and found a correlation between lower HRQoL scores and the incidence of gastroesophageal reflux and recurrent intestinal obstruction [105]. Moreover, scar-related problems were brought up as a significant concern with symptoms such as tension and pain, but also as cosmetic issues [105]. A few children/adolescents mentioned scar issues in free comments in our study but, at the same time, several questions about self-perception were asked within the KIDSCREEN-52, not confirming any differences in comparison with Swedish norms. Furthermore, Poley et al. examined HRQoL in patients born with CDH aged from one to 42 years and found no differences in adolescents and adults over 16 years of age compared with the general population [63]. However, in children one to four years of age they found a significantly lower HRQoL on several domains [63]. In the same manner, Peetsold et al. observed differences between the parents' and children's scoring of HRQoL, where parents tended to score lower than children [45]. In our study, mean T-scores were similar between parents and children in general, but surprisingly there was a low intra-class correlation (ICC) between the children's responses and their parents on all domains, meaning a low concordance between child-parent agreements. According to the KIDSCREEN manual there is a convergent validity between the proxy and child versions and when both answers are available the relationship between them can be considered to be valuable information regarding the different points of view [75]. This can be debated, however, as Berman et al. recently published their results from a Swedish random population sample where they concluded high child-parent agreement in total but item-by-item child-parent agreement was described as slight to fair in general [106]. Longo et al. recently compared answers from the KIDSCREEN-52 in Spanish children with cerebral palsy with their parents and described low correlations between their answers [107]. This clearly shows the difficulties inherent with estimating another person's HRQoL as the definition is subjective per se and should be measured from the individual's perspective and, furthermore, cover different health domains since HRQoL is a multidimensional construct [53]. Being born with a malformation might well provide another view of life and what is to be expected, which is hard to understand for anyone else other than the individual in question. Aaron Antonovsky

wrote 1987 in " *Unraveling the mystery of health: How people manage stress and stay well*" that a sense of coherence is strongly developed if a person sees the world as comprehensible as manageable, and as meaningful [108]. In a qualitative study guided by Antonovsky´s salutogenic theory, young patients with congenital heart disease were studied to gain a deeper insight into their experiences regarding life events and resources [109]. They found that patients with a week and strong sense of coherence did not differ in terms of going through negative life events, but in terms of availability and use of resources to deal with them [109]. Reinforces the results that HRQoL might not be controlled by severity of CDH nor morbidity.

According to other published research on Swedish normative data for KIDSCREEN, Swedish means are known to be higher than European means [75,106], as in this study. Unfortunately, Swedish normative data for the KIDSCREEN-52 is only available for children 12-18 years of age. Berman et al. showed an age difference, where adolescents scored lower wellbeing than pre-adolescents [106]. In our study we did not see any age differences, however, our study population was rather small. It is widely known that for many adolescents puberty can be a sensitive time, and there is no reason to believe that anything else would apply for children with CDH.

### 5.4 PSYCHOSOCIAL FUNCTION

In Study IV we found that parents of children born with CDH scored within the normal range on the behavioral, emotional and social scales. Furthermore, children born with CDH seemed, according to their parents, to have normal levels of school and social competence. There were, however, less than half within the group who were reported to have an activity level within the normal range.

There are a few other studies of CBCL in children born with CDH that have, however, shown various results. Peetsold et al. described that 21% of children born with CDH had total problem scores in the clinical range compared with the 10% of their reference population [45], whereas in our study none was in the clinical range and 10% of the children aged 6-18 years were in the borderline range. Similar to our study, Peetsold et al. did not see any correlation to the severity of the malformation [45]. Madderom et al. found 26% of the CDH survivors within a clinical to borderline range regarding total scale, 26% in the internalizing- and 15% in the externalizing scale, which is not significantly different, however, from their reference population [47]. This is in contrast to the 10% of children 6-18 years old and 9% of the young adults with an internalizing behavior in our study.

Madderom et al. did not see any significant differences between children with or without ECMO support [47], while significantly more children in our study with a history of needing ECMO had an internalizing behavior in the group of children 6-18 years old. An internalizing behavior at the age 6-18 years is based on anxiety, withdrawn and somatic complaints without a specific medical reason. In a study of five-year old children with a previous history of ECMO support for different reasons (meconium aspiration syndrome, CDH, sepsis or persistent pulmonary hypertension), CBCL scores did not differ from the reference population [110]. In our study, there were 18 children with a history of ECMO support and nine of the children were within the 6-18 year age group. The group as a whole showed large variations and although the differences were significant, it is probably wise to interpret the results with caution because they refer to a small material.

