Patient-reported outcomes in children and adolescents born with esophageal atresia

Condition-specific aspects of health-related quality of life and coping

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To the patients and their families

"The important thing is not to stop questioning. Curiosity has its own reason for existing. One cannot help but be in awe when he contemplates the mysteries of eternity, of life, of the marvelous structure of reality. It is enough if one tries merely to comprehend a little of this mystery every day. Never lose a holy curiosity"

Albert Einstein

Abstract

Background
Survival rates in children with esophageal atresia (EA) have reached 90-95%, but they are at risk of chronic morbidity, mainly related to esophageal and respiratory dysfunction. Knowledge of condition-specific health-related quality of life (HRQOL) and coping is needed in order to properly understand the impact of the disease and treatment in the child's daily life.

Aim
The aim was to advance knowledge of condition-specific aspects of HRQOL and coping among children and adolescents with EA, including to develop and establish the field test version of a condition-specific HRQOL questionnaire for children with EA.

Methods
The study design followed international guidelines for the development of a patient-reported outcome measure. A systematic literature review of HRQOL in patients with EA was conducted in Pubmed, Cinahl, and PsycINFO, from inception to January 2015. Ten standardized focus groups with 30 Swedish families of EA children 2–17 years old were held to capture the child and parent perspectives of HRQOL and coping. The reported experiences were content analyzed. The HRQOL experiences were used for item generation of pilot questionnaires which, after translation from Swedish to German, were offered to a cross-cultural sample of 89 families of EA children 2–17 years old. Predefined psychometric criteria were used in the pilot test in order to eliminate or revise poor items for the field test questionnaire. The shortened questionnaires were analyzed for internal reliability and convergent and known-groups validity.

Results
Twelve studies (published 1995-2014) were included in the literature review. Five articles (published 2003–2014) described HRQOL among EA children. The studies had employed four different HRQOL questionnaires, and HRQOL results were heterogeneously reported. A standardized condition-specific HRQOL questionnaire for children with EA was needed. Thirty families of children with EA (18 children 8–17 years old, 32 parents of children 2–17 years old) participated in the focus groups (response rate 100%) and produced 1371 HRQOL statements, which formed the basis of two age-specific versions of pilot questionnaires. The 30-item pilot questionnaire for children aged 2–7 years was completed by 34 families (parent report), and the 50-item pilot questionnaire for children aged 8–17 years was completed by 52 families (51 child-report, 52 parent-report) from Sweden and Germany, with a response rate of 96% in the total sample. After omitting poorly performing items, the field test questionnaire for children aged 2–7 years (parent report) consisted of 18 items and three domains *(Eating, Physical health & treatment,* and *Social isolation & stress)*, and the field test questionnaire for children 8–17 years old consisted of 26

items with four domains *(Eating, Social relationships, Body perception,* and *Health & well-being)*. The initial reliability and validity of the shortened questionnaires were adequate. The focus groups also generated 590 coping statements, which revealed nine different coping strategies *(Problem solving, Avoidance, Confronting, Recognizing responsibility, Seeking social support, Positive reappraisal, Emotional expression, Acceptance, Distancing)* that were used in nine situational contexts. The majority of coping experiences (68.6%) were described by children with severe EA and by their parents.

Conclusions
Following the need for advancement in the field, the perspectives of children with EA and their parents have been incorporated into the field test version of the first condition-specific HRQOL questionnaire for EA children. The foremost HRQOL issues are related to eating, physical health and social dimensions; in children 8–17 years old, body perception issues are also prominent. Condition-specific coping strategies seem to be adopted at an early age and may affect HRQOL. The findings shed light on issues of relevance for follow-up routine care, and can improve the evaluation of pediatric surgical care and treatment. Future research is warranted.

Keywords: Esophageal atresia, Rare condition, Patient-reported outcome, Quality of Life, Coping, DISABKIDS

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Sammanfattning på svenska

Esofagusatresi (EA) är en sällsynt missbildning av matstrupen, som innebär att matstrupen är avbruten. Behandlingen är kirurgisk och rekonstruktionen av matstrupen äger i majoriteten av fallen rum inom barnets första levnadsdagar. Överlevnaden har ökat avsevärt de senaste decennierna och uppgår idag till 95%. Efter operationen har barn med EA en risk för kronisk sjuklighet, framförallt beträffande matstrupens och luftvägarnas funktion.

Syftet med denna avhandling var att öka kunskapen om hur barn med EA upplever att det dagliga livet påverkas ur ett fysiskt, socialt och psykologiskt perspektiv (hälsorelaterad livskvalitet) samt hur de hanterar svårigheter som uppstår till följd av sin specifika sjuklighet (coping). Ett huvudändamål var att i samverkan med barn och deras föräldrar utveckla ett frågeformulär som specifikt fångar livskvalitetsaspekter som är viktiga för barn med EA.

För att uppnå detta syfte, genomfördes först en systematisk litteraturöversikt, dvs en undersökning för att beskriva hur det nuvarande kunskapsläget såg ut avseende hälsorelaterad livskvalitet hos barn, unga och vuxna med EA. Från 1995 och fram till januari 2015 hade 12 studier genomförts, varav fem studier (publicerade 2003-2014) handlade om hälsorelaterad livskvalitet hos barn. Studierna hade använt fyra olika frågeformulär (inget frågeformulär var specifikt för EA) och resultaten av hälsorelaterad livskvalitet beskrevs på olika sätt. Ett frågeformulär som tog hänsyn till specifika aspekter relaterat för barn med EA behövdes således. Därför genomfördes tio sk fokusgrupper med 30 familjer; med 18 barn 8-17 år och med 32 föräldrar till barn 2-17 år. Fokusgrupperna samlade 4-6 barn respektive föräldrar i grupper, där de diskuterade erfarenheter utifrån frågor som ställdes av en forskare. Fokusgruppdiskussionen syftade till att fånga barns och föräldrars perspektiv på barnets hälsorelaterade livskvalitet. Samma frågor ställdes i alla fokusgrupper.

Med hjälp av de livskvalitetserfarenheter som barn och föräldrar beskrev, skapades preliminära frågor till ett formulär för barn 2-7 år (föräldern svarar) och ett formulär för barn 8-17 år (barn och förälder svarar). Frågorna efterliknade de livskvalitetsområden som barn och föräldrar beskrivit, och deras sätt att formulera sig på. Frågeformulärens kvalitet utvärderades genom ett pilottest (ett förtest innan en större undersökning) där sammanlagt 86 familjer; 65 familjer från Sverige och 21 familjer från Tyskland deltog (96% svarsfrekvens i hela undersökningen). Genom förutbestämda kriterier möjliggjorde pilotstudien att antalet frågor kunde kortas ner och att de bättre frågorna kunde behållas inför den sista kvalitetsundersökningen av frågorna, som kallas ”Field test”. Field test versionen för barn 2-7 år bestod av 18 frågor med tre områden; *Ätande, Fysisk hälsa & behandling* och *Social isolering & stress* och för barn 8-17 år bestod den av 26 frågor indelad i fyra områden; *Ätande, Sociala relationer, Kroppserfarenhet* och *Hälsa & välbefinnande.* Enligt pilottestet var tillför-

litlighet (intern reliabilitet) och giltigheten (validitet) god i de förkortade frågeformulären. I barns och föräldrars beskrivningar från fokusgrupperna framkom också att barn med EA använde nio olika typer av strategier för att hantera svårigheter till följd av sin sjuklighet, och att dessa användes i nio olika typer av situationer. Strategier beskrevs av majoritet av de barn som hade en svår EA och deras föräldrar (405 erfarenheter, 68.6%).

Genom dessa studier har vi idag fått mer kunskap om specifik hälsorelaterad livskvalitet hos barn och ungdomar med EA. Ur denna synpunkt verkar ätande, fysisk hälsa och sociala dimensioner vara framträdande livskvalitetsaspekter. Därutöver verkar erfarenheter av operationsärr hos barn i åldersgruppen 8-17 år vara viktiga aspekter för livskvaliteten. Sammantaget är detta en viktig kunskapsutveckling för den uppföljning som barnen behöver efter operationen, samt för möjligheten att bättre utvärdera barnkirurgisk vård. Ett frågeformulär som detta kan efter Field test, också användas av patientföreningar, i kvalitetsregister och översättas till fler språk för att öka kunskapen om diagnosspecifik hälsorelaterad livskvalitet. Barn med EA verkar i tidig ålder ta till sig olika strategier att hantera svårigheter på grund av sin sjuklighet. För sjukvården är det viktigt att tidigt identifiera och stödja framgångsrika strategier i förhållande till barnets hälsa och hälsorelaterade livskvalitet. Mer forskning om livskvalitet hos barn med EA och coping strategier behövs.

List of publications

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

I. **Dellenmark-Blom M., Chaplin J. E., Gatzinsky V., Jönsson L. & Abrahamsson, K. (2015)**
Health-related quality of life among children, young people and adults with esophageal atresia: a review of the literature and recommendations for future research.
Quality of Life Research, 24, 2433–45

II. **Dellenmark-Blom M., Chaplin J. E., Gatzinsky V., Jönsson L., Wigert H., Apell J., Sillén U. & Abrahamsson K. (2016)**
Health-related quality of life experiences among children and adolescents born with esophageal atresia: development of a condition-specific question naire for pediatric patients.
Journal of Pediatric Surgery, 51(4):563-9

III. **Dellenmark-Blom M., Chaplin J.E. Jönsson L., Gatzinsky V., Quitmann J.H. & Abrahamsson K. (2016)**
Coping strategies used by children and adolescents born with esophageal atresia – a focus group study obtaining the child and parent perspective.
Child: Care, Health and Development, 42(5):759-67

IV. **Dellenmark-Blom M., Abrahamsson K., Quitmann J.H., Sommer R., Witt S., Dingemann J., Flieder S., Jönsson L., Gatzinsky V., Bullinger M., Ure B.M., Dingemann C., & Chaplin J.E. (2017)**
Development and pilot-testing of a condition-specific instrument to assess the quality-of-life in children and adolescents born with esophageal atresia.
Diseases of the Esophagus, accepted for publication.

Contents

List of Abbreviations

ALTE	Apparent life threatening event
BMI	Body mass index
CHQ	Child Health Questionnaire
DIF	Differential item functioning
EA	Esophageal atresia
EA-QOL questionnaire	Esophageal atresia Quality-of-Life questionnaire
EMA	European Medicine Agency
ES	Effect size
FDA	Food Drug Administration
GER	Gastro-esophageal reflux
GERD	Gastro-esophageal reflux disease
GIQLI	Gastro Intestinal Quality of Life Index
HRQOL	Health-related quality of life
IRT	Item response theory
ISOQOL	International Society for Quality of Life Research
ISPOR	International Society for Pharmacoeconomics and Outcome Research
MCS	Mental component summary
PEDSQL	Pediatric Quality of Life Inventory
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
PCS	Physical component summary
SF-36	36-Item Short Form Survey from the RAND Medical Outcomes Study
RD	Rare disease
TEF	Tracheoesophageal fistula
TM	Tracheomalacia
WHO	World Health Organization

Introduction

Esophageal atresia (EA) is a rare congenital malformation characterized by a discontinuity of the esophagus (1). Children born with EA need surgery within 48 hours after birth. Since the first successful primary esophageal repair took place by Haight in 1941 (2), survival rates have increased dramatically and now reach 90-95% (3-5). However, chronic morbidity among the surviving children remains both frequent and complicated. Morbidity is related to dysphagia, gastroesophageal reflux disease (GERD), and respiratory disorders such as wheezing, chronic and/or a barky cough and recurrent airway infections (6). Poor health may also be a result of associated malformations, which are present in about 50% of the children (7).

Criteria to evaluate medical outcomes have become increasingly supplemented by patient reported outcome (PRO) standards, among them health-related quality of life (HRQOL)(8). The term HRQOL is multidimensional and refers to the impact of disease and treatment on social functioning, psychological functioning, physical functioning and well-being from the patient's perspective. Knowledge of the patient's perspective is needed in order to thoroughly understand the impact of the disease and treatment in daily life. This knowledge is essential for clinical practice, health-care policy and for research (8-12). According to the international standards of PROs for pediatric patients, children are content experts of their lives and should be involved in the development of a PRO measure (PROM)(13). Moreover, condition-specific HRQOL measurements are sensitive for clinical characteristics in small and heterogeneous populations. Among children with chronic conditions, coping strategies can buffer against a negative psychosocial development and HRQOL across childhood and toward adulthood (14, 15). In patients with EA, several authors (16-18) have discussed the possible positive impact of coping strategies on the EA patient's HRQOL; however no empirical study of coping used by EA children was reported at the start of this research project.

Given this background, research efforts are needed and hence, the aim of this thesis was to describe current knowledge of HRQOL in EA patients and the subsequent need for advancement in the field. Moreover, to gain the child and parent perspective on condition-specific HRQOL and coping in order to more completely understand the possible consequences of EA. In the long-term, this serves to better address the needs of care, improve the evaluation of pediatric surgical care and to enhance the health and HRQOL in children and adolescents born with EA.

Esophageal atresia

History

Esophageal atresia (EA) was first described in 1670, when William Durston portrayed how he was called to the delivery of conjoined twins, one of whom was born with EA. In 1697, Thomas Gibson characterized EA with a distal TEF (19). It would persist several centuries, and more precise until 1939, until Dr William Ladd (20) in Boston and Dr Logan Leven (21) individually reported the operation of the first EA survivors. Two years later, 1941, Dr Cameron Haight, conducted the first successful primary esophageal repair (2) and in 1947, Dr Philip Sandblom carried out the first surgery on a patient with EA in Sweden (22). Since then, survival rates of children with EA have improved considerably, and interest of long-term outcomes of EA patients has increased (18, 23, 24).

Anatomy and classification

There are several subtypes of EA. A classification system made by Vogt in 1929 represents the first anatomical categorization of EA (25). Another classification system that is very commonly used today was reported by Gross in 1953 (1). Kluth has given the most detailed and recent classification in 1976 (26). The main subtypes of EA including their frequency are illustrated according to Gross in Figure 1.

A 7%	B 1%	C 86%	D 2%	E 4%
Isolated EA	EA with proximal fistula (TEF)	EA with distal TEF	EA with proximal and distal TEF	Only TEF (H-type)

Figure 1. Presentation of subtypes and their frequency according to the classification system Gross. The red color illustrates the esophagus, and the gray color represents the windpipe. From left to right: Gross A is an interrupted esophagus without any connection to the windpipe. Gross B is an interrupted esophagus with a connection to the windpipe from the upper (proximal) esophageal segment. Gross C is an interrupted esophagus with a connection to the windpipe from the lower (distal) esophageal segment. Gross D is an interrupted esophagus with a connection to the windpipe from both the proximal and the distal esophageal segments, and Gross E refers to an isolated tracheoesophageal fistula. The illustration is reprinted with permission from Dr. Vladimir Gatzinsky.

Embryology and Etiology

In the fourth week of gestation, the early forgut normally separates into the respiratory and digestive tubes. This process is not fully understood, but there have been two main theories used to explain how the respiratory foregut, separates from the gastrointestinal foregut. The first theory postulates that the evagination of the tracheal diverticulum starts with the primitive digestive tube, which proliferates in the caudal direction and leads to a separation of the trachea and the esophagus. The second theory assumes that there is an active growth of a mesenchymal septum, which is formed in the coronal plane of the primary digestive tube, and separates the foregut lumen into ventral (respiratory) and dorsal (gastrointestinal) structures. Failure in completion of such a process results in tracheoesophageal malformation (27). In experimentally induced EA-TEF in rat-models, a close relationship between EA and tracheobronchial malformations, including tracheomalacia (TM), has been observed (28, 29), the neurological supply of the esophagus has shown to be abnormal (30), and the development of respiratory tract innervation to be delayed and abnormally controlled (31). Few genes and genetic pathways have however been identified as involved in the development of EA-TEF in human or animals. Instead, the majority of cases seem sporadic. The current belief is that the etiology of EA-TEF is multifactorial and includes genetic as well as environmental factors (32, 33).

Epidemiology

Although EA is considered as the most common malformation of the esophagus, it is a rare condition (34) with a reported prevalence of 2.4 per 10 000 births (35, 36). EA seem to be more common in Caucasians and the occurrence is associated with increased maternal age (3, 37). A small predominance in males and a higher frequency in twins have been demonstrated (38, 39).

Associated anomalies

Associated anomalies are present in approximately 50% of EA patients. The most frequently associated anomalies are cardiovascular (24-31%), anorectal and other digestive anomalies (21-23%), urogenital (19-21%) and musculoskeletal (14-29%) conditions (7, 40). The incidence of associated anomalies is higher in patients with isolated EA and least common in patients with TEF only. VACTERL is an acronym for a condition when the patient with EA has two or more malformations of the **V**ertebral, **A**norectal, **C**ardiac, **T**racheo-esophageal, **R**enal and **L**imb system. The CHARGE association (**C**oloboma of the eye, **H**eart anomaly, **A**tresia choanal, **R**etarded growth, **G**enital hypoplasia and **E**ar deformities) may include EA. The reported frequency of VACTERL in patients with EA is around 10%-20% and of CHARGE association 1-2%. About 5-8% of patients with EA have chromosomal abnormalities (40-42).

Diagnosis

It is difficult to detect EA prenatally. The suspicion of EA is based on the presence of polyhydramnios and the absence of the gastric bubble, however these are non-specific criteria. The majority of children with EA are therefore diagnosed postnatally

(43, 44). After birth, the EA child presents with excessive salivation, regurgitation, choking and coughing during the first feeding and can also show episodes of cyanosis. A primary sign of EA is when a nasogastric catheter is not possible to pass to the stomach. The EA diagnosis can be confirmed by a plain X-ray (Figure 2) with the nasogastric cathether in place. If a distal TEF is present, air in the stomach will be present on the X-ray and abdominal distension may be evident. If absence of air in the gastrointestinal tract is observed, this indicate an isolated EA. This is important preoperative information since it determines the initial surgical approach. The diagnosis of an isolated TEF may be delayed until after the child develops problems with coughing during feeding and recurrent airway infections. A broncoscopy together with esophagoscopy are often needed to verify the diagnosis (6, 44).

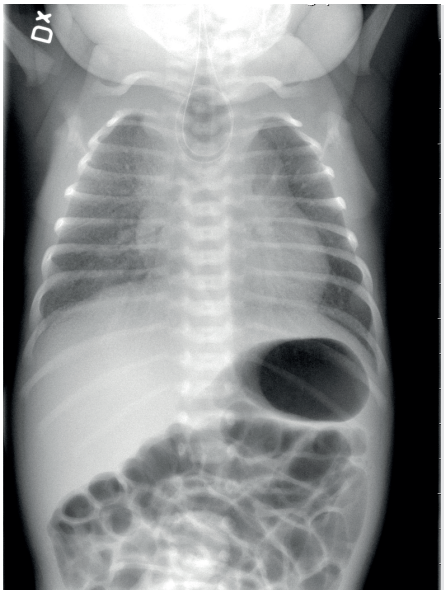


Figure 2. Plain x-ray of a child born with esophageal atresia

Risk factors of mortality and classification

Classification systems for EA have been developed to assess risks with regard to mortality. The Waterston classification, proposed in 1962 (45), described three different risk groups in relation to birth weight, the presence or absence of pneumonia and complications from associated congenital anomalies. In the Montreal classification system, two main factors, dependence on mechanical ventilation and associated major malformations, are considered to be of high prognostic significance (46). In the Spitz classification (47), the risk for mortality is assessed by using three different groups with regard to the two main factors birth weight and cardiac malformations. All of the three different classification systems have been shown to have prognostic value (48-51). However, the Waterston and Spitz classification seem more widely accepted (48-50), with reservation for some modifications in line with medical advances e.g. for birth weight and/or cardiac malformations (52-54).

Preoperative treatment

Once the diagnosis of EA has been confirmed, the aim of the preoperative care is to enhance the child's general state and thereby optimize conditions for surgery. Neonatal care includes stabilization of the infant's respiratory status with intention to avoid endotracheal intubation (6). However, mechanical ventilation may be needed, and children who are prematurely born and/or have low birth weight are more likely to require this (43). The infant should be placed in supine position with the head elevated. A suction tube drainage of the upper esophageal pouch is positioned to prevent aspiration. The vital signs of the infant is monitored, vascular access is ascertained and maintenance of fluids commenced. Antibiotics and acid suppression could be used with the intention of diminishing the postoperative complications. Preoperative information which might influence the planning or outcomes of surgery are collected. Preoperative screening for associated anomalies, especially cardiovascular (including determination of the side of the aortic arch) and renal anomalies, is performed (43, 44).

Surgical treatment

The surgical treatment depends on the type of EA. A bronchoscopy can be used to determine the location of a possible fistula or any other structural abnormality (6, 43, 44, 55). The standard operative approach for EA with a distal TEF is via a posterolateral right thoracotomy. The entrance to the thoracic cage is between the fourth and fifth ribs. If the aortic arch is right-sided, some authors advocate a left-sided thoracotomy. In order to preserve muscle and innervation, alternative skin incisions have been recommended (56, 57). The thoracoscopic approach for EA-TEF repair has been implemented to varying degrees at centers (58, 59), but an international study of the management of EA patients, showed that open surgery in EA patients is favored by the majority of surgeons (59). A metaanalysis from year 2016 evaluated the efficacy and safety of thoracoscopic repair versus conventional open repair, and demonstrated that there were similar complication rates of leaks and strictures for EA-TEF repair. Thoracoscopic repair had earlier time to extubation and the first oral feeding including a shorter hospital stay, but was associated with a longer operative time (60). Tovar and Fragoso have described that there is little doubt about the benefits of minimal invasive surgery over thoracotomy for reducing pain, scars and musculoskeletal sequelae, but, this is into the hands of experienced surgeons. In most large centers it is difficult to gain the skills for this particular operation in EA infants (61). Although the thoracoscopic technique in EA repair has demonstrated some benefits over thoracotomy, still evaluations including long-term outcomes are needed before it can be considered as golden standard.

The procedure in the EA-TEF repair include that the fistula is divided close to its entry into the trachea and the tracheal defect is sutured. The proximal blind end of the esophagus is mobilized to provide an anastomosis between the two esophageal ends. In most cases, it is feasible to perform a primary anastomosis of the two esophageal ends. The long (or wide) gap EA, however, presents a challenge for pediatric surgeons. Although, there is no consensus of the definition of long (or wide) gap

EA, the major problem is that the distance between the two esophageal ends is too long to conduct a primary anastomosis. If a primary anastomosis cannot be made within the first days of life, a gastrostomy is inserted for enteral feeding. A TEF should always be closed. In isolated EA, the lower esophageal segment tends to grow more than the child during the first months of life. The distance between the two esophageal ends is regularly measured radiologically. Approximately at three to four months, the majority of patients can be operated with a delayed anastomosis. Elongation techniques for long-gap EA with attempt to extend the esophagus sufficiently to bridge the gap are used by a number of surgeons (59). Using the Foker technique (62), progressive lengthening of both esophageal ends is completed by external traction of sutures attached to the ends and exteriorized through the thoracic wall. The Foker technique has shown favorable results, but also a high rate of postoperative complications (63-65) and has been understood as a procedure for selected patients (66). It has also been pointed out that randomized and prospective studies that demonstrate the efficacy of mechanical traction in long-gap EA patients are lacking (63).

In cases where esophageal anastomosis is impossible or after failure of previously mentioned procedures, esophageal replacement with gastric, jejunal or colonic tissue can be performed for re-establishment of the digestive tract continuity (6, 42).

The isolated TEF is most often operated using a cervical approach, however some patients might need a thoracotomy (67).

Outcomes

Survival

Since year 1941 when Haight conducted the first successful primary esophageal repair on a patient with EA (2), survival rates have increased dramatically and now reach 90-95%. Mortality is stated to be limited to cases with coexisting severe life-threatening defects (5, 41). The improved survival rates are multifactorial and can be explained by medical advances in neonatal intensive care, anesthesia, respiratory and nutritional treatments, antibiotics and surgical techniques (6).

Early morbidity

Early postoperative complications can have a negative impact on the future course of morbidity (68-70). Anastomotic leakage occurs in 8-25% and is one of the most commonly reported early postoperative complications (71-74). The majority of anastomotic leakages are minor and they usually resolve using a conservative treatment with a chest drain, antibiotics and non-enteral feeding. Major anastomotic leakages require revisional surgery (70). Anastomotic leakage is associated with subsequent anastomotic stricture formation (72), and anastomotic strictures such as a narrowing that needs dilatation are reported in 21-80% (41, 71, 75, 76). In turn, anastomotic strictures are related to the presence of GER (74, 76) as well as to the development recurrent chest infections (68).

Children with long-gap EA are at increased risk for the development of anastomotic

complications including anastomotic strictures (68, 69, 71, 74).

About 2-12% of children with EA develop recurrent fistula (42, 69, 71), which often presents within a few months after primary esophageal repair with symptoms such as coughing and choking during feeds, apneic or cyanotic attacks or recurrent respiratory tract infections. A recurrent fistula can be closed using endoscopic techniques or open surgery (70, 77, 78).

TM is defined as a collapse of the tracheal lumen causing luminal obstruction during expiration and cough, and is reported as clinically significant in 10-50% of the patients (68, 69, 79, 80). TM is usually more common in younger children and in children with EA and TEF (76, 79). The trachea is weak due to a reduction and/or atrophy of the tracheal cartilage and/or an increase in the length of the transverse muscle (81). The tracheal collapse is generally found in the area at or above the TEF in the distal third of the trachea at the level of the aortic arch. The flaccid trachea is easily compressed between the aorta anteriorly and the often dilated esophagus posteriorly, which contributes to the TM pathophysiology. While mild-to-moderate TM is characterized by a barky cough, stridor and/or recurrent respiratory infections, severe TM is presented with dyspnea, recurrent pneumonia and cyanosis. In infants, severe TM may contribute to recurrent dying spells (68, 79). These can be referred to as Apparent Life Threatening Event (ALTE); an apnea which usually occur within the child's first year, typically during or directly after feeding, crying or coughing, and which results in color change and marked change in muscle tone of the infant. Stimulation or resuscitation to awaken the infant and facilitate continuous breathing may be required. Children with severe TM may need surgical interventions such as aortopexy (71, 79).

