Short and Long-Term Outcomes of Congenital Diaphragmatic Hernia

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master of Philosophy

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September 2021

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Acknowledgements

I would like to thank my supervisors Professors Paul Losty and Ian Sinha for their continued guidance throughout this thesis. I also thank Dr Sok-Leng Kang and Dr Joyce Lim for their helpful comments on Chapter 4. I thank my mother for her constant support.

I dedicate this thesis to Rhiannon.

Abstract

Congenital diaphragmatic hernia (CDH) is a serious disease occurring in 1 in 3000 births. Essentially, failure of diaphragmatic closure in-utero leads to herniation of the abdominal contents into the thoracic cavity, causing lung hypoplasia and pulmonary hypertension. The current mortality rate is 30%-50% but for newborns that require ECMO support, a higher mortality rate of 60% is evident. The infants that do survive to hospital discharge may be left with complex long-term health problems, across multiple body systems. It is estimated that the prevalence of chronic lung disease (CLD) may affect up to 50% of all CDH patients. Neurological complications, such as motor and cognitive defects, and gastrointestinal morbidity, including severe gastroesophageal reflux disease (GORD) are also notable.

This thesis focuses on both the short- and long-term outcomes of Congenital Diaphragmatic Hernia and consists of three main studies.

Study I systematically reviews outcome reporting in observational studies and randomised controlled trials of post-natal interventions in CDH. With complex disease comes a variety of management strategies, and the need for these to be evaluated in robust clinical trials. However, no consensus currently exists on which outcomes should best be measured. This study aimed to review the selection, measurement, and reporting of outcomes in CDH. The outcomes were classified into seven domains modelled on the patient journey. The most frequent domains were 'short-term markers of disease activity' and outcomes relating to 'hospital interventions and medication'. Long term outcomes were reported infrequently. There was heterogeneity in outcome reporting, primary outcomes were also variable and not always clearly stated. There is a clear need for a Core Outcome Set to standardise outcome reporting.

Study II, a systematic review, focuses on short term outcomes in CDH, specifically the risk of Respiratory Syncytial Virus (RSV) bronchiolitis. Given uncertainties surrounding upcoming RSV epidemics, debate exists around whether palivizumab (RSV prophylaxis) should be given to CDH

infants. This study aimed to evaluate the risk of RSV bronchiolitis hospitalisation and whether palivizumab prophylaxis modulates this risk. We included three retrospective cohort studies: A single study found CDH to be an independent risk factor for RSV hospitalisation (OR 3.30, 95% CI 2.01-4.4). Two studies compared RSV hospitalisation rates in CDH patients who had palivizumab vs those that did not. The pooled Risk Ratio was 1.11 (95% CI 0.29-4.23, p=0.88). Overall, the quality of evidence was considered poor, and one study was industry-funded.

Study III considers the long-term sequelae of CDH. This study is a systematic review focusing on cardiorespiratory outcomes and health related quality of life in CDH survivors over 2 years of age. Indices of lung function, radiological outcomes, cardiopulmonary exercise testing, and health related quality of life were often reduced. Findings on the prevalence of asthma or reactive airway disease were mixed and there was some evidence of persistent pulmonary hypertension. Three papers reported late death (>2 years), five due to respiratory cause, one of which was pulmonary hypertension.

This thesis has highlighted that the outcomes of CDH survivors, both short and long term, should not be overlooked. Where not already available dedicated follow-up clinics for CDH survivors should be established. Further research into various aspects of CDH survivorship is required.

Abbreviations used in this thesis

CDH	Congenital Diaphragmatic Hernia
GORD	Gastro-Oesophageal Reflux Disease
HRQoL	Health Related Quality of Life
MDT	Multidisciplinary Team
Alder Hey	Alder Hey Children's Hospital
CF	Cystic Fibrosis
RCT	Randomised Controlled Trial
CCAM	Congenital Cystic Adenomatoid Malformation
EXIT	Ex-Utero Intrapartum Treatment
FETO	Fetoscopic Endoluminal Tracheal Occlusion
RR	Risk Ratio
CI	Confidence Interval
NICU	Neonatal Intensive Care Unit
HFOV	High Frequency Oscillatory Ventilation
ECMO	Extra Corporeal Membrane Oxygenation
iNO	Inhaled Nitric Oxide
OI	Oxygenation Index
PDE inhibitor	Phosphodiesterase Inhibitors
EST	Exogenous Surfactant Therapy
MIS	Minimally Invasive Techniques
LHR	Lung to Head Ratio
O/E	Observed: Expected
APGAR score	Appearance, Pulse, Grimace, Activity, Respiration Score

pO$_2$	Partial pressure of Oxygen
PHT	Pulmonary Hypertension
PICO	Population, Intervention, Comparison, Outcome
RSV	Respiratory Syncytial Virus
COPD	Chronic Obstructive Pulmonary Disease
COS	Core Outcome Set
PRISMA	Preferred Reporting Items for Systematic review and Meta-Analysis
CENTRAL	Cochrane Central Register of Controlled Trials
LL	Leonie Lewis
IS	Ian Sinha
MINORS Criteria	Methodological Index for Non-Randomised Studies
N/A	Not Applicable
NIRS	Near Infrared Spectroscopy
CPET	Cardiopulmonary Exercise Testing
ECG	Electrocardiogram
CDHi	CDH International
COMET	Core Outcome Measures in Effectiveness Trials
CASP	Critical Appraisal Skills Programme
OR	Odds Ratio
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
CT	Computerised Tomography
MRI	Magnetic Resonance Imaging
ATS	American Thoracic Society
ERS	European Respiratory Society

SD	Standard Deviation
TLC	Total Lung Capacity
RV	Residual Volume
FRC	Functional Residual Capacity
$PaCO_2$	Partial pressure of carbon dioxide
FiO_2	Fraction of inspired oxygen
RVsp	Right Ventricle Systolic Pressure
Kco	Diffusion capacity for carbon monoxide corrected for alveolar volume
V/Q	Ventilation/Perfusion
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
NEJM	The New England Journal of Medicine

Chapter 1: Introduction

CDH is a severe congenital abnormality characterised by a defect in the diaphragm and herniation of abdominal organs into the thoracic cavity (1). Lung hypoplasia and pulmonary hypertension are invariably present and linked to the high mortality rate (2, 3). As depicted in **Figure 1** there are various types of hernia defect. A posterolateral (Bochdalek) hernia accounts for around 90% of cases (4-7). An anterior or retrosternal (Morgagni) hernia, accounts for some 2-9% of hernias (7) and may often be asymptomatic in the neonatal period (8). Rarely complete diaphragmatic agenesis, the severest phenotype, may be encountered in newborns.

Figure 1: Representation of anterior (Morgagni) hernia, posteriolateral (left and right Bochdalek) hernia and diaphragmatic agenesis. Inspired by Marlow and Thomas, 2013 (9)

Morgagni Hernia

Inferior Vena Cava

Diaphragmatic Agenesis

Oesophagus

Aorta

Bochdalek Hernia
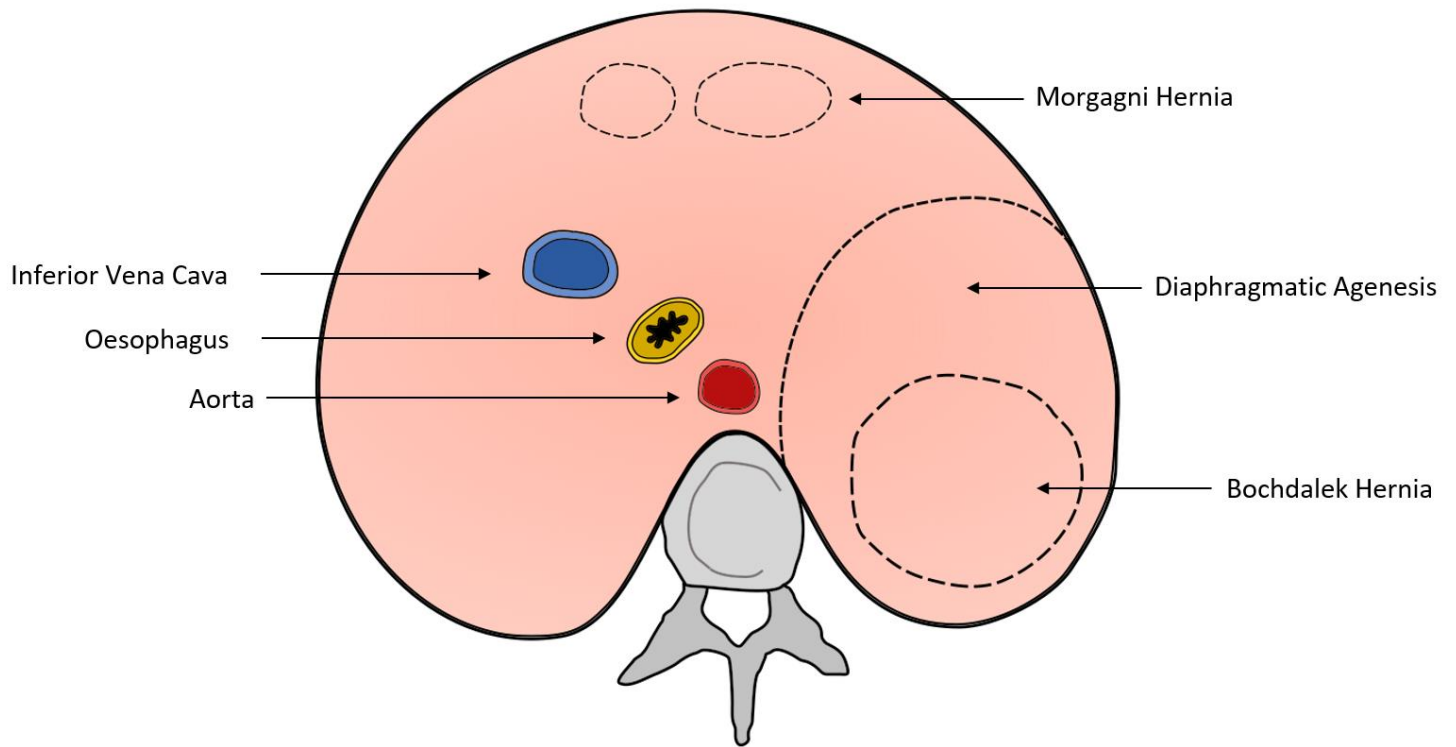
Emergency surgery was once considered to be the best treatment option from as early as 1925 (10, 11). Ladd and Gross are credited with the first successful neonatal repair in 1940 (12). Yet descriptions of lung hypoplasia and corresponding poor survival outcomes did not emerge until the 1950's, and emergency surgery remained the mainstay of treatment up to the mid-1980s (13).

