General discussion and recommendations

Background

The studies in this thesis focussed on the long-term pulmonary and physical sequelae of severe congenital anatomical foregut anomalies and/or treatment with neonatal ECMO and on possible predictors of these sequelae. The ultimate objective was to investigate whether children at risk can be identified early and to prevent or reduce these sequelae.

The long-term (longitudinal) outcomes on lung function, exercise capacity and motor performance, and the possible risk factors associated with these outcomes were investigated in **chapters 2, 3, 4, and 5**. The perspectives of patient and parents on these long-term outcomes in **chapters 6 and 7**, and the potential use of a screening tool to identify children at risk for motor problems in **chapter 7**. Finally, in **chapter 8**, we evaluated the effects of a standardized high intensity training program and/or an online coaching program on exercise capacity and therewith motor performance. All children and their parents were seen within the framework of our standardized multidisciplinary follow-up program.

In this chapter we place the main findings of our studies in a broader perspective. In addition, recommendations for future research and implementation of our findings in patient care are given.

Risk on long-term morbidity

Congenital diaphragmatic hernia

In **chapters 2 and 3** we described the longitudinal lung function and exercise capacity in school-aged children with CDH who had received either neonatal ECMO treatment or conventional ventilation only. We assessed lung function longitudinally at 8 and 12 years of age and exercise capacity from 5 up to 12 years of age. Lung function[1-7] and exercise capacity[5,8-15] have both been studied by others, but the results are contradictory. Most of these studies had a cross-sectional design, small sample sizes and/ or evaluated lung function or exercise capacity in children born several decades ago. As since then important advances in surgical and neonatal management have been made,[16] we evaluated more recent longitudinal data on lung function and exercise capacity in relatively large cohorts of CDH patients within the framework of a prospective follow-up program.[11,17]

Figure 1 graphically displays our main findings on lung function and exercise capacity, and its predictors in CDH patients. The study in **chapter 2** revealed deterioration of airflow obstruction from 8 to 12 years, irrespective of ECMO-treatment. Longer duration of mechanical ventilation was associated with significantly more airflow obstruction. Remarkably, despite the fact that lungs in CDH are underdeveloped and hypoplastic at birth, static lung volumes that should be considered as an indirect parameter of lung

size, were within normal ranges. This can be partly due to the wide variability of pulmonary hypoplasia in these patients.

Diffusion capacity corrected for alveolar volume was reduced at both ages, but remained stable. Clinical factors such as the need for patch repair, type of initial ventilation, duration of mechanical ventilation, treatment with inhaled nitric oxide or treatment with neonatal ECMO, were not found to be of influence on the reduced diffusion capacity.

The results in **chapter 3** showed that exercise capacity was significantly below the norm at 5, 8 and 12 years of age, and declined significantly over time. This decline of exercise capacity was also irrespective of ECMO treatment. We found a positive correlation between diffusion capacity and exercise capacity. Moreover, children who had been longer hospitalized initially, had lower exercise capacity outcomes.

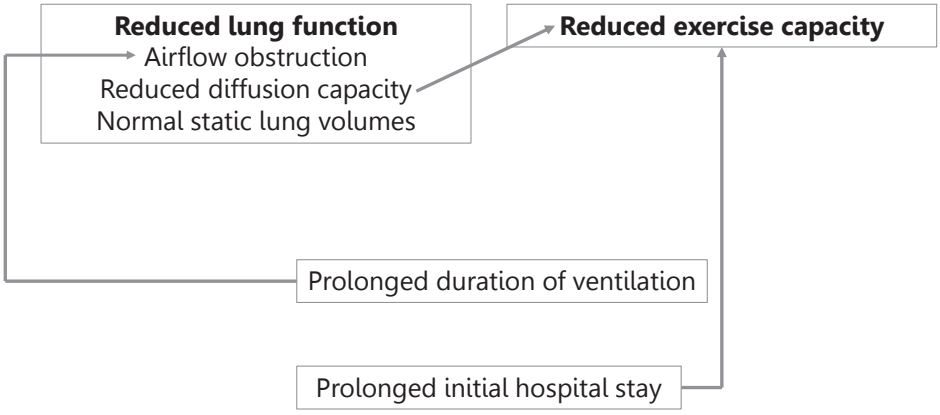

Figure 1 - Main findings on lung function and exercise capacity and its predictors in children with congenital diaphragmatic hernia

We assumed that children who were most critically ill after birth due to severe lung hypoplasia, might be at the highest risk for impaired lung function and exercise capacity at school age. ECMO-treated neonates with CDH are the most critically ill children and have often more severe lung hypoplasia than those not treated with ECMO. They need longer mechanical ventilation, which carries the risk of developing chronic lung disease (CLD). This might be reflected by more severe airflow obstruction and reduced exercise capacity. In our studies, the ECMO-treated patients indeed had longer duration of mechanical ventilation, more often CLD, more airflow obstruction and lower exercise capacity than those not treated with ECMO. Their prolonged initial hospital stay also reflects their severity of illness. However, ECMO-treatment was not a determinant of airflow obstruction or reduced exercise capacity. ECMO-treatment may have spared the lungs from the high inspiratory oxygen levels and high inspiratory pressures that cause a chronic inflammatory reaction of the lungs.[18,19]