Long-term morbidity

Long-term esophageal morbidity is common in patients with EA. Dysphagia is observed in 55-85% of the patients with EA (24, 82, 83). Causes of dysphagia are several and involve dysmotility, anastomotic strictures, eosinophilic esophagitis, esophageal outlet obstruction and gastro esophageal reflux (GER)(84). Dysphagia can lead to feeding problems such as difficulty swallowing certain foods, food refusal, coughing and choking during meals, and the need to eat slow (85-87).

About 35-75% of patients suffer from GERD (44, 71, 83). Many patients are treated with antireflux medication, and the proportion requiring fundoplication ranges from 10-50% (88). The presence of GER can lead to the development of esophagitis, which in turn is a risk for Barrett's esophagus, metaplasia in the esophagus. Barret's esophagus has been confirmed by histology in 36-43% of adolescents and adults with EA, with the presence of gastric metaplasia in the majority of cases (89, 90). Barret's esophagus is a risk factor for adenocarcinoma (91), which has (so far) been reported in three adults with repaired EA (92). Seven cases of squamos cell carcinoma have also been described in the adult EA population (93). Gastric metaplasia is probably of less clinical importance in terms of the likelihood of malignant

transformation, although there is a risk of transforming with time into intestinal metaplasia (90).

Patients with long-gap EA are at increased risk for the development of esophageal morbidity such as dysphagia and GERD (68, 69, 71) and Barret's esophagus (89), as well as for the development of feeding difficulties (86, 94).

Respiratory morbidity is also frequent among EA survivors, and restrictive as well as obstructive pulmonary abnormalities have been observed (80, 95). Among etiological factors are TM, associated respiratory malformations, GER, esophageal strictures and scoliosis (76). Around 30-55% of the children are reported to have chronic and/or barky cough, recurrent respiratory infections, wheezing and to have a doctor-diagnosed asthma (80, 82). A recent metaanalysis showed that respiratory morbidity in adults with EA remained common; 35% of the patients suffered from wheezing, 24% had recurrent respiratory tract infections, 22% had doctor-diagnosed asthma and 15% had persistent cough (96).

After providing a summary of the literature, IJsselstijn et al. (97) in the year 2016 concluded that EA patients are at risk of physical growth problems. Individual studies (86, 98, 99) have demonstrated that children with EA may be small for age due to esophageal as well as to respiratory morbidity, but that a growth catch-up may occur during the first five years of life (98). Prospective and longitudinal studies to gain knowledge of EA patients' growth profiles are warranted; it is unsure whether growth problems persist into adolescence and adulthood (97). A study published in the year 2016 showed that in 37 adults with EA (83.8% Gross C, 67.6% associated anomalies, 18-44 years old), 24% of the patients had body mass index (BMI) < 18.5 kg/m^2 (100).

Deformities of the thoracic wall including scoliosis, which often become apparent later in life, are due to congenital causes such as associated rib-vertebrae anomalies and due to earlier thoracotomy, prior rib resection and division of serratus anterior and latissimus dorse muscles or their nerve supply (101). The frequency of scoliosis after EA repair is dependent on the definition of scoliosis, and reports on the presence of scoliosis varies between 8-56% of cases (24, 102). Sistonen et al. (24) summarized the Helsinki experience of long-term results among EA patients, and found a shoulder asymmetry in 80% and chest wall deformities in 15% of the patients. Furthermore, a winged scapula has been observed in 24% of the patients who underwent a standard posterolateral thoracotomy for EA-TEF repair (102).

Patient-reported outcomes

Patient-reported outcome (PRO)

Since several aspects of the disease and treatment may only be known by patients themselves (9, 13), the patient's perspective is essential in order to thoroughly understand the impact of disease and treatment in daily life. A PRO is defined as any report that comes directly from the patient without any interpretation by a clinician or anyone else. The report regards signs, symptoms, functions or multidimensional constructs such as quality of life and health experiences (11). It represents the subjective experience of health and functioning, including the positive as well as the negative aspects. PROMs are indexes, scales or questionnaires that aim to measure one or more aspects of a PRO (103).

Insights into the patient's view is required in order to properly understand the disease and treatment

PRO assessment

Several guidance documents offering standards for developing, assessing, implementing and analyzing PROs have been produced. Regulatory agencies like the US. Food and Drug Administration, FDA, (11) and the European Medicines Agency (EMA) (104) have described guidelines for the assessment of a PRO in the context of medical product development. The FDA guidelines are more extensive, provide an overview of PRO development, evaluation and of the use of PRO instruments and are regarded as international standards within the medical field (11). Furthermore, professional associations provide international recommendations for PROMs, like the International Society for Quality of Life Research (ISOQOL) (105, 106) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (13, 107-111). In summary, these documents highlight that the adequacy of a PROM- whether it is existing, modified, or newly developed- depends on its conceptual framework, validity (content validity, construct validity, criterion validity), reliability (internal consistency, reproducibility) and responsiveness (ability to detect change). A definition of each of these terms is provided in the Figure 3. In addition, interpretability, burden, administration form and cultural adaptations are important aspects in order to understand the quality of a PROM (11, 112).

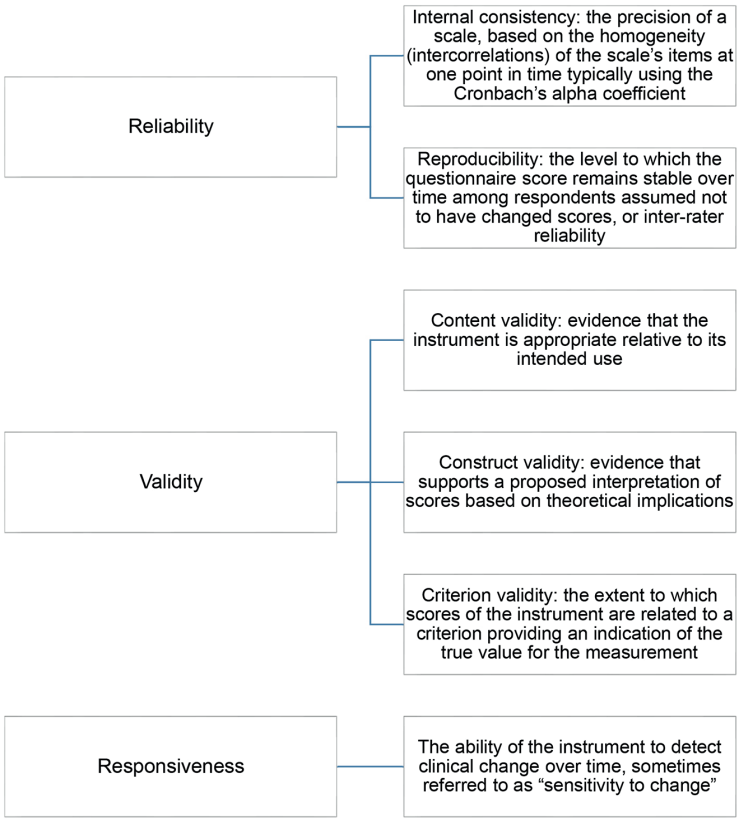


Figure 3. Definitions of the terms reliability, validity and responsiveness, as described by the Scientific Advisory Committee of the Medical Outcomes Trust Quality of Life Research 2002:11;193–205

The development of a PROM

The process of developing a PROM is outlined in Figure 4. During the development of a PROM, the conceptual framework and psychometric properties should be established (103). The first step in the development of a PROM is to *specify the target PRO concept* of interest e.g. signs, symptoms, functions or quality of life, including to formulate inclusion/exclusion criteria for the target population of interest e.g. disease, treatment, symptomatology, age and culture.

The next step in the PROM development is a *concept elicitation*. Concept elicitation is used to identify constructs that reflect the patient's view, and is established mostly through focus groups and/or individual interviews. Besides focus groups and individual interviews with patients, clinicians, family members, researchers, a literature review represents another source of information. The concept elicitation can give

information of aspects, which the patients feel are important and words and phrases that patients use to describe the target concept. Consequently, a concept elicitation helps to establish primary evidence for content validity of an instrument (11, 109, 110, 113).

After the PRO concept has been elicited, the *item generation* process starts. The item generation refers to the creation of a list of issues that are relevant to the target concept and target population. When the item generation have incorporated input from patients that represent variations in severity of disease, age, sex, ethnicity and language groups, item coverage are more easily achieved (11, 109, 110). An exact sample size for qualitative studies to reach item comprehensivess cannot be predefined. Instead, it depends on the quality of the data collection and the participants in the focus groups or in the individual interviews. However, data saturation can help to determine when a qualitative study can be regarded as comprehensive. The term data saturation refers to the state when information occurs repeatedly, and whereby the collection of more data can be assumed not to reveal more information of value (103, 114). The first generated list of items usually constitutes a large item pool.

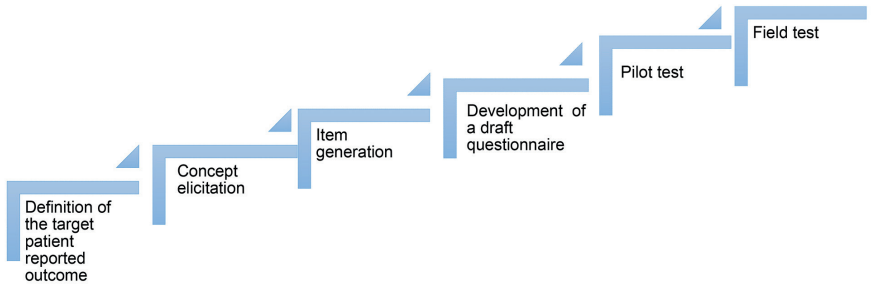


Figure 4. Different phases in the development of a patient-reported outcome measure

The next phase in a PRO development involves the *creation of a draft questionnaire*, which includes a reduction of items, formation of scales and wording of questions. Item reduction can be performed by a group of researchers (usually representing an expert team), who according to predefined criteria (11), determines the inclusion or exclusion of items that will form the draft questionnaire. Examples of item inclusion criteria are a high reported frequency of a certain item and a representation of an item in different subgroups (age, gender, severity of disease). Instead, items which are considered not to clearly capture the concept of interest, are too narrow to have universal applicability, or that seem confusing, are excluded (11, 115). A decision should also be made regarding the response scale and the recall period of the PROM, in order to adequately convert the items into questions. The aim is to formulate the questions clearly, so they are easy to understand and easy to respond to from the patient's perspective (103).

A cognitive interviewing is a qualitative research technique to determine whether concepts and items are understood by patients in the same way that instrument developers intend. Usually, the respondent completes the questionnaire and provides input to the item relevance, clarity and adequacy. Such information can support reduction of poor items and can help to improve the questionnaire format, wording of items and improve the response options from the respondent's perspective (11, 113). If the PROM is intended to be of international use, it must be translated into a different language. The translation of items does not only include a linguistic translation, but also semantical and cultural adaptations. In the international recommendations, provided by the ISPOR task force (111), several steps are included in the translation process; preparation, more than one (independent) forward translation, reconciliation of the two forward translations, at least one back translation, back translation review, harmonization, cognitive debriefing, review of results and finalization, proofreading and final report.

After a draft questionnaire has been constructed, *a pre-test (pilot test)* should be performed. By conducting a pilot test, the initial psychometric properties of the questionnaire can be determined. In addition, the pilot test is important because it gives opportunity to identify and solve potential problems with the questionnaire. This aids the selection of the better performing items for the *field test* questionnaire version. The purpose of the field test is to determine and confirm the acceptability, validity, reliability and the responsiveness before it is implemented for general use. The field study involves a larger group of patients who are representative to the full range of the intended responders (11, 103).

Quality of life

Quality of life (QOL) is regarded as one of the core concepts within PRO research (116). The explicit term QOL did not exist at Aristoteles time (384-322 BC), but Fayers (103) described in a historical summary that the QOL concept has roots in his work. Though, the most evident evolvement of the QOL concept is observed as late as the twentieth century. In 1948 the World Health Organization (WHO) declared that health is not merely the absence of disease, but the state of complete physical, mental and social well-being (117). In a historical review, provided by Bullinger (12), the term QOL is said to be used in social science literature since the 1940s. It was first established within political economy.

In the 1960s the concept of QOL was developed to represent the well-being of a population and was investigated from an intercultural perspective in various countries. At this stage, the assessment of QOL encompassed mortality, opportunities for education and access to medical care and socioeconomic indicators such as productivity. An individual focus of QOL was slowly introduced when the quality of the American life was investigated as an overall composite of different life domains. Moving from the discussions in the 1970s of what QOL is and how it should be assessed, the 1980s was described to represent a corresponding development of QOL measurements and the 1990s involved the first implementation of QOL instruments

in clinical studies (12). Today, the international definition of QOL refers to a multidimensional construct that encompasses physical, psychological and social health and well-being from the individual's perspective. The QOL concept includes the individuals' perception of their position in life in relation to cultural systems and personal goals, expectations and concerns including personal and spiritual beliefs (118, 119).

From a generic quality of life perspective, it seems relevant to feel physically fit, to be socially integrated, to feel psychological stable and to be able to fulfill daily roles in a safe environment

Health-related quality of life

While the term QOL is a broad concept, the term health-related QOL (HRQOL) more specifically refers to the patients' subjective perception of health. Even though widely valued aspects of life, such as income, freedom and quality of the environment can affect health, they are regarded as more distant from health and generally not included in the HRQOL concept (101). Instead, the HRQOL concept is defined as the positive and negative impact of a medical condition and its treatment on daily life, physical, psychological and social functioning, and well-being as perceived by the patient (12, 119). Behavioral or function-oriented dimensions regarding patients' capacity to fulfill everyday life "roles" are included in the concept (116). In the past decades, an increased interest to improve HRQOL in patients has led to a need for valid measurements of HRQOL. Outcomes in medical care are not only evaluated through criteria such as survival and morbidity rates, but additionally by the use of HRQOL standards (8, 116, 120).

HRQOL assessment

Interviews and focus groups may be used to elicit the patient's view on HRQOL. However, the use of questionnaire is advantageous because of well-established psychometric criteria and the number of respondents which can complete the HRQOL questionnaire at the same measurement occasion (12, 116). There are two main methods to assess HRQOL, namely the generic and specific approach (119). Generic HRQOL questionnaires measure HRQOL from a general population perspective, i.e. independent of health state (12, 119). Generic HRQOL assessments also include preference-based measures which yield both single and multi-attribute utility values anchored at scores of death and perfect health. This type of generic instruments are

derived from economic and decision theory. The scores can be integrated into cost-utility analyses as the weightings for quality adjusted life years (121). Since generic instruments measure HRQOL at a general population level, comparisons can be made between unhealthy and healthy people and between patients suffering from different diseases. Generic HRQOL questionnaires may not, though, be sensitive to specific clinical characteristics. Another approach to assess HRQOL is to focus on aspects that are specific to an area of primary interest; specific to a disease (such as asthma, diabetes) and/or to a population of patients (such as frail elderly, children, people with gastrointestinal symptoms). Although specific HRQOL questionnaires do not allow comparison of outcomes to healthy references, they can be expected to provide more clinically relevant information (12, 119, 122-124). A specific HRQOL instrument can be used to assess burden of illness, compare outcomes in patients that underwent different treatments, and to provide standards for population characteristics relating to severity level (122, 123). Specific HRQOL instruments are more likely to be able to collect clinically meaningful information to patients also in small and heterogeneous populations (119, 122).

An important perspective of HRQOL assessment also regards the person who answer the HRQOL instruments. Since HRQOL is a subjective experience, the self-report is the primary source of information. Proxy-reported HRQOL is the report by someone other than the patient, who reports as if he or she is the patient. A proxy-report is not a PRO (125). A proxy-report differs from an observer-report, since the observers, which can be caregivers or clinicians, report only his or her observation. Observer-reported information does not represent the patient's perspective (11). For patients who have difficulties or cannot respond for themselves e.g., infants or patients with cognitive impairment, either proxy-reported or observer-reported HRQOL can be used (11, 13, 126).

QOL /HRQOL assessment in children and adolescents: particular conceptual, methodological and regulatory issues

There are a number of circumstances that differ QOL/HRQOL assessment in children and adolescents compared to adults (125, 127). Advancement in the development of HRQOL measures in pediatric populations has resulted in papers describing critical methodological issues for pediatric PROM research (127). Some of the key issues are age-appropriateness in relation to QOL/HRQOL content, adequacy of data collection methods and utility of parent proxy-reports (121, 125).

QOL/HRQOL content

Children's QOL/HRQOL may depend on interactions between the child and the social environment. In contrast to adults, children have decreased ability to influence their context. The social contexts; the family, peer relationships and school environment may interact with the impact of disease and treatment, and thus the child's perception of HRQOL (13, 125). Children and adolescents are also experiencing a rapid developmental change (127) and there may be different HRQOL issues that are important at different child ages (125).

Specific gender differences may be present during childhood and adolescence e.g. self-esteem and physical self-image may differ between girls and boys, where girls have been found to display more problems than boys (120).
Consequently, HRQOL questionnaires for pediatric populations should address those issues and incorporate such aspects (120, 125).

Assessment of quality of life in children differ to that in adults. In particular, considerations to a rapid developmental change with age-appropriate content and adequate data collection methods are needed

Adequacy of data collection methods

Cognition, language level and social interaction skills affect the reliability of the self-report of QOL/HRQOL. Focus groups and individual interviews require the children to have social interaction skills and ability to express themselves. Focus groups and individual interviews with children younger than 8 years may be challenging, and children in ages 5-7 years may need age-adjusted methods such as drawings (13, 128, 129). Given the challenge of data collection from younger children, researchers may choose to conduct both focus groups and individual interviews, since this can offer rich information as the result of group dynamics in a focus group, and a confirmation or complementary information based on individual interviews (13).
Regarding the assessment of QOL/HRQOL using questionnaires, reliability and validity of information provided by children depends on the complexity of the constructs. Children seem to reliably self report more concrete QOL/HRQOL domains between 4- 6 years of age compared to subjective or abstract QOL/HRQOL domains. In young children aged 5–7 years, the self report of QOL/HRQOL often requires support from an interviewer or the QOL/HRQOL report is given by a proxy or an observer. From child age 8 years, many QOL/HRQOL questionnaires are usually presented to children for self report as well as to their parents for observer report or proxy report (125).

From child age 8 years, quality of life questionnaires can usually be presented to children for self-report

Parent reported HRQOL

In summary, parent reported HRQOL may provide valuable information that would otherwise be unobtainable in young or severely disabled children, but their reports are affected by their position to and knowledge of their child (13, 120, 125). The parents knowledge of the child's HRQOL may also be affected by age and severity of disease (130). The proxy question has been investigated by assessing the degree of agreement between parent- and child-report in HRQOL assessments. In 2013, three general findings from empirical studies were summarized by Eiser and Varni (130):

- In healthy children, parents typically rated the child's HRQOL better than themselves, whereas in children with chronic health conditions, parents typically rated the child's HRQOL worse than children themselves.
- Agreement between child- and parent-report was more likely to be found on objective physical domains such as walking and running, but less in terms of emotional functioning, social functioning, and symptom experience.
- Parents' report of the child's HRQOL was related to their own emotional well-being. The most consistent finding is that parents (most studies have been conducted on mothers) who report a higher level of emotional distress, typically depressive symptoms, also report more negative perceptions of their child's HRQOL (130).

Differences in child- and parent-reports have sometimes been regarded as "methodological error" and led to argumentation about who is "right". Eiser and Varni (2013) suggested that there is no correct view, but rather different perspectives on how the child feels and functions. Instead, the focus should be given to the clinical meaning of discrepancies (130). The general consensus is that the child is the primary source of HRQOL information, and that the parent-reported information is additional and complementary (13, 130). Parent- and child- versions of HRQOL instruments should therefore include the same items and domains in order to make comparisons between self- and proxy-reports more meaningful (130).

The evolution of pediatric PROMs with focus on QOL/HRQOL assessment

Advancement in medical care and health technology have resulted in improved life expectancy and increased prevalence of children with chronic diseases. The past decades have shown a corresponding growing interest in assessing HRQOL in children and adolescents with a rapid development of HRQOL measurements and the subsequent use of HRQOL instruments in research as well as in clinical practice (8, 120, 131).

In 2001, Eiser and Morse (132) identified 19 generic and 24 disease-specific measures of HRQOL in children with chronic disease, approximately 50% were established in the US. Many measures were regarded as appropriate for children and covered a broad age range. However, there was a large variability in the definitions of HRQOL, a lack of precision of the content of overall HRQOL and an overlap between measures of HRQOL, health and functional status. There were disease-specific HRQOL questionnaires for e.g. for asthma, cancer and epilepsy, but for several pediatric conditions, a generic HRQOL measurement was stated to be the only possible option. Very few measures were available for children younger than 8 years. Studies were needed to better understand the child and parent reported HRQOL (132).

In 2003, Schmidt and Bullinger, concluded that the most known QOL/HRQOL instruments had undergone a cross-cultural adaption, but a cross-cultural evaluation was still needed in children with chronic health conditions (133). Two years later, De Civita et al. addressed the need to have an empirical basis to generate items in a questionnaire and to select specific domains. This would help to avoid confusion between the concepts QOL and HRQOL. A higher involvement of children defining HRQOL was addressed, and still, a better understanding of the relationship between child-parent ratings of QOL/HRQOL was required (134).

In 2006, Bullinger et al. (120) declared that in HRQOL research of pediatric populations, children of younger age than 13 years were underrepresented and that most HRQOL instruments that were being developed were proxy-reported. While empirical investigations were less prevalent, theoretical and conceptual work constituted about half of the publications. About a third of the HRQOL instruments were disease-specific.

Reaching year 2008, Solan et al. (131) concluded that the development of HRQOL instruments for children and adolescents, particularly with regard to disease-specific instruments, had advanced. Many questionnaires met the accepted standards for psychometric properties; however, still the inclusion of children in the PROM development was underlined.

In 2013, specific recommendations for pediatric PROM development in medical contexts were provided by the ISPOR task force: Good Research Practices for the

PRO Assessment of Children and Adolescents (13). Five good research practices for pediatric PRO in medical contexts were presented.

- The developmental differences and age-based criteria for the administration form should be considered. Specific age cutoffs should be determined individually for each PRO instrument and tested with cognitive interviews in each new target population.
- Content validity of pediatric PRO instruments can be assessed through the inclusion of children in qualitative research.
- Informant-reported outcomes include both proxy and observational measures. The reports should measure observable content as much as possible.
- The instrument should be designed and formatted appropriately for the target age group, e.g. aspects such as vocabulary and reading level, response scale, recall period, length of instrument should be taken into consideration.
- Cross-cultural issues should be addressed. Content validity and measurement approach of a pediatric PRO instrument need to be re-examined within each new culture.

Good progress, but still, pediatric PRO research had a long way to go. In 2014, Huang et al. (135) concluded that there was still confusion between the concepts QOL, HRQOL and functional status. Moreover, the same domain name across different instruments did not ensure the same underlying definition (or measurement) of the same construct. In addition, different psychometric methods had been used to evaluate different PROMs. Item response theory (IRT) could support the information whether items truly measure different levels of the same underlying latent construct. Similar to other studies (125, 136), Huang et al. (135) underlined the need to investigate the HRQOL instruments' responsiveness to clinical change. Without information of responsiveness and minimally important differences, difficulties will arise to understand and monitor the PROs over disease or developmental trajectories. The need to investigate response shift was also described, since the interpretation of PROs may change along with new experiences or neurocognitive development stages in children. A need for a life-course theory to generate latent constructs of PROs for children and adults with chronic conditions was needed, to facilitate comparison of PROs across childhood and adulthood (135).

Examples of generic QOL and HRQOL measurements in children and adolescents

Reflecting the last decenniums' evolution with regard to generic HRQOL questionnaires, a selected sample of four generic HRQOL instruments, are introduced as examples for multidimensionality, self-report and psychometric testing. These instruments are the Child Health Questionnaire (CHQ) (137-139), the Pediatric Quality of Life Inventory (PEDSQL)(140, 141), the KIDSCREEN (142-145) and the DISABKIDS (146-148) and are presented in more detail in Table 1.

Coping with chronic disease

The literature on coping with chronic illness has expanded during the last decades and for this, various reasons can be observed. Since people today of industrialized societies are living longer, the risk of experiencing a chronic disease has increased. Moreover, medical advances have led to an increased survival rates in former life-threatening diseases such as in children with congenital malformations. Chronic conditions during childhood may be accompanied by physical, sensory, cognitive and neurological disabilities (149, 150). In a Swedish report, 9% of the girls and 11% of the boys in ages 0-15 years suffered from a chronic disease that considerably had affected the daily life during at least 3 months of the last year or lead to continuing medical treatment (151). Corresponding to a larger number of people suffering from chronic disease and greater life expectancy of previously life-threatening diseases, an interest has grown to explore not only HRQOL and psychosocial functioning, but also what mediates or moderates such outcomes. Questions have arisen of how individuals, who earlier had limited chances of survival, today manage to live with chronic morbidity and to adjust successfully. Therefore, parallel to the development of QOL/HRQOL research, literature on coping and psychosocial adaptation with chronic disease has expanded (152).

New survivor groups of children with former life-threatening diseases give rise to questions, how they manage to live with chronic condition and adjust successfully

Stress, Adaptation and Coping

People encounter two types of stressors; major life events and daily hassles. Originally, major life events (e.g. death of a significant person, parental divorce) were considered to be the critical stressors, instead of the daily hassles, which are defined as irritating, frustrating and distressing demands that plague us daily (e.g. feeling left outside, feeling different, being bullied by peers, failing at school, or feeling ill). Stressors can affect people due to the frequency and/or due to the intensity. Chronic disease and/or disability may lead to specific stressors in context of major life events and daily hassles. Such stressors are considered as added on to common stressors that all people experience (153). Successful adaptation to stressful situations is important with respect to the development of mental and physical health/disorder and/or improved/impaired HRQOL (14, 154). Coping is a particular adaptation, which occurs in individuals when they are confronted with stressful and demanding situations (14, 153).