Management of CDH has since steadily progressed towards a strategy of delayed elective surgery and gentle ventilation to avoid lung barotrauma.

This first chapter introduces CDH describing my time spent at the multidisciplinary (MDT) clinic held at Alder Hey Children's Hospital. This chapter then discusses the embryology, pathophysiology, and aetiology of CDH. The prevalence, diagnosis, and management of CDH is also examined, before considering the long-term outcomes associated with CDH survivorship, the importance of robust outcome reporting, and finally the utility of systematic reviews.

1.1 CDH Clinic at Alder Hey Children's Hospital

In order to gain experience in CDH, I attended four MDT clinics at Alder Hey Children's Hospital. Alder Hey is a large specialist children's hospital located in Liverpool, England. It is one of the largest children's hospitals in the UK and Europe. It has a dedicated surgical team providing healthcare for infants born with CDH and is widely credited with establishing the world's first neonatal surgical unit in 1953.

I found it fascinating that despite the high mortality rate associated with CDH I had the privilege of witnessing clinical interviews and specialist consultations with survivors of all ages ranging from newborns to adolescents at clinic with their families.

The focus of the CDH clinic was threefold. Firstly, it was multidisciplinary. The clinical team comprised of a university paediatric surgeon who specialised in CDH, a paediatric respiratory consultant, and a dietician. The clinic highlighted the crucial need for different healthcare professionals in managing this rare condition.

Secondly, was the holistic approach that the clinic took to children with CDH. The reason for this was to create a comfortable environment where the children and their families were able to talk openly. Often the children were keen to tell us about which sports they played, such as swimming or football. This highlighted that key indicators for health outcomes important to children may not be the same as clinicians. This was an area I wanted to explore further.

Thirdly, it was apparent that there were many varied sequelae linked to CDH, involving both short- and long-term clinical outcomes. Some of these were troublesome, whereas others were not.

What I took away from the clinic was that the goal of long term follow up is to make sure these children have a happy and healthy childhood whilst transitioning smoothly into adulthood. The focus of clinic was therefore not only how these children were at that instance, but also how their health and lifestyle would be progressing into adulthood.

It was for these very reasons that I chose to undertake a thesis on CDH and was privileged to work with a world-renowned specialised team.

1.2 Embryology, pathophysiology, and aetiology of CDH

1.2.1 Embryology of the respiratory system and diaphragm

The embryology behind the Bochdalek hernia is not completely understood. The understanding that does exist behind the development of the Bockdalek defect is based on the Carnegie staging of human embryos.

In the developing embryo growth of the diaphragm is closely linked to lung development. The lungs begin to grow at week 4 of gestation into the pericardioperitoneal canals (which connect the pleural and peritoneal cavities). The lungs begin to fill, then overfill these canals. The lungs expand into the body wall. The body wall is then split into the body wall proper and the pleuroperitoneal folds. These pleuroperitoneal folds appear at the 5th week, and eventually fuse with the oesophagus and the septum transversum to close the pericardioperitoneal canals to create the diaphragm. As the lungs expand, a muscular rim from the body wall migrates into the diaphragm. Myoblasts from the muscular rim migrate into the membranous pleuroperitoneal folds to form the muscular diaphragm **(14, 15)**. This process is represented in **Figure 2**.

Figure 2: Embryology of the diaphragm. Inspired by Sadler and Langman, 2019 (14)
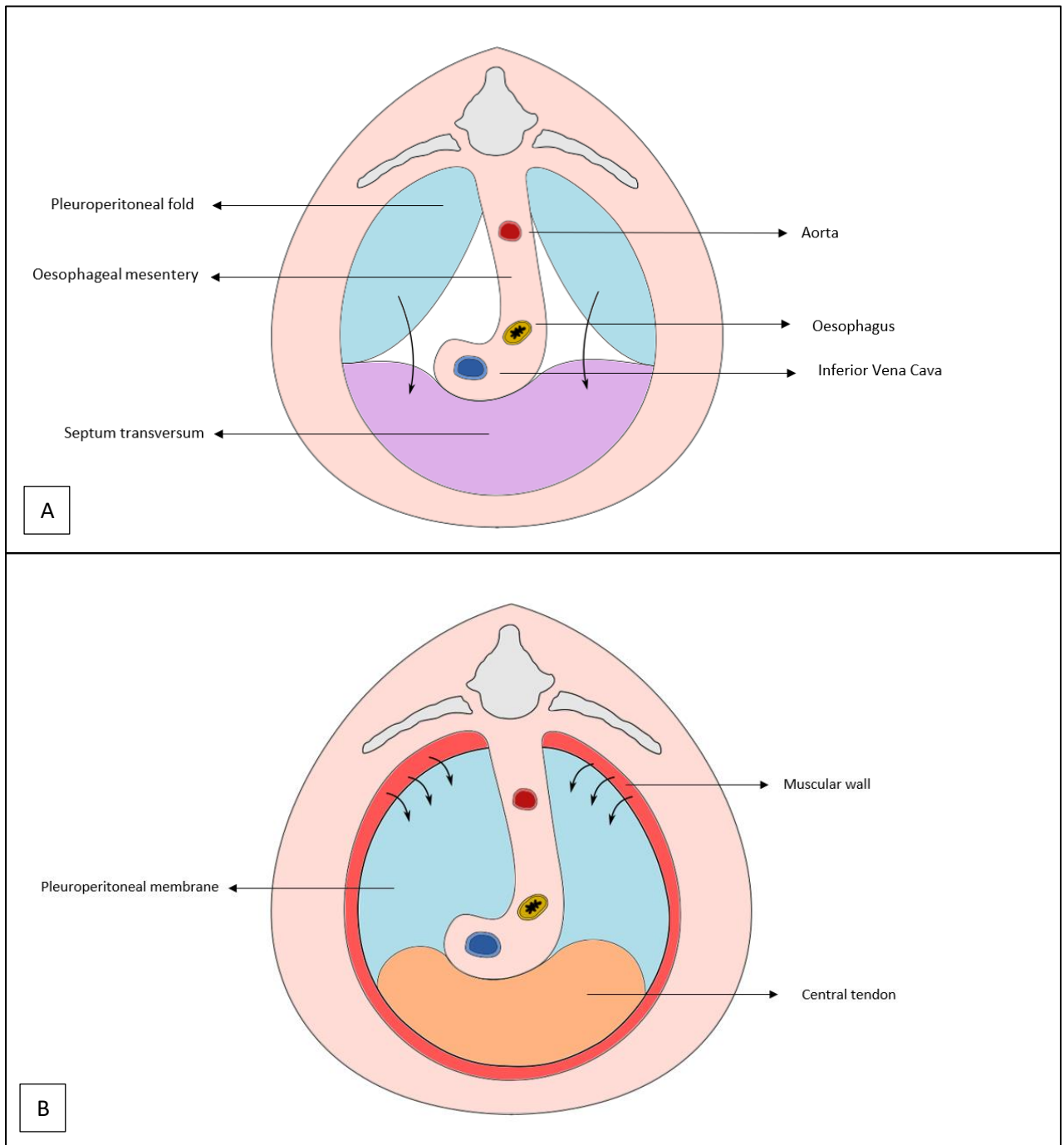
Legend: (A) shows the pleuroperitoneal folds at the 5th week beginning to grow over the septum transversum. (B) shows the diaphragm at the 4th month of development. The pleuroperitoneal membrane forms the central tendon of the diaphragm and muscle cells migrate from the periphery.

To understand the mechanism of lung hypoplasia in CDH, knowledge of lung embryology is also needed.

Lung development is divided into five stages (**Figure 3**) (16):

- The Embryonic stage (up to week 7)

- The Pseudoglandular stage (from 7 to 17 weeks)

- The Canalicular stage (from 17 to 27 weeks)

- The Saccular stage (from 28 weeks to term)

- The Alveolar stage (from late foetal period until at least 8 years of age)

Figure 3: Stages of lung development. Inspired by Kajekar, 2007 (17)

Embryonic stage (up to week 7)

- Lung bud differentiation
- Trachea and bronchi development
- Pulmonary vein and artery development

Pseudoglandular stage (weeks 7 to 17)

- Terminal bronchiole development
- Epithelial cell differentiation (goblet cells)
- Neural network development
- Pre-acinar blood vessels
- Foetal breathing movements

Canalicular stage (weeks 17 to 27)

- Primitive alveoli
- Type I cells (gas exchange), Type II cells (secrete surfactant)

Saccular stage (28 weeks to term)

- Alveoli saccules and capillary network
- Maturation of the neural network
- Development of the extra-cellular matrix

Alveolar stage (from the late foetal period)

- Development of the alveoli, nerves, and capillaries

The first stage of lung development begins at the 4th week of gestation, during the embryonic stage of development. The 'lung bud' or 'diverticulum' begins as an outgrowth of the foregut. This expands and separates from the foregut, leaving the dorsal part of the foregut to develop into the oesophagus, and the ventral part to become the trachea and lung bud. The lung bud is invaded by mesenchyme and the distal end branches into two. At week five the lung buds begin to enlarge to form the right and left bronchi then divide further. The developing lungs fill the pericardioperitoneal canals **(14)**.

During the Pseudoglandular and Canalicular stages the diverticulum further divides to form the bronchial tree and bronchioles. The Saccular stage sees further branching and formation of alveoli. This continues after birth during the alveolar stage, up until around 8 years of age **(14)**.

