Summary

SUMMARY

Introduction

Nowadays, the majority of newborns with severe congenital anatomical anomalies survive due to advances in specialized intensive care and surgery. With the increased survival, the focus of attention should shift from mortality to morbidity, and be directed towards improvement of long-term outcomes from childhood into adulthood.

In **chapter 1**, a short literature review revealed that most studies on morbidities in children with severe congenital anatomical anomalies born several decades ago, had often a cross-sectional design, small sample sizes, and reported contrary results. The important advances in surgical and neonatal management made since then warrant longitudinal evaluation of these morbidities on the basis of more contemporary data. Furthermore, perspectives of the child and parents on the pulmonary and physical morbidities, the possible impact on quality of life, but also strategies to prevent or diminish impaired outcome have remained unstudied. Therefore, the studies included in this thesis have focussed on longitudinal long-term pulmonary and physical outcomes of children born with congenital diaphragmatic hernia (CDH), esophageal atresia (EA) and/or treated with neonatal extracorporeal membrane oxygenation (ECMO), and on the perspectives of the child and parents on these outcomes. In addition, an intervention program to prevent or diminish impaired outcomes was proposed. The children included in the studies were followed by a specialized multidisciplinary team in the Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands and/or Radboud University MC - Amalia Children's Hospital, Nijmegen, the Netherlands.

Part 1 Risk on long-term pulmonary and physical morbidity

This part on the long-term risk of morbidity concerned children born with CDH (chapters 2, 3 and 4) and children born with EA (chapter 5).

In **chapter 2** we described the longitudinal lung function of 76 CDH patients (27 treated with ECMO), born between January 1999 and June 2009, from 8 to 12 years of age. In addition, possible determinants of impaired lung function were assessed. The study revealed airflow obstruction at both ages, which was more severe in the ECMO-treated children. Longer duration of mechanical ventilation was associated with significantly more airflow obstruction. The severity of airflow obstruction deteriorated from 8 to 12 years, irrespective of having received neonatal ECMO treatment. We did not find clinical variables significantly associated with this deterioration airflow obstruction. The static lung volumes were normal, though diffusion capacity corrected for alveolar volume was reduced at both ages. These two parameters had not significantly changed from 8 to

12 years. Interestingly, the airflow obstruction in the children treated after introduction of the postnatal treatment protocol of the CDH EURO Consortium was more severe than that in the children born earlier. This result supports the assumption that with the decreased mortality after the introduction of the postnatal treatment protocol, the survivors might be facing more severe lung hypoplasia. This is subject of further study.

In view of the increased risk of pulmonary morbidity and deterioration of lung function at school age in children with CDH, we longitudinally evaluated in **chapter 3** the maximal exercise capacity in these children aged 5 to 12 years, and its relation to lung function and several clinical variables. A total of 107 children (30 treated with ECMO), born between January 1999 and May 2012, performed 191 reliable exercise tests. At ages 5, 8 and 12 years, the mean SDS endurance time was significantly below the norm. The maximum endurance time in the ECMO-treated patients was significantly lower than that in the non-ECMO-treated patients. The exercise capacity had declined between 5 and 12 years of age, irrespective of ECMO-treatment. Duration of initial hospital stay and diffusion capacity corrected for alveolar volume were associated with SDS endurance time. Other variables were not significantly associated with exercise capacity: timepoint of assessment, gestational age, use of a new postnatal treatment protocol of the CDH EURO Consortium, patch repair, ventilator free days in the first 28 days of life, type of initial mechanical ventilation, congenital cardiac malformation, FEV_1, TLC, and sports participation. Determinants for deterioration of exercise capacity remained unclear in this study. We concluded that both the ECMO-treated and non-ECMO-treated CDH patients had decreased exercise capacity at the age of 8 and 12 years. It even deteriorated between these ages, for unknown reasons. Risk stratification for decreased exercise capacity may be important to offer timely intervention.

Our follow-up program has yielded many prospectively collected data on long-term morbidities. The study in **chapter 4** is one of the firsts outcome studies of our group and formed - with other studies - the basis for further research. The study in this chapter compared intelligence and motor function at eight years of age of 35 children with CDH, either treated with (n=16) or without (n=19) neonatal ECMO, between January 1999 and December 2003. It confirmed the assumption that CDH patients are at risk for motor problems. Motor problems were found in 16% of all children with CDH (specifically ball skills were affected), which proportion is significantly higher than the 5% in the reference population. No significant differences between the treatment groups were found in the motor domain. Intelligence was normal for both treatment groups; with significantly lower scores, however, for the ECMO-treated children. Problems with concentration (low working-speed) and behavior (attention problems; reported by the mothers) were significantly more apparent for both treatment groups compared to normative data.

Health status was significantly lower than Dutch normative data, except for emotional functioning; school performance and feelings of competence were not affected. We concluded that children with CDH, whether or not treated with neonatal ECMO, are at risk for long-term morbidity especially in the areas of motor function, concentration and attention. But, despite their impairment, these children have a well-developed feeling of self-competence.

In **chapter 5** we evaluated maximal exercise capacity and its relation to lung function in 63 children with EA, born between January 1999 and August 2007, at the age of eight years. Moreover, we studied possible determinants of exercise capacity and lung function. The test outcomes showed reduced exercise capacity, airflow obstruction and low lung volumes. Exercise capacity did not correlate with airflow obstruction, diffusion capacity, respiratory problems or symptoms of gastroesophageal reflux, but was positively associated with total lung capacity and negatively weight for height. Spirometric parameters were negatively associated with congenital cardiac malformation, duration of ventilation and persistent respiratory morbidity. We concluded that the relatively small reduction in total lung capacity could not fully explain the decreased exercise capacity. We speculate that diminished physical activity as a result of a chronic disease state with recurrent respiratory tract infections and physical growth failure may be also a determining factor, which should be addressed in multidisciplinary follow-up clinics for EA-patients.