Table 1. Characteristics of four well-established generic health-related quality of life questionnaires for

Questionnaire (reference number)	Purpose	Year/Country of origin	Respondent/ Age band	Number of items	Dimensions
Child health questionnaire; CHQ (137-139)	To measure health-related quality of life in healthy children and adolescents and those with acute and chronic conditions	1996/USA	Child/ 10–18 Parent/ 4–18	87 98/50/28	Physical functioning, bodily pain, role/social-physical, general health perception,role/social-emotional/behavior, mental health, general behavior, self-esteem,parental emotional impact, parental time impact, family impact
Pediatric Quality of Life Inventory; PedsQL 4.0 (140-141)	To measure health-related quality of life in healthy children and children with acute or chronic conditions	2001/ USA	Child and parent/ 5–18 Child and parent/2-4	23 21	Physical functioning Social functioning Emotional functioning School functioning
KIDSCREEN (142-145)	To assess children's and adolescents' subjective health and well-being applicable for healthy and chronically ill children and adolescents	2001-2004/ Austria, Czech Republic, France, Greece, Hungary, Ireland, Poland, The Netherlands, Spain, Sweden, Switzerland, United Kingdom and Germany	Child and parent/ 8-18 years	52/27/10	Physical Well-being, Psychological Well-being, Moods and Emotions, Self-Perception, Autonomy, Parent Relations and Home Life, Social Support and Peers, School Environment, Social Acceptance (Bullying), and Financial Resources
DISABKIDS; DCGM (146-148)	To asses chronic-generic and condition-specific health-related quality of life in children and adolescents with chronic health conditions	2001-2007/ Austria, France, Germany, Greece, The Netherlands, Sweden, United Kingdom	Child and parent/ 8-16 years Child and parent/ 4-7 years (and older children who are cognitively impaired)	37/12/6	Independence, Emotion, Social inclusion, Social exclusion, Limitation, and Treatment Chronic-generic health-related quality of life

† different results on retest reliability have been reported
‡ Item generation and reduction is described for the Pediatric Cancer Quality of Life Inventory, from which the PedsQL 4.0 is derived
§ measurement of longitudinal change in quality of life, was performed after the field test

Scale	Evidence of reliability	Evidence of validity	Example of responsiveness	Strengths (+) and weaknesses (-)
Each item consists of 4-6 response options depending on the item	Internal consistency Reproducibility†	Construct validity Criterion validity	Chronic pain, fatigue	+ captures all core dimensions of quality of life, available in many countries, well evaluated - the self-completion is very long and it was not constructed based upon qualitative research in children, retest reliability has shown different results, different child-parent items, self-report for younger children is lacking
5-point response scale scored as Never to almost always. Adjusted to a 3-point scale for children aged 5-7 years	Internal consistency Reproducibility	Content validity‡ Construct validity Criterion validity	Cardiac disease, pediatric orthopedics clinic setting and rheumatic disease	+ captures all quality of life core dimensions, well documented psychometric properties in many countries, available for a large age span, provides several condition-specific or symptom-specific measurements - was initially not cross-culturally developed, version 4.0 was derived from 1.0 and not directly from qualitative research on children, school-dimensions may be difficult to answer for ill children not attending school
5-point scale from never to always	Internal consistency Reproducibility	Content validity Convergent validity Criterion validity	Changes in mental health status of Spanish children and adolescents§	+ simultaneous development of quality of life measurement in 13 European countries, Rasch-scaled dimensions, participation from children and their parents in evaluation of the questionnaire throughout the project, works well for use in clinical settings - a measurement for young children is lacking
5-point scale from never to always/smiley faces from very happy to very sad	Internal consistency Reproducibility	Content validity Convergent validity Criterion validity	NA	+ cross-cultural evaluation with participation of children and parents throughout the project, well-documented psychometric properties, a standardized measurement available in many countries, measure chronic-generic and condition-specific health-related quality of life, available for a large age span - lack of evidence for responsiveness

Coping definitions started to appear in the 1970s, but one of the most influential coping definitions has its roots from Lazarus and Folkman in the 1980s, who meant that coping was rather process-oriented than trait-based. Stress was said to occur due to specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person (155). Individuals orient their thoughts and behaviors toward the goals of resolving the stressful source or of managing emotional reactions following stress. According to the model, coping with disease-related stress includes all purposeful attempts to manage stress, regardless of their effectiveness (156). Lazarus and Folkman (155) meant that an individual's appraisal of the degree of stress and the availability of coping resources determine the ability to adapt. Given this background, coping must be distinguished from defense mechanisms which are rigid and automatically generated, intra-psychic efforts directed at decreasing anxiety and danger. Instead coping strategies are flexible, integrated, and environmentally attuned efforts that are concerned with the management of both internal and external demands as well as with the personal resources (152).

Particular aspects related to coping with chronic disease during childhood and adolescence

The ways in which children and adolescents cope with stress may affect their health outcomes and psychosocial adjustment (157). In 2009, Skinner et al. (154) declared that the understanding of childhood coping can contribute to higher knowledge of how difficulties shapes the development of children and adolescence, and in turn, how their development relates to risks, resilience and competence (15). Coping in children and adolescents must be understood from a developmental perspective, since the organization and flexibility of coping will undergo qualitative and quantitative shifts from early childhood to adolescence. Children's cognitive, emotional, language, memory are likely to affect the ways cope with disease-related difficulties (14, 154, 158). Coping is described to evolve during childhood; starting with stress responses guided by reflexes during the neonatal period, via behavioral schemes during infancy, adding regulation, which will be supplemented by coping through direct action during preschool age. In middle childhood, cognitive coping and during adolescence, more sophisticated cognitive efforts are present (14, 15, 154). Schmidt et al. (14) also declared that coping is a developmental process, with behavioral strategies being more prominent at an early child age and where the evolution will form cognitive and flexible coping strategies. A broad framework of coping also considers how the child's temperament, socialization and normative patterns surrounding the child will shape the child's coping (14, 158). From the perspective of emotional regulation, the attachment theory (interpersonal context) can provide information as to why some individuals are able to resourcefully use different strategies, in contrast to others who use rigid ways of coping (14). In children with chronic health condition, the concept of patient participation may be considered as a further elaboration of coping. In view of coping, patient participation can be used to describe the self-management in relation to the desirable health outcomes. When supporting the active role in children with chronic conditions, the child is guided by their interaction with medical care and is put in a position where they can influence their own

development (14). Indeed, the development of coping is complex and may be formed by interpersonal factors, environmental characteristics and disease-related aspects (14, 158).

Very many subtypes of coping have been identified in children and adolescents with chronic conditions, among them seeking social support, self-reliance, problem-solving, social isolation, wishful thinking, positive restructuring and distancing (15, 153). In 2012, Compas et al. (15) summarized a broader framework for childhood coping that were empirically tested and validated. Accordingly the elements of coping with chronic illness in childhood and adolescence consisted of three control-based factors, as viewed in Figure 5. The summary of previous literature on coping efficacy showed that secondary control coping (e.g. cognitive reappraisal, positive thinking, acceptance) is related to successful adaptation to chronic illness, disengagement coping (e.g. avoidance, distancing) is associated with poorer adjustment, and findings for primary control (e.g. problem solving) coping of mixed outcomes (15). Such categorizations can be used to assess the impact of coping on health, psychosocial functioning and HRQOL and to more easily try to measure a person's inclination to respond to a range of stressful situations in a particular way (152).

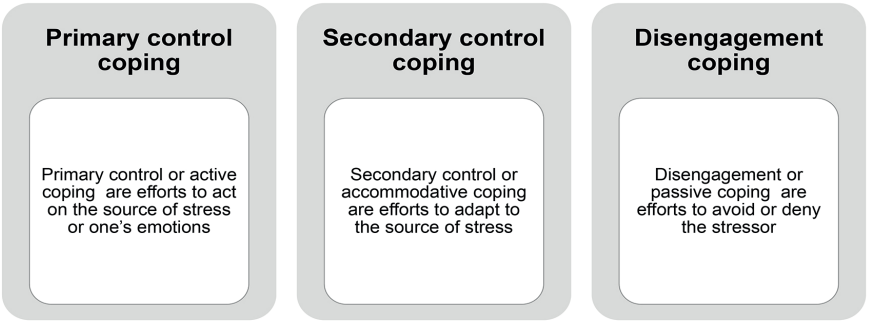


Figure 5. A model for childhood coping summarized by Compas et al. 2012

The evolution of pediatric coping measurements

In the late 1980s research on coping in children and adolescents was in its earliest stages (159). Most conceptualizations of coping in children and adolescents were initially based on models of coping in adults and measures of coping had been developed for adults and applied to children and adolescents with little or no modification. The majority of models of coping, which was based on adults, did not specifically address the developmental perspective of coping (157). However, the field of coping with stress during childhood and adolescence has made some advancement in the past 20 years (15, 157). In 2003, Schmidt et al. (14) showed that in terms of coping with pediatric chronic illness, in 14 studies, children's as well as parents' views on coping were assessed. However, more studies assessed parents' view on cop-

ing compared to the children's view on coping. In addition, the parents' views were mostly related to their own coping strategies with the burden that the child's chronic disease might lead to. Five years later, in 2008, Blount et al. (160) identified nine coping measurements for children; six were general coping measurements and three regarded pain-specific coping. Four of six general coping instruments were classified as well-established. Conclusions were drawn that there was a need to give attention to the quality and characteristics of pediatric coping measures. In previous research, future coping measurements have been recommended to focus on the situational context and content of coping, in order to increase the likelihood of capturing the multifaceted ways that one use coping during childhood and adolescence (14, 15, 153).

Examples of self-report coping measurements for children and adolescents

A selected sample of four self-reported coping measurements for children and adolescents is presented in Table 2. These instruments are the Kidcope (161, 162), The Responses to Stress Questionnaire (163, 164), the Children's Coping Checklist (165), the Coping with a Chronic Disease –CODI (166, 167) Only one coping measurement for children and adolescents (Coping with a chronic Disease) is available in Swedish (according to a literature research) (Table 2).

Coping strategies used by patients with EA

Several authors (16-18) have argued that coping is more efficient in the EA population due to the nature of a congenital condition and that such coping capacities could lead to better outcomes than in acquired diseases (17, 18) and in healthy people (16). Consequently, this would explain why higher levels of HRQOL in children with EA are found compared to patients with diabetes or asthma (17), and why more satisfaction and gratefulness to life after esophageal replacement is observed in patients with EA compared to patients who acquired caustic stenosis (18). One study by Deurloo et al. (168) investigated coping used by adults with EA and demonstrated that adults who reported negative consequences from EA in open-ended questions, had impaired physical functioning on the 36-item Short Form Survey (SF-36) (145). They also had reduced scores on the physical and gastrointestinal symptom domains and on the total scores of the Gastro Intestinal-Quality of Life-Index (GIQLI) (169). Patients who reported a negative influence in terms of limitation demonstrated low acceptance and high helplessness according to the Illness Cognition Questionnaire (170). Adults who reported positive consequences from EA, even with impairment on the physical role scale on the SF-36 had higher scores on perceived disease benefit (168). However, despite the importance of establishing good coping strategies early in life, no empirical study of coping used by EA children seem to have been reported in the literature at the start of our research project.

PROMs in rare disease- particular conceptual, methodological and regulatory issues

PRO assessment in rare disease (RD) meets particular conceptual and methodological challenges. Corresponding to more diagnostics and treatment modalities that evolved for RDs, key issues for demonstrating safety, efficacy, effectiveness and clini-

cal meaningfulness through PRO assessment have been increasingly reported (126, 171-173). In children and adolescents with RDs, a joint use of generic and disease-specific instrument can give a more valid understanding of HRQOL. Although some RDs have received attention in terms of HRQOL assessment (122), disease-specific instruments are often lacking despite that these may provide a higher degree of content validity than generic ones. This may be explained by a number of challenges that exist in the development, analysis and interpretation of PROMs in RD contexts. These challenges include the availability of suitable measures, recruitment difficulties, complexity of data collection methods and heterogeneity of outcomes (122, 126). Indeed, the small number of patients may impede the recruitment of patients for the development or the validation of a PROM. If the heterogeneity in the RD is large, discrete outcomes across the population may be difficult to measure (126). ISPOR special interest group for RD has released several documents (173,174) to elucidate key challenges, issues and recommendations in RD research, including PRO assessment. The ISPOR task force for RD provides recommendations to overcome some of the specific challenges in PRO assessment that are caused by the small number of patients and heterogeneity in the condition in RD. In the available literature, it is, among others, recommended to use a variety of information sources on the PRO concept of interest; registries, literature, clinical experts, patients and caregivers. Moreover, patient advocacy groups for recruitment of patients and the use of patient clinic visits for time assessment have been recommended (122, 126, 173, 174). Qualitative studies are emphasized to understand disease experience in recognized subgroups, regions or other factors affecting the disease or treatment. Moreover, core signs and symptoms should be the focus during the development of a PROM. When traditional methods in PROM development cannot be followed, this should be documented (173, 174).

In the year 2015, FDA published a document on Guidance for the Industry on common issues in RDs and declared that the definition of a study endpoint includes the selection of a patient assessment to be used as an outcome measure. The suitability of the available patient assessment tools, the modification of existing ones or the recognition of a new PROM development must be considered early in the research process in order for it to be reliable (171).

Application of pediatric PROMs

With efforts to improve health and well-being among pediatric patients, an increased utilization of standardized pediatric PROMs has been observed. This has enabled evaluation of disease, treatment and health care from the patient perspective in research, clinical practice and health policy (8-10, 120, 175). HRQOL measures can be used to determine the effects of treatments and psychosocial interventions in research, but can also be used for comparative and evaluation studies in health policy (12). In 2009, FDA released their Guidance for Industry (11), which clarified that PROMs should be used to measure treatment benefits or risks in clinical trials. The HRQOL assessment in the individual patient can provide information of a patient's health state, which is relevant in clinical practice. The application forms

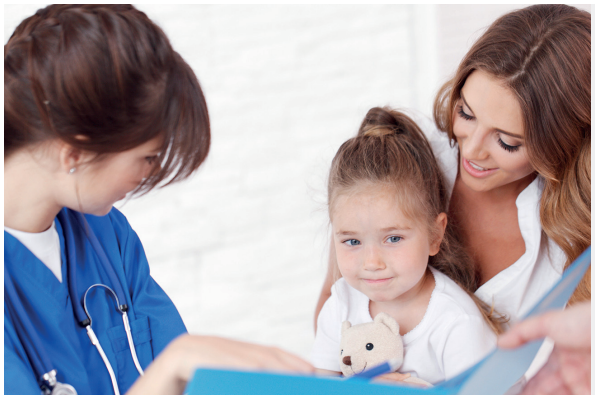
Table 2. Characteristics of four different coping questionnaires for children and/or adolescents

Questionnaire (references)	Aim	Year of development/ Country of origin	Respondent	Number of items	Dimensions
Kidcope (161-162)	To assess coping thoughts and behaviours in children and adolescents	1988/USA	Child 7-12/ Child 13-16	15/10	Three subscales measuring ten coping strategies: avoidant coping (distraction, social withdrawal, wishful thinking, resignation); negative coping (self-criticism, blaming others) and active coping (problem solving, emotional expression, cognitive restructuring, social support)
Responses to Stress Questionnaire (163-164)	To measure volitional coping efforts and involuntary responses to specific stressful events or specified domains of stress	1991/USA	Child 11-19 years	57	Primary control engagement coping, secondary control engagement coping, disengagement coping, automatic engagement and disengagement stress responses that do not reflect coping
Children's coping checklist (165)	To describe coping efforts in children	1996/USA	Child 9-13 years	54	11 subscales, to be subsumed into the following five primary scales: problem focused coping, positive reframing, distraction, avoidance and support seeking strategies
Coping with a Chronic Disease (166-167)	To assess coping thoughts and behaviours in children with chronic health conditions	2001-2006/ Austria, Germany, Greece, the Netherlands, Sweden, United Kingdom	Child 8-18 years	28	Six coping strategies; acceptance, avoidance, cognitive-palliative, distance, emotional reaction, wishful thinking

†content analysis of children's responses according to a semi-structured interview combined with items from a literature review of coping during childhood and adolescence
‡ different results of factor loadings and scale structure have been described

Scale	Reliability	Validity	Strengths (+) and weaknesses (-)
2-point response scale to confirm the use or not (yes/no) and how effective they perceived the coping strategy was for them in that specific situation (not at all to a lot).	Reproducibility	Convergent validity Criterion validity	+ measures the perceived effect of a coping strategy, covers a broad age range, one of the more commonly used coping questionnaires in children - was developed a long time ago and was not derived from qualitative research in children, could need further psychometric evaluation
4-point frequency scale from not at all to a lot, additional information to describe specifically how they employed that particular coping strategy	Internal consistency Reproducibility	Convergent validity Criterion validity	+good psychometric properties, covers a broad aspects of stress responses -was developed many years ago, only for use in a narrow age band, many items can be exhausting for children to complete, involuntary responses cannot be understood as coping
4-point frequency scale from never to always	Internal consistency Reproducibility	Content validity† Convergent validity‡	+ one of the more recent developed questionnaires that partly was developed based on child interviews - many items to complete may be exhausting for children, measures coping in a more narrow age range, factor loadings and scale structure varies in psychometric evaluations
5-point Likert scale from never to always	Internal consistency	Content validity Convergent validity	+ the most recently developed questionnaire that uniquely was constructed cross-culturally and was derived from qualitative research on children, directed to assess stress response due to a chronic health condition, covers a broad age band -Could need further psychometric evaluation such as test-retest reliability and criterion validity

of PROMs in clinical practice include the function as screening tools and monitoring tools. They can serve as a method to promote patient-centered care, serve as a decision aid and as a method to facilitate communication amongst multidisciplinary teams (176, 177). In RD, a standardized HRQOL assessment can help to not only identify health care needs, but also to assess the progress in health status (122). In pediatric clinical settings, several studies have revealed positive outcomes after applying PROMs into pediatric routine care. The evaluation of the young patients' self-reported HRQOL in clinical practice can improve the patient–physician communication and the information provided to the family (178-180). A Swedish study published in year 2016, showed that children with chronic conditions experienced that the HRQOL assessment during a patient encounter provided them with insights about their health and that they felt encouraged to make lifestyle changes when outcomes were discussed with the health care professionals (181).



The evaluation of young patients' self-reported HRQOL in clinical practice can improve the patient-caregiver communication and the information provided to the family

Studies on coping can contribute to a better understanding of how the ways children and adolescents cope with disease-related stress affect outcomes of health, HRQOL and psychosocial adjustment. Children's utilization of coping strategies may differ between different diagnosis and ages (14, 153, 182), but it has also been shown that the most frequently used coping strategy was assessed by the children as the most effective (182). Coping assessment has been recommended to be incorporated into pediatric treatment programs, for example in childhood asthma (183). Coping interventions, including psychosocial-educational interventions, can be used to strengthen positive behavioral, emotional and social outcomes in children with chronic conditions (184-186).

Aim

The thesis is a part of a larger research project with the long-term aim to address the needs of care, improve the evaluation of pediatric surgical care and treatment and to enhance the health and HRQOL in children and adolescents born with EA. The overall aim of the thesis was to describe current knowledge of HRQOL in EA patients and the subsequent need for advancement in the field. Moreover, to gain the child and parent perspective on condition-specific HRQOL and coping in order to more completely understand the possible long-term consequences of EA. Specific aims included

- To review the literature on HRQOL among EA patients across all ages, to conduct a metaanalysis of the effect of EA on HRQOL and to describe the questionnaires that have been used in order to improve knowledge within the field (paper I)
- To describe condition-specific HRQOL experiences as reported in focus groups by Swedish children and adolescents with EA and by their parents (paper II)
- To describe the development of the "Esophageal atresia Quality-of-Life questionnaire" (EA-QOL questionnaire), a condition-specific HRQOL questionnaire for children and adolescents born with EA (paper II, IV)
- To evaluate item and scale characteristics when using the EA-QOL pilot questionnaire in Sweden and Germany (paper IV)
- To establish the EA-QOL field test questionnaire (paper IV)
- To increase the understanding of coping processes among children with EA by obtaining the child and parent perspective, and thereby to create the groundwork for a condition-specific coping questionnaire (paper III)

Patients and methods

Patients

Patients and methods of the specific papers I-IV are presented in Table 3. Regarding the empirical studies, families of children with EA were recruited from Queen Silvia Children's Hospital, Gothenburg Sweden (paper II, III, IV) and from the Center of Pediatric Surgery, Hannover Medical School, Hannover, Germany (paper IV). The methodological work included qualitative as well as quantitative methods. All procedures complied with the Helsinki Declaration (187) and were approved by the regional ethical committees in Gothenburg, Sweden and Hannover, Germany.

Table 3. An overview of aim, patients and methods of paper I-IV

	Study aim	Patients	Methods to collect data	Year of data collection	Data analysis
Paper I	To review the literature on health-related quality of life in patients with EA and describe the questionnaires used	Estimated as 589 patients (158 children, 433 adults) and 214 parents who participated in twelve studies	Systematic literature review including a metaanalysis	Inception - Jan 2015	Content-analysis Synthesize of results Metaanalysis
Paper II	To describe the health-related quality experiences reported by children with EA and by their parents and the subsequent establishment of a condition-specific health-related quality questionnaire	30 families of children with EA 2-17 years; 18 children 8-17 years, 32 parents of children 2-17 years	Medical records review Standardized focus groups	2014	Content analysis Descriptive statistics
Paper III	To describe coping strategies among children and adolescents with EA and the situational context in which coping strategies are used, from the child and parent perspective. To provide groundwork for the development of a condition-specific coping questionnaire	30 families of children with EA 2-17 years; 18 children 8-17 years, 32 parents of children 2-17 years	Medical records review Standardized focus groups	2014	Content analysis Descriptive statistics
Paper IV	To describe the results from a pilot test – including the initial validity and reliability- when using a condition-specific HRQOL questionnaire for children and adolescents with EA in Sweden and Germany	86 families (21 German, 65 Swedish) of children with EA 2-17 years old; 51 children 8-17 years old, 86 parents of children 2-17 years old	Medical records review Questionnaire study Cognitive debriefing	2015-2016	Psychometric statistical analysis Content analysis Descriptive statistics

Abbreviation: EA, esophageal atresia

Overall study design

The study design followed the international guidelines for the development of a PROM provided by the FDA (11), the international recommendations for PROM in children and adolescents (13) and the emerging practices for PROM in RD provided by the specific ISPOR task force (172, 173). Particularly, methodological experiences were collected from the European DISABKIDS project for children with chronic health conditions (188). The overall aim of the DISABKIDS project was to develop and to support the use of standardized instruments of HRQOL, coping and health care needs in children with chronic health conditions. Thereby, the aim was to enhance HRQOL and independence of children with chronic health conditions. Seven different pediatric chronic health conditions (asthma, juvenile rheumatic arthritis, epilepsy, cerebral palsy, diabetes mellitus, atopic dermatitis and cystic fibrosis) were included in the initial project. Studies were conducted in collaboration between seven different European countries (France, Germany, Greece, the Netherlands, Sweden, Austria and the United Kingdom) (188). The DISABKIDS project used the definition of HRQOL as physical, social and mental components of QOL, and distinguished between chronic-generic and condition-specific HRQOL measurements. The condition-specific questionnaires were cross-culturally developed in at least two counties (188). A patient-derived nature of questionnaire development was used throughout the project. The methodology includes seven work phases, which reflects the stepwise process; literature review, focus groups, item development, translation, pilot study, field test and implementation of the questionnaire (147, 148).

The focus group is led by a trained moderator and helps to collect experiences on a specific topic based on discussions among 3-6 participants

The start of the project is a review of the literature on HRQOL assessment in the particular population. Criteria for severity of disease are developed by experts to prepare the empirical studies. Standardized focus groups - composed according to the child's severity of disease, age and gender – are held. Each focus group consists of discussions among 4-6 participants, which is led by a trained moderator. The aim of the focus groups is to incorporate children's and adolescents' views on HRQOL into the development of the PROM; the reported HRQOL experiences are used to generate items for a preliminary questionnaire. Items are translated from a linguistic and semantical point of view. The questionnaire undergoes an item reduction pro-

cess; and is evaluated for validity and reliability in its shortened version. A primary evaluation of the questionnaire is conducted through a pilot test, which includes a cognitive debriefing, and lastly in a field test, using a larger study sample of the target population. The questionnaire can thereafter be implemented in clinical studies including intervention studies and comparative studies (188).

Preparation for empirical studies

Multidisciplinary expert team

As a ground for the EA project, a Swedish-German multidisciplinary expert panel (pediatric surgeons, psychologists and a pediatric nurse) was established. The aim of the expert team was to ascertain pediatric surgical expertise of EA, methodological knowledge of PROM development and cross-cultural understanding of the specific Swedish and German contexts during the studies of condition-specific HRQOL and coping.

Criteria for severity levels of EA

Four inclusion criteria for severe EA were defined by the expert team under consideration of previously reported research on severity of EA (68, 69, 71, 79, 189-191) and an international review from pediatric surgeons. A child was regarded to have severe EA fulfilling one or more criteria (A-D) as described in Table 4. Each associated anomaly was discussed in relation to the term disability, as an umbrella term for impairments (problems in body function or structure as a significant deviation or loss), activity limitations and/or participation restrictions (192). All congenital conditions regarded to cause disability were documented.

Table 4. Inclusion criteria for severe esophageal atresia

Severe EA	A)	The primary anastomosis was delayed and/or EA replacement was accomplished
	B)	Major surgical revision (open surgery) of the EA correction performed for causes as recurrent TEF or anastomotic leakage
	C)	Severe tracheomalacia/ tracheobronchomalacia verified through a flexible broncoscopy with a macroscopic estimation of an anteroposterior collapse documented as excessive, severe and/or of ≥75% during cough or expiration (79). The most recent bronchoscopy was considered valid
	D)	Presence of at least another congenital health condition resulting in disability according to the definition provided by the International Classification of Disability and Health (192). The term disability is an umbrella for impairments (problems in body function or structure as a significant deviation or loss), activity limitations or participation restrictions. Each associated anomaly was discussed by the expert team until consensus was reached

Abbreviations: EA, Esophageal atresia; TEF, tracheoesophageal fistula

Review of medical records

The clinical data collected for the whole research project included prenatal diagnosis, neonatal data (gestational age at birth, birth weight, Apgar score, multiple birth), type of EA according to the Gross classification, presence of associated anomalies

(cardiovascular, anorectal, gastrointestinal excluding anorectal, uro-genital, limb, vertabrae-rib, choanalatresia, eye, ear, central nervous system, respiratory, other), presence of syndrome or chromosomal abnormality, information regarding the surgical repair (time of esophageal surgical repair, type of surgical treatment, time period for postoperative mechanical ventilation, postoperative complications such as recurrent fistula, anastomotic leakage, sepsis, wound infection, pneumothorax, trombosis or other adverse events), need for revisional surgery, presence of dilatation before the first hospital discharge, length of stay at the pediatric surgical ward. Moreover, the number of dilatations and presence of TM verified by bronchoscopy until the time of the study was noted. Based on data in the medical records, the child was categorized as fulfilling or not fulfilling the severity criteria A, B, C, D. The number of fulfilled criteria for severe EA was noted as well.