The pulmonary vascular bed develops at the same time as the airways. There are varying reports of whether vessel growth drives development of the airways or vice versa (18, 19). Regardless, both the vascular bed and the alveoli must develop correctly to allow for sufficient gas exchange. Blood vessel development occurs continually whilst the lungs are growing. This mostly occurs by vasculogenesis, the growth of new blood vessels from the recruitment of mesenchymal progenitor cells, as early as 34 days of gestation (18, 20).

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1.2.2 Pathophysiology of CDH

The hernia is located on the left side in 78-84% of cases, the right side in 13-20% of cases, and is bilateral in <5% of cases (5, 6, 21, 22). Right sided defects are associated with a higher mortality than left sided defects, particularly with liver herniation (23). This has been attributed to the size of the defect often being larger (24), and liver herniation resulting in vena cava compression, reduced preload and impaired cardiac output (25).

Lung hypoplasia occurs on the ipsilateral side of the diaphragmatic defect, and the contralateral lung can also have a degree of hypoplasia (26, 27).

The hypoplastic lung has fewer airways, and scarcer and smaller alveoli. Lung growth is closely linked to pulmonary vascular and diaphragm development (28). The vascular bed has a significant reduction in size and number of arterial branches.

The pulmonary vasculature has thickened media and tunica adventitia, thus contributing to the lethal pulmonary hypertension seen in CDH (1, 27, 29-31).

1.2.3 Aetiology of CDH

The mechanism of diaphragmatic defect formation is currently not fully understood. There are varying hypotheses surrounding CDH. In 1981, Nitrofen, a herbicide, was found to induce CDH in rats (32). Since then, many theories surrounding CDH have been based on this model (33). One such theory is the 'dual hit' hypothesis. This implies that lung development is impaired before diaphragm formation, and after, by mechanical compression from the herniated abdominal organs (34, 35).

Another theory is the 'smooth muscle' hypothesis. This suggests a fault in the mesenchyme leads to both the diaphragmatic defect and lung hypoplasia (36). This theory would also explain the abnormal development of vascular smooth muscle leading to the pulmonary hypertension seen in CDH.

Further understanding is gained at a molecular level, where disruptions in the retinoid signaling pathway have been seen in animal models and humans with CDH (37-39). Retinoic acid has been suggested as a treatment to upregulate expression of genes involved with lung formation in the hypoplastic lung affected by Nitrofen (38, 40). Yet use of retinoic acid has been controversial (41).

Higher levels of vasoactive substances, such as Endothelin-1, in animal models and humans with CDH have also been reported. This causes vasoconstriction and can lead to pulmonary hypertension (42, 43).

In rodents with Nitrofen-induced CDH, the transforming growth factor β pathway has also been shown to be affected (44-46).

1.2.4 Genetics and environmental factors associated with CDH

The cause of CDH is multifactorial, with both environmental and genetic factors contributing. Most cases of CDH are sporadic, although it is thought 2% of cases are familial (47, 48). These familial cases can be autosomal recessive, autosomal dominant, or X-linked (4).

There are various rare syndromes where CDH can feature. Fryns syndrome is the most common; this is an autosomal recessive syndrome, where amongst other features, CDH is present (4). CDH is also a feature of the Donnai-Barrow , Coffin-Siris, and Cornelia de Lange syndromes (49).

Genes identified and associated with CDH include (4, 50-53):

- Wilms tumour 1 gene (Denys Drash, Meacham, Beckwith-Wiedemann, WAGR syndromes)

- Glypican-3 gene (Simpson-Golabi-Behmel syndrome)

- Fibrillin1 gene (Marfan syndrome)

- Epihrin-B1 gene (Craniofronto-nasal syndrome)

Examples of syndromes associated with CDH are summarised in **Table 1**.

Table 1: Syndromes associated with CDH

Syndrome	Gene	Inheritance pattern	Key features
Fryns	Unknown (49)	Autosomal recessive (49)	CDH, pulmonary hypoplasia, hypoplasia of the distal phalanges and nails, flat nasal bridge, dysplastic ears, micrognathia, orofacial clefts (49)
Donnai-Barrow	Unknown (49)	Autosomal recessive (49)	CDH, omphalocele, hypertelorism, absent corpus callosum, myopia, severe sensioneural hearing loss (49)
Brachman/Cornelia-de-Lange	*NIPBL, SMC1A* (49)	Autosomal dominant/sporadic, X-linked (49)	Mental retardation, short stature, microbrachycephaly, confluent eyebrows, long philtrum, thin upper lip, limb abnormalities (49)
Craniofrontonasal	*EFNB1* (49)	X-linked dominant, more severe females (49)	Hypertelorism, craniosynostosis, broad bifid nose (49)
Beckwith-Wiedemann	*CDKN1C, NSD1* (49)	Autosomal dominant (49)	Macrosomia, omphalocele, macroglossia, ear creases (49)
Simpson-Golabi-Behmel	*GPC3* (49)	Autosomal recessive (49)	Macrosomia, coarse facial features, hypertelorism, protruding jaw and tongue, wide mouth, polydactyly (49)

CDH has been reported in various chromosomal abnormalities including Trisomies 13, 18, 21, and Turner's syndrome (4). CDH can also be associated with congenital cardiac defects, including ventricular septal defects, tetralogy of Fallot, aortic coarctation, ductus arteriosus, and patent foramen ovale (60-62).

1.3 Diagnosis of CDH

1.3.1 Prevalence

The prevalence of CDH is around 1/2500-1/3000 births (7, 63, 64). In different studies the ratio of CDH in males to females varies widely from 0.6 to 1.58 (6). It is estimated that 6% of CDH pregnancies result in spontaneous abortion or still-birth (22, 65).

Although CDH is often regarded as a rare disease, the prevalence of CDH is not dissimilar to Cystic Fibrosis (CF), one of the most common genetic life-limiting conditions in Caucasian children (66). Despite their similar prevalence, CF services are more advanced, with molecular therapies now available (67). It is the use of robust randomised controlled trials (RCTs) and research funding that has advanced therapeutic options for CF (68, 69). In comparison, treatments for CDH are lacking.

1.3.2 Prenatal diagnosis

Up to 56% of CDH cases are diagnosed antenatally and are usually detected on routine 20-week foetal ultrasound scan (22, 65, 70, 71). The ultrasound shows the stomach or bowel within the chest cavity and the mediastinum displaced (72). Other alternative diagnoses, such as diaphragmatic eventration, congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration or bronchogenic cysts, can give a similar picture.

Prenatal diagnosis has allowed families to make informed decisions surrounding the pregnancy or planning of perinatal care. Many foetuses with prenatally detected CDH often have associated anomalies, meaning the survival rate here is lower than in those with a postnatal diagnosis (22, 73, 74).

It is therefore important to offer parents amniocentesis or chorionic villus sampling to allow for accurate karyotyping. Counselling should also be offered and explain the unpredictable course of newborns with CDH. Parents may choose to opt for termination of pregnancy, the rates of which are around 19-24% in CDH (22, 65). Delivery should ideally be arranged at a tertiary obstetric centre (21, 75).

1.3.3 Early and late presentation of CDH

Typically, the infant presents with profound respiratory failure immediately after birth or shortly after. The infant may have low oxygen saturations, a high respiratory rate, increased work of breathing, and other signs of respiratory distress. Mediastinal shift may be apparent on clinical examination, the infant may have a scaphoid abdomen, and bowel sounds may be heard within the chest (35).

X-ray will reveal lung hypoplasia, bowel loops within the chest, and mediastinal shift away from the side of the hernia (76).

Very occasionally the patient may not present with respiratory failure. Instead, the patient can be asymptomatic or present later with intestinal obstruction, abdominal pain, or recurrent chest infections (77). Some cases may not be detected for months or even years.

1.4 Management of CDH

1.4.1 Antenatal management

In 2015 Grivell *et al* (78) conducted a Cochrane review of three studies evaluating antenatal management options in congenital diaphragmatic hernia. The main prenatal interventions include (a) foetal tracheal occlusion and (b) antenatal corticosteroid administration. Both methods aim to improve lung growth in the developing foetus.

Foetal Surgery

Various methods have been trialled in foetal intervention to improve lung growth. Firstly, in-utero repair of the diaphragm was attempted, this was achievable, although outcomes were no better than postnatal repair (79).

A further strategy was tracheal occlusion, a method that centred on the idea that congenital laryngeal atresia resulted in lung hyperplasia (80). This was originally done via hysterotomy and tracheal clipping, which was then reversed at the time of delivery by an ex-utero intrapartum treatment (EXIT) procedure. This involves performing a Caesarean section and working on the foetal upper airway, whilst they are still attached to the placenta (35). There is little evidence currently to recommend in-utero open hysterotomy guided tracheal clipping for foetuses with CDH (78).

This demanding maternal foetal operation was subsequently replaced by minimally invasive guided 'fetoscopic' endoluminal tracheal occlusion (FETO), where a detachable balloon at 26-28 weeks gestation is secured in the foetal trachea, causing accumulation of fluid within the lungs, designed to physically stretch and accelerate lung growth. The balloon is later deflated by image guided puncture or retrieved by foetal tracheoscopy between 32 and 34 weeks (81, 82). FETO is strictly reserved for 'high risk' foetuses with the worst chance of survival. Preterm birth and premature rupture of amniotic membranes is a frequent complication of FETO (83).

The Cochrane review undertaken by Grivell *et al* (78) included two RCTs comparing FETO to standard postnatal management (84, 85). Differences between the study methods were such that the RCTs could not be combined into a meta-analysis. The first trial, involving 24 women, included no suitable data on perinatal mortality. There were no differences in long term infant survival when comparing FETO vs. standard postnatal management (risk ratio (RR) 1.06, 95% confidence interval (CI) 0.66 to 1.69) (84). The second trial, including 41 women, did not report perinatal mortality. There was a small reduction in mean gestational age at birth (mean difference -1.80 weeks, 95% CI -3.13 to -0.47). There was no clear difference in risk of preterm birth (RR 1.75, 95% CI 0.78 to 3.92) or preterm rupture of membranes (<37 weeks) (RR 1.47, 95% CI 0.56 to 3.88). Long term survival was apparently better with FETO vs. standard postnatal management (RR 10.50, 95% CI 1.48 to 74.71) (85).