We assume that a number of factors lead to CLD, such as distorted airway architecture[20] due to pulmonary hypoplasia and ventilator induced lung injury. The development of the lungs is also affected by pulmonary vascular maldevelopment.[21] Capillary growth and alveolar growth are intricately connected. Deficient capillary growth will probably result in inhibited alveolar development, particularly in the ipsilateral lung. While normal lung growth is caused by alveolar multiplication,[22,23] several studies suggested that lung growth in CDH is the result of expansion of already existing alveoli.[21,24] This implies that there may be little postnatal catch-up growth, especially in children with severe lung hypoplasia. Lung hypoplasia with vascular maldevelopment and limited catch-up growth will probably contribute to the development of CLD – and affect lung function and exercise capacity later in life. Studies on lung morphology in childhood and adulthood may be useful to identify patients at risk for impaired lung function and exercise capacity.[20] The first studies on lung morphology in young adults have shown functional and (micro)structural changes of the lungs, even in those who were only shortly ventilated after birth and those with mild lung hypoplasia.[20,21] It can be speculated that some degree of emphysema is present that contributes to impaired lung function and reduced exercise capacity. The high residual volume total lung capacity (RV/TLC) ratio found in this study supports the assumption of emphysema. Others have suggested that a high RV/TLC ratio is probably the result of chest wall deformity.[25]

Only few of the CDH patients included in the study presented in **chapter 3** reported lower respiratory tract infections treated with antibiotics in the last year, atopy, or gastroesophageal reflux symptoms. Therefore, we assume that the distorted airway structure due to hypoplasia and ventilator-induced lung injury plays a determined role in the development of lung injury.

The standardized postnatal treatment protocol developed by the CDH EURO Consortium in 2008 has led to an important change in the treatment of children born with CDH.[16] This protocol was implemented in our department in 2007. On the basis of the initial reports on mortality rates and on the prevalence of CLD after introduction of this protocol,[26] we hypothesized that with the introduction of the protocol in our department, more children with severe lung hypoplasia would survive, albeit with a greater probability of CLD and impaired lung function. This hypothesis is confirmed by the study presented in **chapter 2**, in which we evaluated lung function of children treated with the protocol between 2007 and 2009. Analysis of our data showed significantly more severe airflow obstruction in eight-year-old children with CDH treated after the introduction of the protocol than the eight-year-olds treated before its introduction. Nevertheless, this hypothesis might as well be refuted on the grounds of the fact that ECMO treatment – usually applied in children with more severe lung hypoplasia– was more frequent before the introduction of the protocol.[27] Nevertheless, the UK ECMO trial, which is the only trial

so far that evaluated the effect of ECMO over conventional ventilation on lung function, showed a slightly better lung function in ECMO-treated patients than in those who were conventionally ventilated.[19] The authors concluded that ECMO patients might have been spared prolonged ventilation and subsequent barotrauma. The question is whether the same holds true for neonates with CDH. We have to bear in mind that the UK study was highly underpowered with respect to CDH. The study group of neonates who survived and underwent lung function assessment included only three (6%) children with CDH.[19]

Esophageal atresia

Another group of children born with severe anatomical anomalies who are at risk for lung function problems and reduced exercise capacity are children born with EA. In the study presented in **chapter 5,** we evaluated airflow obstruction and low lung volumes in eight-year-old children born with EA. Diffusion capacity corrected for alveolar volume was normal. Spirometric parameters were negatively associated with congenital cardiac malformation, duration of ventilation and persistent respiratory tract infections. We did not find any predictors of lower lung volumes (Figure 2). Others have suggested that chest wall abnormalities are associated with abnormal lung function.[28,29] Pleural scarring after multiple thoracotomies could probably lead to restrictive lung disease.[29] In our study, however, the type of repair (thoracotomy/ thoracoscopy) was not associated with impaired lung function. Lung function during the first year was also similar irrespective of the type of repair.[30]

Based on the available literature on the high prevalence of gastroesophageal reflux disease (GERD) in the first years of life,[31] the consensus guidelines recommend to treat all infants with EA with proton pump inhibitors (PPIs) up till the age of one year and to continue PPI treatment in those with symptomatic GER thereafter.[32] Although conservative therapy is always the first-line approach for these patients, in 30-64% of them fundoplication is ultimately required, often before one year of age.[32] One quarter of the participants in our study underwent a Nissen fundoplication in the past. At school age, GER symptoms were reported by 25% of all patients and 8% still needed PPI treatment. Some authors have suggested that EA patients with a history of GERD are at risk of impaired pulmonary function later on in life.[33] In our study, we did not find a correlation between impaired lung function and a Nissen fundoplication in the past or symptoms of gastroesophageal reflux at the age of eight.

We found reduced exercise capacity in the eight-year-old EA patients. In a previous study of our research group, with largely the same cohort, we found reduced exercise capacity also at the age of 5 years.[10] Exercise capacity at both ages was not significantly different, suggesting that reduced exercise capacity persists when the children get older. We found that children with a smaller total lung capacity had more often reduced

exercise capacity. Although weight for height was below normal at this age, exercise capacity was more reduced in children with higher weight for height (Figure 2). We concluded that the relatively small reduction in total lung capacity could not fully explain the decreased exercise capacity.