The DISABKIDS focus group manual

The DISABKIDS focus groups manual consists of eight questions focusing on the child's health care needs, QOL and coping processes (193). The aim of the questions is to promote a discussion among the focus group participants. In order to gain an understanding of the relevance and adequacy of the DISABKIDS focus group questions for EA families, the eight questions were pretested prior to the empirical use. The pretest included individual structured interviews with five Swedish health care professionals (one child nurse assistant, four pediatric nurses, and one pediatric surgeon who were not a part of the author group, total experience of 151 years in the field of pediatric surgical care). All participants provided their view on the relevance and appropriateness of the focus group questions. They also gave their perspective of the impact of EA in the child's life and the wording that children with EA and their parents used to describe their situation. Based on the results, standardized follow-up questions were documented in order to improve the discussions among children with EA, and among their parents.

Moderator training

Before the focus groups were conducted, all moderators took part of the DISABKIDS focus group manual and underwent training in focus group methodology. Meetings were held to go through the DISABKIDS manual and to strengthen the standardization of the procedure.

Literature review and metaanalysis (paper I)

Data collection

The literature review reflected a systematic approach with the aim to detect articles from a number of different sources and include articles based on pre-defined criteria (194). A broad literature search was conducted among the databases Pubmed, Cinahl and PsycINFO in order to identify articles up to January 2015 that included empirical information of HRQOL in EA patients. Searches were performed without limitations with respect to publication year, language employed or accessibility to full-text articles. A combination of keywords and database specific terms were used

(respiratory AND esophageal chronic disease OR congenital anomaly OR digestive system abnormalities OR esophageal atresia) AND (psychology OR psychosocial needs OR well-being OR health outcome OR quality of life OR health related quality of life) AND (questionnaire OR instrument OR patient-reported outcome).
Studies with the aim to describe HRQOL among EA patients were included. Since the term HRQOL is multidimensional, reports on single domains, psychological impact or symptoms were excluded. Sixteen literature reviews of patients with chronic conditions related to EA were read throughout, but no additional articles were identified through manual search of references from them. The process of article selection is outlined in Figure 6.

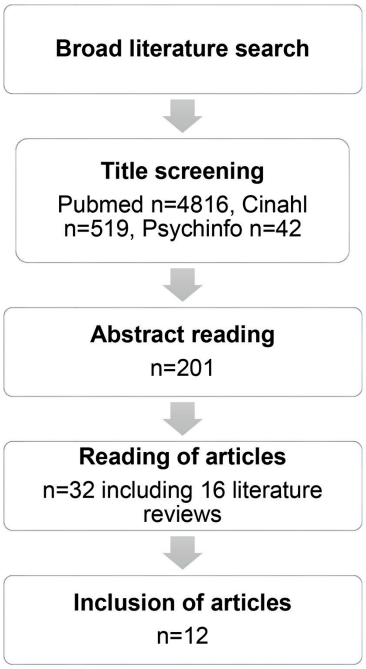


Figure 6. Description of the step-wise search for empirical studies of health-related quality of life in patients with esophageal atresia

The doctoral student had the main responsibility for screening the titles and abstracts. Articles that were identified at this stage were then independently read and discussed with two more authors to ensure an unbiased selection in the final inclusion. In order to trace the psychometric characteristics of the questionnaires used to measure HRQOL in EA patients, a new database search in PubMed, CINAHL and PsycINFO was completed. If this information was sparse, contact was attempted with the author responsible for the development of the questionnaire.

Data analysis

In order to advance knowledge within the field, the following information of studies of HRQOL among children, young people and adults with EA was described

- Characteristics of articles (year of publication, objective of the study, study de-

sign, HRQOL questionnaire used, study participants, response rate, location for data collection, control/reference group).

- Questionnaires that had been used in HRQOL evaluation. As a framework to the describe the questionnaires used in evaluation of HRQOL in EA patients, the questionnaires were appraised for adherence to the desirable attributes outlined by the Scientific Advisory Committee of the Medical Outcomes Trust, namely the conceptual design, validity, reliability, responsiveness, interpretability, patient burden, modes of administration and cultural/language adaptations (112).
- The empirical HRQOL findings. With the intention of conducting a systematic literature review (194) and receiving a comprehensive understanding of HRQOL, a metaanalysis of the effect size in HRQOL scores for patients with EA compared to healthy references/controls was conducted. Effect sizes (ESs) were calculated as Cohen's d and we relied on Cohen's criteria for standardized interpretation, and considered an ES >0.2 small, >0.5 moderate, and >0.8 large (103). I^2 statistic was calculated to assess the degree of heterogeneity (195).

Focus group study (II, III)

Participants

During the period 1997–2013 at the Queen Silvia Children's Hospital in Gothenburg, Sweden, 135 children with EA survived (91.8%) and were eligible for recruitment at the time of the Swedish focus group study. 73 children (54.0%) were categorized as cases of severe EA. Focus groups were stratified for child gender and families of each five children with mild-to-moderate EA and five children with severe EA (one or more of the criteria A-D) were selected in three age groups (0–7, 8–12, 13–17 years). In total, a number of 30 families were contacted and accepted the study invitation.

Data collection

Informed consent to participate in the study was obtained from each family. In addition to information given to the legal guardians, children 12-17 years old received written information for children, and adolescents 15-17 years old gave written informed consent.

Separate focus group discussions with the Swedish children and their parents took place during year 2014 and were digitally recorded. The DISABKIDS focus group manual (193) with eight questions focusing on issues of health, HRQOL and coping, formed a standard basis for discussions with both children and parents. All participants were asked questions about the nature and extent to which the EA condition has continued to affect the child's daily life including in school, spare time, at home and in the family. All focus groups participants were given opportunity to discuss questions about the impact of esophageal morbidity, respiratory morbidity, growth retardation, surgical scar and associated anomalies. Discussions were facilitated by

the moderator, who ensured that all participants had an opportunity to contribute. A research assistant who was present during the child focus groups was responsible for taking field notes of non-verbal communication and group interactions, which were used to create a better understanding of the verbal findings. In the focus groups with parents of children with EA, field notes were made by the moderator.
All parents also completed a structured questionnaire of family characteristics regarding parent characteristics (age, gender, marital status, native ethnicity, the family's living area, parental health, educational level, occupation, income per household, need of financial support, number of persons living in the household). The questionnaire also contained questions about the child's current health status including weight, length, presence of esophageal morbidity (GERD, dysphagia, impact on meal situation) and respiratory disorders (doctor-diagnosed asthma, wheezing, cough, dyspnea), medical treatment and child school situation.

Data analysis

Content analysis of health-related quality of life experiences
A patient-derived approach was used in the data analysis. The focus group discussions were transcribed verbatim and the transcripts were content analyzed with the intention to be consistent with the FDA guidelines of a PRO (11), i.e. to preserve the report given by the focus group participant. HRQOL experiences were extracted from the focus group text and documented in Excel 2010. Each HRQOL experience was concisely formulated as a HRQOL statement. The reporting participant information (child age, child gender, severity of EA, child-proxy-report) was noted. All participant information was printed on a card with the HRQOL statement. HRQOL statements were card sorted into domains, which can be defined as grouping of HRQOL statement that share a common feature. A term that characterized the content of the categories was chosen (Figure 7). Statistical analysis was performed using SPSS 22.0. Descriptive statistical analysis of the clinical and sociodemographic data, the frequency and distribution of HRQOL statements according to domains, severity of EA, child gender, age group (0-7, 8-12, 13-17 years), child and proxy reports was performed.

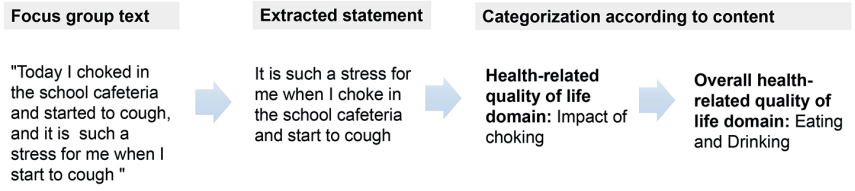


Figure 7. Example of the categorization process

In a further categorization process, the content HRQOL domains were (deductively) assigned to the three main dimensions of HRQOL – physical, social and emotional HRQOL. An example is given in Figure 8. The frequency and distribution of the HRQOL dimensions were analyzed in relation to the HRQOL domains.

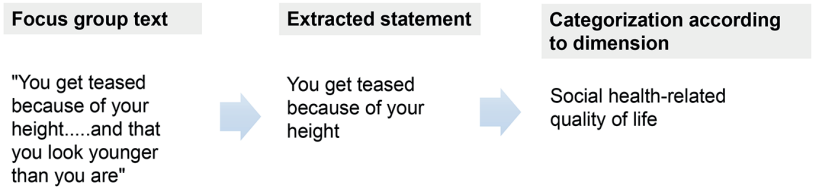


Figure 8. Example of the deductive categorization process of health-related quality of life core dimensions (physical, social and emotional)

The development of a questionnaire

The focus group results were used to derive items for the development of a draft HRQOL questionnaire. The primary item generation and item selection were based on the following criteria: high frequency of repeated statements was an indication of importance to the patients; if semantically equivalent, they were replaced by a single HRQOL statement covering that concept; HRQOL statements that were described across subgroups of EA (severity, child gender, child age, child and proxy report) was central; ambiguous statements were identified and removed. After items had been generated, HRQOL statements were adjusted to a format where they could be answered using a five-point Likert scale from never to always and within a recall period of four weeks. In sum, the draft HRQOL questionnaire was completed through a multistage process including item generation, card sorting, item writing and discussions which involved several researchers in the expert team.

Content analysis of coping processes

The coping definition provided by Lazarus and Folkman (155) was used as a theoretical and broad concept for identification of coping experiences in the transcripts of the focus group discussions. Hence, coping was considered as a cognitive or behavioral activity to manage specific external or internal demands experienced as stressful or exceeding the individual's resources. Similarly to the bottom-up approach used for the development of the EA-QOL questionnaire, each identified coping statement was added to an Excel file with participant information (child age, child gender, severity of EA, child-proxy-report). All coping statements were then submitted to a card-sorting procedure (166) performed by several researchers, who sorted the statements into categories of coping strategies that shared similar content and that were given a descriptive label. The procedure was repeated for situational context (Figure 9). The type of coping strategy, situational context, child gender, age group (0–7, 8–12, and 13–17 years), severity of EA, presence of associated anomaly and child and proxy-report were analyzed using descriptive statistics.

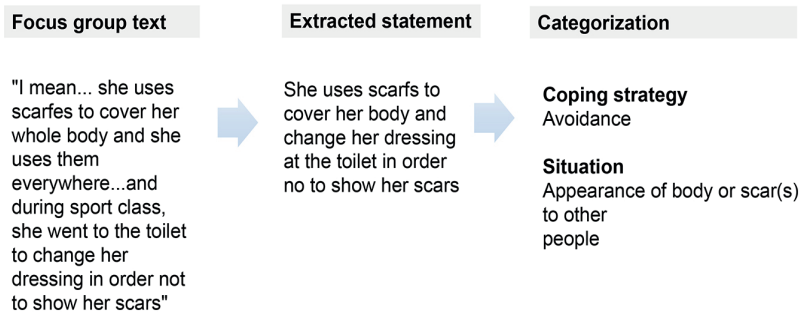


Figure 9. Example of the categorization process of coping strategies and situations in which they were described to be used

Framework analysis of coping used by children and adolescents born with EA

As illustrated by the example in Figure 10, the coping statements were also categorized deductively based on the framework of childhood coping as primary control (e.g. problem solving, social seeking, confronting, emotional expression), secondary control coping (e.g. cognitive reappraisal, positive thinking, acceptance), disengagement coping (e.g. avoidance, distancing)(15).

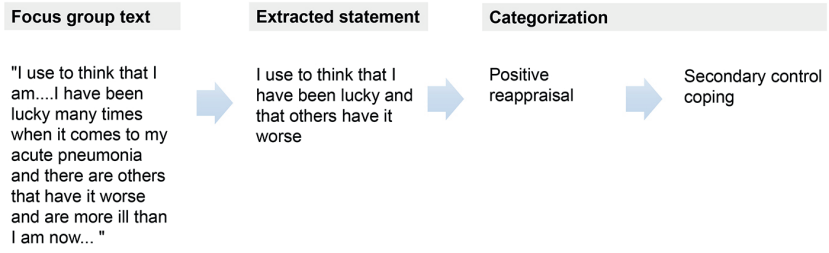


Figure 10. Example of the categorization of coping into primary control coping, secondary control coping or disengagement coping

Rigor

In the categorization processes, category saturation was confirmed through comparison analysis; one focus group was analyzed one at the time and analysis of multiple focus groups served as proxy for theoretical sampling (114). In order to ensure correct classification, item selection, reformulation as questions and thereby objectivity, analysis of the statements was performed and approved by several researchers. Moreover, quotes were used illustrate the HRQOL and coping domains that were recorded and identified in the focus group discussions.

Pilot study of the EA-QOL questionnaire (paper IV)

Study participants

Families of EA children aged 2–17 years were recruited from the Queen Silvia Children's Hospital, Sahlgrenska University Hospital in Gothenburg Sweden and the Center of Pediatric Surgery Hannover, Hannover Medical School, Germany during October 2015 to February 2016. Children younger than 8 years or children or children who suffered from cognitive impairments, were represented by the parent. The sample size was determined by the requirements of the whole project and by the total eligible EA population at the respective centers. In order to make the most of the patient population size and preserve a sample of at least 100 families in the field test of the EA-QOL questionnaire, the Swedish families who had attended the focus groups were also considered qualified for participation in the pilot study since, on average, 13.5 months had passed since their previous participation. In total, 89 EA families were invited and agreed to participation: 68 Swedish families (26 of children aged 2–7 years, 42 Swedish of children 8-17 years old and their parents) and 21 German families (10 German parents of children 2-7 years old and 11 German children aged 8–17 years) and their parents. In total a subsample of 31 families were invited and accepted participation in the cognitive debriefing: all 21 German families and the 10 Swedish families, who had not attended the focus groups.

Data collection

Medical records

As previously described (Review of medical records (pp.51-52), medical records were reviewed for child clinical data, and children were categorized as cases of severe EA or mild-to-moderate EA according to criteria A-D (p.51)

Questionnaires

Postal questionnaires were used, except for the 31 families who participated in the cognitive debriefing at the hospital, who completed the questionnaires during their visit.

- Parents completed a structured questionnaire regarding sociodemographic information and parent, child and family characteristics (see p.55)
- Parents of children 2–7 years old completed 30 condition-specific HRQOL questions and children aged 8–17 years and their parents completed 50 condition-specific HRQOL questions.
- The participants completed an age-specific version of the generic HRQOL measure PedsQL 4.0, which is available for children aged 2–4 years, 5–7 years, and 8–18 years (141). The questionnaires for children older than 4 years are composed of 23 items comprising 4 HRQOL dimensions; physical functioning, emotional functioning, social functioning and school functioning. The questions are answered on a 5-point Likert scale from never to almost always. The toddler version consists of 21 items covering the same 4 HRQOL dimensions. The PedsQL 4.0 Generic Core Scales have resulted from an extensive iterative

process of individual and focus group interviews, item generation, cognitive interviewing, pretesting and field testing in over 25. 0000 healthy children and children with different chronic health conditions. The instruments have demonstrated reliability, validity, sensitivity and responsiveness for self-report in child age 5-18 years and parent proxy report for ages 2-18 years (141).

- Children 8-17 years and their parents completed the DISABKIDS-short version (188). The short version assigns the three dimensions mental, social and physical components of HRQOL and the items can be combined to produce a total score. The DISABKIDS-short version was derived from the same conceptual background as the long-version of 37-Likert-scaled items in six HRQOL areas; Independence, Emotion, Social Inclusion, Social Exclusion, Limitation and Treatment (147). The instruments have demonstrated good convergent validity in pediatric patients with different chronic conditions as well as good reliability in the child version and the proxy version (188). Parents of children 4- 7 years answered the DISABKIDS Smiley version (196). The DISABKIDS-Smiley measure consists of 6 items with Likert scaled smiley faces from very happy to very sad, and has been shown to have acceptable convergent validity and reliability measured as Cronbach's α.

Cognitive debriefing

Participants in cognitive debriefing completed the EA-QOL pilot questionnaire and rated item importance (yes/no), item clarity (yes/no) and the adequacy, sensitivity to answer the question (yes/no). They were face-to-face interviewed and given an opportunity to discuss their thoughts about the items with the researcher, who documented their open answers and made field notes about the non-verbal communication.

Data analysis

Data analysis for the pilot test was performed using SPSS 22.0. Descriptive statistics were used for child clinical data and family characteristics.

Item characteristics

Items of the EA-QOL pilot questionnaire were coded 1–5, with higher points representing better HRQOL. Item descriptive statistics included mean, standard deviation, skewness, kurtosis, and percentage of missing values. Inter-item correlation was determined using Spearman's rho (r_s). Item-specific clinical sensitivity was evaluated using the Mann–Whitney U test for group differences between patients with severe EA (one or more of the criteria A-D, p. 51) and patients with mild-to-moderate EA. Differential item functioning (DIF) was used to detect item equivalency across groups (197). Uniform and non-uniform DIF for child gender and subgroups of the older age group (8–12 and 13–17 years) were assessed using ordinal logistic regression with severity of EA as a covariate to avoid confounding. Descriptive statistics were used to evaluate item importance, clarity, and adequacy as rated by participants in the cognitive debriefing, and content analysis was used for the subsequent interview findings.

Criteria for item exclusion, rephrasing or exclusion
Predefined criteria (11) were used to include, reword, or omit an item for the field test version of the EA-QOL questionnaire.

Criteria that supported item inclusion: Item-specific clinical sensitivity for group differences between patients with severe EA and patients with mild-to-moderate EA ($p<0.05$). Qualitative information supporting item comprehensiveness, clarity and importance to patients. An item regarded as clinically important to EA as evaluated by the expert group.

Criteria that supported item exclusion: Skewness or kurtosis >2.0, missing proportion >5%, DIF for child gender and age subgroup 8–12 vs.13–17 years, item importance rated <70%, item clarity <80% and item adequacy <80% in cognitive debriefing, Spearman's rho > 0.7 for inter-item correlation. Qualitative information supporting item redundancy, ambiguity or unimportance for patients. For each domain scale, a Cronbach's alpha coefficient of at least 0.7 was expected, and an item-total correlation over 0.3. Within each hypothesized HRQOL domain, item deletion that would increase alpha by at least 0.02 was used as criteria to support item exclusion (146).
If an item fulfilled a statistical criteria supporting item deletion and at the same time fulfilled a criteria for item inclusion, it was discussed by the multidisciplinary Swedish-German expert group and was considered as candidates for rephrasing. In the evaluation of the EA-QOL questionnaire for children 8-17 years old, child-report was considered as primary information. The parent-report was regarded as complementary information. It was as a strength if the parent-reported item fulfilled a criteria for item inclusion or did not fulfil a criteria for item exclusion. In summary, items that fulfilled one or more criteria for exclusion in child-report, but not in the parent-report, were considered as candidates for inclusion in the field test version. However, they were discussed by the expert group before final decision.

The HRQOL domains
After reducing poorly performing items, the remaining items in the shortened EA-QOL questionnaire versions were linearly transformed to a 0–100 scale. HRQOL domains were identified through a combined-item content analysis and inter-item correlation. Descriptive statistics of each domain and total scores included mean, SD, range. The scale scores were examined in relation to the extremes of the scaling range, that is, the maximum possible score (ceiling effect) and the minimum possible score (floor effect).

Internal reliability
The reliability of the HRQOL domains was estimated using item-total correlation and Cronbach's alpha coefficient (internal consistency).

Known-groups validity
Known-groups validity was tested by examining expected HRQOL differences between patient groups with different EA severity, using two tests. The hypothesis was that

- Patients who fulfilled one or more criteria for EA severity A-D (taking the overall severe morbidity that may affect EA patients into consideration) would report lower total scores than children with mild-moderate EA ($p<0.05$).
- Patients who fulfilled one or more criteria A-C (related to severe esophageal and respiratory function) would report lower total scores than children with mild-to-moderate EA ($p<0.05$).

Convergent validity

Convergent validity was assessed using r_s between the total scores of the shortened EA-QOL questionnaire and of the already validated HRQOL questionnaires PedsQL 4.0 and DISABKIDS. The r_s 0-0.19 was considered as very weak, 0.20–0.39 weak, 0.40–0.59 moderate, 0.60-0.79 strong and r_s >0.8 as very strong.

Results

Literature review and metaanalysis (paper I)

Articles identified and questionnaires used

Twelve articles (published 1995-2014) were identified and included (16, 17, 168, 189, 198-205). Five articles described HRQOL among children and adolescents (17, 189, 199, 203, 205), one of these articles also reported on HRQOL among adults (189), and seven articles described HRQOL among adults only (16, 168, 198, 200-202, 204). All reported studies were based on patient materials recruited from Europe. In total, 15 different HRQOL questionnaires were used to assess HRQOL in patients with EA. Psychometric evaluation of the questionnaires specifically with regard to the EA population was not reported.

The HRQOL studies of pediatric patients with EA are presented in Table 5. The first article appeared in year 2003 and was conducted by Ludman et al. (199). The authors investigated outcomes in EA children operated with gastric transposition as measured by a modified version of the GIQLI, which from the beginning was developed for adults (169, 206). The four other studies employed established generic HRQOL instruments for pediatric populations. A study from Netherlands conducted by Peetsold et al. (203) used the CHQ (137, 207-209), two studies from France completed by Legrand et al. (17) and Lepeytre et al. (205) used the PedsQL 4.0 (140, 141) and a German study by Dingemann et al. (189) used the KIDSCREEN-27 (144). The largest study sample size was 57 for children and 63 for parents. An overview of characteristics of the questionnaires used in the pediatric EA population is given in Table 6.

The eight HRQOL studies of adults with EA are presented in Table 7. The first adult population study regarded HRQOL of EA patients with colon interposition and was reported by Ure et al. in year 1995 (198). In the adult population studies, study sample sizes varied from eight to 128 patients. The oldest patient was 54 years. As seen in Table 8, twelve different questionnaires were used (169, 170, 200, 206, 210-222) to assess HRQOL among adults with EA. The most commonly used were the symptom-specific GIQLI (169, 206), which was used in six studies, but as a modified version in two studies (although without any new validation reported). The generic SF-36 (223, 224) was used in four studies of EA adults. Six questionnaires measured aspects of HRQOL and were used only in combination with other HRQOL assessments. Three studies measured disease- or symptom-specific HRQOL for other conditions than EA, and four questionnaires had limited documentation of their content and field test results (Table 8).