Since this earlier Cochrane review further landmark studies have just been published. These were two new international randomised trials comparing FETO to standard postnatal management in moderate and severe CDH (86). The primary outcome of both TOTAL trials was survival to hospital discharge from the neonatal intensive care unit (NICU). The 'moderate severity' trial involved 12 FETO centres and 46 neonatal care facilities across 15 countries. 196 pregnant women carrying foetuses with CDH were included. The results of the trial showed no reduction in survival rate at discharge (RR 1.27, 95% CI 0.99 to 1.63, p=0.06), and survival rate to 6 months of age without oxygen supplementation (RR 1.23, 95% CI 0.93 to 1.65). The incidence of premature rupture of membranes (44% vs. 12%, RR 3.79, 95% CI 2.13 to 6.91) and preterm birth (64% vs. 22%, RR 2.86, 95% CI 1.94 to 4.34) were both higher in the FETO group (86). The trial in 'severe' CDH included 10 FETO centres and 26 neonatal centres across 12 counties. 95 women participated. There was an increase in survival to discharge when using FETO compared to expectant care (40% vs 15%, RR 2.67, 95% CI 1.22-6.11, p=0.009). Survival rate to 6 months was identical to survival to discharge. Premature rupture of membranes (47% vs 11%, RR 4.51, 95% CI 1.83-11.9) and preterm birth (75% vs 29%, RR 2.59, 95% CI 1.59-4.52) were again both higher in the FETO group.

Antenatal steroids

Antenatal steroids are recommended for babies at risk of preterm delivery to improve lung growth in the foetus. The Cochrane review by Grivell *et al* (78) identified only a single inadequately powered RCT comparing antenatal steroids to placebo. The trial published in 2006 involved only 32 women. No differences in incidence of perinatal mortality, days of mechanical ventilation or shorter hospital stay were found (78, 87). Further large-scale trials are needed to answer unresolved questions.

Other areas of research

Research into stem cell therapy is a promising nascent field in an effort regenerate hypoplastic lung growth and also towards engineering diaphragm tissue substitutes (88-90).

Newborn Delivery

Where possible, elective delivery should occur in a tertiary obstetric centre with expert surgical services available. There is no current evidence to support caesarean section for CDH unless there are specific maternal indications (91). The baby should be emergently intubated and ventilated, although bag-mask ventilation should be avoided at all costs to prevent gaseous distention of the stomach (41).

1.4.2 Post-natal management

In the last 30 years there has been a paradigm shift away from emergency surgery towards stabilisation of labile physiology with a focus on gentle ventilation and delayed elective operation. It is strongly recommended that immediately after birth the infant is intubated and ventilated to achieve stabilisation in order to avert severe hypoxaemia and pulmonary hypertension (7).

Ventilation

Up to the 1980's aggressive ventilation techniques led inexorably to significant pulmonary barotrauma and increased mortality. Therefore, 'gentle' ventilation and 'permissive hypercapnia' is now the accepted best form of management to avoid ventilator induced lung injury (75). This was first suggested by Wung *et al* , working in New York City in 1985 (92). Permissive hypercapnia is associated with fewer complications, particularly pneumothorax, and gentle ventilation has convincingly shown better survival outcomes (93).

High frequency oscillatory ventilation (HFOV), aims to avoid barotrauma by keeping mean airway pressures limited at 18-20cmH$_2$O. The advantages of which have been historically well reported (94-96), however, a recent randomised clinical trial has not shown that HFOV reduces mortality rates compared to conventional ventilation. There was also suggestion of longer ventilation time and higher use of ECMO following HFOV vs. conventional ventilation (97).

If HFOV is not sufficient to achieve adequate patient oxygenation, then inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO) can be used. Due to its high risk of complications, ECMO is reserved for only the most unwell infants (93).

ECMO

ECMO is an artificial life support system. In the same way as a cardiopulmonary bypass machine, ECMO pumps blood from the body, adding oxygen to the blood with a membrane oxygenator system and removing carbon dioxide, returning oxygenated blood to the patient's body. Babies can be maintained on ECMO for days to 2-3 weeks for stabilisation (98) to allow the lung to rest and amelioration of pulmonary hypertension. ECMO is however associated with significant morbidity and many long-term survivors are left with neurodisability (99). For these reasons ECMO should be used only in those infants most at need.

Potential candidates for ECMO are those infants with an oxygenation index (OI) over 40, those unable to maintain preductal saturations over 85% or a postductal saturation over 70%, those with systemic vascular hypotension resistant to inotropes, a blood pH of less than 7.15, or a raised CO_2 on blood gas analysis (100). ECMO is commonly used, although not widely supported by robust Level 1 evidence.

A Cochrane review in 2008 examined RCTs comparing neonatal ECMO to conventional ventilatory support. They included four trials of infants with respiratory failure, two of which included infants with CDH. All four trials showed that ECMO benefited mortality rates (RR 0.44; 95% CI 0.31 to 0.61), though this was most notable in infants without CDH (RR 0.33, 95% CI 0.21 to 0.53). The authors of these studies concluded that the benefit of ECMO for infants with CDH remains unclear (101). At the time of writing no further RCTs investigating ECMO use in babies with CDH have been conducted since.

Inhaled Nitric Oxide

As previously mentioned, nitric oxide is produced by the vascular endothelium and relaxes the blood vessels. iNO has been shown to reduce pulmonary artery hypertension in infants with CDH (102), and can be useful also in stabilising patients prior to ECMO (7, 103). Despite the potential of iNO, the overall clinical benefits remain controversial (7, 75, 104, 105).

The NINOS study, a large RCT showed that despite improvements in early oxygenation, inhaled nitric oxide did not improve overall mortality rates or indeed reduce the need for ECMO in CDH (106).

An alternative to iNO for managing pulmonary hypertensive crises are the PDE inhibitors. The PDE 5 inhibitor Sildenafil enhances the vasodilation caused by nitric oxide, making it potentially useful in CDH (7, 107). The PDE 3 inhibitor Milrinone has also been reported to reduce pulmonary hypertension in CDH (100, 108).

Perfluorocarbons

Liquid ventilation was first developed for exploring space flight for astronauts in the 1950's. Perfluorocarbons, a liquid medium capable of carrying large amounts of oxygen and carbon dioxide, fills and ventilates the lungs. Its use has been proposed for CDH, however early trials were halted due to high mortality levels and FDA (Food and Drug Administration) support being withdrawn (109, 110). A more recent published study examining perfluorocarbon use in CDH infants on ECMO found patient lung size doubled on radiology screening but persistent pulmonary hypertension did not improve (111).

Surfactant

Despite some published reports of surfactant deficiency in CDH, no studies have shown benefits for exogenous surfactant therapy (EST) in CDH infants and it is suggested that EST should likely be strictly reserved for only those babies who are born extremely premature < 32 weeks (75, 100, 112, 113).

Post-natal surgery

The mainstay of treatment for CDH is surgery to remove the herniated intestines from the chest cavity and repair the diaphragm. The best timing of such surgery has been long debated (114, 115). Most centres now favour stabilisation first, followed by delayed elective surgery.

CDH it is most often repaired by classical open surgery. The procedure involves a subcostal or transverse muscle incision to gain access, the abdominal viscera are then returned to the abdomen, and the diaphragm is repaired through primary repair when possible using non-absorbable sutures (116).

If the defect is large and primary repair is not feasible a patch can be used. Patches can be prosthetic material such as Goretex or bio-prosthetic such as Surgisis Gold.

At times, abdominal closure can be difficult, and the abdominal wall may also need a prosthetic patch (8). Jester, 2018 (8) recommended folding the diaphragmatic patch into a cone shape to allow for additional space in the abdominal cavity to avoid abdominal compartment syndrome.

As a less commonly used alternative to open surgery, minimally invasive techniques (MIS) can be attempted by thoracoscopy (116). However, reports have shown thoracoscopic surgery to be associated with significant recurrences, increased operation times, and worsening acidosis and hypercapnia during surgery (117-121). Nevertheless, thoracoscopic repair is also associated with possibly quicker patient recovery times, less post-operative pain, lower risk of abdominal adhesions, and a better aesthetic outcome (8). The patient should ideally be of a good birthweight and very stable before attempting thoracoscopic repair. It should be noted that infants born with larger diaphragmatic defects (Grades C or D (122)) are more likely to be at risk of significant hernia recurrence.

The infant is positioned laterally with the affected side up, and the table tilted so gravity helps reduce the herniated viscera from the thoracic cavity into the abdomen. Stab incisions are made for the camera and two working ports. When reducing the abdominal viscera, the spleen should be handled carefully as damage causing bleeding can mean having to convert to open surgery. Primary closure can be difficult in larger defects, in these instances a Gore-Tex patch should be used instead (8).

Prophylactic fundoplication at the time of diaphragmatic hernia repair to reduce the risk of gastro-oesophageal reflux disease (GORD) has also been suggested, however, studies have not shown clear benefits (123).

CDH patients may have a period of stability and improvement in oxygenation post-surgery known as the 'honeymoon' period, then begin to deteriorate 6 to 24 hours later due to worsening pulmonary hypertension post-surgery (35). A sudden deterioration in oxygenation could also be due to pneumothorax.

A pneumothorax may occur in ventilated patients and present as a sudden drop in respiratory and cardiac parameters. This carries a high mortality, although diagnosis from chest x-ray should be made with caution. The hypoplastic lung may not fill the thorax and so be mistaken for a pneumothorax. Other surgical complications include small bowel obstruction, pleural effusion, recurrent herniation, and chylothorax. Routine postoperative chest drains should not be used however as they can lead to overinflation of the lung and air leaks. If a pleural effusion or chylothorax cause respiratory distress or mediastinal shift needle aspiration can be tried initially, then a chest drain should be later considered (8, 124). Octreotide can also be used to treat chylothorax (125).

Hernia recurrence can occur in some 7% of children who have had a primary repair (126, 127) and there have also been reports of up to 44-46% of survivors having recurrence following a patch repair (116). By contrast various 'high-volume' CDH centres have reported much lower rates of recurrence (<10%) (128, 129). A prosthetic patch is less likely than a primary native repair to expand with the child as they grow.