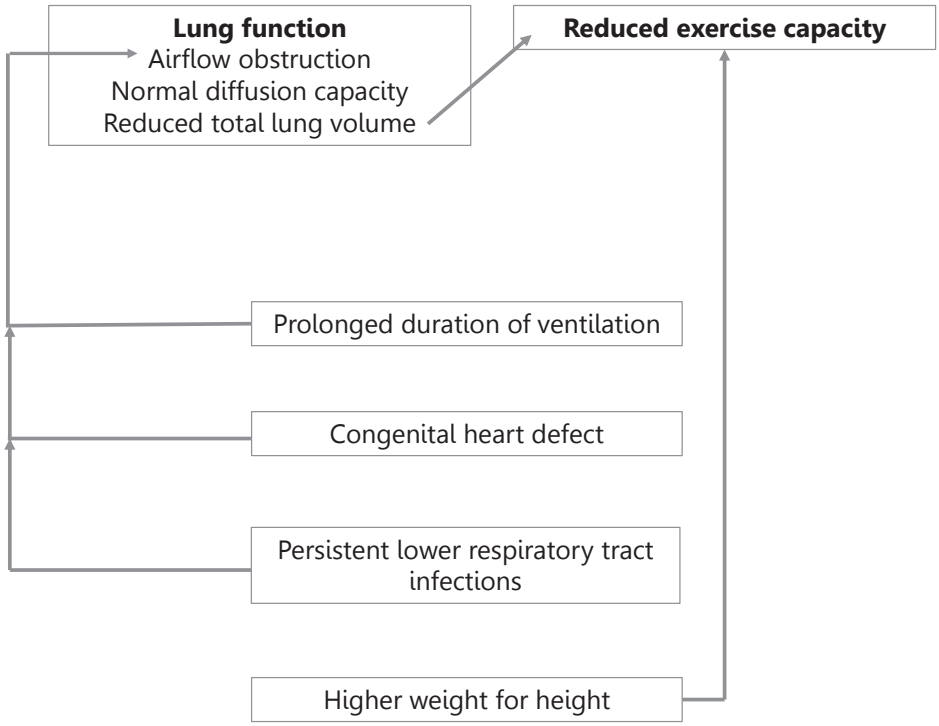

Figure 2 - Main findings of lung function and exercise capacity and its predictors in esophageal atresia patients

We hypothesized that tracheomalacia is a contributing factor to reduced exercise capacity. Tracheomalacia is not only seen during the first years of life in EA-patients, but usually persists until school age.[34] It can be assumed that the increased airflow obstruction due to tracheomalacia contributes to poor exercise capacity.[35] In our study, forty percent of the children reported signs of tracheomalacia. Still, the airflow obstruction -which was usually mild- did not correlate with the exercise capacity. A limitation of our study described in **chapter 5** is that we did not objectify the severity of tracheomalacia with bronchoscopy or an expiratory CT scan. So, besides total lung capacity and weight for height, from our data it is not clear what factors contributed to reduced exercise capacity. Also airflow obstruction, persistent respiratory morbidity or gastrointestinal

morbidity were not associated with reduced exercise capacity. These results are is in line with findings from other studies.[36,33]

As the relatively small reduction in total lung capacity and the weight for height in these children could not fully explain the reduced exercise capacity, we assume that physical inactivity is a contributing factor. Tracheomalacia with recurrent lower respiratory tract infections and physical growth failure over the years may contribute to physical inactivity from an early stage onwards, and hence lead to a poor exercise capacity at older age.

The findings from our studies indicate that both children with CDH and EA are at risk for pulmonary morbidity and reduced exercise capacity. However, the lung function problems and the determinants of impaired lung function and exercise capacity differ between these two severe congenital anatomical anomalies. In CDH patients, a distorted airway structure due to pulmonary hypoplasia and ventilator-induced lung injury presumably plays a significant role in the development of lung disease. In patients with EA, recurrent respiratory tract infections, possibly aggravated by gastroesophageal reflux and tracheomalacia, contribute to lung disease. The children who were most critically ill after birth, have the highest risks for long-term pulmonary morbidity and reduced exercise capacity.

Besides reduced exercise capacity, the findings is this thesis and in various other studies of our research group,[12,37] showed that these critically ill born children also have in common that they participate less in sport activities compared to healthy Dutch peers.[38,39] This is mainly at pre-school age (Table 1). Also children with other chronic conditions, such as cystic fibrosis, participate less in physical activities than healthy peers.[40]

Table 1 - Percentages of children participating in organized sports

	Pre-school age	School-age
Dutch norm population[a]	74	87
CDH[b]	53	74
EA[c]	55	80
Neonatal ECMO[d]	60	78

[a] van der Cammen-van Zijp MHM et al., Eur J Appl Physiol 2010; van der Cammen-van Zijp et al., Scand J Med Sci Sports 2010 [38,39]

[b] Chapters 2 and 3 of this thesis

[c] Chapter 5 of this thesis and Harmsen et al., Arch Dis Child Fetal Neonatal Ed 2017 [37]

[d] van der Cammen-van Zijp et al., Eur Respir J 2011 [12]