Table 5. Presentation of studies of health-related quality of life in children with esophageal atresia

Study (reference)	Objective of the study	Publi-cation year	HRQOL questionnaire	Reporter in the study (age in years)	
Ludman et al. (199)	To explore the HRQOL in patients with EA after gastric transposition	2003	GIQLI (modified version)	Patient (10-22) Parent (2-18)	
Peetsold et al. (203)	To evaluate HRQOL and its deter-minants in children and adolescents with EA	2010	CHQ-CF87 CHQ-PF50	Patient (10-18) Parent (9-13)	
Legrand et al. (17)	To evaluate the outcome of patients with EA type III focusing on the presence of late sequelae and HRQOL	2012	PEDSQL 4.0	Patient (9-18) Parent (9-18)	
Lepeytre et al. (205)	To evaluate the medium-term health status and HRQOL of children born with EA type III	2013	PEDSQL 4.0	Patient (8-13) Parent (3-13)	
Dingemann et al. (189)	To evaluate long-term HRQOL in adult and pediatric patients registered in at patient group with a complex form of EA/complicate course after primary repair	2014	KIDSCREEN-27	Patient/Child (8-18) Parent (0-18)	

Abbreviations: CHQ, Child Health Questionnaire; EA, Esophageal atresia; GIQLI, Gastro Intestinal Quality of life Index; HRQOL, Health related quality of life;
PEDSQL, Pediatric Quality of Life Inventory; TEF, Tracheoesophageal fistula, an opening between the esophagus and the wind-pipe

	Sample of patients with EA (size)	Control/Reference group (size)	Response rate (%)	Location for data collection
	Patients who had undergone gastric transposition (28)	Group I: patients who had undergone cervical esophagostomy and gastrostomy without attempt at esophageal anastomosis (13) vs. Group II: patients who had undergone previous attempts at reconstruction or replacement (15)	Patient (68) Parent (79)	Hospital
	Patients born with EA with or without TEF excluding prematurely born children or children with severe mental retardation (63) and their parents (31)	Healthy references of Dutch adolescents (475) for CHQ-CF87 and healthy references of parents of Dutch school schoolchildren (353) for CHQ-PF50	Patient (58) Parents (77)	Home
	Patients with EA type III (81)	Healthy reference group (5079), Reference group for children with chronic diseases (574)	Patient (70)	Hospital
	Patients with EA type III (20) and parents of children with EA type III (68)	Healthy reference group (4762), Reference group for children with chronic diseases (1982)	Patient (80) Parent (65)	Telephone / Home
	Complicated EA defined as; delayed anastomosis more than three months, esophageal replacement, major surgical revision, more than ten dilatations of the esophagus Children (29), Parents(63)	Healthy references for the KIDSCREEN-27 (number not reported) Subgroups of complicated EA are compared	Patient (98)	Not reported

Table 6. Overview of characteristics of the questionnaires used to assess health-related quality of life Committee of the Medical Outcomes Trust

Questionnaire (reference number)	Aim ot the questionnaire	Reliability		Content validity	Construct validity	Criterion Validity	
		Internal consistency (Cronbach's alpha)	Reproducibility (time duration re-test, interrater)				
Child Health Questionnaire (137,207-209)	To measure the HRQOL in healthy children and adolescents and those with acute and chronic conditions	Yes	Yes	Patients	Yes	Yes	
Gastrointestinal Quality of Life Index (169,206)	To assess HRQOL specifically for adult patients with gastrointestinal disease	Yes	Yes	Adult patients Health professionals Relatives	Not reported (Convergent)/Yes	Yes	
KIDSCREEN-27 (144)	To assess children's and adolescents' subjective health and well-being	Yes	Yes	Patients Parents	Yes	Yes	
Pediatric Quality of Life Inventory 4.0 (140,141)	To measure HRQOL in healthy children and children with acute or chronic conditions	Yes	Yes	Patients Parents (PedsQL 1.0)	Yes	Yes	

Abbreviation: HRQOL, health-related quality of life; PedsQL, Pediatric Quality of Life Inventory

among children with esophageal atresia based on review criteria described by the Scientific Advisory

	Responsiveness	Interpretability	Cultural and/or translational adaptation	Alternative forms	Respondent burden/administrative burden
	Sensitive to disease change in chronic pain or fatigue	Yes	Yes	Yes	Answer 6 items per minute/Administration time 5–25 minutes. No training is necessary for administration
	Sensitive to improved HRQOL in patients before and after surgery	Yes	Yes	No	Minimal burden /Not reported
	Not reported for KID-SCREEN-27	Yes	Yes	Yes	Respondents answer in 10-15 minutes /No training is necessary for administration
	Sensitive to clinical change in cardiac disease, pediatric orthopedics clinic setting and Rheumatic disease	Yes	Yes	Yes	Respondent completion < 4 minutes / No training is necessary for administration

Table 7. Presentation of studies of health-related quality of life among adults with esophageal atresia

Study	Objective of the study	Publi-cation year	HRQOL questionnaire	Reporter in the study (age in years)
Ure et al. (198)	To assess functional results and HRQOL in patients with colon interposition for long-gap EA	1995	GIQLI, Spitzer QL Index, VAS 1-100 for overall HRQOL	Patient (20-27)
Ure et al. (16)	To determine the long-term HRQOL in patients who underwent primary anastomosis or colon interposition for EA	1998	GIQLI, Spitzer QL Index, VAS 0-100 for overall HRQOL	Patient (20-31)
Koivusalo et al. (200)	To compare the HRQOL of adult patients with EA with that of the general population	2005	GIQLI (modified version), Health Disease and Education, RSRQLI, SAQ, SF-36, VAS 1-100 for overall HRQOL	Patient (24-54)
Deurloo et al. (168)	To investigate the generic HRQOL after correction of EA in a large adult population and compare it with the generic HRQOL of a healthy population, investigate factors which influence HRQOL and explore HRQOL by asking open-ended questions	2005	ABS (modified version), EORTC-OES18 (modified version), GIQLI (modified version), ICQ, SF-36, Three additional questions regarding limitations, positive and negative experiences with EA	Patient (16-48)
Deurloo et al. (201)	To evaluate esophageal function after correction of EA in adults and to investigate the association between complaints, esophageal function and HRQOL	2008	GIQLI, SF-36	Patient (18-42)
Burgos et al. (202)	To assess the results in adult patients who had undergone esophageal replacement with colon during childhood	2010	Interview on subjective perception of well-being and familial and professional adaptation Karnofsky performance status index	Patient (19-48)
Gatzinsky et al. (204)	To measure dysphagia following EA and investigate whether there is a correlation with early risk factors, symptoms of GER and HRQOL	2011	SF-36v2	Patient (25-40)
Dingemann et al. (189)	To evaluate long-term HRQOL in adult and pediatric patients registered in a patient group with a complex form of EA/complicate course after primary repair	2014	GIQLI, WHO-5	Patient/ Adult (18-47)

Abbreviations: ABS, Affect Balance Scale; EA, Esophageal atresia; GER, Gastro esophageal reflux; EORTC, European quality of life; ICQ, Illness Cognition Questionnaire; KPS, Karnofsky Performance Status; RSRQLI, The Respiratory from the RAND Medical Outcomes Study; Spitzer QL Index, Spitzer Quality of Life Index; TEF, Tracheoesophageal fistula;

	Sample of patients with EA (size)	Control/Reference group (size)	Response rate (%)	Location for data collection
	Adults who underwent colon interposition for long-gap EA (6) and parents (2)	Healthy reference group for GIQLI (150), Patients with cancer and other chronic diseases for Spitzer QL Index (number not reported), Patients with cancer for VAS (number not reported)	Patient (100) Parent(100)	Hospital
	Patients with primary anastomosis (50) Patients with colon interposition (8) (Patients with EA Vogt I, II, IIa-c)	Patients with primary anastomosis (50) vs. Patients with colon interposition (8) for GIQLI, VAS, Spitzer QL Index, Healthy reference group for GIQLI (150)	Patient (82)	Hospital
	Patients with EA with or without TEF and with TEF without EA (159)	Healthy control group for GIQLI,RSRQLI, SAQ (163) Finnish healthy references for SF-36 (2175)	Patient (80)	Home
	Patients with EA with or without TEF and with TEF without EA (119)	Healthy Dutch references (607) for SF-36 Patients with EA and with (34) and without (63) concomitant congenital anomalies for ABS, EORTC-OES18, GIQLI, ICQ, SF-36	Patient (82)	Home
	EA who had undergone primary end-to-end anastomosis for EA with distal TEF (25)	Patients with (10) vs. without dysphagia (11), Patients with (7) vs. without self-reported GER (14)	Patient (80)	Home
	Patients who underwent colon interposition for esophageal replacement (EA, 34, caustic injury 34, other, 4) Patients interviewed (30)	No control group	Patient (57)	Telephone interview/ Home, Hospital
	EA with TEF (79)	Healthy Swedish references (140)	Patient (92)	Home
	Complicated EA defined as; delayed anastomosis more than three months, esophageal replacement, major surgical revision, more than ten dilatations of the esophagus Adults (28)	Healthy reference group for GIQLI (150), Reference values for WHO-5 from patients with diabetes and patients with psychiatric disorders, Subgroups of complicated EA are compared	Patient (98)	Not reported

Organization into Research and Treatment of Cancer; GIQLI, Gastro Intestinal Quality of Life Index; HRQOL, Health-related Symptoms–Related Quality of Life Index; SAQ, Strategy and Attributional Questionnaire; SF-36, 36-Item Short Form Survey VAS/Uniscale, Visual Analogue Scale/Uniscale for overall HRQOL; WHO-5, World Health Organization-5- Well- Being Index

Table 8. Presentation of questionnaires used to assess health-related quality of life among adults with Outcomes Trust

Questionnaire (reference number)	Reliability		Content validity	Construct validity	Criterion Validity	
	Internal consistency (Cronbach's alpha)	Reproducibility (time duration re-test, interrater)				
Affect Balance Scale (210-211)	Yes	Yes	Healthy people	Yes/ Not reported (discriminant)	Yes	
European Organization into Research and Treatment of Cancer – Esophageal cancer-18 (212-214)	Yes	Not reported	Patients Health professionals	Yes	Yes	
Gastrointestinal Quality of Life Index (169,206)	Yes	Yes	Patients Health professionals Relatives	Not reported (convergent) /Yes	Yes	
Health Disease and Education (200)	Not reported	Not reported	Not reported	Not reported	Not reported	
Illness Cognition Questionnaire (215)	Yes	Yes	Patients Health professionals Researchers	Yes	Yes	
Karnofsky Performance Status (216-217)	Not reported	Yes	Not reported	Not reported (convergent) /Yes	Not reported	
The Respiratory Symptoms–Related Quality of Life Index (200)	Not reported	Not reported	Pulmonologist Pediatric Surgeons	Not reported	Not reported	
36-Item Short Form Survey from the RAND Medical Outcomes Study SF-36 (223-224)	Yes	Yes	No (compared with other generic health surveys)	Yes	Yes	
The Spitzer Quality of Life Index (218)	Yes	Yes	Health professional Patients Relatives Healthy people	Yes	Not reported	
The Strategy and Attributional Questionnaire (219)	Yes	Yes	Not reported	Yes	Yes	
Visual Analogue Scale/Uniscale for overall HRQOL (220)	Yes	Yes	Patients	Yes/ Not reported (disciriminant)	Yes	
World Health Organizaion-5 Well–Being Index (221-222)	Yes	Not reported	Not reported	Yes	Yes	

Abbreviations: HRQOL, Health related quality of life

esophageal atresia, according to criteria described by the Scientific Advisory Committee of the Medical

	Responsiveness	Interpret-ability	Cultural and/or translational adaption	Alternate forms	Respondent burden/administrative burden
	Change in affect variables is age-related, although these changes are relatively small	No	Yes	No	Minimal burden/ No training is necessary for administration
	Sensitive to change over time in patients with different severity of disease and treatments	Yes	Yes	No	Completion of generic and disease-specific questionnaires in about 15 minutes /Not reported
	Sensitive to improved HRQOL in patients before and after surgery	Yes	Yes	No	Minimal burden /Not reported
	Not reported	Not reported	Not reported	Not reported	Not reported
	Not reported	No	No	No	Not reported
	Correlation with worsening in function in patients with cancer	No	No	No	Not reported
	Not reported	Not reported	Not reported	Not reported	Not reported
	Sensitive to change in health status and health perception, for different medical conditions and treatments	Yes	Yes	Yes	2–10 minutes/ Administrative burden minimal
	Not reported	No	Yes	No	Physician < 1 minute
	Not reported	No	Yes	No	Not reported
	Not reported	No	No	No	Respondent burden minimal
	Sensitive to treatment response in patients within psychiatric services	Yes	Yes	No	Respondent burden minimal

The HRQOL findings

Overall HRQOL

Legrand et al. (17) showed that overall HRQOL was reduced as compared to healthy children, but was higher when compared to children with asthma and diabetes. Other articles reported that overall HRQOL among children with EA was similar to a healthy reference group (205) or did not report overall HRQOL (189, 203). Ludman et al. (199) showed that patients who underwent gastric transposition as a primary procedure had fewer symptoms, and also higher HRQOL compared to children who had undergone gastric transposition of secondary causes.

Koivusalo et al. (200) demonstrated that adults with EA had a reduced HRQOL according to the Respiratory Symptoms–Related Quality of Life Index. In addition, three studies (16, 189, 198) showed that HRQOL was reduced in adults with complicated EA (patients who had undergone colon interposition, delayed esophageal surgical repair more than three months, other esophageal replacement, major surgical revision, more than ten dilatations). In 2005, Deurloo et al. (168) showed that patients with concurrent presence of congenital anomalies had a negative influence on the indigestion scale of the European Organization into Research and Treatment of Cancer – Esophageal cancer-18 (212-214). In total two studies (16, 200) reported that overall HRQOL in adults with EA was not reduced according to the SF-36 (200) and/or the GIQLI (16, 200). Three studies (168, 201, 204) did not report the overall HRQOL of the SF-36, but only the physical component summary (PCS) and mental component summary (MCS).

Factors associated with lower overall HRQOL among children with EA were prematurity, barky cough, GERD and dyspnea on exertion (17); a prior gastrostomy procedure, pneumonia, current asthma, and hospitalization due to respiratory and esophageal illness (205); higher age (203). In the Lepeytre et al. study (205) there was no statistical difference in overall HRQOL when age groups were compared (ages three to five, five to eight, eight to thirteen years). In adults with EA, no independent factors have been identified to negatively influence the overall HRQOL.

Physical function and general health

The general health (child- and proxy-report) and the physical summary scale (proxy-report) was lower among children with EA according to the Peetsold et al study (203). In the Legrand et al. study (17), physical health was reduced in children with GERD. Peetsold et al. (203) also showed that the general health was dependent on GERD; in fact by the frequency and characteristics of reflux symptoms. General health was also dependent on the number of associated malformations; the more anomalies present, the lower general health. A regression analysis showed that age at follow-up affected general health and the physical summary scale. Within the regression model, the physical summary scale in 13-18 year olds reduced when age at follow-up increased by one year. In two other articles (189, 205), physical function/wellbeing was not impaired among children with EA compared to healthy refer-

ences. Six children with delayed esophageal primary anastomosis, had better physical well-being than healthy references and other subgroups of complicated EA in the Dingemann et al. study (189).

In adults with EA, four articles (16, 168, 189, 198) reported impaired general or physical health (symptoms) compared to healthy references, three of them (16, 189, 198) considered patients with complicated EA. In the Deurloo et al. study (168), 8% of adults described physical limitations due to EA. According to the clinician-reported Karnofsky Performance Scale (216, 217), 6% of adults following colonic interposition had a poor functional outcome (202). In the Deurloo et al. study (201) patients with dysphagia showed impaired general health, PCS (SF-36) and physical well-being (GIQLI). However, in a Swedish study (204) there were no correlation between the PCS of SF-36 and self-reported dysphagia.

Psychological function and psychosocial aspects
In children, Peetsold et al. (203) showed that EA children had impaired mental health according to proxy-report. Legrand et al. (17) described an impaired emotional function in children with dyspnea at rest and dysphagia. No difference in psychological functioning was found between children with EA and healthy references according to two other studies (189, 205). Dingemann et al. (189) showed that children with complicated EA were reported better psychological well-being in the proxy-report. No differences in psychological function were identified in children who had undergone gastric transposition for primary compared to secondary indications (199).

Dingemann et al. (189) demonstrated that 23% of adults with complicated EA had poor well-being scores answering WHO-5 (221, 222), which may be understood as an indication of depression. In the Deurloo et al. (168) study, 33% of adults had experienced negative consequences of EA due to dysphagia, fatigue and surgical scars. Also Koivusalo et al. (200) reported patient complaints with respect to the scar, with minor to significant complaints in approximately 50% of adults with EA, and 11% of adults with EA made complaints of a disfigured or winged scapula. No article reported worse MCS of the SF-36 (168, 200, 204) or worse emotional function of the GIQLI (16, 198) in adults with EA compared to healthy references. However, adults with EA scored lower on the vitality scale of the SF-36 in the Deurloo et al. study (168). No significant difference in psychosocial functioning among adults with EA compared to healthy controls were recognized in the Koivusalo et al. study (200) using the Strategy and Attribution Questionnaire (219). Burgos et al. (202) reported that a majority of adults after colonic interposition described satisfactory well-being during interviews. In the Deurloo et al. study (168), 14% of adults described positive experiences from EA, and the most commonly described sentiment was a gratefulness to be alive. These adults had lower scores on the physical role scale of the SF-36, but scored higher on perceived benefits at the same time as they demonstrated a high impact on reducing the consequences of the condition (i.e low acceptance) as measured by the Illness Cognition Questionnaire (170). Dysphagia (201, 204) and GER

(201) did not have a negative influence on the MCS of the SF-36 and the presence of concomitant congenital anomalies in EA adults did not influence the positive well-being, when using a modified form of the Affect Balance Scale (210, 211).

Social function, school function and family function

Children with EA had reduced social or school functioning in two studies (17, 189). Children with complicated EA had diminished social HRQOL functioning (189) and children with EA combined with associated malformations had lower school functioning (17). At the same time, no negative influence on the dimension school environment among children with complicated EA was found compared to healthy children (189). In another study (205) children with EA type III (8-13 years) had higher social HRQOL scores. In two studies (189, 203), children with EA rated better family functions compared to healthy references, one of which considered six children who had underwent delayed anastomosis (189). No study (16, 168, 189, 198, 200-202, 204) reported any reduced social functioning in adults with EA, and additionally, Deurloo et al. (201) showed that the presence of esophageal dysfunction did not negatively influence social functioning.

Metaanalysis

Five eligible studies were included in the meta-analysis of overall HRQOL (Table 9). As is shown in Figure 11 showing Forest Plots of self-reports from patients with EA compared with healthy reference populations, they provided a total of seven ESs estimates. Four of these reached statistical significance, $p<0.05$ for moderate to large ESs which indicated worse overall HRQOL for patients with EA. Using Cohen's criteria (103), the pooled estimate of the effect of EA was small for overall HRQOL and I^2 indicated large heterogeneity (195).

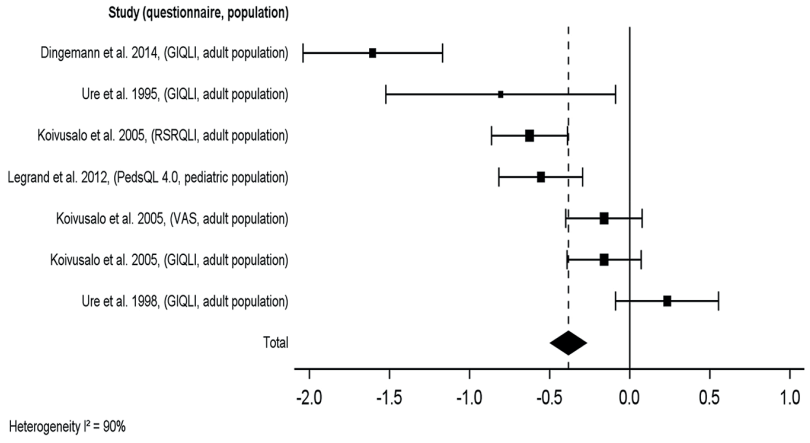


Figure 11. Forest plot showing metaanalysis of overall health-related quality of life in patients with esophageal atresia compared to healthy references/controls

Table 9. An overview of overall health-related quality of life in patients with esophageal atresia, according to studies that were included in the meta-analysis

Study (questionnaire, population)	Patients with esophageal atresia			Healthy references/ controls				
	N	Mean	SD	N	Mean	SD	Cohen's d (95% CI)	P-value
Dingemann et al. (GIQ-LI, adult population)	27	105.1	12.3	168	125.8	13	-1.6 (-2.0;-1.2)	**<.0001**
Legrand et al. (PedsQL 4.0, pediatric population)	57	77	13	5079	83.91	12.47	-0.6 (-0,8;-0.3)	**<.0001**
Koivusalo et al. (GIQLI, adult population)	128	121.9	16.4	163	124.3	13.8	-0.2 (-0.4;0.1)	0.18
Koivusalo et al. (RSRQ-LI, adult population)	128	55.3	7.2	163	58.9	4.3	-0.6 (-0.9;-0.4)	**<.0001**
Koivusalo et al. (VAS, adult population)	115	80	13	163	82	12	-0.2 (-0.4;0.1)	0.19
Ure et al. (GIQLI, adult population)	50	111.5	8	150	107.6	18.7	0.2 (-0.9;0.6)	0.15
Ure et al. (GIQLI, adult population)	8	92.2	26.5	150	107.6	18.7	-0.8 (-1.5;0.1)	**0.028**

Advancement of future research

This literature review provided new information in the field of HRQOL in patients with EA. Up to January 2015, available reports were limited to relatively small patient samples recruited from Europe and HRQOL was heterogeneously measured. HRQOL was incoherently described and definite conclusions on HRQOL in children, young people and adults with EA were difficult to draw. Consequently, the development of a standardized condition-specific HRQOL questionnaire for the EA population was needed. This in turn could contribute to more valid, reliable findings on which to assess patients' health care needs and to provide a better understanding of the patient's life situation. Previous research was taken into consideration in order advance the forthcoming empirical studies. e.g.

- It was clear that future HRQOL research should include cross-cultural approaches and collaboration between centers. This would increase the sample sizes and enable a cultural evaluation of HRQOL.
- The majority of the pediatric population studies had used different inclusion/exclusion criteria for study participation. We decided that, although the EA population is heterogeneous, all children with EA should be invited to participate in the study. The aim was to gain a proper overall insight of condition-specific HRQOL. In addition, the sample size is paramount in PROM development. In case the child was not able or willing to answer, a proxy-measurement was decided to be used.
- Knowledge of HRQOL in children younger than eight years of age was sparse and they studies had used different HRQOL questionnaires in different subgroups of EA. We decided to advance knowledge of HRQOL among young

children with EA from 2 years of age.

- Only two studies (189, 205) of HRQOL among children with EA described a response rate that exceeded 70% in the child-report, one of which included study participants recruited from a patient advisory support group (189). Of the studies that had the highest response rate and described their location for data collection, the questionnaires were completed in the patient's home. We decided to establish strategies that would improve the response rate, since the number of patients is principal in PROM development for a rare condition. Postal questionnaires sent home to the family were decided to be used. Every family should be given an oral invitation by the same researcher according to a standardized protocol. This should be followed by a written invitation/information. Three reminders; one reminder on telephone, one written postal reminder which provided new questionnaires and one last telephone reminder should be given during the data collection period.
- The studies of HRQOL in EA children provided important information of clinical data and study designs. We collected similar clinical data to be able to repeat clinical hypothesis testing and in addition to the chronic-generic DISABKIDS questionnaire, we decided to use the PedsQL 4.0 questionnaire, which was the most frequently used in the pediatric EA population and which was available for toddlers. This would increase generalizability.
- The literature review confirmed that further studies of coping strategies used by children with EA were needed.

Focus group participants (paper II, III)

Ten focus group discussions were held (19.2 hours, mean 1.9 hours). All 30 families participated as planned (response rate 100%) and were represented by 18 children (8-17 years) and 32 parents of children (2-17 years). Table 10 presents the characteristics of the focus group participants. Of the children, 53.3% were males and 76.7% underwent primary anastomis. At follow-up, 33.0% used anti-reflux medication and 46.6% bronchodilators or inhaled steroids. Within the last year, 20.0% of the children had been admitted to hospital care and 80.0% had visited the pediatric specialist outclinic service. Of the children (n=15) who were regarded to have severe EA, seven children underwent a delayed primary anastomosis or an esophageal replacement procedure (criteria A), five children had revisional surgery for causes as recurrent TEF or anastomotic leakage (criteria B), five children had severe TM as estimated through a broncoscopy (criteria C), and four children had at least one other congenital health condition resulting in disability (criteria D). In the majority of families, the proxy-report was provided by the mother (Table 10).

Table 10. Characteristics of focus group participants

Variables	Frequency (%)	Mean/Median(SD)	Min/Max
Child background information			
Male	16(53.3)		
Gestational week		36/37(3)	30/41
Birth weight (kilograms)		2.4/2.5(0.7)	1.1/3.4
Associated anomalies	16(53.3)		
Cardio-vascular	4(13.3)		
Gastro-intestinal (excluding anorectum)	2(6.7)		
Anorectal	2(6.7)		
Uro-genital	6(20.0)		
Limb	3(10.0)		
Vertebral-skeletal	6(20.0)		
CNS	2(6.7)		
Eye	2(6.7)		
Esophageal repair			
Primary anastomosis	23(76.7)		
Delayed primary anastomosis	4(13.3)		
Esophageal replacement	3(10.0)		
Focus group follow-up			
Child age		9/10(5)	2/17
Need of gastrostomy	2(6.7)		
Growth retardation (weight and/or height < 2 SD)	7(23.3)		
Medication intake	20(66.7)		
Anti-reflux medication	10(33.3)		
Bronchodilators or Inhaled steroids	14(46.7)		
Other	9(30.0)		
Esophageal dilation	18(60.0)		
Additional school support	5(16.7)		
Family information (Proxy-representatives, total number=32)			
Two parents at home	25(83.3)		
Mother	26(81.3)		
Parental age (years)		41/40(6)	28/59
Healthy parent	29(90.1)		
National descent Swedish	26(81.3)		

Condition-specific HRQOL experiences (paper II)

1,371 HRQOL statements (experiences) were recorded, and nine overall HRQOL areas were identified. The reported frequency of each overall domain and examples of representative focus group quotes are given;

Eating and drinking (n=368, 26.8%)

The HRQOL experiences which regarded *Eating and drinking* reflected food issues, impact of choking, nutritional intake, school cafeteria experiences, fluid intake matters, and impact on children's parties due to eating problems.

"I need to think of drinking a lot when I eat in order for the food not to get stuck, and it's hard"

(16-year-old girl, mild-to-moderate EA)

Relationships with other people (n=283, 20.6%)

The domain *Relationships with other people* included HRQOL experiences of social exclusion, loneliness, understanding and support from school, friends, family, expression of empathy to others, confidence in finding a partner.

"They use to call me things like "pig" in school because of my cough"

(8-year old boy, severe EA)

General life issues (n=202, 14.7%)

The domain *General life issues* incorporated experiences of physical activity like sport and play, sleep and perceived general health.

"She is negatively affected during sports because of her breathing difficulties"

(Mother of 16-year-old girl, mild-to-moderate EA)

Communicative/interactive processes (n=161, 11.7%)

The domain *Communicative/interactive processes* included experiences of communication with other people, other people's questions and wonderings and the children's need to explain their health condition to other people due to EA.

"The most difficult thing with EA is to find someone who did not ask about the scars"

(12-year-old boy, severe EA)

Body image issues (n=109, 8.0%)

The domain *Body image issues* referred to HRQOL experiences of surgical scar(s), winged-scapula, scoliosis and to the experience of being small and/or short for age.

"She feels that it very difficult when her scars are visible to others"

(Mother of 11-year old girl, severe EA)

Bothersome symptoms (n=81, 5.9%)

The domain *Bothersome symptoms* included experiences of respiratory symptoms, acid reflux and vomiting that was described to impact the child.

"It is tough that I have to throw up food all the time"

(8-year-old girl, severe EA)

Impact of health care use and medical treatment (n=78, 5.7%)
The HRQOL experiences of *Impact of health care use and medical treatment* referenced medical treatment including the need of dilatation of the esophagus, having a gastrostomy button and impact on school absence.
"He needs to have shorter days in preschool because of EA"
(Mother of a 6-year-old boy, severe EA)

Confidence (n=65, 4.7%)
The overall HRQOL domain *Confidence* referred to perceptions of oneself and of confidence in the future due to EA.
"EA makes me feel that I am special"
(12 year-old boy, severe EA)

Additional difficulties due to concomitant anomalies (n=24, 1.8%)
This domain consisted of HRQOL experiences reflecting concomitant anomalies and the complexity of living with several malformations.
"He is so bothered by using the button (urinary stoma)"
(Mother of 6-year- old boy, severe EA)

Distribution of HRQOL experiences
The major part (66.9%) of the HRQOL statements was generated from children with severe EA and their parents. With respect to gender distribution, 730 (53.2%) were for males and 641 (46.8%) were for females, respectively. A number of 247 (18.0%) HRQOL statements were expressed by parents of children 2-7 years old. The remaining 1174 HRQOL statements were produced by families of children 8-17 years old. Of all HRQOL statements, 716 (52.2%) were child reports. The distribution of HRQOL areas according to child age group, child gender, severity of EA and child/proxy report are presented in Table 11.