Biological patches and absorbable sutures are the most likely factors linked to an increased risk of hernia recurrence (8). Since most recurrences generally occur within the first two years of repair and are usually asymptomatic, regular surveillance chest x-rays are often recommended to detect hernia recurrence (8).

1.5 Prognosis in CDH

Survival rates for CDH are estimated between 50 and 80% (22, 23, 65, 81, 122, 130, 131). This value is wide ranging, though depends strongly on the patient population and associated disease and management factors. Specialised 'high volume' centres (delivering >5-6 CDH cases per year) have reported survival rates of up to 90% (132). It is unclear, however, if all infants are included in these mortality figures. For example, whether the infants who are not fit for surgery are included here. Increasing numbers of terminations of CDH pregnancies also pose a hidden mortality perhaps not fully accounted for in these studies (133).

Infants with an additional major birth defect, such as congenital heart disease, or chromosomal abnormality, alongside CDH, have a much lower chance of survival (73, 134). One study reported a survival rate of only 19% in these higher risk infants, compared to 63% for isolated CDH (22).

There are various proposed methods to predict CDH prognosis antenatally, none of which are wholly ideal. Unfortunately, the reliability of each parameter is low, and they are best used in conjunction with each other. A prognostic index scoring tool has been developed to calculate prognosis in CDH (134).

Predictive factors include size of the defect, position of the liver, foetal lung to head ratio, and whether the hernia is bilateral or not.

The size and type of hernia defect can be classified according to the CDH international study group grades A to D (122). A grade 'A' defect is surrounded by muscle, a 'B' defect has a small portion of chest wall without diaphragmatic tissue, a 'C' defect has a larger portion of chest wall without diaphragm, and a 'D' defect is missing all or nearly all the diaphragmatic tissue. Knowing the grade of defect is vital for surgical repair and can be useful for calculating prognosis.

Measurement of foetal lung to head ratio (LHR) is calculated on ultrasound scan and can be used to determine prognosis (135, 136). Inconsistencies in measurement however mean that absolute LHR is not always accurate at predicting prognosis, and various studies have advised against its use (137). The ratio between observed and expected (O/E) LHR has been suggested as a better alternative, more accurate, measurement (138). An O/E LHR <20% has been associated with a higher mortality (139).

Foetal MRI imaging has also been used to calculate lung volume against total foetal body volume, another potential prognostic indictor for CDH (134, 140). Echocardiography can be deployed to predict left ventricle hypoplasia (LVH), whilst the McGoon Index uses the diameter of the pulmonary vasculature to predict survival (134).

Prescence of the liver in the thoracic cavity predicts a poorer prognosis (141), and babies with right sided CDH are often thought to have poor outcomes when the liver is located in the thoracic cavity (23). The degree of liver herniation can also be measured as liver herniated to thoracic volume ratio (142).

Foetal stomach position is another prognostic indicator. If the foetal stomach is in the abdominal cavity then the prognosis is stated to be much more favourable (135).

Post-natal prognostic factors include 'birth weight, APGAR score, post-ductal partial pressure of oxygen (pO2), age at presentation, side of the hernia, need for and the duration of ECMO' (143-145).

1.6 Long term outcomes in CDH

1.6.1 Cardiorespiratory outcomes

Pulmonary hypertension (PHT) is a leading cause of mortality in CDH. The baby usually presents with poor oxygenation and a marked difference in pre- and post-ductal arterial oxygen saturations (146).

Echocardiography shows a 'raised pulmonary vascular resistance and high right ventricular pressures' (147). At times, the transition from foetal to the newborn circulation can be severely impaired and the pressure in the pulmonary vascular bed will remain high. This is due to blood flow through the lungs being reduced and instead blood bypassing the pulmonary circulation via the foramen ovale or the ductus arteriosus with right to left shunting (146, 148).

As mentioned before, the abnormal precocious development of smooth muscle in the blood vessels will lead to pulmonary hypertension (1). There can also be an imbalance of vasodilating and vasoconstricting factors in the circulation (149). Nitric oxide, mostly produced by the endothelial cells, causes smooth muscle relaxation and iNO has been suggested as a therapy for PHT, although its use in CDH is controversial (105, 150, 151).

Pulmonary hypertension may be a temporary phenomenon in around 50% of babies and can resolve within the first few weeks of life (13, 102). Other infants will have persistent pulmonary hypertension despite therapeutic interventions, and this can be a key factor in early and late CDH mortality. As explained previously the adoption of 'gentle ventilation' has avoided ventilator induced lung injury (13). Despite this, there are still CDH survivors with long-term pulmonary hypertension.

CDH survivors may also have other respiratory co-morbidities including but not limited to; increased risk of respiratory tract infections, reduced lung function, and asthmatic symptoms. This is discussed further in Chapter 3 'Short term outcomes in CDH: Respiratory Syncytial Virus Bronchiolitis' and Chapter 4, 'Long term outcomes in CDH: cardiopulmonary outcomes and health related quality of life'.

1.6.2 Gastrointestinal outcomes

GORD is a common finding in CDH. Explanations for which have been centred around the defective diaphragm distorting the anatomy of the gastro-oesophageal junction, and the presence of a shorter oesophagus (152). Anti-reflux medications can be useful for management. However, the GORD may lead to difficulty feeding, oral aversion, failure to thrive, and some infants may have recurrent aspiration which worsens respiratory morbidity. In such cases, gastrostomy feeding, or fundoplication surgery can be helpful (153, 154). One study found gastrotomy tube feeding was used in 43.9% of infants (155).

Other gastrointestinal complications that may follow successful CDH repair is risk of adhesions after surgery which can threaten intestinal obstruction (156).

1.6.3 Neurological outcomes

CDH is associated with various neurological complications, most likely due to recurrent episodes of hypoxia in the neonatal period. Neurodevelopmental delay is recorded in up to 30-70% of survivors (63). Motor delay, such as hypotonia and asymmetry, as well as speech and language problems are prevalent. Sensorineural hearing loss can also be present in CDH survivors (43, 157) and has been linked with aminoglycoside therapy (158), prolonged mechanical ventilation, and ECMO use (159, 160). Furthermore, there are now emerging reports of increased rates of autism spectrum disorder in CDH vs the healthy general population (161).

1.6.4 Musculoskeletal outcomes

For children with significant respiratory distress, indrawing of the sternum during breathing can lead to the development of pectus excavatum (8). Scoliosis is also prevalent in CDH and can develop before birth or later in childhood (162).

1.6.5 Health Related Quality of Life (HRQoL)

With any serious congenital abnormality comes the risk of reduced HRQoL in survivors. This is discussed more fully in Chapter 4 'Long term outcomes in CDH: cardiopulmonary outcomes and health related quality of life'.

1.7 Systematic reviews

This thesis consists of three systematic reviews. I chose to focus on this research methodology as the systematic review is considered to be amongst the highest level of evidence (163). **Figure 4** depicts the hierarchy of evidence.

Figure 4: Hierarchy of evidence. Inspired by Murad et al, 2018 (163)

Originally developed in the 1970's (164), systematic reviews 'search, appraise and collate all relevant empirical evidence in order to provide a complete interpretation of research results' (165). The Cochrane collaboration was founded in 1993 to facilitate the production of systematic reviews. The logo is based on key findings from an iconic systematic review performed by Crowley *et al (166)* published in the 1990's. Various studies had published the benefits of the use of Corticosteroids in premature babies, though, no healthcare professional had synthesised the evidence until the publication by Crowley. It was this leading systematic review that was so influential in persuading obstetricians to adopt the use of maternal corticosteroids for preterm babies and likely saved thousands of lives.

The systematic review follows strict, reproducible methods. It is this robust process that distinguishes the systematic review from a narrative review. The narrative review provides a broad summary without guidelines (164, 167). The differences defining systematic vs narrative reviews are summarised in **Table 2**.

Table 2: Comparison of systematic and narrative reviews (167)

Systematic review	Narrative Review
Aims to minimise bias	May introduce bias through selective presentation of results
Preplanned methodology with predefined outcome measures	No preplanned methodology defining outcome measures
A set search strategy	No set search strategy
Comprehensive systematic searching including predefined databases and unpublished data	Often not predefined, systematic search of databases and does not include unpublished data
Documented, explicit methodology so it is possible to replicate by another independent researcher	Undocumented methodology which is difficult to replicate by another independent researcher
Systematic quality assessment of studies documented	Unlikely to include quality assessment of studies
Often involves a team of researchers	Usually written by one expert/researcher
May include numerical aggregation of data (meta-analysis)	Does not usually include statistical analysis
Conclusions based on a series of set and predefined outcome measures	Conclusion based (at best) on findings of the identified studies but more likely on the opinion of the reviewer

A systematic review includes the following steps. Firstly, a research question is constructed using the PICO (population, intervention, outcome, comparison) model. This forms the basis of the literature search. A protocol is developed, then the search of all relevant literature is conducted. Screening of studies is usually undertaken by two or more reviewers. The final step is data extraction and synthesis (164). Statistical methods (meta-analysis) can be applied where appropriate (167). The structured process of the systematic review improves transparency and researcher objectivity (164).

A systematic review allows for strengths and weakness of evidence to be summarised (167). It also allows for the identification of research gaps and methodological concerns (165).

 This synthesis of evidence within the context of its quality is far superior to drawing conclusions from a handful of selected papers out of context. The evidence becomes more accessible to clinicians and families and allows for shared decision making informed by the best evidence.

A variety of systematic reviews have been undertaken in CDH and some have guided advances in clinical practice. Most notably a Cochrane review of studies comparing early vs late surgical repair in CDH, led ultimately to a change in practice (114) with elective or delayed operative repair now being preferred by many centres (76).

1.8 Aims and outline of this thesis

The aim of this thesis is to use systematic review methodology to better understand the short- and long-term outcomes of Congenital Diaphragmatic Hernia, with a particular focus on the cardiorespiratory system. The following chapters are summarised here as a guide for the reader:

With numerous management options, and multiple outcomes to measure along with this, comes the need for robust outcome reporting. Study I - Chapter 2 - is a systematic review of outcome reporting in observational studies and RCTs addressing post-natal interventions in CDH.