CDH = congenital diaphragmatic hernia; EA = esophageal atresia; ECMO = extracorporeal membrane oxygenation

One of the possible explanations for our findings of reduced exercise capacity and sports participation is that the parents of these critically ill born children consider their child more vulnerable than do the parents of healthy peers. For this reason, and also because pulmonary morbidity[2,5,41] and growth failure[42,43] persist for years, parents might be reluctant to encourage physical activities. This may, in turn, put them at risk of reduced exercise capacity and gross motor function problems, and consequently reduced participation in physical activities (Figure 3). Similar problems occur in other survivors of critical illness in the neonatal period.[44] This phenomenon has also been described for chronic diseases such as cystic fibrosis, asthma, and congenital heart disease.[45] It is also possible that motor problems as a result of a chronic disease state, lead to being reluctant in engaging in physical activities with peers, and finally to reduced exercise capacity.

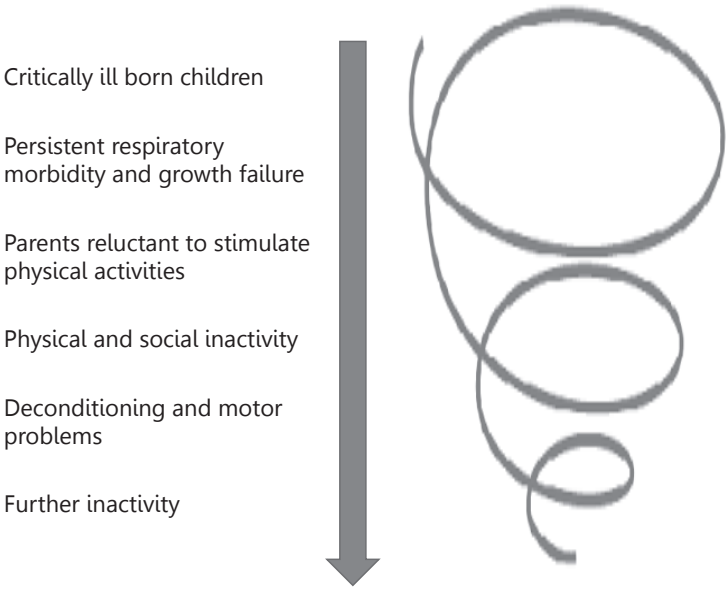

Figure 3 - Negative spiral of physical inactivity

Indeed, we found that patients with CDH, EA and/or treated with neonatal ECMO are at risk for motor problems (**chapters 4, 6, 7, and 8**). A previous study of our research group showed that motor problems even deteriorate between 5 and 12 years of age in ECMO survivors, which included 49 children with CDH.[15] In children with EA, motor performance remained stable between 5 and 8 years of age.[46] The study presented in **chapter 8** focused on physical activity of children with severe congenital anatomical anomalies and/or treated with neonatal ECMO, which we will discuss in more detail later on in this chapter.

Taken together, children born with severe anatomical foregut anomalies and/or neonatal ECMO treatment are at risk for impaired lung function, reduced exercise capacity and motor problems. These findings highlights the importance of a long-term follow-up program with screening of these morbidities, and stress the need for early risk stratification and targeted intervention.

Screening of morbidity and the patient- and proxy-reported long-term outcomes

We showed that children with severe anatomical anomalies and/or treated with neonatal ECMO are at risk for long-term pulmonary sequelae and physical sequelae. The patients' and parental perspectives on this sequelae has hardly been studied.

We hypothesized in **chapter 6** that children who had been treated with ECMO in the neonatal period develop motor problems and reduced exercise capacity, have a low self-perception of motor competence and are reluctant to engage in physical activities with their peers. This, in turn, might negatively influence their perception of social competence and also affect feelings of self-worth and their health-related quality of life. Interestingly, although motor problems occur more often in these children than in healthy peers, they felt more competent in the motor domain and the social domain, and also perceived their self-worth better than did healthy peers.

This positive perception of motor competence and self-worth indicates that these children 'overrate' their actual motor performance – a phenomenon known as superiority bias.[47] We suppose that the parents may consider their child more vulnerable than healthy peers and extra applaud them when motor milestones have been reached. Moreover, as motor function problems in neonatal ECMO survivors already exist at preschool age and seem to persist,[15] it can be speculated that these children have an altered perception of normal motor function. The phenomenon of overrating motor performance, has been reported also in chronic conditions like attention deficit/ hyperactivity disorder and osteogenesis imperfecta.[48,49] This issue has hardly been studied in children who were critically ill in the neonatal period. A study of 6-year-old children born preterm found an association between self-perceptions of physical competence and actual motor performance.[50]

The past decades have also seen developments in the pediatric physical therapist profession, such as a shift to a more demand-oriented approach. This approach implies carefully addressing the patient's request for help and come to an agreement with the patient regarding the treatment. In view of our findings, the children who join our follow-up program will probably not acknowledge the need for and actively seek professional assistance. Therefore, the demand-oriented approach is not appropriate for these children. In our opinion, pro-active monitoring of morbidity, with targeted advice on a physical life-style and/or intervention, is of utmost importance for these children's long-

term health. Especially because reduced participation in daily life physical activities can finally lead to a greater risk for secondary disease (Figure 3).[51]

Our routine follow-up assessments of physical functioning are relatively lengthy and costly to administer and take place in the hospital, which can be stressful for the children and parents. Therefore, we hoped that impaired physical functioning could be identified with the use of screening tools, so that follow-up visits would be only necessary for children with functional problems. In the study presented in **chapter 7,** we evaluated the usefulness of the Movement-Assessment-Battery for children Checklist, second edition (MABC-2 Checklist) as screening tool to identify children at risk for motor problems. This questionnaire was filled out by the parents.