Physical, social and mental HRQOL
The HRQOL domains referenced physical, social and mental perspectives of HRQOL. In the total sample, 596 (43.5%) HRQOL statements were regarded as physical HRQOL, 589 (43.0%) as social HRQOL and 186 (13.5%) HRQOL statements as mental HRQOL. Table 12 provides a description of each domain in descending order of the reported statement frequency with regard to the core dimensions of HRQOL. Different composition (%) of the reported HRQOL experiences with regard to physical, social and mental HRQOL was observed for children 2-7 years (n_{tot}=247 HRQOL statements), and for children and adolescents 8-17 years (n_{tot}=1174 HRQOL statements) as shown in Figure 12 and Figure 13.

The EA-QOL pilot questionnaire versions (paper I, IV)
All 1371 HRQOL statements that were subjected to content analysis were included in item reduction procedures. Based on predefined criteria (p.56), 58 unique items

Table 11. HRQOL areas and their distribution according to severity of esophageal atresia, child gender, child age group and child/proxy report

Overall domain	Frequency (%)		Frequency (%)		Frequency (%)		
	Mild-moderate EA	Severe EA	Male	Female	Proxy 2-7	Children 8-17	Proxy 8-17
Eating and drinking	100(7.3)	268(19.5)	201(14.7)	167(12.2)	79(5.8)	193(14.1)	96(7.0)
Relationships with other people	94(6.9)	189(13.8)	140(10.2)	143(10.4)	44(3.2)	127(9.3)	112(8.2)
General life issues	67(4.9)	135(9.9)	127(9.3)	75(5.5)	45(3.3)	91(6.6)	66(4.8)
Communicative/ interactive processes	65(4.7)	96(7.0)	72(5.2)	89(6.5)	16(1.2)	100(7.3)	45(3.2)
Body issues	52(3.8)	57(4.2)	52(3.8)	57(4.2)	13(0.9)	47(3.4)	49(3.7)
Bothersome symptoms	30(2.2)	51(3.7)	39(2.8)	42(3.1)	17(1.2)	52(3.8)	12(0.9)
Impact of health care use and medical treatment	18(1.3)	60(4.4)	55(4.0)	23(1.7)	11(0.8)	52(3.8)	15(1.1)
Confidence	25(1.8)	40(2.9)	33(2.4)	32(2.3)	6(0.4)	49(3.6)	10(0.7)
Additional difficulties due to concomitant anomalies	3(0.2)	21(1.5)	11(0.8)	13(0.9)	16(1.2)	5(0.4)	3(0.2)
Total	454(33.1)	947(66.9)	730(53.2)	641(46.8)	247(18.0)	716(52.2)	408(29.8)

Abbreviations: EA, Esophageal atresia; HRQOL, health-related quality of life

Table 12. Distribution of HRQOL domains in relation to physical, social and mental HRQOL

	No. of HRQOL statements (%)		
Overall HRQOL domain	**Physical**	**Social**	**Mental**
Eating and Drinking (ntot=368)	254	73	41
Relationships with other people (ntot=283)	5	274	4
General life issues (ntot=202)	190	7	5
Communincative/interactive processes (ntot=161)	0	157	4
Body issues (ntot=109)	13	47	49
Bothersome symptoms (ntot=81)	65	6	10
Impact of health care use and treatment (ntot=78)	46	15	17
Confidence (ntot=65)	2	8	55
Additional difficulties due to concomitant anomalies (ntot=27)	21	2	1
Total (ntot=1371)	596 (43.5)	589 (43.0)	186 (13.5)

Abbreviation: HRQOL, health-related quality of life

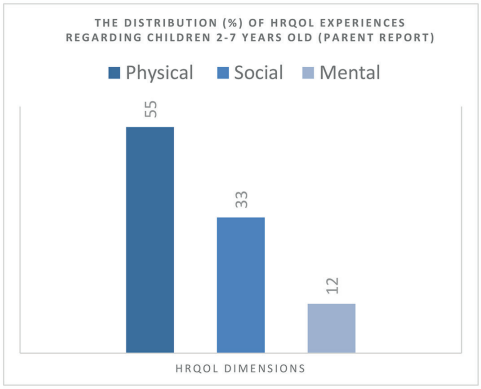


Figure 12. The distribution of health-related quality of life (HRQOL) experiences (n_{tot}=247) reported in focus groups with parents of children with esophageal atresia 2-7 years with regard to physical, social and mental HRQOL

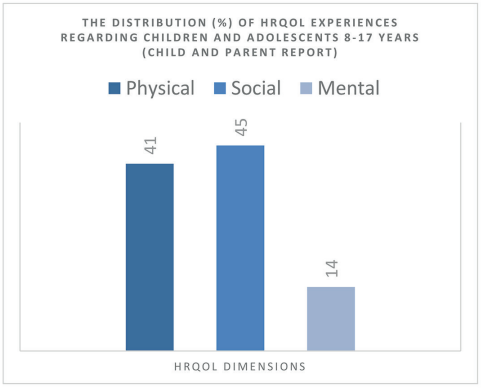


Figure 13. The distribution of health-related quality of life (HRQOL) experiences (n_{tot}=1174) reported in focus groups with children with esophageal atresia 8-17 years old and their parents, with regard to physical, social and mental HRQOL

for children 2- 7 years (parent report only) and 118 unique items for children 8-17 years (child and parent report) were identified and reworded to comply with the answer format of a 4-week recall period and a 5-point Likert scale from never to always. During the data analysis, it was evident that the detailed HRQOL aspects including the composition/distribution of the HRQOL statements, and the wording used by parents of children 2-7 years old differed from results in children 8-17 years old to that extent that two age-specific scales were developed. In order to support further item reduction and test the items for face validity, four parents of children 2-7 years, four children 8-17 years and their parents completed the pre-pilot questionnaire and undertook a cognitive interview concerning item relevance, clarity and adequacy. Following the pre-pilottest, 30 items were included in the pilot questionnaire for children 2-7 years and 50 items for children 8-17 years (Figure 14).

A German translation and adaptation process was completed. Following a standardized procedure, focus groups with families of children 2-17 years were conducted in Germany and were content analyzed using the Swedish detailed descriptive protocol

of HRQOL domains as a proxy for theoretical sampling. This confirmed content validity. The EA-QOL pilot questionnaires were also translated from Swedish, to English and German using an internationally recommended procedure (111).

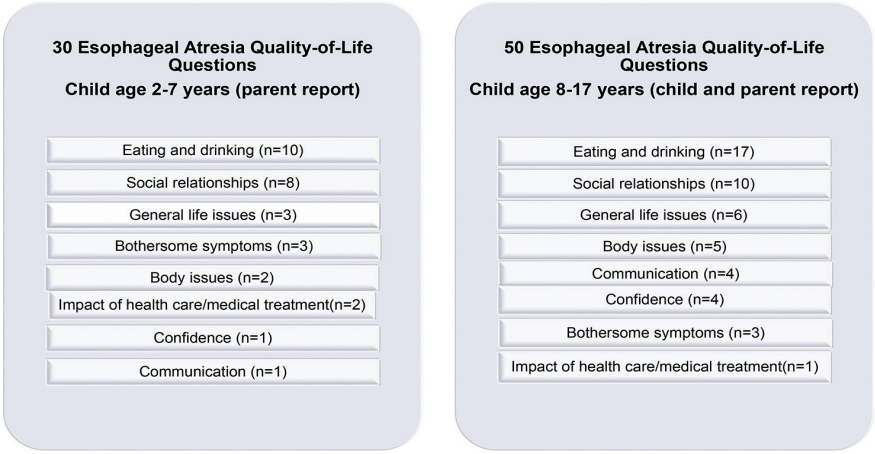


Figure 14 . The Esophageal Atresia Quality-of-Life pilot questionnaires for children 2- 7 years old (parent report) and children 8-17 years old (child and parent report).

The pilot testing of EA-QOL questionnaires for children and adolescents born with EA (paper IV)

Study participants

In total 86 of 89 families that were given the questionnaires, completed them, which was a response rate of 96% in the total sample. The population characteristics of 34 EA children aged 2–7 years and 52 families of EA children aged 8–17 years (51 reports came from children) are presented in Table 13.

Table 13. Description of characteristics of participants in the pilot study

	Children 2–7 years (ntot=34)		Children 8–17 years (ntot=52)	
	No (%)	Median (Min/Max)	No (%)	Median (Min/Max)
Child background				
Male	19 (55.9)		27(51.9)	
Gestational week		37.0 (33–41)		37 (28–43)
Birth weight, kg		2.5 (1.7–3.7)		2.7 (1.1–3.8)
Associated anomalies	23 (67.6)		25 (48.1)	
Cardiovascular	9 (26.5)		12 (23.1)	
Anorectal	5 (14.7)		3 (5.8)	
Urogenital	6 (17.6)		8 (15.4)	
Vertebrae–rib	8 (23.5)		7 (13.5)	
Limb	5 (14.7)		2 (3.8)	
Esophageal repair				
Primary anastomosis	30 (88.2)		44 (84.6)	
Delayed primary anastomosis	1 (3.0)		6 (11.5)	
Esophageal replacement	3 (8.8)		2 (3.9)	
Follow-up				
Child age in years		5.5 (2-7)		13(8-17)
Esophageal dilation	14 (41.2)	0(0-11)	27 (51.9)	1(0-90)
Doctor diagnosed asthma	10(33.3)†		13(25.5)‡	
Parental information				
Proxy report, mother	27 (79.4)		47 (90.4)	
Age in years		38 (29-58)†		45 (30-64)‡
Cohabiting partner	28 (90.3)†		41 (80.4)‡	
University-educated	16 (51.6)†		24 (47.1)‡	

† 3 missing
‡ 1 missing

Among children 2-7 years old, 18 (52.9%) patients were regarded to have severe EA, and among children 8-17 years old, 24 (46.2%) patients were regarded to have severe EA. Table 14 presents children with severe EA and the criteria that were fulfilled for inclusion. Two EA children 2-7 years old and three children 8-17 years old only fulfilled criteria D, i.e. to have another congenital condition regarded to cause disability.

Table 14. Presentation of children with severe esophageal atresia in relation to the inclusion criteria 1-4

	Children 2-7 years old (ntot=18)	Children 8-17 years old (ntot=24)
	No. of children	No. of children
A. The primary anastomosis was delayed and/or EA replacement was accomplished	4	8
B. Major surgical revision (open surgery) of the EA correction performed for causes as recurrent TEF or anastomotic leakage	6	9
C. Severe tracheomalacia/ tracheobronchomalacia verified by a broncoscopy and based on macroscopic estimation of an anteroposterior collapse documented as excessive, severe and/or of ≥75% without limitation of the child's age at the bronchoscopy	9	9
D. Presence of at least one other congenital health condition resulting in disability	13	10

Study participants in the cognitive debriefing

In the cognitive debriefing, 16 parents of children aged 2–7 years participated (child median age 4 years, 12 boys, 9 children with severe EA according to criteria A-D, 10 German families) and 15 children aged 8–17 years and their parents (child median age 12 years, 8 boys, 6 children with severe EA according to criteria A-D, 11 German families).

Item characteristics, item reduction and examples of the decision-making process of item exclusion, rewording, and inclusion

Taking into account the predefined criteria presented in the method section (p.60) and after expert group consensus, 12 items were omitted from the 30-item questionnaire for children aged 2–7 years and 24 items were eliminated from the 50-item questionnaire version for children aged 8–17 years. Table 15 gives an overview of the reasons for excluding the items. All questions in the pilot questionnaires are presented in the Appendix with the decision of item exclusion, rewording and inclusion.

Items excluded from the field test version of the EA-QOL questionnaire for children 2–7 years old (parent report) showed different problems as defined by the predefined criteria for item exclusion (Table 15). However, many items also performed well, and among the 18 items that were included in the field test questionnaire for children 2–7 years old (parent report), 14 items did not demonstrate any problem according to the predefined criteria for item exclusion. Five of the included items demonstrated item-specific clinical sensitivity (parents of children with severe EA reported significantly lower scores than parents of children with mild-to-moderate EA ($p < 0.05$, two-tailed). Two items were discussed and were improved in their wording before inclusion in the field test version. One item was improved in translation because of significant DIF for child gender. Another item ("Is it hard for your child to explain to others what he/she can and cannot do?") was included in the field test version

Table 15. Overview of characteristics of the excluded items from the EA-QOL pilot questionnaire for children 2-7 years old (parent report) and children 8-17 years old (child and parent report)

	No of items in the EA-QOL pilot questionnaire		
	Children 2-7 years old (parent report)	**Children 8-17 years old (child report)**	**Children 8-17 years old (parent report)**
Skewness > 2.0	1	6	1
Kurtosis > 2.0	1	8	2
Missing proportion >5%	4	5	12
Differential item functioning for child gender	0	7	3
Differential item functioning for child age group 8-12 and 13-17 years old	0	3	4
Spearman's rho > 0.7 for inter-item correlation	0	3	8
Ratings in cognitive debriefing, importance < 70%	0	10	2
Ratings in cognitive debriefing, clarity < 80%	0	1	0
Ratings in cognitive debriefing, adequacy < 80%	4	1	0
Complaints in qualitative findings in cognitive debriefing interviews	9	4	15
Failed internal consistency reliability	4	1	0

Abbreviations: EA, esophageal atresia; QOL, quality of life

without any rewording, despite reaching missing values of 8.8%. Reasons for inclusion were related to the item uniqueness with no other item to cover the same aspect (comprehensiveness), the item importance emphasized by parents who participated in cognitive debriefing interviews, and the satisfactory results for internal reliability. Items excluded from the EA-QOL field test questionnaire for children 8–17 years old showed different problems as defined by the predefined criteria. The rate of missing values in the parent report and the cognitive debriefing partly reflected difficulties for parents of children who were fed only by a gastrostomy to answer some of the items regarding eating. However, many items regarding eating performed well according to the predefined criteria and were rated as clear, important, and adequate by the majority of children and/or their parents. The cognitive debriefing interviews also revealed that it was difficult for a parent whose child was cognitively impaired to answer some of the questions e.g. regarding social relationships and scar experiences.

Among the 26 items that were included in the field questionnaire for children 8–17 years old, 10 items in the child report did not demonstrate any problem according to the predefined criteria for item exclusion. In responses given by children 8-17 years old, 3 items did not show any problem except than a higher r_s with other items/

similarity, but were excluded due to this reason. In the child report, a further nine items fulfilled at least one of the criteria for item exclusion at the same time as they achieved criteria for item inclusion and did not demonstrate any problem in the parent report. They were discussed by the expert team before inclusion in the field test questionnaire. One example of a decision-making process concerned the item "Do you have the strength to play sports (e.g. running, playing football) and play as you friends do?". This item exceeded kurtosis > 2.0 in the child report, but performed well in every other aspect including in the parent report. The expert group decided to include it, but reword the item to "Do you have the strength to play sports (e.g. running, playing football) and play as children your age do"?". The reason for rewording was that children may choose friends who perform at the same level as themselves; the new question will ask the children from a broader frame of reference. Five items that fulfilled one or more criteria for item exclusion in the child report, but not in the parent report, were included without rewording. An example was the item "Is it a problem that you vomit after eating?". This item exceeded skewness and kurtosis > 2.0 in the child report, indicating better HRQOL. According to expert consensus, the item distribution on the response scale could be expected since only a subgroup of EA children may recognize this problem. The item was also regarded to be clinically important with an anticipated ability to identify worse HRQOL for this clinical subgroup of patients.

In total, 7 items that were included in the field test version for children 8–17 years old showed item-specific clinical sensitivity for child report (children with severe EA rated significantly lower scores than children with mild-to-moderate EA, $p < 0.05$, two-tailed). Three of these items also showed item-specific clinical sensitivity for the parent report (parents of children with severe EA rated significantly lower scores than parents of children with mild-to-moderate EA, $p < 0.05$, two-tailed).

The 18-item EA-QOL questionnaire (parent report)

Description of HRQOL domains and internal reliability
Table 16 shows descriptive statistics for three domains, *Eating, Physical health & treatment,* and *Social isolation & stress*, on the final 18-item EA-QOL questionnaire version for children aged 2–7 years. Cronbach's alpha reached satisfactory levels for all domains. The lowest mean was found in the domain *Physical Health & treatment*. The floor effects for the subscales varied from 2.9-9.1% and the ceiling effects varied from 2.9-6.1%. The largest floor (9.1%) and largest ceiling effect (6.1%) was found in the domain *Social isolation & stress*.

Known-groups validity of the 18-item EA-QOL questionnaire (parent report)
Table 17 shows the descriptive statistics of total scores of the shortened EA-QOL questionnaire for children with mild-to-moderate EA and severe EA aged 2-7 years (parent report) with the results of known-groups validity. As seen, children aged 2–7 years with severe EA had significantly lower total scores on the 18-item EA-QOL questionnaire version than children with mild-to-moderate EA according to parent-

report, in the two known-groups validity tests (Table 17).

Convergent validity of the 18-item EA-QOL questionnaire (parent report)
The total scores on the 18-item version correlated moderately with the total scores on the PedsQL 4.0 for children aged 5–8 years (n=20 parents of children aged 5–7 years, r_s=.58,) and very weakly with the total scores on DISABKIDS-6 (n=27, r_s=.058).

The EA-QOL field test version
Questions selected for the final field test version of the EA-QOL questionnaire for children aged 2–7 years (parent report) are shown in Figure 15. The EA-QOL questionnaire for children 2-7 years old starts with a presentation of the questionnaire as a "Quality of Life questionnaire for young children born with esophageal atresia" and the subheading is "Hello! how is your child feeling? That is what we would like to know". Following an introduction of the questionnaire, an example of how to answer a question on the 5-point response scale from never to always, the items are presented according to their HRQOL domain, which is labeled in a way that is easily understood by parents.

Table 16. Descriptive statistics and reliability of the Esophageal Atresia Quality-Of-Life questionnaire for children 2-7 years old (parent report)

Domain	No. of items	Mean	Range	SD	Floor (%)	Ceiling (%)	Cronbach's α
Eating	8	61.1	12.5–100.0	23.0	2.9	2.9	0.80
Physical function & treatment	6	58.4	20.8–95.8	20.2	2.9	2.9	0.72
Social isolation & stress	4	60.9	0–100.0	30.0	9.1	6.1	0.73
Total score	18	60.2	26.4 –91.7	18.3	2.9	2.9	0.84

Table 17. Descriptive statistics of total scores of the shortened Esophageal Atresia Quality-Of-Life questionnaire for children 2-7 years old (parent report) and the results of known-groups validity of using Mann-Whitney U-test

Severity of EA	n	Mean (SD)	Median (Range)	z(U)	p-value (two-tailed)
Mild-moderate EA	16	68.7(17.9)	71.5(26.4-91.7)	-2.6(67.5)	0.007
Severe EA (criteria A-D)	18	52.6(15.4)	54.3(29.4-86.1)		
Mild-moderate EA	18	69.0(16.9)	71.5(26.4-91.7)	-3.1(53.0)	0.001
Severe EA (criteria A-C)	16	50.2(14.4)	49.9(29.4-86.1)		

Abbreviation: EA, esophageal atresia

ABOUT YOUR CHILD'S EATING	
1.	Is it hard for your child to eat because food sticks in his/her throat?
2.	Is it difficult for your child to eat a full meal?
3.	Does eating stress your child?
4.	Can your child eat at the pace he/she wants?
5.	Is your child worried when he/she chokes on food?
6.	Does your child avoid eating because he/she is afraid of choking?
7.	Is it a problem for your child that he/she vomits?
8.	Is it a problem for your child to eat food at a party or when he/she is out with friends?
ABOUT YOUR CHILD'S PHYSICAL HEALTH AND TREATMENT	
9.	Does your child get tired easily when he/she plays games or sports?
10.	Does your child have less strength than other children during physically demanding activities?
11.	Are your child bothered by respiratory problems (e.g. coughing, phlegm, or difficulty breathing)?
12.	Is it a problem for your child that he/she gets respiratory infections easily?
13.	Does your child hate taking medicine?
14.	Does your child's health condition make it difficult for your child to sleep at night?
ABOUT YOUR CHILD AND OTHER PEOPLE	
15.	Is it a problem for your child that his/her health condition involves absence from preschool/school?
16.	Is it hard for your child to explain to others what he/she can and cannot do?
17.	Does it bother your child that people make comments about him/her?
18.	Does it bother your child that people get frightened when your child makes noise (e.g. breathing, clearing his/her throat, coughing, running)?

Figure 15. The Esophageal atresia Quality-of-life questionnaire field test version for children aged 2-7 years old (parent report)

The 26-item EA-QOL questionnaire (child report)

Description of HRQOL domains and internal reliability (child report)
Table 18 shows descriptive statistics for four scales, *Eating, Social relationships, Body perception,* and *Health & well-being*, on the final 26-item EA-QOL questionnaire version for children aged 8–17 years (child report). Cronbach's alpha reached satisfactory levels for all domains. The lowest mean was found in the domain *Social relationships*. The floor effect of each domain varied from 2.0-3.9% and the ceiling effects 7.8-23.5%. The domain *Body perception* reached the largest ceiling effect (Table 18).

Known- groups validity of the 26-item EA-QOL questionnaire (child report)
Table 19 provides information of descriptive statistics of the total scores of the shortened EA-QOL questionnaire for children with mild-to-moderate EA and children severe EA aged 8-17 years and the results of known-groups validity (child report). As shown, children aged 8–17 years with severe EA reported significantly lower total scores on the 26-item EA-QOL questionnaire version than children with mild-moderate EA in both tests of known-groups validity (Table 19).

Convergent validity of the 26-item EA-QOL questionnaire (child report)
The total score on the 26-item version correlated strongly with the total scores on DISABKIDS-12 (n=51,r_s=.70,) and moderately with the total scores on PedsQL 4.0 (n=51,r_s=.50) for the child report.

Table 18. Descriptive statistics and reliability of the Esophageal Atresia Quality-Of-Life questionnaire for children 8-17 years old (child report, n=51)

Domain	No. of items	Mean	Range	SD	Floor (%)	Ceiling (%)	Cron-bach's α
Eating	8	80.8	25.0–100.0	18.3	2.0	18.0	0.80
Social relationships	8	73.1	31.3–100.0	18.6	3.9	7.8	0.75
Body perception	5	79.1	20.0–100.0	20.2	2.0	23.5	0.74
Health & well-being	5	79.0	10.0–100.0	18.9	2.0	19.6	0.74
Total score	26	77.6	23.1–98.1	15.4	2.0	4.0	0.90

Table 19. Descriptive statistics of total scores of the shortened Esophageal Atresia Quality-Of-Life questionnaire for children 8-17 years old (child report) and the results of known-groups validity of using Mann-Whitney U-test

Severity of EA	N	Mean (SD)	Median (Range)	z(U)	p-value (two-tailed)
Mild-moderate EA	28	80.4(18.5)	86.0(23.1-98.1)	-2.7(177.0)	0.006
Severe EA (criteria A-D)	23	74.2(10.5)	76.0(56.7-94.2)		
Mild-moderate EA	31	79.3(18.0)	85.6(23.1-98.1)	-2.1(200.5)	0.035
Severe EA (criteria A-C)	20	74.9(10.5)	76.4(56.7-94.2)		

Abbreviation: EA, esophageal atresia

The 26-item EA-QOL questionnaire (parent report)

Description of HRQOL domains and internal reliability (parent report)
Table 20 shows descriptive statistics for four scales, *Eating, Social relationships, Body perception,* and *Health & well-being*, on the final 26-item EA-QOL questionnaire version for children aged 8–17 years (parent report). Cronbach's alpha reached satisfactory levels for all domains. The lowest mean was found in the domain *Body perception*. The floor effects varied from 2.0-3.8% and the ceiling effect from 3.8-19.2%. The HRQOL domain Body perception demonstrated the largest ceiling effect (Table 20).

Known- groups validity of the 26-item EA-QOL questionnaire (parent report)
Table 21 shows descriptive statistics for the total scores of the shortened EA-QOL questionnaire for children with mild-to-moderate EA and children with severe EA aged 8-17 years including the results of the known-groups validity tests (parent-report). As seen, parents of children aged 8–17 years with severe EA did not significantly report lower total scores on the 26-item EA-QOL questionnaire version than children with mild-moderate EA in any of the known-groups validity tests (Table 21).

Convergent validity of the 26-item EA-QOL questionnaire (parent report)
The total score on the 26-item version correlated moderately with the total scores on DISABKIDS-12 (n=51,r_s=.60,) and strongly with the total scores on PedsQL 4.0 (n=51,r_s=.66) for the parent report.

Table 20. Descriptive statistics and reliability of the Esophageal Atresia Quality-Of-Life questionnaire for children 8-17 years old (parent report, n=52)

Domain	No. of items	Mean	Range	SD	Floor (%)	Ceiling (%)	Cron-bach's α
Eating	8	77.9	40.6-100.0	18.1	2.0	13.5	0.79
Social relationships	8	74.7	21.9-100.0	18.2	2.0	3.8	0.78
Body perception	5	70.2	0-100.0	25.9	3.8	19.2	0.86
Health & well-being	5	71.2	25.0-100.0	20.6	2.0	13.5	0.71
Total score	26	73.9	31.0-98.1	16.5	2.0	3.8	0.88

Table 21. Descriptive statistics of total scores of the shortened Esophageal Atresia Quality-Of-Life questionnaire for children 8-17 years old (parent report) and the results of known-groups validity of using Mann-Whitney U-test

Severity of EA	n	Mean (SD)	Median (Range)	z(U)	p-value (two-tailed)
Mild-moderate EA	28	76.0(17.5)	76.9(31.0-98.1)	-1.1(264.0)	0.272
Severe EA (criteria A-D)	24	71.3(15.3)	72.1(43.3-96.0)		
Mild-moderate EA	31	76.2(17.0)	76.0(31-98.1)	-1.3(213.0)	0.187
Severe EA (criteria A-C)	21	71.1(15.3)	69.2(43.3-96.0)		

Abbreviation: EA, esophageal atresia

The EA-QOL field test version
Questions selected for the final field test version of the EA-QOL questionnaire for children and adolescents 8–17 years are shown in Figure 16. The EA-QOL questionnaire starts with a presentation of the questionnaire as a "Quality of Life questionnaire for children and adolescents born with esophageal atresia". The subheading is "Hello- how are you feeling? That is what we would like to know". Following an introduction and example of how to answer a question on the 5-point Likert scale

from never to always, the items are presented according to their HRQOL domain which is labeled in a way that is easily understood by children.