In Chapter 3 - Study II focuses on short-term outcomes in CDH, specifically the risk of Respiratory Syncytial Virus (RSV) bronchiolitis. Given uncertainties surrounding upcoming RSV epidemics, debate exists whether palivizumab (RSV prophylaxis) should be given to CDH infants.

This study aims to evaluate the risk of RSV bronchiolitis hospitalisation and whether palivizumab prophylaxis may modulate this risk.

In Chapter 4 - Study III considers the long-term sequelae of CDH. This study is a systematic review focusing on cardiorespiratory outcomes in CDH survivors over 2 years of age and adults with CDH. Cardiorespiratory outcomes here include pulmonary hypertension, lung function, radiological outcomes, functional outcomes, and risk of asthma, emphysema, and chronic obstructive pulmonary disease (COPD).

Finally, Chapter 5 provides a discussion of the overall findings in the thesis from these individual studies, their strengths and limitations, as well as potential future directions for research.

Chapter 2: Outcome reporting in CDH

2.1 Background

As described earlier, there are wide-ranging post-natal management strategies that aim to improve both short- and long-term outcomes of infants born with CDH. These include 'gentle' ventilation with electively scheduled delayed surgical repair, as well as the use of ECMO, nitric oxide, and sildenafil (131). Despite available post-natal therapies there is currently no internationally agreed consensus as to which 'best outcomes' should be measured in studies seeking to evaluate these interventions in CDH. Outcomes may be selected on the basis of, for example, their financial cost or time constraints rather than those perhaps which would be most informative for health-care teams and parents. The selection of outcomes in this way can be problematic.

Heterogeneity can exist between such studies. Firstly, outcomes can be measured using different methods or at different time points. This may lead to limitations in comparing studies or combining the results as systematic reviews or meta-analyses (168).

Secondly, outcomes can be at risk of selective reporting. This occurs when outcomes are measured and analysed but not fully reported. Often insignificant outcomes are omitted from papers for brevity of journal submission and editing. This however can risk reporting bias (169). It has been found that studies with statistically significant results are more likely to be published in healthcare journals (170, 171).

Without a standardised set of outcomes, studies also risk choosing outcomes that prove to be irrelevant. Outcomes should be chosen with the patients, parents, and clinicians in mind, rather than those that would be most convenient for the researchers (168, 172). There is perhaps uncertainty about which outcomes are most relevant. CDH impacts on various aspects of the lives of its survivors, and the outcomes selected should reflect this (173).

As healthcare has improved steadily over decades, outcomes which were previously considered of merit, may no longer be relevant today (172). This uncertainty in choice of outcome may underpin the heterogeneity between studies.

The development of a Core Outcome Set (COS), a standardised set of outcomes, would preferably yield a robust consensus for health professionals regarding CDH (173). A COS would also hopefully reduce heterogeneity, reporting bias, and clinically irrelevant outcomes (168, 174). In order to develop a robust COS, it must first be critically determined which outcomes are currently reported in CDH.

The aim of this chapter is to analyse outcome reporting data available in published studies of CDH, with a view to designing and developing a valid COS for future research studies.

2.1.1 Objectives

1) To review studies of post-natal interventions in CDH to see which outcomes are measured, and if there are any gaps in outcome reporting or non-uniformity between studies.

2) To examine trends in outcome domains reported in published studies during 2000-2020.

3) To determine any associations (if any) between outcomes with regard to study quality, study type, or patient age group.

2.2 Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (175). A protocol was developed which defined - (I) study objectives, (II) selection criteria, (III) assessment of study quality, (IV) data extraction and (V) analysis.

2.2.1 Search strategy

We searched Cochrane Central Register of Controlled Trials (CENTRAL), a large database of randomised trials, from January 2000 to December 2020, using the heading term 'Congenital Diaphragmatic Hernia'. We chose not to review papers before the year 2000 due to a shift towards supportive management around that time. The database was last searched on 03/03/2021.

Two researchers (LL and IS) screened potential studies based on title and abstract. The selected studies were then read in full to screen for eligibility.

Studies included were published RCTs and observational studies describing any post-natal care interventions in CDH. There were no limitations set on the age of study participants.

Studies excluded were duplicates, abstract-only papers, papers published before 2000, and those not in the English language. Studies of pre-natal intervention(s) for CDH (including FETO and peri-natal cord clamping) and animal studies were also excluded.

2.2.2 Data extraction and quality assessment

Data from selected eligible studies were extracted by the primary author (LL). Extracted data included study characteristics and main results.

Study characteristics included: (a) study design, (b) single or multi-centre study, (c) number of patients, (d) age of patients, and (e) intervention(s).

Study results consisted of: (i) outcomes reported, (ii) primary outcome reporting, and whether the study focused on (iii) short- or long-term outcomes. Outcomes were then grouped into categorical domains.

The study authors assessed observational study quality using the methodological index for non-randomised studies (MINORS) criteria (176). Study quality for RCTs was assessed using the Cochrane risk of bias tool for randomised trials (177).

2.2.3 Data analysis

Outcomes from each published study were categorised by discussion between reviewers into seven predetermined domains. Domains were based on Sinha *et al's* paper on outcomes in paediatric asthma (173), and modelled on the CDH patient journey throughout their hospital stay and then post hospital discharge (**Figure 5**): (a) CDH surgical repair; (b) short-term markers of disease activity; (c) hospital interventions and medications; (d) adverse effects of therapy; (e) hospital discharge; (f) long-term markers of disease activity; (g) functional health status. Outcomes were also classified as short-term (measured at <1 year) or long-term (measured at >1 year).

Figure 5: The Seven Outcome Domains Modelled on The Patient Journey
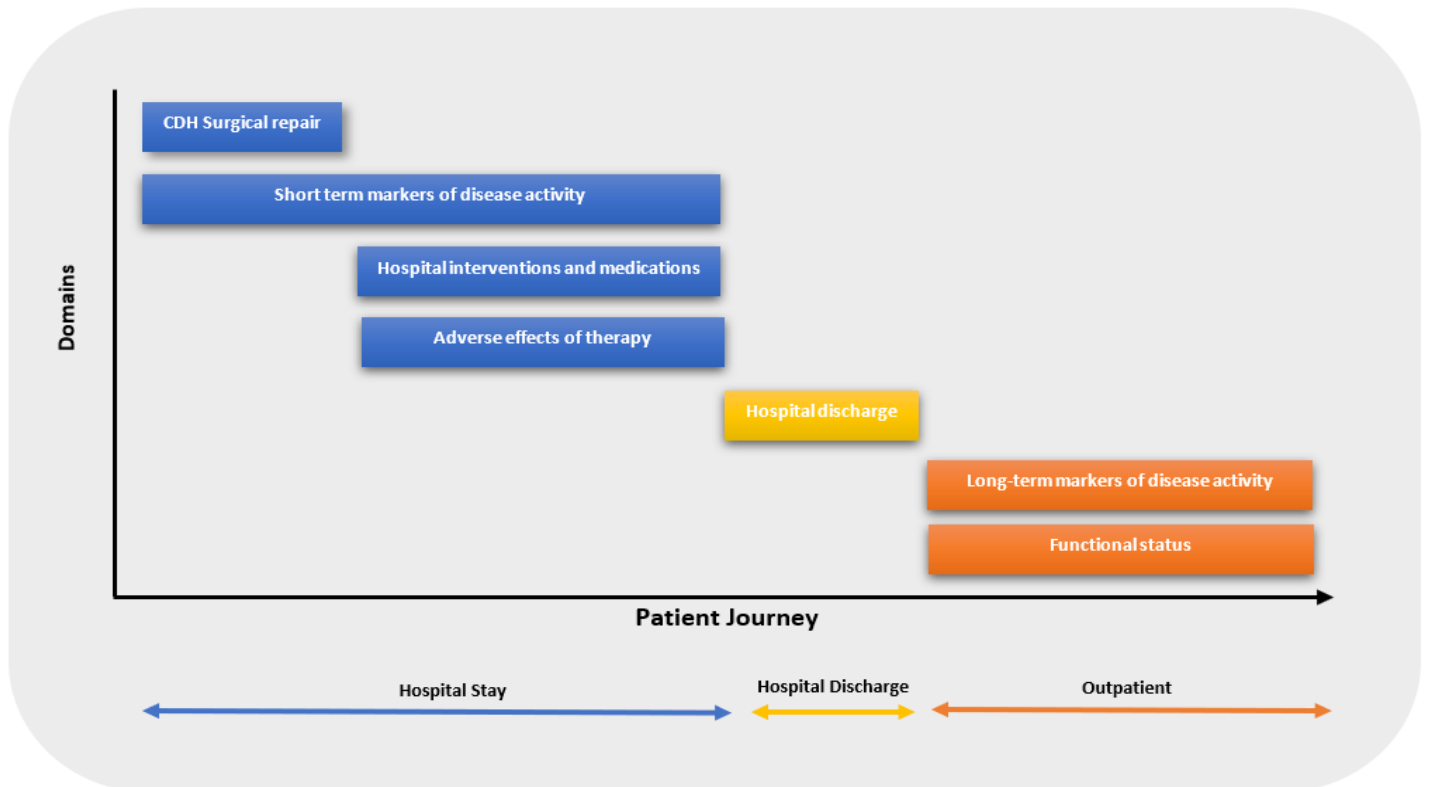
Study interventions were further categorised into (a) use of ECMO, (b) cardiopulmonary drugs, (c) anti-reflux drugs, (d) neurocognitive training, (e) inspiratory muscle training, (f) ventilation strategies, (g) surgical CDH repair, (h) surgical CDH repair with mode of ventilation. Occasionally a study intervention was not explicitly listed and therefore defined as 'unclear'.

To determine how trends in outcome reporting changed over time, studies were classified by year of publication and presented as a moving window. The twenty years spanning 2000 to 2020 were split into seventeen 5-year long periods, each overlapping the previous by 4 years, starting at 2000-2004, followed by 2001-2005 continuing up until 2016-2020.

To determine outcome reporting by age category, each study was then classified by the age range of patients. Categories were newborns (<28 days), infants (<1 year), children and adolescents (<18 years), or a combination of children and adults (>18 years).