We found low sensitivity of the MABC-2 Checklist in our population, to the effect that half of the children with impaired functioning would not have been identified with the use of this tool alone. The question is whether the parents could reliably estimate the child's performance. A high percentage of the parents of our population tended to overrate their child's motor performance. So, not only the children themselves, but also their parents could have an altered perception of the child's physical functioning. We assume that the parental internal standards of physical health might have changed by noting their child's critical state in the intensive care unit. This phenomenon is called a response shift. Parents of critically ill children who suffered from meningococcal septic shock, reported better long-term physical and psychosocial health-related quality of life of their children than the parents of the Dutch normative population. These parents reported that the child critical illness made them appreciate life more fully and they were less worried about 'futilities' in life.[52] A positive response shift is also seen in parents of children with less life-threatening situations, such new-onset epilepsy.[53]

From our findings it is clear that the MABC-2 Checklist filled out by the parents could not replace our routine follow-up assessment of actual motor performance. Moreover, our findings demonstrated the need for follow-up assessments and providing education to the child and parent. Especially when outcomes as evaluated by clinicians differ from parental perceptions, and parents overestimate the child's performance. This may have implications for the approach to motivate the children and their parents to undertake physical activities, and to adhere to physical therapy and therapeutic advice to improve the child's physical functioning.

The specificity of the MABC-2 Checklist, however, was acceptable. Therefore, the checklist may well serve to indicate the prevalence of normal motor function in (multicenter) outcome studies in our population. National and international collaborative initiatives for children with rare anomalies/diseases are increasing, requiring standardization of assessments and management,[54,55] and facilitation of multicenter research.[55,56] International standardization of assessments and management can be difficult because of differences in geographical distances for home-hospital transfers and differences in

resources to provide adequate multidisciplinary follow-up. In a first step towards the development of international evidence-based guidelines, the MABC-2 Checklist can be considered useful for evaluation of the prevalence of normal motor function in (multicenter) outcome research.

Treatment of patients at risk

Given the increased risk for long-term persistent respiratory morbidity, reduced exercise capacity, and motor function problems, with even deterioration of exercise capacity at school-age, we stress the importance of rehabilitation strategies to improve physical functioning. Therefore, the trial described in **chapter 8** aimed to demonstrate whether reduced exercise capacity –and secondarily motor function problems– in children with neonatal respiratory failure could be improved. We questioned, however, whether persistent respiratory morbidity hampers improvement of exercise capacity.

Our single-blind, randomized controlled trial (RCT) showed significantly improved exercise capacity and motor performance in the intervention groups and in the control group (receiving standard of care) as well. Comparison with the findings of the few RCTs available on improving exercise in children is difficult because of the differences in study population, intervention type and primary outcome parameter.[57-61] The children included in the other studies did not have the same ethnicity, age and underlying diagnosis as in our RCT.

We preferred high intensity interval training (HITT) over endurance training as HIIT has been shown to be beneficial in RCTs with healthy or obese children,[59,60] and corresponds with the intensity of physical activities in the everyday life of school-aged children. Maximal exercise capacity was measured on a treadmill using the Bruce-protocol with reference values for healthy Dutch children.[38,39] We preferred treadmill testing over bicycle ergometry because children have relatively underdeveloped knee extensors, which is often the limiting factor of the bicycle test.[62] The maximal endurance time served as criterion of maximal exercise capacity and was our primary outcome parameter. A strong correlation between maximal endurance time and maximal oxygen uptake has been reported by Cumming and coworkers.[63] We used the maximal endurance time rather than the peak oxygen consumption as measure of exercise capacity, mainly for reasons of feasibility. Wearing a mask may lead to loss of cooperation and to submaximal results, especially in the younger children. We did use cardiopulmonary exercise testing (CPX), which includes breath gas analysis, in young adults born with neonatal respiratory failure before the era of ECMO, nitric oxide administration, and high frequency ventilation. Wearing a mask was quite feasible for these young adults. The results demonstrated that residual lung hypoplasia did not play an important role on exercise capacity.[64] Currently,

research with CPX in our department is performed in young adults born with CDH and we consider CPX in our follow-up program for school-aged children.