In contrast to our study, Bouman et al. found in a small CDH cohort consisting of 11 children, increased levels of emotional and behavioral problems in comparison with the general population and further recommended an intense follow-up in order to detect children with psychological and social problems [111].

Kubota et al. studied psychological consequences after major neonatal surgery including children born with CDH, anorectal malformations and esophageal atresia, and found higher total T-scores in children who underwent multiple surgery and home medical treatment than in those who underwent single surgery without home medical treatment [112]. Early exposure to anesthesia and surgery has previously been identified as significant independent risk factors for learning disabilities but not, however, to emotional or behavioral outcome [113]. Kubota et al. did not see any correlations with scores of CBCL and LOS, which is in line with our results. The total T-score in the CDH population in the study by Kubota et al. was 55.3±10.8 [112], while children at the same age in our study had a total T-score of 47.2±8.5. In several previous comparisons of the CBCL 6-18 in different societies, it has been found that Swedish and Scandinavian norm data are significantly lower than many other countries [114-116]. It has not yet been explained, however, why Swedish parents score low.

In an earlier published article, where data for the Swedish normal population of the older version of CBCL concerning preschool children are described [117], scores were much lower than in other parts of the world but similar to other Scandinavian countries. Even with the new version of CBCL, the lower Scandinavian scores have been confirmed in an

international comparison of preschool children's behavioral and emotional problems [116]. Since no new Swedish standard data are available after changing the CBCL questionnaires, there is no possibility of making a comparison with the Swedish normal population. However, for the 1.5-5 year age group, new national Danish normative data are available which are consistent with data from this study [118].

In our study we found large differences in the activity scale among boys (6.2±2.8) and girls (8.4±3.3) born with CDH aged 6-18 years. In a published study from Norway, Jozefiak et al. presented Norwegian normative data on CBCL, which has been confirmed as being representative to Swedish normative data [114]. Further Jozefiak et al. showed similar activity in both boys and girls (9.2± 2.7), much higher than in our study population. The underlying reasons for the low activity rates among children and adolescents born with CDH have not been further elucidated in this study, however, an explanation may be the reduced lung function that many children born with CDH live with. There is, of course, no reason to believe that boys would have worse lung function than girls, but on the other hand there are traditional differences between sports that boys and girls often exercise. A speculation could be that it is easier for girls to find traditional sports to exercise that do not require as much physical effort.

The findings from the qualitative data showed that there was a clear trend in what worried parents of children of different ages. Parents of the youngest children were very concerned about complications related to CDH and respiratory tract infections and, furthermore, they were generally worried that something would happen to their children. Parents of older children were more concerned about how the children would handle the future. One possible cause of the shift in anxiety could be that the first few years may have passed by relatively well and even though the children had respiratory tract infections the parents were able to cope and focus more on the future. Overall, parents who expressed concerns were those who had children with some kind of sequelae, and therefore it was natural to express such a reaction. The number of parents who answered the question about being concerned were among the younger group of 80%, while 58% of the parents of the older children did the same, which also reinforces this reflection.

The young children's parents used strikingly emotional words when describing their children, "she has survived against all the odds" and "he is a real fighter, simply amazing". Most children born with CDH undergo a very intensive first period of life, and these

memories are likely to remain very strongly among the parents. Even parents of the older children left strong descriptions of their children's best episodes, however, no longer with words such as "survivors".

## 5.5 REFLECTIONS ON METHODOLOGY

All four studies are based on different questionnaires, where mostly quantitative but also some qualitative data were collected and analyzed. In the first study, the aim was to assess perceived physical function in the study population, and we compiled a study-specific questionnaire. An instrument should be used carefully and the results and conclusions drawn from Study I must be interpreted with caution since the instrument has not been validated. Measurements from a reliable questionnaire are consistent over time, repeatable and reducible [119]. The questionnaire we used has been published and is free for others to repeat and reduce. Furthermore, multi-item scales are more reliable since responses from several questions can reduce the impact of the variability [119] and, therefore, many questionnaires consist of scales or domains including many questions reminiscent of each other. Validity can be increased further if the questions are both negatively and positively formulated because the reliability increases. To choose a questionnaire with tested psychometrics is therefore preferable. However, if you never ask the questions of interest you will never obtain the answers to these questions either. The questionnaires used in Studies II-IV have the strength of being reliable and they have been validated in a Swedish context. In addition, both the SPSQ and KIDSCREEN-52 have Swedish normative samples available, while the CBCL refers to multicultural normative values. It has already been discussed within this thesis that cultural differences exist, and an updated Swedish reference population would have been beneficial for Study IV.