ABOUT YOUR EATING	
1.	Do you feel it is a problem that food get stuck in your throat when you eat?
2.	Does your health condition restrict you from eating any food?
3.	Do you get any pain when you eat because of your health condition? (e.g. when food sticks in your throat, heartburn, stomach ache)?
4.	Do you need to think of drinking a lot when you eat?
5.	Are you afraid when you choke?
6.	Does choking make it hard for you to eat?
7.	Can you eat at the pace as children your age?
8.	Is it a problem that you vomit after eating?
ABOUT YOU AND OTHER PEOPLE	
9.	Do you feel like the only one who was born with esophageal atresia?
10.	Is it complicated to explain to others what esophageal atresia is?
11.	Do others call you names (e.g. because you are small, have an unusual cough, eat slowly, or because you have a surgical scar)?
12.	Do you feel that others are staring at you (e.g. when coughing, choking, dressing in the locker room)?
13.	Do you get tired of people asking about the scar/scars?
14.	Do others say mean things about you?
15.	Is it easy for you to fit among children your age?
16.	Does it feel awkward when others ask you about esophageal atresia?
ABOUT YOUR SCARS AND YOUR BODY	
17.	Do you feel different because you have scars?
18.	Are you careful about what you wear because of your scar /scars?
19.	Do you feel awkward when your scar/scars are visible to others (e.g. new people, partner, people in the locker room, or in the swimming pool)?
20.	Do you feel that you are not perfect because you have scars?
21.	Is it a problem for you that are smaller than children your age?
ABOUTH YOUR HEALTH AND WELL-BEING	
22.	Do you have the strength to play sports (e.g. running, playing football) and play as other children your age?
23.	Are you bothered by breathing difficulties if you exercise and play?
24.	Do you have trouble sleeping at night because of your health condition (e.g. acid reflux, heartburn, or respiratory problems)?
25.	Are you worried about your future because of esophageal atresia? (e.g. school, friends, partner, work)
26.	Does esophageal atresia make you sad?

Figure 16. The Esophageal atresia Quality-of-Life questionnaire field test version for children aged 8-17 years old (child report)

Condition-specific coping experiences (paper III)

In the ten focus groups, a total of 590 coping statements (48.3% child reports) were recorded. Nine coping strategies were identified and the same type of coping strategies were described by parents and by children. The coping strategies described to be used by children and adolescents with EA are presented in relation to the three model of childhood coping; *Primary control coping, Secondary control coping* and *Disengagement coping* in relation of the reported frequency. An illustrative quote from the focus groups is given.

Primary control coping, 295 (50.0%)

Problem solving (ntot=116, 19.7%)
Problem solving (56 child reports, 60 parent reports) referenced experiences of the child's contemplation of decisions, planning of behavior or of activities, preparation of oneself for situations, finding of alternative solutions and an active focus to solve health-related problems.
"He chews more and drinks a lot when he eats meat, because he wants to be able to eat what he likes and the same as the rest of us"
(Mother of 3-year-old boy, severe EA)

Confronting (n=70, 11.9%)
Confronting (30 child reports, 40 parent reports) referred to experiences where the child recognized and approached difficulties due to their health condition or tried to overcome them.
"He tries to play football, even though he doesn't have the same physical strength as his peers and feels he is much smaller than they are"
(Mother of 12-year old boy, severe EA)

Seeking of social support (n=63, 10.7%)
Experiences of *Seeking of social support* (25 child reports, 38 parent reports) considered the child's active search for understanding and support from parents, peers, teachers and the doctor.
"When I feel ill, I go to my mother and seek her knowledge, because she is the expert of my condition and knows when my health is bad"
(15-year old boy, severe EA)

Emotional expression (n=46, 7.8%)
Emotional expression (21 child reports, 25 parent reports) strategies reflected experiences of showing and demonstrating anxiety, worry, fear, resignation, anger and resistance to deal with health-related difficulties.
"I am afraid of and I don't want to lose my button (gastrostomy), because I have had it my whole life"
(8-year old girl, severe EA)

Secondary control coping, 169 (28.6%)

Recognition of responsibility (n=71, 12.0 %)
Recognition of responsibility (41 child reports, 30 parent reports) was constituted by experiences of the child's active initiatives to learn more of one's health or treatment, strategies to learn from experience, to take care of health-related problems or challenges on their own and to show self-consciousness and independence.
"I have learned that I need the time of 20 minutes to finish my meal in order not to have pain or problems with vomiting"
(15-year old boy, severe EA)

Positive reappraisal (58, 9.8%)
Experiences of *Positive reappraisal* (32 child reports, 26 parent reports) were defined as statements where the child re-evaluated negative experiences as positive ones, found strength through difficulties, created pride and prestige out of difficulties, identified benefits of having the disease, experienced to be in 'luck and that others can have it worse'.
"She finds something positive with every visit at the hospital, like visiting the play therapy"
(Mother of 17-year old girl, mild-to-moderate EA)

Acceptance (n=40, 6.8%)
Experiences of *Acceptance* (20 child reports, 20 parent reports) were defined as adjustment to a demanding situation or to own (impaired) ability, humor and jokes, tolerance to endure stress, feelings of being used to the problems.
"I'm not bothered by my scars being visible to others, because they are a part of me"
(13-year old boy, mild-to-moderate EA)

Disengagement coping, 126 (21.4%)

Avoidance (n=95, 16.1%)
Experiences of *Avoidance* (45 child reports, 50 parent reports) were defined as behavior and thoughts that aimed to avoid situations, conceal problems or hide difficult emotions related to EA.
"I don't shower the same time as my class mates after sport class because of my scars"
(14-year old girl, severe EA)

Distancing (n=31, 5.3%)
The experiences (15 child reports, 16 parent reports) of downgrading, eliminating, suppressing and/or lessening the significance of problems to cope with problems caused by EA was defined as *Distancing*.
"She doesn't want to take medications even though she needs to, because she says she is tired of being ill and going to the hospital"
(Mother of 15-year old girl, mild-to-moderate EA)

Distribution of coping statements
Table 22 shows the distribution of coping statements with regard to child gender and child age group 2-7, 8-12 and 13-17 years. *Primary control coping* was most commonly reported in all child age groups. Experiences of *Disengagement coping* were rarely described to be used by children 2-7 years old (Table 22). The distribution of coping statements according to severity of EA, and presence/absence of associated anomaly is shown in Table 23. The majority of the aggregated coping statements were generated by or on behalf of children with severe EA (68.6%) and children with associated anomalies (61.9%).

Situations in which coping experiences were used
Condition-specific coping experiences (n_{tot}=590 statements) were reported in nine

Table 22. Distribution of coping statements with regard to child gender and child age group 2-7, 8-12 and 13-17 years

Coping strategy	Child gender		Child age group		
	Female	Male	2-7	8-12	13-17
Primary control coping	140(23.7)	155(26.3)	77(13.1)	127(21.6)	91(15.4)
Problem solving	54	62	28	47	41
Confronting	35	35	17	33	20
Seeking social support	31	32	17	28	18
Emotional expression	20	26	15	19	12
Secondary control coping	71(12.0)	98(16.6)	28(4.7)	64(10.8)	77(13.1)
Recognizing responsibility	32	39	15	23	33
Positive reappraisal	20	38	6	26	26
Acceptance	19	21	7	15	18
Disengagement coping	60(10.2)	66(11.2)	15(2.5)	53(9.0)	58(9.8)
Avoidance	48	47	13	49	33
Distancing	12	19	2	4	25
Total number of statements	271(45.9)	319(54.1)	120(20.3)	244(41.4)	226(38.3)

Table 23. Distribution of coping strategies according to severity of Esophageal Atresia, and presence/absence of associated anomaly

Coping strategy	Severity of esophageal atresia		Associated anomaly	
	Mild-moderate	Severe	Presence	Absence
Primary control coping	80(13.6)	215(36.4)	192(32.5)	103(17.5)
Problem solving	40	76	76	40
Confronting	14	56	48	22
Seeking social support	12	51	39	24
Emotional expression	14	32	29	17
Secondary control coping	56(9.5)	113(19.2)	101(17.1)	68(11.5)
Recognizing responsibility	21	50	45	26
Positive reappraisal	17	41	26	32
Acceptance	18	22	30	10
Disengagement coping	49(8.3)	77(13.1)	72(12.2)	54(9.2)
Avoidance	42	53	59	36
Distancing	7	24	13	18
Total number of statements	185(31.4)	405(68.6)	365(61.9)	225(38.1)

different situational contexts. The nine situational context referred to problems and stress experienced with nutritional intake (38.5%), communication of one's health condition (13.2%), self-perception when experiencing troublesome symptoms (10.0%), appearance of body or scar(s) to other people (9.7%), physical activities like sport and play (7.3%), sleep (5.8%), hospital care (5.6%), stigmatization and social

exclusion (5.1%) and medication intake (4.9%). The reported frequency of statement in relation to each situational context and the three-model of *Primary coping, Secondary coping* and *Disengagement coping* is shown Table 24. Coping experiences assigned as *Primary coping, Secondary coping* and *Disengagement coping* were described in all situations, but with different frequency depending on situation (Table 24).

Table 24. The reported frequency of each situational context in relation to the three-model coping Primary coping, Secondary coping and Disengagement coping

	Primary control coping (ntot=295)	Secondary control coping (ntot=169)	Disengagment coping (ntot=126)
Situational context			
Nutritional intake	133	59	35
Communication of one's health condition	44	10	24
Self-perception	13	36	9
Appearance of body or scar(s) to other people	12	23	22
Physical activities like sport and play	30	3	10
Sleep	27	6	1
Hospital care	14	17	3
Stigmatization and social exclusion	16	4	10
Medication intake	6	11	12

A conceptual model of coping

Based on the study results on coping processes among children and adolescents with EA and in combination with previous literature concerning coping in children with chronic conditions (14, 15, 153) a conceptual (hypothesis) model was developed (Figure 17).

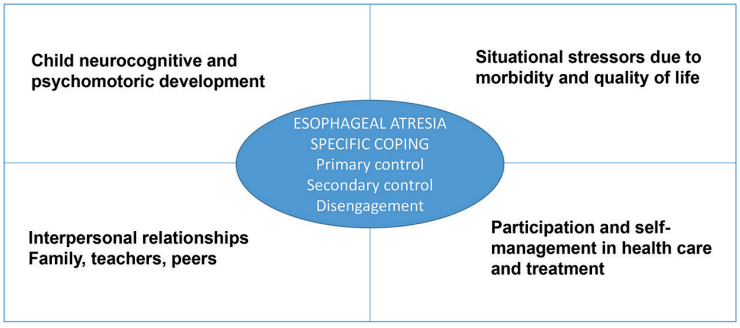


Figure 17. Conceptual model of coping for children and adolescents with esophageal atresia

Childhood coping, categorized according to the three-factor model described in the Compas et al. study (15), served as the starting point for the conceptual model to show that the use of primary control, secondary control, and disengagement coping by children with EA may be influenced by four main components. The conceptual model suggests that four main components – the child's neurocognitive and psychomotor development, situational stressors due to morbidity and QOL, interpersonal relationships and participation and self-management in health care and treatment- are closely interrelated to each other as well as to the child's choice of coping strategy.

The study results of coping used by children with EA indicated that the coping strategy may reflect the child's age. The developmental approach to childhood coping has been stressed by several authors (14, 15, 158). Therefore, the child neurocognitive and psychomotor development ought to be a part of the coping model. Situational stressors due to morbidity and QOL, as shown in our study of coping among children with EA, may also characterize coping. Interpersonal relationships such as with the family, teachers, and peers can also be assumed to affect coping processes in children with EA. In fact, the attachment theory can help to understand the child's coping response (14). In EA children, the family context can be anticipated to be important in view of the fact that parents learn to be the expert on their child's needs from birth onwards, and that children learn to seek proximity, support and autonomy in relation to their primary caregivers. In addition, our HRQOL studies showed that social dimensions are prominent HRQOL issues for EA children, which sheds light on the importance of their interpersonal relationships. The patient's participation in the health care context may also influence coping, as described by Schmidt et al. (14) that participation in health management is as a part of the coping concept in pediatric chronic disease. With emphasis on follow-up care for children with EA (225), the care context can also be assumed to shape the use of coping strategies in children with EA. In this manner, the conceptual model of coping in children with EA makes the assumption that there are developmental, situational, relational, and health care mechanisms that continuously will shape coping processes in children with EA.

A conceptual model of HRQOL

Based on our study results (paper I, II, III, IV) among children and adolescents with EA, in combination with results presented in previous literature, a conceptual (hypothesis) model (Figure 18) was developed that can increase the understanding of HRQOL in the EA population. Furthermore, it presents hypotheses that can be tested in future studies. The conceptual model describes the following relationships to HRQOL: The type of EA (including associated anomalies) and the surgical treatment of EA determine functional outcomes, which in turn is assumed to affect the generic as well as condition-specific HRQOL in children and adolescents with EA. The condition-specific HRQOL for young children with EA is defined as the components of *Eating, Physical Health & treatment*, and *Social isolation & stress*. The condition-specific HRQOL for children 8–17 years old consists of the HRQOL domains *Eating, Social relationships, Body perception* and *Health & well-being*. There are two main mediating factors that determine why or how effects on HRQOL occur. First, there are clinical mediators – early severe postoperative complications, level of severity of disease, frequency of esophageal and respiratory symptoms, and adherence to follow-up care service. Second, there are psychosocial mediators – child coping style and coping skills, and family impact or parent burden. The effect of EA on HRQOL depends on moderating factors (which determine the strength of the HRQOL outcomes): child gender, child age, child resilience, family socioeconomic status, and culture.

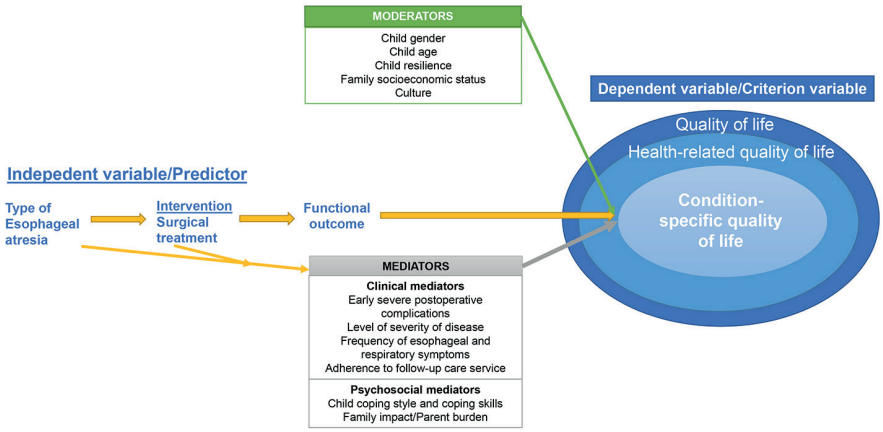


Figure 18. A conceptual model of HRQOL for children and adolescents with esophageal atresia

Discussion

The overall aim of this thesis was to advance knowledge of condition-specific aspects of HRQOL among children and adolescents born with EA and the coping strategies they use. This thesis showed that, as of January 2015, only twelve articles have reported the empirical measurement of HRQOL among patients with EA, and no articles were found prior to 1995. Articles reporting on HRQOL among patients with EA have only recently started to include younger patients among the study groups. Since the literature review was completed, four more HRQOL studies of EA patients have been published, none of which had used a patient-derived questionnaire development to assess disease-specific aspects of EA and three of which concerned children and/or adolescents (226-229). Using a patient-derived approach, this thesis demonstrates that aspects specific to EA may affect children and adolescents in the overall quality of their daily lives, and that children with EA use several coping strategies to deal with different health-related problems.

Discussion related to HRQOL

Following international standards for the development of a PROM (11, 13, 173, 174), the EA-QOL questionnaires uniquely incorporate highly valued characteristics from the EA family's viewpoint. Previous studies have shown that factors related to the severity of esophageal and respiratory morbidity negatively affect generic HRQOL in children with EA (17, 205). The EA-QOL questionnaires are designed to more specifically elicit the patient's experience of the impact of the EA-related morbidity. According to our results, HRQOL issues concerning food, meals and nutritional intake were prominent across childhood and adolescence, and were therefore incorporated as questions in the domain *Eating* of both age-specific EA-QOL questionnaires. It has previously been shown that feeding difficulties are associated with postoperative EA in childhood (85-87, 230), including food refusal, needing more time to eat a meal, difficulty swallowing certain foods, coughing, and choking (85-87).

Aspects of eating are important for a good condition-specific quality of life in children with esophageal atresia

In the Baird et al. study (94), the majority of children with EA type C reported feeding difficulties in the subclinical range; whereas children born extremely prematurely or those with non-type C demonstrated severe feeding difficulties. Khan et al. (230) showed that feeding milestones of children with long-gap EA after primary repair were found not to be significantly different from those of a control group, but there was much greater variability in attaining milestones in the long-gap EA group. Two other studies (85, 86) have shown that feeding difficulties may lessen with time and become more infrequent in older children. However, in a recent study of adults with EA (83.8% type C, mean age 25.3 years), adults with EA having BMI<18.5 kg/m^2 still had feeding problems such as severe postprandial fullness, the need to eat slowly, and severe difficulties swallowing dry solid foods (100). As the first QOL study of EA patients reported from the US, Waleed et al. (227) developed their Swallowing Dysfunction Questionnaire for adult patients (without involving any patients in the questionnaire construction) and showed that, within a recall period of seven days and a median age of 40 years (range 18-63 years), as many as 82.2% of adults with EA reported some problem with swallowing. Although both soft and dry food were accepted by patients, 15–20% of patients always had difficulty, discomfort, or pressure when swallowing hard food. Coughing or choking when swallowing was uncommon, but 75% of patients increased intake of thin liquid to help swallowing.

Consequently, many studies confirm that feeding problems are a common complication in EA patients (230). Earlier studies reflect the use of different measurements, different subsamples of EA and reporters, but also that the follow-up studies of esophageal morbidity and its impact on the child are of clinical interest and importance. In view of future research, the EA-QOL questionnaires offer the composition of age-specific HRQOL questions that can give information on the perceived impact on food and meals from a physical, social, and emotional HRQOL perspective. The wording of items, derived from focus groups, are the children's or parents' own way to express themselves. This has increased the possibility to gain reliable information about eating issues from a child and parent perspective.

According to the results of our studies, social dimensions were also pronounced HRQOL issues among children and adolescents with EA. Earlier studies of HRQOL in children with EA have shown impaired social HRQOL in children with complicated EA or impaired school functioning in children with EA and associated anomalies (17, 189). Other studies of psychosocial functioning (231-233) have shown a larger use of special education services among children with EA compared to healthy references, especially in children with additional sequelae (232, 233). Two studies have reported behavioral problems (232, 234) at the same time, as another study (231) has reported an improved perception of social acceptance among adolescents compared to the general population.

Previous literature regarding psychosocial functioning and social HRQOL in young EA children is sparse. Complementing previous studies, our results highlighted that

there may be social issues of relevance to young EA children. The EA-QOL questionnaire asks the children (or parents) about relationships, communication, and social interaction with others as a result of EA. From this perspective, it is central to identify children who are at risk of impaired social HRQOL by assessing condition-specific HRQOL, and to be able to promote a good social HRQOL.

In our findings, items regarding social dimensions were more comprehensive in the EA-QOL questionnaire for children 8–17 years old compared to the version for younger children. This may reflect an increased importance of social issues in children older than 8 years. From a developmental perspective, this is consistent with the cognitive maturation and the growing importance of peer relationships, school, and leisure time that are associated with increasing age. The international standards of PROM development in children (13) recommend an age-specific approach. This was supported also by the characteristics of underlying morbidity reported to affect the children. As previously known, respiratory disorders may become more infrequent as the child gets older (98, 190). In line with those studies, the HRQOL problems caused by physical health and respiratory disorders were differently manifested in the different child age groups. Bothersome symptoms, impact on play, respiratory infections, and medication intake characterized the common features in the young children's lives. In the HRQOL domain *Physical health & well-being* in the EA-QOL questionnaire for children aged 8–17 years, the impact on sport and play due to respiratory problems showed internal consistency with items of emotional well-being, i.e. a broader perception of health, in these children. Growth retardation may also become more infrequent with increased age of the child (98). From a HRQOL perspective, the possible impact of one's own body size may become more evident as the child's cognitive function matures in combination with the expansion of their social world after school start. This is in agreement with the HRQOL domain *Body perception* in the EA-QOL questionnaire for children 8–17 years old, which elicits responses from the children (or their parents) regarding the impact of surgical scars on their perception or behavior.

Social dimensions are prominent and may be negatively affected in school-aged children and teenagers with esophageal atresia

HRQOL questions regarding surgical scars have not previously been reported in a valid HRQOL instrument for children with EA. Interestingly, the ceiling effect in child and parent report of the HRQOL domain *Body perception* was 23.5% and 19.2% respectively. This indicates that around a quarter (patients) and around a fifth (parents) scored at the maximum of the scaling range, but also that the majority of the children within a recall period of four weeks to some extent perceived themselves to be negatively impacted by body issues. In comparison to our study results, three earlier studies have reported results of EA children's perceptions of their physical appearance. In 1984, Lindahl et al. (235) examined aspects of physical and psychological development in 33 children with EA without significant associated anomalies, and found that these children had a normal body image. Faugli et al. (231) showed that EA adolescents (n_{tot}=21) rated better physical appearance scores on the Self-Perception Profile for Adolescents compared to the general adolescent population. Using the Self-Perception Profile for Children, Bouman et al. (232) showed that children with EA who had more physical problems had a negative perception of their physical appearance. However, the issue of surgical scars has been more specifically examined in HRQOL investigations of adults with EA. Koivusalo et al. (200) found that 50% of adults had complaints about their thoracic scar, although 34% had only minor complaints. Deurloo et al. reported that 9% had negative daily life experiences due to their scars (168). Surgical methods used for EA repair may differ between the conducted studies, and importantly with respect to future studies, both a muscle sparing approach and a thoracoscopic technique have been implemented to date (43, 44). In line with the view expressed by Laberge and Blair (236) that we should find out what the patients' perceptions and feelings are about their scars before we assign our importance to them, the EA-QOL questionnaire for children 8–17 years old will allow such an assessment in future research.

Discussion related to coping

In order to improve our understanding of condition-specific aspects of HRQOL among children and adolescents with EA, we also need to better understand the coping processes. It is interesting that several authors (16-18, 189) have implied that coping strategies used by EA patients lead to better outcomes, but that no study at the start of our project had reported the effect of coping on health, psychosocial functioning, or HRQOL outcomes in pediatric patients with EA. This thesis so far presents the only reported study of the coping strategies used by children with EA. Although this study is of a descriptive nature, it has increased the understanding of coping strategies in several ways. Coping strategies were described to be used by young EA children when morbidity may be particularly apparent (98). This suggests that coping strategies adopted at an early age may shape the child's development and perceptions of HRQOL. Having the condition from birth, EA children have no experience of anything else and must at the same time learn to adapt to their health condition. Attachment theory (237) may shed light on further special circumstances concerning EA children. Parents are supported to take care of their EA child before the first hospital discharge and become the expert on their child. In turn, children learn how to seek their parents' proximity and support, find security, strive

for exploration and autonomy as well as activation and deactivation based on the attachment behavioral system. As a cumulative interactive process, coping experiences are embedded in developmental organization and may lay the groundwork for the evolvement of behavioral and cognitive processes (14). These circumstances may form the early behavioral coping strategies such as seeking social support, recognizing responsibility, and problem-solving.

Parents of EA children may experience emotional strain (189, 238). Although two studies using child report (189, 203) have reported improved family functioning in EA families compared to healthy references, children with chronic disease may have to cope with the impact of the disease and treatment on the family (14). From this perspective, the health care support given to EA families may be of particular importance to influence the early adoption of coping strategies in the EA child.

Parents of children with esophageal atresia are educated to become the child's expert and children may learn how to seek support, proximity and autonomy

Nutritional intake is a part of everyday life that is independent of the child's age, and the experience of stress can be associated with the frequency of stressful situations (153). In combination with esophageal morbidity in the study sample, this may explain why the majority of coping strategies were reported in nutritional intake situations. With increased age, the EA child's self-perception and social awareness of other people grow. New stressors may appear, such as the appearance of surgical scars or communication with others about their health condition. In parallel, the child's coping strategies increase in scope and flexibility (166). This could result in the child's choice of other coping strategies. In summary, coping in EA children may be characterized by disease-specific and age-related stressors.

In this study, the majority of coping experiences were reported by children with severe EA (or their parents) as well as by those of children with EA and associated anomalies (or their parents), and this was seen in the different types of coping strategies. Hampel et al. (239) showed that coping with everyday stressors was improved in children and adolescents with chronic illness compared to healthy controls. Hence, coping with a chronic illness may lead to more effective coping with everyday stressors. This may be one of the explanations for study results where generic

overall HRQOL was not impaired in EA pediatric patients compared to healthy references (205, 226).

Previous literature (153) has suggested that instruments used to assess coping strategies used by children with chronic disease should include situational details, thus capturing the multifaceted ways that youngsters appraise different types of stressors and deal with them. Our study of coping provided the groundwork for the development of a condition-specific coping measurement (240) (the EA-COPE questionnaire, which is currently being pilot tested). This can allow hypothesis testing of the relationship between primary control coping, secondary control coping, and disengagement coping (15) and HRQOL outcomes, and further refine explanations of why or how HRQOL effects occur among EA patients in accordance with the conceptual model.