The few previous RCTs on improving exercise capacity in children evaluated exercise capacity only immediately after the program, but not on the long run. Based on our observation that one year after the intervention exercise capacity was even slightly better than after three months in all three study groups, we propose that this sustained improvement is due to lifestyle changes on physical activity. The well-developed pro-active coping competencies of the parents probably have contributed to a change from a semi-active to an active lifestyle. Other studies have confirmed that children's physical activity can be promoted by parental behaviour.[65,66] Role modeling, which includes a parent's interest in physical activity as well as efforts to be active, could facilitate children's activity.[65] And also parental support in the form of encouragement, involvement (i.e., participating in physical activities with the child), and facilitation such as providing opportunities for the child to be active (e.g., transportation to school and sport clubs), leads to a more physically active lifestyle in children.[65,66] The more significant physically active school-home transfers and the increase in time on sports, which both correlated with the improvement of exercise capacity, support our assumption that the pro-active coping competencies of the parents have contributed to a change from a semi-active to an active lifestyle. Besides, the children of the parents who reported a good physical health status of themselves had better exercise capacity than those whose parents reported lower physical health status. Therefore, we recommend extra counselling and education for the parents with a less well-developed coping competence and the parents who report a low physical health status. Follow-up assessments can be extended with the evaluation of the parents pro-active coping competencies and health status by questionnaires or standardized questions. Methods as shared decision making and/or motivational interviewing can be used for the counselling and education of families.[67] Shared decision is a method where clinicians and patients make health decisions together using the best available evidence. In this approach, the clinicians' role is to help patients become well-informed, help them develop their personal preferences for available options, and provide professional guidance where appropriate. Choosing one's own treatment goals seems important for successful self-management to change behavior.[68,69] Although some people can change behaviour on their own, others require more support. Motivational interviewing is a style of counseling that can help resolve the ambivalence that prevents patients from realizing personal goals. Both motivational interviewing and shared decision making are patient-centered methods that have been associated with improved patient outcomes. Studies of shared decision making found improvements in patients' ability to self-manage long-term conditions and adherence to treatment.[70] For motivational interviewing, several studies have found positive results on lifestyle change outcomes and on psychological outcomes.[71-73] The principles and

methods of motivational interviewing are highly valued by practitioners frustrated with the ineffectiveness of the traditional prescriptive advice giving.[73] In the study in **chapter 8**, we have used the principles of motivational interviewing and shared decision making in the treatment groups.

We assume that improvement in the children's physical functioning could improve their social functioning and vice versa (Figure 4). The children in our RCT reported improvement in the physical domain and the social domain as well. As the social environment of the child seem to be important for health-related behaviour, efforts to change the child's health-related behaviour should also focus changes in the social environment. This does not only include family habits and activities, but also for example, participation in sport clubs, gymnastics, in public areas, and activities with classmates at and after school.

The currently available guidelines on physical activity for children provide recommendations only on the duration of moderate to vigorous activities. Not only the duration of activities, but also the intensity of these activities are important for maintaining a good physical health condition, and also for improvement.[74,75] Therefore, counselling of patients and their parents should not only include standardized questions on the type, the frequency, and the social environment in which physical activities take place, but also on the intensity of these activities.

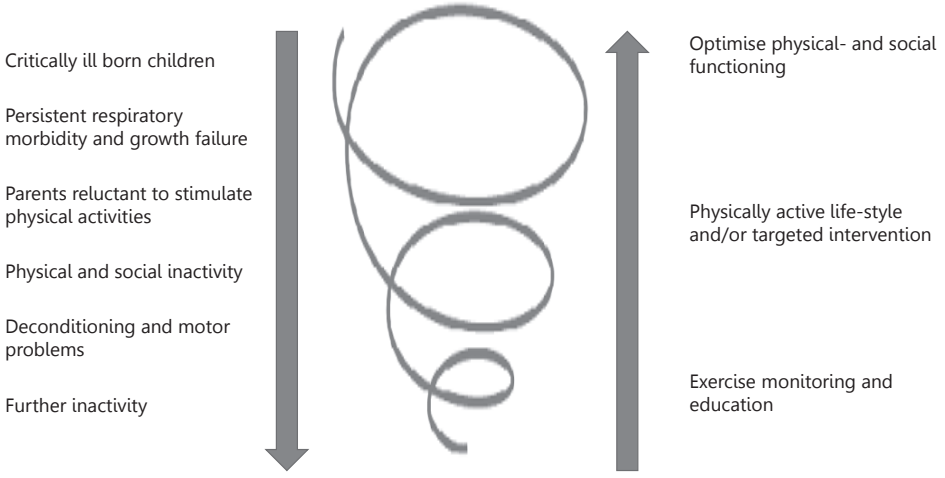

Figure 4 - Positive spiral of physical activity and/or targeted intervention

In general, the increased use of technological devices has resulted in more sedentary behaviour in children and adults as well.[76-78] Children in Europe spend approximately 8 hours per day sedentary.[79] The adverse relationship between sedentary behavior and morbidity and mortality in adults has become more apparent.[80] There is no convincing evidence for the relationship between childhood sedentary behavior and various health

outcomes,[81,82] but sedentary behavior appears to track from childhood into adulthood.[77] Therefore, it is disturbing that the children in our study spent much time sedentary, which amount did not change during the study period. Especially, when we take into account that this not even include school-time sedentary behaviour, such as sitting in the classroom and doing homework. Close monitoring of sedentary and physical activities, and counselling with education from an early stage onwards could reduce sedentary behaviour and improve physical activity and should be part of routine care. Finding a balance between (necessary) sedentary activities and physical activities is probably important for success. Moreover, the facts that children spend much time sitting on school days, schools could also be an important setting to integrate health promotion interventions.