Another limitation that must be addressed is the sample size, especially in Studies II-IV. Even though analysis did not show any significant differences between non-responders and study participants, the loss must be considered as a potential weakness. Congenital diaphragmatic hernia is a rare malformation and, moreover, Sweden is a small country which, combined, challenges the sample size. Multicenter studies would of course have been valuable in order to increase the numbers of participants. One of the strengths of performing research in Sweden is the PIN number which makes it possible to follow patients over time and reach everyone, not just the most or lest severely affected patients. This decreases the risk for selection bias and losing patients to follow-up.

There are published results that indicate differences in mortality and morbidity in children born with, and treated for, CDH at different types of hospitals, low versus high volume centers, access to ECMO and so forth. This issue touches upon external validity, to what extent a result is generalizable or not. Results from our studies provide an indication of how the children who were treated in Stockholm during this period are doing later in life, and it is possible that the results cannot be generalized to other parts of the country but probably to other ECMO centers with similar resources to ourselves.

# 6 CONCLUSIONS

This thesis has contributed to a deeper understanding on how life can be for children, adolescents, their parents, and young adults born with CDH in some of the long-term aspects of this condition. As described in *Studies I* and *III*, parents of children and adolescents born with CDH viewed their physical function and HRQoL as being good. Furthermore, the conclusion from *Study II* was that overall parental stress was normal in comparison with parents of healthy children. Moreover, *Study IV* showed no behavioral or emotional problems according to parents of children born with CDH. Further, children aged 6-18 years of age born with CDH seemed to be socially competent and function well in school and during their leisure time. However, when it came to physical activities, less than half in the group of children born with CDH reached normal levels. In conclusion, children born with CDH are managing well, **but** in all four studies there were exceptions and those shall be clearly stated; children born with a severe form of CDH and their parents seem to be in need of extra health care support from professionals, not only during the first intensive period but also for many years to come. Follow-up programs can be valuable to ensure that nothing is missed, but resources must be invested for those patients who benefit from them.

# 7 FUTURE RESEARCH

As I wrote in the preface, there are three main perspectives from which to view how the children are managing in terms of health, quality of life and psychosocial function, namely, the perspectives of health care providers, parents, and the individuals themselves. I have also written in this thesis that the only one voice which can actually tell the "truth", is the individual's own. It remains, however, that in most of the studies I have been obliged to ask the parents. I do not in any way diminish their stories but I think, as a researcher and as a parent myself, that we are all really most interested in the children's own experiences. And that is what I would like to know more about in the future.

The background data for all four studies were collected retrospectively. This was possible due to the Swedish PIN which allows patients and their medical records to be tracked. The downside of having to trust retrospectively-collected material is that you are limited to what is actually documented and, in some cases, the medical records consisted of a large amount of information which made it time-consuming to find the detail we were looking for. As well as the introduction of a structured follow-up program, we started to collect data prospectively, which raised the quality of information and made it easier to continuously compile results. Since both national and international centers follow the same follow-up programs, results are easy to compare. This, I think, is crucial for ensuring a good quality of care for both parents and children, but also for the healthcare professionals themselves.

Further, all the four studies were cross-sectional, which enabled us to collect all the data at one time and thereby not lose any patients in extensive follow-ups. Nevertheless, we have captured the situation as it appears right now but we cannot say anything about how it will evolve for the children and their parents over time. I am hoping to get the chance to follow the younger group of children in these studies over time, in order to obtain a more holistic view of how it actually can be to grow up with CDH.

Another issue that captured my interest during this journey, and really surprised me in the beginning, was something that happened when we sent out the first information about the study to the participants. A few young adults answered that they did not want to participate because they did not think they were born with CDH. Hopefully, they were managing well and did not need any follow-up or support, but we cannot know for sure. There were also a

few who answered and wanted to come for a follow-up since they had different kinds of problems. Several of them did not really know what their condition had been or what they had been through when small. It became very clear to our team that we, as health care providers, had completely failed in the last part of our pediatric care assignments to tell the adolescents about their medical history and prepare them for the future. This is also something I would like to know more about.

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