The support given to the families of children with esophageal atresia may be of outmost importance to help the child deal with health-related difficulties and achieve a successful adjustment

Implications of the results

Aiming for excellent care and treatment, the joint evaluation of survival, morbidity and patient-reported outcomes is fundamental, and the advantage of the EA-QOL questionnaire is the possibility to evaluate HRQOL outcomes even in young children. Tovar and Fragoso (61) argued that the gold standard in the treatment of EA patients remains a good anastomosis with survival, limited sequelae, and "good QOL". In order to properly design interventions that improve HRQOL in EA patients, we must first fully understand what HRQOL is from the perspective of the EA child. In addition to generic HRQOL questionnaires, in which questions are asked in a more general way, it is paramount that HRQOL instruments can provide clinically relevant information and that we can also understand what factors affect HRQOL. Our knowledge is dependent on the nature of the questions that we ask patients with a rare condition, and disease-specific questions benefit the evaluating potential of an instrument (241). The EA-QOL questionnaires showed promising results in the pilot test, as a potential discriminative instrument (241) that can assess the burden of illness and improve the exploration of who in this population is facing a larger or lesser burden of illness. Asking condition-specific HRQOL ques-

tions, this study showed that children with severe EA, as defined in this study, had reduced HRQOL. After the field test, the EA-QOL questionnaires can be implemented to compare HRQOL outcomes in patients who have undergone different surgical techniques. As a secondary endpoint (11), the HRQOL information can improve the evaluation of treatments and can help to give further evidence for the use of a particular surgical method. Such evaluation can be especially valuable when there is no consensus regarding surgical methods, such as in the case of esophageal replacement procedures (242).

Our studies of HRQOL and coping have also revealed information of importance to new parents. If they ask questions regarding HRQOL in EA children, we can today improve HRQOL information concerning condition-specific HRQOL; aspects that do and that do not seem to impact EA children, and the known groups of severe EA children who seem to be at risk of impaired condition-specific HRQOL. We can also point out that EA children seem to adopt coping strategies at an early age, and stress the subsequent expected importance of parental involvement in supporting effective strategies.

The ESPGHAN-NASPGHAN Guidelines for the Evaluation and Treatment of Gastrointestinal and Nutritional Complications in Children With Esophageal Atresia-Tracheoesophageal Fistula which were published in 2016 (225) were based on a systematic literature search from inception to March 2014 and expert consensus, and highlighted the need for follow-up care for children with EA. In March 2014, our studies were not yet published. Based on available data, the authors of the ESPGHAN-NASPGHAN guidelines (225) concluded that gastrointestinal and respiratory symptoms and associated anomalies may negatively affect HRQOL and recommended long-term medical and psychosocial support for these patients and families. In recent publications, follow-up care by multidisciplinary teams are strongly advocated (44, 84, 97, 243), but the opportunities for families to have a long-term follow-up care varies between centers (59).

Our study results are in agreement with these studies and can further possibly advance the HRQOL information. The study results can be used to improve information to EA children and/or their parents during their postoperative visits to the outpatient clinic. This information can help them to be better prepared for situations such as communication with peers regarding their health condition, other people's reactions to their surgical scars, and feelings of social isolation. From a clinical point of view, physicians and nurses can in this way be assumed to facilitate a good condition-specific HRQOL in EA children.

An implementation of a PROM into clinical practice, can possibly improve information provided to the families of children with esophageal atresia and help them to become more prepared to deal with situations that may affect the children

As observed in other pediatric chronic conditions (178, 180, 181), implementation of a PROM instrument in clinical practice can be used specifically to improve the child-caregiver communication about the child's health. Moreover, our study results concerning coping can help physicians, nurses, and families during follow-up care to recognize the efficacy of coping strategies in relation to outcomes. From a clinical perspective, the noticeable use of coping strategies in nutritional intake situations motivates future studies of the efficacy of coping on esophageal morbidity and condition-specific HRQOL (such as the HRQOL domain Eating). In a study by Puntis et al. (86) regarding growth and feeding outcomes in 124 children with EA, strategies such as "hurrying over food" were a frequent antecedent of choking in children with EA, and behaviors such as "liberal fluid intake during meals", were preventative of choking (86). Presse et al. (100) reported compensatory eating behavior in 37 adults with EA, and the most common were "the need to drink while eating" and "the need to eat slowly". Underweight EA patients reported significantly more often having severe postprandial fullness and "the need to eat slowly" compared to adult patients with EA with BMI>18.5 kg/m^2. In addition to medical treatments directed at the underlying cause of dysphagia, feeding adaptation and effective strategies are other treatment options (225). In the medical field, coping can be viewed from the concept of patient participation in self-management strategies to reach the preferred health outcomes of the patient's own therapeutic process (14). Although underweight patients in the Presse et al. study (100) also had severe difficulties swallowing dry foods as an indication of dysphagia, it would be interesting to investigate such outcomes and add the coping strategy perspective.

Another perspective on the importance of coping assessment or coping interventions in clinical practice is the use of disengagement coping among EA children. Interventions to improve coping should be targeted at young children before maladaptive coping patterns become entrenched (14). EA patients (or their parents) may not actively seek health care support (17, 86). At the same time, patients with EA are at risk of chronic conditions and diminished HRQOL into adulthood (16, 189, 198, 200). A systematic approach to education and advice for EA children and their families, covering ways to deal with nutritional intake, medical treatment, hospital care, and

social aspects of life, could possibly better prepare adolescents for transition to adult care, as well as improve health and HRQOL outcomes. From the perspective of pediatric health care, this would be a crucial step toward designing appropriate support to ease the child's burden and facilitate independent development into adulthood. Only one intervention study of transition from pediatric to adult care has been reported: Dingemann et al. (228) showed that a transition education program, given to adolescents with EA and their parents, did lead to satisfaction and increased transition-specific knowledge among the patients in the intervention group, though their generic HRQOL did not change. The international ESPHAGAN-NASHPAGAN guidelines (225) advocated that the transitioning from pediatric to adult care for patients with EA should be established to ensure that lifelong comprehensive care is provided for all patients with EA. Further studies are needed and should include coping interventions.

Condition-specific aspects of HRQOL and coping can also provide relevant information to stakeholders such as patient advisory support groups and teachers at the preschool or school. In previous research on other health conditions, PROMs have also been found valuable in describing the population in a standardized way, identifying outcomes in different levels of morbidity, predicting relevant clinical events, evaluating the efficacy of medical and/or psychosocial treatments to support the patient's health, and improving HRQOL (8, 11, 14, 126, 127). In research on EA patients, standardized PROM criteria can enable generalizability of the results in describing the population and can help us to compare outcomes, for example between different cultures. Standardization will also make longitudinal studies of EA-QOL over life trajectories possible, starting when the child is two years old.

Methodological discussion – study strengths and weaknesses

Our attempts to develop a PROM for children and adolescents with EA is a reflection of the methodological progress as well as the medical advances in the EA field. From a methodological standpoint, PROM development has moved forward from high-prevalence diseases in adult populations to children with chronic conditions, and finally to rare pediatric conditions (8, 120, 122, 131). In line with most recent advancement in PROM research, the development of item banks is becoming more common (115, 178). Using IRT methods for different health domains, this is a way to achieve a standardized metric by drawing from an item pool. However, this always requires large statistical data, which complicates the evaluation of condition-specific HRQOL assessment in RD. Rare pediatric conditions pose specific challenges to PROM development, analysis, and interpretation of data (13, 126, 173, 174). The international practices for PROM development described by the respective ISPOR task forces for children are recently published and practices for PROM development for populations with a RD are emerging (13, 173, 174). We have strived to be compliant with the international standards of PROM development, which is a study strength.

The literature review reflected a systematic approach, and although articles were included in the review based on a broad literature search, predefined criteria, and decision made by several authors, there is always a risk that articles of relevance for the understanding of HRQOL in EA patients may have been excluded. In order to address the methodological quality of the included articles, the HRQOL assessments were viewed in relation to attributes outlined by the Scientific Advisory Committee of the Medical Outcomes Trust (112). In a systematic literature review, clinical heterogeneity of the study population should be described (194). In our study, this was completed in table format by describing each study population and by using I^2 statistics in the meta-analysis. The estimate of the effect of EA on HRQOL presented in the metaanalysis- although reflecting underlying study heterogeneity - has increased the understanding of HRQOL in EA patients. It is a study strength that the literature review as a methodological step, strengthened the preparation of the empirical studies.

Content validity is one of the most central aspects in a condition-specific instrument for a RD, and may prevent future measurement error (173, 174). Items and domains reflected in the scores of a PROM should be important to the target population and comprehensive with regard to patient concern (109). Both age-related versions of the EA-QOL questionnaires have strong content validity. Accordingly, the patient and parent input to item generation of the questionnaires is well documented, and the understanding of the questionnaires has been evaluated through cognitive debriefing (13, 109). As recommended, children and adolescents were involved as effective content experts (13), through qualitative research. Parents were considered as important providers of complementary HRQOL information (130), and the EA-QOL questionnaires parent form can be considered to be informant-reported (13).

The overall HRQOL domains were identified across the child age groups. However, at an item level, the detailed content, the wording, and the distribution across subgroups varied between younger children (parent report) and the HRQOL descriptions of children from 8 years of age (child and parent report). Hence, two age-specific HRQOL questionnaires for children with EA were developed. One advantage of a developmental approach toward the concept condition-specific HRQOL is a stronger content validity in each of the age groups. However, in line with Huang et al. (135), this can also be viewed as a disadvantage since we did not develop a latent construct of condition-specific HRQOL based on a life-course theory approach, which complicates comparison of condition-specific HRQOL across early childhood and adolescence.

Considering the developmental approach toward the concept of coping, the study results indicated that coping strategies used by EA children may shift and become more advanced with increased age. Many authors (14, 15, 158) have promoted a developmental perspective to childhood coping, and Skinner et al. (158) explained that theory and evidence have shown five main developmental stages during childhood when coping processes are likely to undergo significant qualitative and quantitative

changes: infancy to toddlerhood, ages 5 to 7, late childhood to early adolescence (about ages 10 to 12), early and middle adolescence (about ages 12 to 16), and middle and late adolescence (about ages 16 to 22). As a study weakness, further details of coping used by EA children from an age perspective cannot be known without conducting further studies.

The focus group study is strengthened by the response rate of 100% and the fact that all participants have contributed information. Similar to the European DISABKIDS project (148), other strengths are the efforts that were made to retain the patient report and the condition-specific aspects during the categorization of HRQOL and coping experiences. Interpretation bias was minimized through consensus among several researchers and the use of field notes. In addition, presentation of the categorization process and focus group quotes strengthened rigor. Nevertheless, generalization of the focus group findings is limited due to the small patient sample and the single-center study design. Although they were compared to the results of focus groups held in Germany (results in manuscript in preparation), the Swedish focus groups served as the primary source for item generation of the EA-QOL questionnaires. Even though the number of statements in a focus group may give an indication of the importance of a certain domain, it must be interpreted with caution. Focus group data are not appropriate for statistical testing; the focus group studies were descriptive and do not describe the statistical differences between subgroups of EA, which limits the scope for interpretation of the data. Regarding HRQOL, statistical testing was conducted in the pilot study of the EA-QOL questionnaires (and currently of the EA-COPE questionnaire) using a larger sample size of EA families than used in the focus groups.

In the pilot test of the EA-QOL questionnaires, item reduction to reduce poorly performing items was shown to be complex. In compliance with the international standards (11, 173, 174), we tried to meet the challenges in PROM development by using predefined criteria to select items for the field test, and careful attention by experts to interpret the study results from a methodological and clinical perspective. Through the development of the EA-QOL questionnaire, affirmative questions were discarded. It may therefore be considered as a study weakness of the EA-QOL questionnaires that the majority of HRQOL questions will ask the patient about a negative impact. However, results of the initial validity and reliability of the shortened EA-QOL questionnaires were adequate. The construct validity and internal reliability of the EA-QOL questionnaire for children 2–7 years old were acceptable, with only a very weak correlation to the total scores of the DISABKIDS-6, suggesting that the two instruments measure different constructs.

The construct validity and internal reliability of the EA-QOL questionnaire for children 8–17 years old were adequate. The parent version of the EA-QOL questionnaire for children 8–17 years old achieved acceptable convergent validity, but not known-groups validity for the total scores. However, the EA-QOL questionnaire for children 8–17 years old was primarily developed for children. Still, it is interest-

ing to consider why the scoring made by parents of children with mild-to-moderate EA and parents of children with severe EA was not significant and why the result of known-groups validity was different from the child-report. A high proportion of parents were mothers and university-educated in the pilot study. This can influence the results. According to previous research (130), a possible explanation for the study results is that the parent report is dependent on to what extent the parent is a part of the daily life of their child. This can affect their ability to provide reliable information about the child (130). Yet another explanation for the study results is the communication patterns in the family, which can influence parents' ability to report their children's internal states or feelings. Moreover, the emotional well-being in parents can also affect the rating of their child's HRQOL. However, these characteristics are not known in the participating families of EA children with different severity levels, and this can therefore only be reflected upon.

As already seen in the literature review of HRQOL in EA patients (paper I), HRQOL results may depend on study population characteristics with regard to survival rates, age, the presence of esophageal and respiratory morbidity and associated anomalies. These population characteristics differed between some of the HRQOL studies reviewed in the literature (paper I). The heterogeneity is also a known challenge in PROM development for RD, and the heterogeneity of the EA study population will influence our study results. The effect of heterogeneity can become magnified in combination with small sample sizes. If heterogeneity is large in how the disease presents, as in EA, there may be discrete outcomes that are not measureable across the population (126, 174, 241). In order to address the issue of heterogeneity, we defined criteria for severe EA with thoroughness. These criteria made it possible to stratify the study sample for the focus groups according to severity of EA and to increase the sample size and improve the assessment of known-groups validity (fewer criteria would have reduced the sample size of severe EA). However, an important study weakness is that patients with EA may have fulfilled more than one of the inclusion criteria for severe EA. This means that the known groups of mild-to-moderate and severe EA are heterogeneous.

In view of the aim of the criteria to assess severe EA according to neonatal characteristics, it is successful that early EA-related factors can distinguish between different levels of condition-specific HRQOL. A prediction of the relationship between such factors and condition-specific HRQOL can improve information to the parents around the time for esophageal repair, and early interventions that support a good HRQOL. However, defining severity of EA based on neonatal characteristics and not current health may also be a weakness. The reason is that previous research did not employ a standardized definition of severe EA and the significance of early risk factors for the development of long-term complications is only partly understood (68, 69). Moreover, the criteria for severe TM required a broncoscopy. Although we used a reference for the definition of severe TM and both recruitment centers had similar routines for bronchoscopy examinations, there is a risk of different evaluations. A broncoscopy may also limit future assessments of known-groups validity in

this specific way, since all centers don't perform broncoscopy intraoperatively at time for esophageal repair or provide follow-up care to children with severe respiratory symptomatology.

In the pilot results of the EA-QOL questionnaires, the heterogeneity was reflected in the difficulties for patients with a gastrostomy to answer some of the questions regarding eating, which were the same aspects regarded as important by the majority of patients and parents. Moreover, heterogeneity was observed in the scoring range of each of the HRQOL domains as well as in the ceiling effects of the HRQOL domains *Eating, Body perception* and *Health & well-being* of the EA-QOL questionnaire for children 8-17 years old. Due to heterogeneity, our results should be understood in relation to the specific context in which the studies were performed. Therefore the study population characteristics were carefully described. This showed that the study sample characteristics can be considered as comparable to characteristics presented in previous literature (42, 44, 76) with regard to surgical treatments of EA, esophageal and respiratory morbidity, and associated anomalies. However, there was a rather high prevalence of associated anomalies in the study sample participating in the pilot study, but this has also been reported previously (17, 100, 189).

Small sample size in a rare condition complicates the use of classical test theory methods in PROM development (174). Since small sample size used in the studies will affect the results, non-parametric statistical testing was used, which is also preferable to use with data retrieved from an ordinal scale and on non-normally distributed data (103, 174). In addition, in order to maximize the number of participating patients, recruitment from patient advocacy groups has been recommended (122, 173). However, we gave precedence to recruitment from clinical centers, although some of the patients had previously participated in the focus groups. The condition-specific HRQOL questions cover a recall period of four weeks, but previous participation in focus groups may influence the study results and this is therefore considered a study weakness.

A cross-cultural approach was undertaken through the cognitive debriefing, but differences in the Swedish and German study sample size limited the possibility to conduct a cross-cultural statistical equivalence test. Future research is warranted. A field test, which is ongoing in a larger sample of the EA families, will provide more validation and reliability to the EA-QOL questionnaire. This is central also because some of the items were reworded in the pilot study. The field test of the EA-QOL questionnaires will permit analysis of the questionnaire's factor structure, external reliability (re-test), cross-cultural equivalence in Sweden and Germany, a deeper exploration of differences in child-parent HRQOL ratings and a more advanced clinical hypothesis testing.

Conclusion and future perspectives

Using international standards for PROM development and the framework of the European DISABKIDS project, children with a rare pediatric surgical condition such as EA were placed in the forefront. Thus, the studies in this thesis, being based on child and parent experience, have advanced our understanding of HRQOL and coping among EA children. These studies are the only ones to date that have reported using a patient-derived development of a condition-specific HRQOL questionnaire for children with EA. As a result, this thesis is able to demonstrate that children with EA of all ages may be significantly affected by condition-specific HRQOL issues of eating and social dimensions of relationships, communication, and interaction with others. In addition, from an age-related perspective, physical HRQOL items reflecting issues of respiratory disorders and items concerning medical intake constitute one of the HRQOL domains in the EA-QOL field test questionnaire for young children. Physical health shows internal consistency with items of emotional well-being in the EA-QOL field test questionnaire for children 8–17 years old. Furthermore, body image concerns seem to constitute a part of the overall EA-QOL of the older children and adolescents. This means that the overall QOL of EA children is not merely a composite of the patient's disease-specific symptoms, but also of a relationship between EA-related morbidity and environmental contexts - family, peers, and school- in which the children's lives unfold, as well as of their internal mental states. These perspectives are included in the EA-QOL questionnaire and have adequate initial validity and internal reliability in children 2–7 years old and children 8–17 years old (child report).

As a complement to clinical endpoints such as survival or morbidity rates, the EA-specific parameters can provide important information that increases our understanding of the possible long-term impact of EA and/or surgical techniques from the patient's perspective. Young as well as older children with severe EA are at risk of reduced condition-specific HRQOL, which means that children who undergo a delayed anastomosis or esophageal replacement, and/or a revisional surgery and/or has a severe TM may have a risk for larger illness burden in terms of reduced condition-specific HRQOL.

Coping is adopted at an early child age and the strategies may become more advanced with increased age and seem to be especially present in children with severe EA; hence, coping is an important variable that may influence the outcomes in pediatric patients with EA.

This knowledge can improve future evaluation of pediatric surgery and it sheds light on issues that should be integrated into follow-up routine care. In turn, this will improve the health and HRQOL of children with EA and their families.

From the perspective of the DISABKIDS methodology, a field test and implementation studies of the EA-QOL questionnaires are needed. Based on items generated from standardized focus groups with children with EA 8–17 years old and parents of children 8–17 years old, groundwork for the EA-COPE questionnaire was provided. The EA-COPE questionnaire is currently being pilot tested in larger cross-cultural samples in Sweden and Germany. In the EA-QOL questionnaires, the ongoing studies will permit not only a repeated test for internal reliability and construct validity, but also more advanced psychometric testing, such as of the questionnaire's factor structure, external reliability (re-test), cross-cultural equivalence in Sweden and Germany, differences in child–parent HRQOL ratings and an advanced clinical hypothesis testing. The psychometric testing can eventually include IRT, a test for responsiveness and an evaluation of the clinical meaningfulness of the scoring. Moreover, the ongoing research project includes assessment of family impact and of the parents' HRQOL. Finally, the conceptual model of mediating and moderating factors to impact generic and condition-specific HRQOL can be tested.

The EA-QOL questionnaires and the EA-COPE questionnaires should be translated into more languages and culturally adapted according to international guidelines. Thereafter, studies can include evaluation of different treatment alternatives such as outcomes of different surgical techniques for esophageal replacement or of thoracotomy vs. thoracoscopic esophageal repair. Evaluation of different treatment alternatives through randomized control trials is complicated in rare pediatric surgical conditions. However, observational prospective studies will become important in detecting HRQOL outcomes in different subgroups of patients with EA and their HRQOL over time. A standardized HRQOL assessment, will increase the generalizability in such studies.

Moreover, incorporation of the EA-QOL questionnaire in a quality register would facilitate longitudinal studies of condition-specific HRQOL; this will be important in order to explore HRQOL outcomes in different groups of patients over time. In addition, the EA-QOL questionnaire and the EA-COPE questionnaire can be evaluated for use in clinical practice for individual assessment in order to improve monitoring of the child's health and to guide interventions. The value of the implementation of a PROM should be investigated from a clinician and patient perspective. The questionnaires can also be made available to patient advisory support groups.

Importantly, the methodological experiences of the development of a condition-specific HRQOL instrument for children with EA, can benefit the development of a condition-specific instrument in other rare pediatric surgical conditions, as well as in adults with EA.

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30 condition-specific quality-of-life questions for children and adolescents born with esophageal atresia 2-7 years – parent version			
	Excluded	**Reworded**	**Included**
Is it a problem for your child that he/she vomits?			X
Does your child have to eat particular/special foods (e.g. puréed food, peeled or grated food, or food given via a gastrostomy button) because of his/her health condition?	X		
Does your child find it boring to get different food than other people eat?	X		
Can your child eat at the pace he/she wants?			X
Does eating stress your child?			X
Is it difficult for your child to eat a full meal?			X
Is your child worried about choking?	X		
Does your child's health condition cause him/her to eat slowly?	X		
Does your child have less strength than other children during physically demanding activities?			X
Does your child get tired easily when he/she plays games or sports?			X
Do people make comments to your child because of his/her health condition?	X		
Does it bother your child that people nearby get frightened when your child makes more noise than other children (e.g. breathing, clearing his/her throat, coughing)?		X	X
Do people stare at your child?	X		
Does it bother your child that people make comments about him/her?			X
Does your child's health condition make it difficult for your child to sleep at night?			X
Is it hard for your child to eat because food sticks in his/her throat?			X
Is your child worried when he/she chokes on food?			X
Does your child avoid eating because he/she is afraid of choking?			X
Is your child ashamed of his/her scar?	X		
Can your child go to other children's homes after preschool/school without careful planning?	X		
Does your child feel that other children at the preschool/school understand him/her?	X		
Does your child feel that teachers in the preschool/school give help when needed?	X		
Does your child feel different than other children because of his/her health condition?	X		
Is it a problem for your child that he/she gets respiratory infections easily?			X
Does your child feel self-conscious about his/her problems with restricted airways (e.g. coughing, phlegm, or difficulty breathing)?		X	X
Is it hard for your child being small compared to other children of the same age?	X		
Does your child hate taking medicine?			X
Is it hard for your child to explain to others what he/she can and cannot do?			X
Is it a problem for your child to eat food at a party or when he/she is out with friends?			X
Is it a problem for your child that his/her health condition involves absence from preschool/school?			X
Total number of items	12	2	18

50 condition-specific quality-of-life questions for children and adolescents born with esophageal atresia 8-17 years – child version			
Quality-of-life question	**Excluded**	**Reworded**	**Included**
Do you have the strength to play sports (e.g. running, playing football) and play as your friends do?		X	X
Are you bothered by breathing difficulties when you exercise and play?		X	X
Do you participate in physically demanding activities (such as running, playing football, handball)?	X		
Do you find it difficult to play sports because of your health condition?	X		
Do others call you names (e.g. because you are small, have an unusual cough, eat slowly, or because you have a surgical scar)?			X
Do others say mean things about you?			X
Do you get teased about things in school?	X		
Do you feel that others are staring at you (e.g. when coughing, choking, dressing in the locker room)?			X
Do you have to think about avoiding certain foods because of your health condition (e.g. because of choking, acid reflux or heartburn)?	X		
Does your health condition restrict you from eating any food?			X
Is it a problem if you drink a lot when you eat?		X	X
Is eating unpleasant for you because you choke?		X	X
Do you feel it is a problem that food get stuck in your throat when you eat?			X
Does it bother you that it takes longer to eat for you than it does for your friends?	X		
Do you get any pain when you eat because of your health condition? (e.g. when food sticks in your throat, heartburn, stomach ache)?			X
Can you eat at the pace you want?		X	X
Does it bother you if you get other food in school than your friends?	X		
Do you worry about choking in front of others?	X		
Is it a problem that you vomit after eating?			X
Do you feel that it is a problem for you that you must have special/particular food (e.g. puréed food, nutritional drink, or food through a gastrostomy button)?	X		
Are you afraid when you choke?			X
Is it easy for you to be open with others about esophageal atresia?	X		
Does it feel awkward when others ask you about esophageal atresia?			X
Is it complicated to explain to others what esophageal atresia is?			X
Do you get tired of people asking about the scar/scars?			X
Are you stressed by having to finish your meal in time in the school cafeteria?	X		
Does it feel like you are always the last one to finish when you eat in the school cafeteria?	X		
Is it hard for you to find peace and quiet when you eat in the school cafeteria?	X		
Do you choke or vomit when eating in the school cafeteria?	X		
Is it easy for you to fit in and make friends?		X	X
Do you feel different because you have scars?			X
Are you careful about what you wear because of your scar /scars?			X

Do you feel awkward when your scar/scars are visible to others (e.g. strangers, new people, boyfriend/girlfriend, friends or classmates in the locker room or people in the swimming pool)?			X
Do you feel that you are not perfect because you have scars?			X
Do you have trouble sleeping at night because of your health condition (e.g. acid reflux, heartburn, or respiratory problems)?			X
Does your health condition mean that you have to think about, for example, what you eat, taking medicines on time, sleeping in a raised position (extra pillows) to sleep well?	X		
Do you feel it is a positive thing that you were born with esophageal atresia?	X		
Do you feel sad that you were born with esophageal atresia?		X	X
Is it hard having to take medications?	X		
Do you feel that you can talk to your parents about esophageal atresia?	X		
Do you feel like the only one who was born with esophageal atresia?			X
Do you feel that there are other children like you?	X		
Do you feel small compared to other children your age?		X	X
Is it hard for you to find clothes because of your height or body size?	X		
Does it bother you that you get acid reflux (day and/or night)?	X		
Do you feel that teachers in the school understand that some things are difficult for you because of your health condition (e.g. sports, in the school cafeteria)?	X		
Are you bothered that you have a different kind of cough?	X		
Is it worse for you than for others when you catch a cold?	X		
Do you think about how your future will be because of your esophageal atresia?		X	X
Does esophageal atresia make you feel uncertain when it comes to boys/girls?	X		
Total number of items	24	9	26