We suppose that participation in this study created awareness of impaired exercise tolerance, and there with a more physically active life-style, which might have resulted in improvement over time in all three study arms. This phenomenon is known as the Hawthorne-effect.[83] This assumption also supports our conviction that we should not only provide education on a more physically active life-style and sedentary behaviour, but we also have to reconsider the frequency of our follow-up for guidance and supervision on a physically active lifestyle.

Seeing that for some families it is quite an effort to visit the hospital because of the long home-to-hospital distance, that the hospital setting is stressful, and that the assessments are costly, setting up a network of physicians or pediatric physical therapist near the families' homes should be taken into consideration. Another possibility is the additional use of e-health services in our follow-up program, which requires a good financial and digital infrastructure.

Taking into account that parents might be reluctant in encouraging physical activities from early childhood as they consider their child vulnerable, it is important to assure the parents from an early stage that exercise is essential and safe, which we have demonstrated in this thesis. After childhood, the guidance should probably shift from the parents towards the adolescent.

Strengths and limitations of this thesis

Strengths

Our studies included relatively large numbers of children with rare anomalies, assessed within the framework of our multidisciplinary follow-up program at the ages of 5, 8 and 12 years. The children performed standardized assessments which included norm-referenced tests administered by specialized healthcare providers. The compliance to follow-up is high.

Limitations

Small sample sizes

In this thesis we have made clear that pulmonary- and physical sequelae persist or even deteriorate during childhood. We also have found several determinants of impaired lung function and reduced exercise capacity (**chapters 2, 3 and 5**), but prediction models were hampered by the relatively small sample sizes of these single-center studies. These relatively small sample sizes are a common problem in follow-up studies of children with rare diseases and relatively high mortality rates.

In the studies of this thesis, we only included data of children who performed the standardized assessments of our program. This implies that children with 'severe neurodevelopmental problems' were excluded. We presented the numbers of children who were unable to perform the assessments in each individual study on morbidity (corresponding to 2.5%-7.5% of the study population in chapters 2-5). Considering this, the prevalence of morbidities in children with CDH, EA and/or neonatal ECMO treatment are even slightly higher as presented in our studies.

The results of our intervention study might have been influenced by small sample sizes as well. Randomised controlled trials are considered as highest level of evidence to demonstrate the effect of a clinical study.[84] In this thesis, we showed the findings of the first RCT on physical functioning in children with severe congenital anatomical anomalies and/or neonatal ECMO treatment. Despite nationwide recruitment, the sample size was still relatively small. This may be associated with an increased type 2 error, and this could have been the reason that we were not able to find a significant positive effect of the interventions. As a result, it was not possible to perform a cost-effectiveness analysis. Therefore, the question remains whether a RCT is the appropriate design for studies on rare anomalies. Although multicenter studies with international recruitment could ensure larger sample sizes with adequate statistical power, achievement of the calculated sample size is still not ensured.[85]

Self-report bias

The children and their parents in our RCT were motivated to participate in an intervention program. This may have positively influenced their self-reported baseline assessment scores, which is possibly reflected in their comparable or even better baseline scores compared with normative data. Due to this ceiling effect, the children and parents may have had little room for improvement of the questionnaire scores. Some effects were found only in children with low baseline scores, as self-reported HRQoL for example. Another explanation is the tendency to overrate physical activities in questionnaires.[86] Moreover, we noted that it was difficult for the children to fill out the questionnaires on daily (physical) activity as they were required to recall events in the past weeks or even in the past months. Therefore, our data do not allow concluding what factors contributed to improvement of exercise capacity.

Conclusions and future perspectives

The studies in this thesis have shown that children born with severe congenital anomalies and/or neonatal ECMO treatment are at risk of impaired lung function, reduced exercise capacity and motor problems. Although children with CDH and EA showed similarities in morbidity and its determinants, there are also important differences. While in CDH a distorted airway structure due to pulmonary hypoplasia and ventilator-induced lung injury plays a significant role in the development of lung disease, in EA the recurrent respiratory tract infections, possibly aggravated by gastroesophageal reflux and tracheomalacia, contribute to lung disease. Some of the identified predictors of impaired lung function and reduced exercise capacity, such as the duration of mechanical ventilation and duration of initial hospital stay, reflected the severity of illness in the neonatal period. We therefore suggest that the severity of illness after birth itself is an important predictor of these morbidities. The severity of illness also seems an important predictor of physical growth and neuropsychological outcomes in these children.[87,88] Still, the conclusions on predictors need to be interpreted cautiously in view of the relatively small sample sizes of the single center studies in this thesis. Future multicenter studies could ensure larger sample sizes with adequate statistical power.