2.3 Results

2.3.1 Study search and selection

The search of CENTRAL yielded 126 papers, and after removal of 8 duplicates, 118 papers were screened. Titles and abstracts were then assessed for eligibility, excluding 73 papers. The remaining 45 publications were read in full, and a further 18 papers excluded. We included 27 studies (93, 110, 111, 117, 123, 178-199) of which 13 were RCTs (110, 111, 117, 178-187) and 14 observational studies (93, 123, 188-199). **Figure 6** shows the PRISMA flowchart for the study review.

Figure 6: PRISMA Flow Diagram
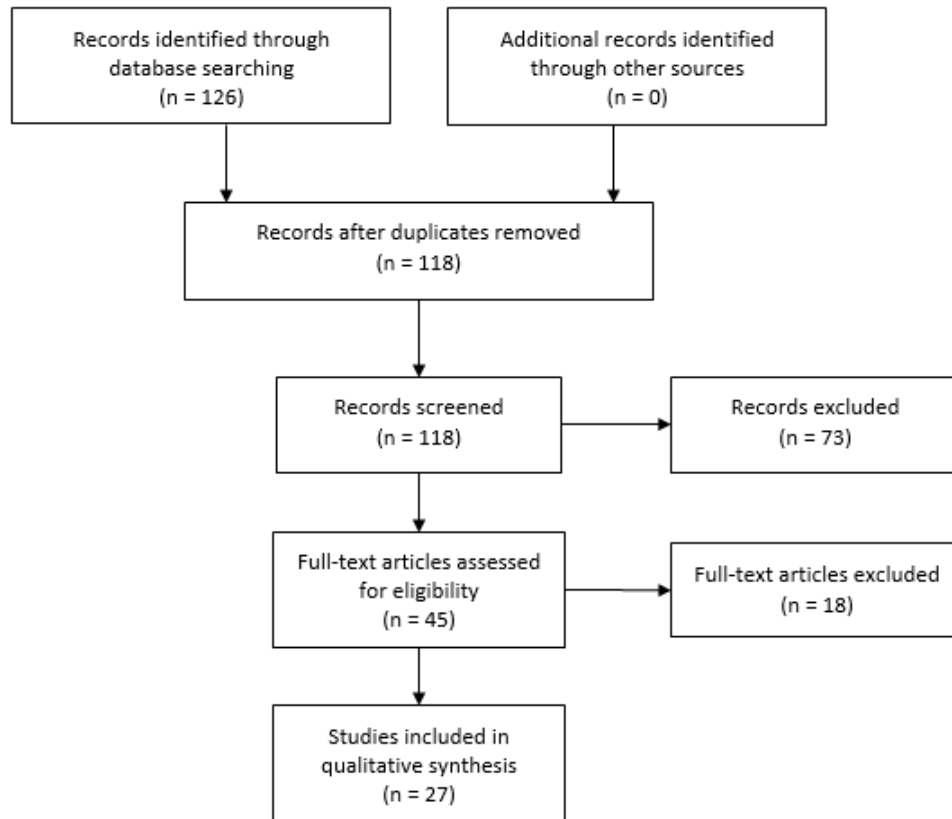
2.3.2 Study characteristics

Overall, the studies included 2596 patients with CDH. The average number of patients with CDH were 96 per publication (range 5-691). 13/27 studies were RCTs (110, 111, 117, 178-187) and 14/27 were observational studies (93, 123, 188-199). 7/27 studies were multicentre collaborative works. Studies emerged from many countries including the UK, the Netherlands, Belgium, the USA, Canada, Japan, Egypt, and Australia.

17/27 studies (63%) involved newborns, 4/27 (15%) infants (178, 188, 193, 196), 4/27 (15%) children and adolescents <18 years (181, 184, 194, 199), and 2/27 (7%) publications described children, adolescents and adult populations (189, 197). No studies included exclusively adults with CDH.

Interventions described amongst these many studies were wide-ranging and classified into 10 category domains, with studies relating to surgical CDH repair, ventilation and cardiopulmonary drugs being the most frequent.

16/27 (59%) of CDH studies reported only short-term outcomes (<1 year); 6/27 (22%) reported only long-term outcomes (>1 year) and 5/27 (19%) examined both short- and long-term outcomes. Study characteristics are summarised in **Table 3**.

Table 3: Table of study characteristics

Study characteristic	Category	Number of studies	Percentage of studies (%)
Year of publication	2000-2004	8	30
	2005-2009	1	4
	2010-2014	2	7
	2015-2019	13	48
	2020	3	11
Study type	Randomised controlled trials	13	48
	Observational studies	14	52
No. of centres	Single Centre	20	74
	Multi Centre	7	26
No. of CDH patients	<25	8	30
	25-49	8	30
	50-99	4	15
	100-299	4	15
	300-700	3	11
Age of patients	Newborns (<28 days) only	17	63
	Infants (<1 year) only	4	15
	Children and adolescents (<18 years) only	4	15
	Children and adolescents (<18 years), and Adults (>18 years)	2	7
	Adults (>18 years) only	0	0
Intervention	Neuro-cognitive training	1	4
	Inspiratory muscle training	1	4
	ECMO	1	4
	Cardiopulmonary drugs (iNO, Milrinone, Treprostinil, Sildenafil)	4	15
	Anti-reflux drugs	1	4
	Patient position (prone or supine)	1	4
	Ventilation	6	22
	Surgical CDH repair	8	30
	Surgical CDH repair and ventilation	2	7
	None/unclear	2	7
Outcomes	Short-term (<1 year)	16	59
	Long-term (>1 year)	6	22
	Both	5	19

2.3.3 Study Quality

 Table 4 shows the Cochrane risk of bias for randomised trials (177) for all trials included in this study. Overall risk of bias was rated as 'low risk' if all domains fell under this category, 'some concern' if the trial had one domain in this category, and 'high risk' if more than one domain showed 'some concern' or at least one domain was 'high risk'. Seven papers showed 'some concern' for risk of bias, and six papers showed a 'high risk' of bias. No papers showed a 'low risk' of bias. The two domains that were rated as 'high risk' were due to the method of measuring the outcome being inappropriate. We used these assessments of study quality later to ascertain any trends in outcome reporting between higher and lower quality RCTs.

Table 5 shows the observational studies as rated by the methodological index for non-randomised studies (MINORS) criteria (176). Non-comparative studies were given an overall score out of 16, and comparative studies a score out of 24. Overall scores ranged from 54%-81%.

(176).

Table 4: Cochrane Risk of Bias For Randomised Trials (n=13) (177)

Primary author	Domain 1: Risk of bias arising from the randomisation process	Domain 2: Risk of bias due to deviations from the intended interventions	Domain 3: Risk of bias due to missing outcome data	Domain 4: Risk of bias in measurement of the outcome	Domain 5: Risk of bias in selection of the reported result	Overall risk of bias
Bestebreurtje**(178)**	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Bishay**(117)**	Low risk	Low risk	Low risk	Low risk	High risk	High risk
Guevorkian**(179)**	Some concerns	Some concerns	Low risk	Low risk	Low risk	High risk
Hirschl**(110)**	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Jacobs**(180)**	Low risk	Some concerns	Low risk	High risk	Low risk	High risk
Moawd**(181)**	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Moustafa**(182)**	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Mychaliska**(111)**	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
NINOS**(183)**	Low risk	Some Concerns	Some concerns	Low risk	Low risk	High risk
Schiller**(184)**	Low risk	Some Concerns	Low risk	High risk	Low risk	High risk
Snoek**(185)**	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Snoek**(186)**	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Wu**(187)**	Some concerns	Some concerns	Some concerns	Low risk	Low risk	High risk

Table 5: Methodological index for non-randomised studies (MINORS) score (n=14) (176)

Primary author	1. Clearly stated aim	2. Inclusion of consecutive patients	3. prospective collection of data	4. Endpoints appropriate to the aim of the study	5. Unbiased assessment of study endpoint	6. Follow up period appropriate	7. Loss to follow up less than 5%	8. Prospective calculation of study size	9. Adequate control group	10. Contemporary groups (no historical comparison)	11. baseline equivalence of	12. adequate statistical analysis	Overall Score
Bevilacqua(188)	2	1	2	2	0	2	1	0	N/A	N/A	N/A	N/A	10/16 (63%)
Bojanic(189)	2	2	0	2	0	1	1	0	2	2	2	0	14/24 (58%)
Boloker(93)	2	2	1	2	2	2	2	0	N/A	N/A	N/A	N/A	13/16 (81%)
Chamond(190)	2	2	1	2	0	2	1	0	2	2	1	0	15/24 (63%)
Cruz(191)	2	2	2	2	2	2	2	0	2	2	1	0	19/24 (79%)
Desfrere(192)	2	2	2	2	0	2	2	0	2	2	2	0	18/24 (75%)
Harting(193)	2	2	2	2	0	2	2	0	2	2	1	2	18/24 (75%)
Kubota(194)	2	1	2	2	1	2	1	0	2	2	0	0	15/24 (63%)
Lally(195)	2	1	2	2	0	2	1	0	N/A	N/A	N/A	N/A	10/16 (63%)
Lawrence(196)	2	2	1	2	2	2	2	0	2	2	1	0	18/24 (75%)
Maier(123)	2	1	2	2	2	2	1	1	2	2	2	2	21/24 (88%)
Mesas Burgos(197)	2	1	2	2	0	2	0	0	2	2	0	0	13/24 (54%)
Okuyama(198)	2	2	0	2	0	2	1	0	2	2	1	0	14/24 (58%)
Turchetta(199)	2	1	0	2	0	1	2	0	2	2	2	0	14/24 (58%)

Items are scored 0 (not reported), 1 (reported but inadequate), 2 (reported and adequate), or N/A (not applicable)

2.3.4 Study results

Domains and outcomes measured

Domains and outcome frequency are illustrated in **Table 6**. Short-term markers of disease activity was the most frequently reported domain (17/27, 63%) of papers, followed by hospital interventions and medications (15/27, 56%), hospital discharge (15/27, 56%), surgical CDH repair (8/27, 30%), functional status (8/27, 30%), adverse effects of therapy (4/27, 15%), and long-term markers of disease activity (3/27, 11%). These findings are depicted in **Figure 7**. **Figure 8** illustrates the most popular 10 outcomes measured.