Part 2 Patient- and proxy-reported long-term outcomes and screening of morbidity

The perspectives of the children and parents on long-term morbidities had hardly been studied. Therefore, we assessed in **chapter 6** perceived motor competence, social competence, self-worth, HRQoL, and actual motor performance in in a nationwide study of 135 neonatal ECMO survivors at the age of eight years. They had received ECMO-treatment within 28 days of birth between 1996 and 2004. Perceived motor competence, social competence, and self-worth were all significantly higher than those in the norm population. Fifty-five percent of the children indicated an impaired HRQoL (less than –1 SD); they scored significantly lower on physical, emotional, social, school, and psychosocial functioning than the norm population. Twenty-two percent of the children had actual motor problems (versus 5% in the norm population). Actual motor performance did not correlate with perceived motor competence, self-worth and HRQoL; only a weak but significant positive correlation was found with perceived social competence. Perceived motor competence was significantly positively correlated with perceived social competence and self-worth. Self-worth correlated positively with all domains of HRQoL. We concluded that eight-year-old ECMO survivors feel satisfied with

their motor and social competence, despite their impaired motor performance. Even though they indicate more problems in the physical, social, and psychosocial domains than do their healthy peers, they do not have a lack of self-worth. They experience even more self-worth than their healthy related peers. Because motor problems in ECMO survivors deteriorate throughout childhood, clinicians should be aware that these patients may tend to "overrate" their actual motor performance. Education and strict monitoring of actual motor performance are important to enable timely intervention.

In **chapter 7**, the perspectives of parents on the child's motor performance was assessed with the aim to determine the value of a proxy-reported questionnaire for early identification of motor problems in the target groups at school age. All children who joined our multidisciplinary follow-up program at the age of five, eight and twelve years, between May 2015 and May 2018, were included. The children performed the MABC-2 Test and their parents filled out - prior to the test - the MABC-2 Checklist. Data of 190 MABC-2 Checklists were analyzed. The sensitivity of the checklist was 57.1%, which means that 42.9% of children with motor difficulties were not identified. We concluded that the MABC-2 Checklist cannot be used as screening tool to identify actual motor problems in school-aged children born with severe congenital anatomical anomalies and/or treated with neonatal ECMO. Nevertheless, these instruments are valuable for clinicians to evaluate parental perceptions on their child's motor performance. Parents who tend to overrate their child's physical performance, may not see the need for or may not adhere to targeted aftercare/intervention. Therefore, strict monitoring of actual motor performance, evaluating parental perceptions of motor performance, and parental education are essential. Moreover, the specificity of the MABC-2 Checklist was acceptable (89.7%), and therefore the checklist may well serve to indicate the prevalence of normal motor function in outcome studies in our population.

Part 3 Treatment of patients at risk

We have shown in part 1 that children with CDH and EA are at risk for long-term persistent respiratory morbidity, reduced exercise capacity, and motor function problems. Moreover, exercise capacity deteriorated between 5-12 years of age in CDH patients, irrespective of neonatal ECMO-treatment. There are no intervention programs to improve the exercise capacity of children with neonatal respiratory failure. The question is whether persistent respiratory morbidity hampers improvement of exercise capacity.

In **chapter 8** we evaluated if decreased exercise capacity can be improved in school-aged children (8 and 12 years) born with anatomical foregut anomalies and/or treated with ECMO. We described the significant improvement of exercise capacity 3 and 12 months after a standardized anaerobic high-intensity interval training and/or online lifestyle

coaching-program, assessed using a nationwide, single blind randomized controlled trial. Improvement of exercise capacity was not only seen in the intervention groups, but also in the control group (receiving standard of care). Motor performance also improved significantly over time in both the intervention groups and the control group.

The change in number of days that participants walk or ride a bike for school-home transfers correlated significantly to the change in mean SDS endurance time. Although scores on a daily activity questionnaire did not significantly change over time, more participants spent an average/or above-average amount of time (>1 hour/week) on sports over time (44.8% at baseline; 57.2% after 3 months; 65.7% after 12 months). Patients of all study groups reported significantly higher HRQoL after 3 and 12 months, in particular on physical and social functioning. The parents of the children scored within the normal range on a pro-active coping competence questionnaire, which indicates that parents considered themselves competent in pro-active coping. Parental pro-active coping did not influence the change in exercise capacity, as this score did not significantly correlate with the change in mean SDS endurance time. Although parents gave a significantly higher physical component score on the health status questionnaire, which indicates being more satisfied with their physical health than the reference population, parental health status did not influence the change in exercise capacity as parental health status and the change in mean SDS endurance time of the participants did not correlate significantly. Parental mental health was normal at all points. We concluded that exercise capacity improved significantly over time, irrespective of the intervention. This implies that residual morbidities are not the only factor responsible for reduced exercise capacity. Enhanced awareness of impaired exercise tolerance might have resulted in improvement over time in all three study arms. Parental pro-active coping competence can stimulate a more physically active lifestyle in their child. Our observations have implications for the counselling of children and their parents. We speculate that parents of children who survived neonatal critical illness consider their child more vulnerable than the parents of healthy children, and may therefore be reluctant to encourage physical activities. Close monitoring and counselling from an early stage onwards could improve physical activity and should be part of routine care. Intervention should be offered on an individual basis.

In **chapter 9** we summarized and discussed the main findings of our study results, and made recommendations for future research and patient care. The findings demonstrate the importance of long-term follow-up of pulmonary and physical morbidities, and show the need for early risk stratification and targeted advice on a physically active lifestyle and/or intervention.