Collaboration networks on an international level –set up to improve healthcare and to facilitate multicenter research in children with rare diseases– are on the rise.[16,55] The CDH EURO Consortium is such a collaboration of a large number of high-volume CDH centers in Western Europe. In 2007, they established a protocol of standardized postnatal management of CDH patients,[55] and in 2016, they evaluated in a RCT the optimal initial ventilation mode in children born with CDH.[85] In this thesis, we presented the first results of the effect of the standardized postnatal treatment protocol on long-term lung function and exercise capacity outcomes. However, more patients treated according to the protocol should be studied to confirm the effect of the protocol on lung function and to demonstrate a possible effect on exercise capacity. Currently, the CODINOS-trial is underway within the collaborative infrastructure of the CDH EURO Consortium, as aimed at identifying the drug of choice for the initial treatment of pulmonary hypertension in children with CDH. The CDH EURO Consortium has also proposed a collaborative project for long-term standardized follow-up in CDH patients using the 'standardized clinical assessment and management plan (SCAMP) methodology.[89,90] This methodology, found successful in the development of management algorithms for children with congenital heart disease,[54,91] will be used to establish uniform and standardized follow-up of CDH patients at an international level.[55] This initiative will make a substantial contribution to improve long-term follow up care and research with a large multicenter cohort. The SCAMP-methodology can be applied widely to improve health care in other rare anomalies/diseases, such as EA. European reference networks such as the European Reference Network for rare Inherited and Congenital digestive tract anomalies, including gastro-

intestinal disorders (ERNICA),[92] may facilitate multicenter collaboration in close contact with patients organizations. This could possibly contribute to larger sample sizes with adequate statistical power in future studies. Networks such as ERNICA could also play a role in the development of optimal screening tools for (early) identification of morbidities, as investigated in **chapter 7**. The question remains whether a RCT is the appropriate design for studies on rare anomalies.

Understanding the pathophysiological mechanism underlying long-term pulmonary morbidity and physical impairments, could aid the understanding of the development and persistence of these morbidities, and to develop effective intervention strategies to improve or even to prevent morbidity. This is important because morbidity in these children persists throughout childhood and even seems to deteriorate. The results of our RCT showed that exercise capacity and motor problems can be improved in children with severe anatomical anomalies and/or ECMO treatment. We assume that a negative spiral of physical inactivity played a role in the development and persistence of reduced exercise capacity and motor problems (Figure 3), but we cannot give a definitive answer on the basis our data. This, too, is a topic for future multicenter research. Nevertheless, this assumption has also been made with regard to other groups of children born critically ill and in children with chronic conditions.[44,93] Thus, physical inactivity could well be the common pathophysiologic mechanism underlying these morbidities. We assume that a more physically active lifestyle due to the well-developed coping competence and physical health status of the parents contributed to improvement of these outcomes (Figure 4). We recommend long-term follow-up of morbidity with monitoring of the child's physical activity and the parent's pro-active competence and physical health status. In the future, the effect of an intervention strategy –including its cost effectiveness– should be investigated in multicenter international randomized controlled trial in these children with severe congenital anatomical foregut anomalies and/or having undergone neonatal ECMO treatment.

Recommendations for clinical practice

- Close monitoring of morbidity and physical activity, with counselling and education on a physical active life-style and/or intervention, from an early stage onwards, should be part of routine care. Recommendations on physical activity for these children should be based on the 'Physical activity guidelines for children'.[94,95] These guidelines recommend 60 minutes or more per day of moderate-to-vigorous physical activity; at least three times a week muscle- and bone strengthening activities; and minimization of sedentary behaviour. Besides, healthcare professionals could recommend a tailor made training program for these children.
- During follow-up assessments, physicians and pediatric physical therapists should actively ask about physical activity and sedentary behaviour in daily life. We recom-

mend the use of standardized questions on the type, the frequency, the intensity of these activities, and the social environments in which these activities take place. Besides, physicians and physical therapists should assure the parents from early childhood on that being physically active and exercising is safe for their children and important for overall health and physical function.

- Follow-up assessments can be extended with evaluating –with the use of questionnaires or standardized questions– the parent's pro-active coping competence and health status. We recommend additional counselling and education for those with a less well-developed coping competence and a low physical health status. Counselling and education could be based on the principles and methods of shared decision making and motivational interviewing.
- Cardiopulmonary exercise testing, with breath gas analyses, to evaluate exercise capacity for clinical practice and/or research purposes should be taken into consideration. The findings can probably contribute to understanding the mechanism underlying reduced exercise capacity. Cardiopulmonary exercise testing serves as a diagnostic tool to distinguish the etiology of exercise intolerance, sorting between pulmonary, cardiac, and peripheral etiology's through distinctive patterns of gas exchange, cardiac, and hemodynamic responses.
- Increasing the frequency of follow-up assessments or setting up a network of physicians or pediatric physical therapist near the family's home should be taken into consideration to provide close monitoring, counselling and education on morbidities and a more physically active life-style. Another possibility is blended care: follow-up assessment supplemented with e-health. To implement e-health in our follow-up program, good financial and digital infrastructures are conditions to should be guaranteed first.

Recommendations for future research

- SCAMPs should be used to investigate optimal long-term follow-up care for children born with severe congenital anomalies.
- Research should focus on the pathophysiological mechanism underlying long-term pulmonary morbidity and physical impairments to understand the development and persistence of these morbidities, and help us to develop effective intervention strategies to improve or even to prevent morbidity.
- Multicenter studies could ensure larger sample sizes, which is important to improve early risk stratification and reaching conclusions on the effects of future clinical trials in these children with rare anomalies.

In conclusion, the findings of our studies demonstrate the importance of long-term follow-up, and stress the need for early risk stratification and targeted advice and/or

intervention in children born with severe anatomical foregut anomalies and/ or having undergone treatment with neonatal ECMO.

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