Domain	Subdomain	Outcome	Number of studies which measured outcome n (%)
CDH surgical repair (n=8, 29.6%)		Timing of repair	4 (14.8)
		Primary or Patch repair	1 (3.7)
		Ease of intubation	1 (3.7)
		% CO_2 exhaled during operation	1 (3.7)
		Intraoperative or postop complications	2 (7.4)
		Conversion to open surgery	1 (3.7)
		Hernia recurrence	2 (7.4)
Short-term markers of disease activity (n=17, 62.9%)	General markers	Medical history and examination	5 (18.5)
		Vital signs	7 (25.9)
	Respiratory markers	Oxygenation index	3 (11.1)
		Evidence of pulmonary hypertension	5 (18.5)
		Lung function testing	1 (3.7)
		Chest X-ray	3 (11.1)
		Pulmonary hypoplasia post-mortem	1 (3.7)
	Neurological markers	Neurological scan – ultrasound scan or near infrared spectroscopy (NIRS)	1 (3.7)
	Gastrointestinal markers	Evidence of gastro-oesophageal reflux disease/pH monitoring	3 (11.1)
	Laboratory markers	Blood gases	8 (29.6)
		Brain Natriuretic Peptide (BNP)	2 (7.4)
Hospital interventions and medications (n= 15, 55.5%)	Interventions	ECMO	8 (29.6)
		Ventilation	10 (37.0)
		Oxygen	5 (18.5)
		Chest tube	1 (3.7)
		Type of feeding e.g. Nasogastric or Gastrostomy tube	2 (7.4)
	Medications	Pulmonary or cardiac drugs	6 (22.2)
		Surfactant	3 (11.1)
		Anti-reflux drugs	1 (3.7)
		Analgesia	2 (7.4)
	Other	Cost of treatment	1 (3.7)
		Intervention 'free' days	1 (3.7)
Adverse effects of therapy n=4, 14.8%)		Treatment failure	1 (3.7)
		Haematological complications	2 (7.4)
		Renal complications	2 (7.4)
		Central line sepsis	1 (3.7)
		Pneumothorax	1 (3.7)
		Electrolyte abnormalities	1 (3.7)
		Dose of intervention therapy	1 (3.7)

Hospital discharge (n= 15, 55.5%)		Mortality rate	13 (48.1)
		Age at death	3 (11.1)
		Hospital discharge rate	2 (7.4)
		Duration of hospital stay/age at discharge	3 (11.1)
		Discharged with treatment/medications	2 (7.4)
Long-term markers of disease activity (> 1 year) (n=3, 11.1%)		History and Clinical examination	2 (7.4)
		Medications	1 (3.7)
		Echocardiogram	1 (3.7)
		Pulmonary function testing and cardiopulmonary exercise testing (CPET)	3 (11.1)
Functional health status (n=8, 29.6%)		Use of a speciality medical clinic	2 (7.4)
		Neurological function	3 (11.1)
		Occupational or speech therapy	1 (3.7)
		Social worker	1 (3.7)
		Education level/school function	2 (7.4)
		Socioeconomic status	2 (7.4)
		Behaviour and attention	2 (7.4)
		Self esteem	2 (7.4)
		Opinion of physical fitness and activity levels	2 (7.4)
		HRQoL - child or carer	3 (11.1)

Figure 7: Domain Popularity

Figure 7: Domain Popularity
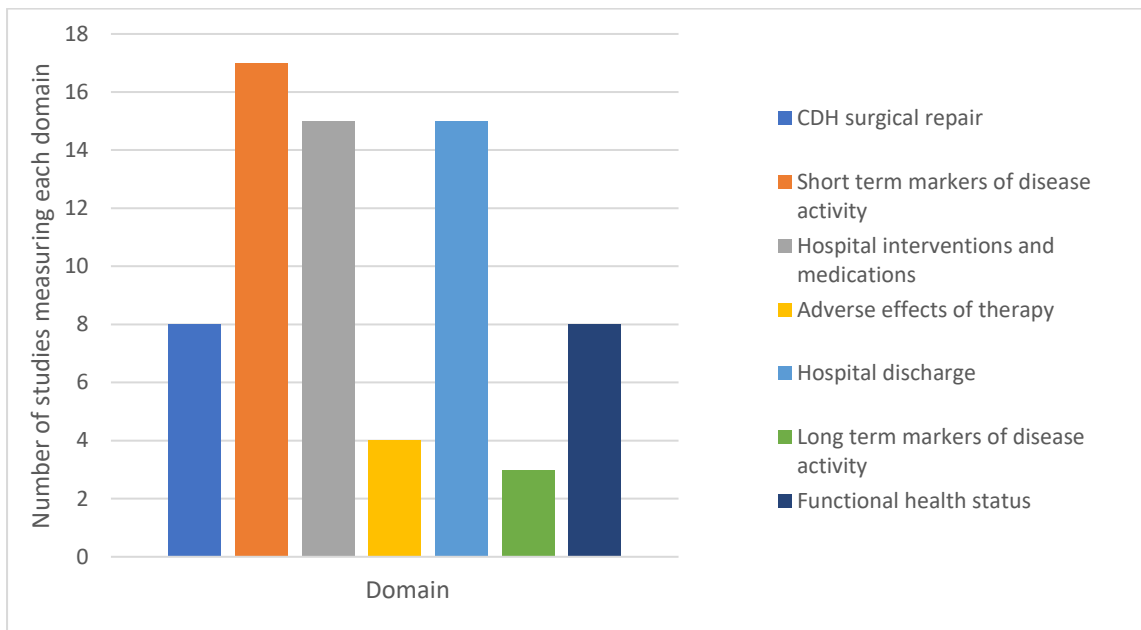
Figure 8: Most Popular Outcome Measured in CDH Health Care Data
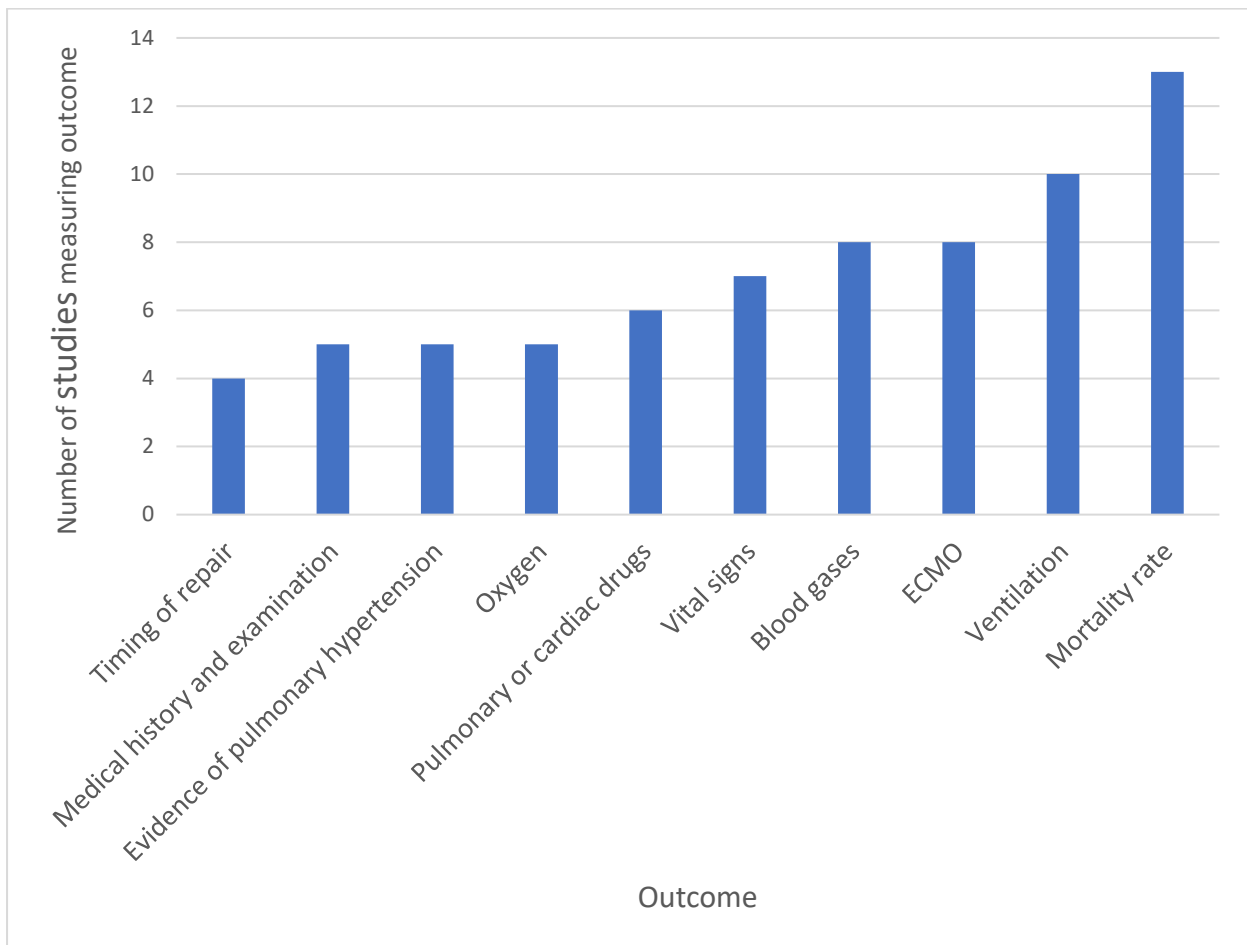
A primary outcome was specified in 10/13 (77%) of RCTs. The remaining 3 (33%) of RCTs reported multiple outcomes but did not specify which was their primary outcome. When a primary outcome was reported these fell into domains relating to CDH surgical repair (intubating status as measured by the Copenhagen scale - time taken to intubate and the number of attempts), short-term markers of disease activity (arterial CO_2 level, and pH monitoring), hospital discharge (mortality/survival rate), long-term markers of disease activity (cardiopulmonary exercise training), and functional status (neurological function). 'Hospital discharge' was the most popular domain for primary outcome, see **Figure 9**.

Figure 9: Frequency with which primary outcomes were selected from the different outcome domains
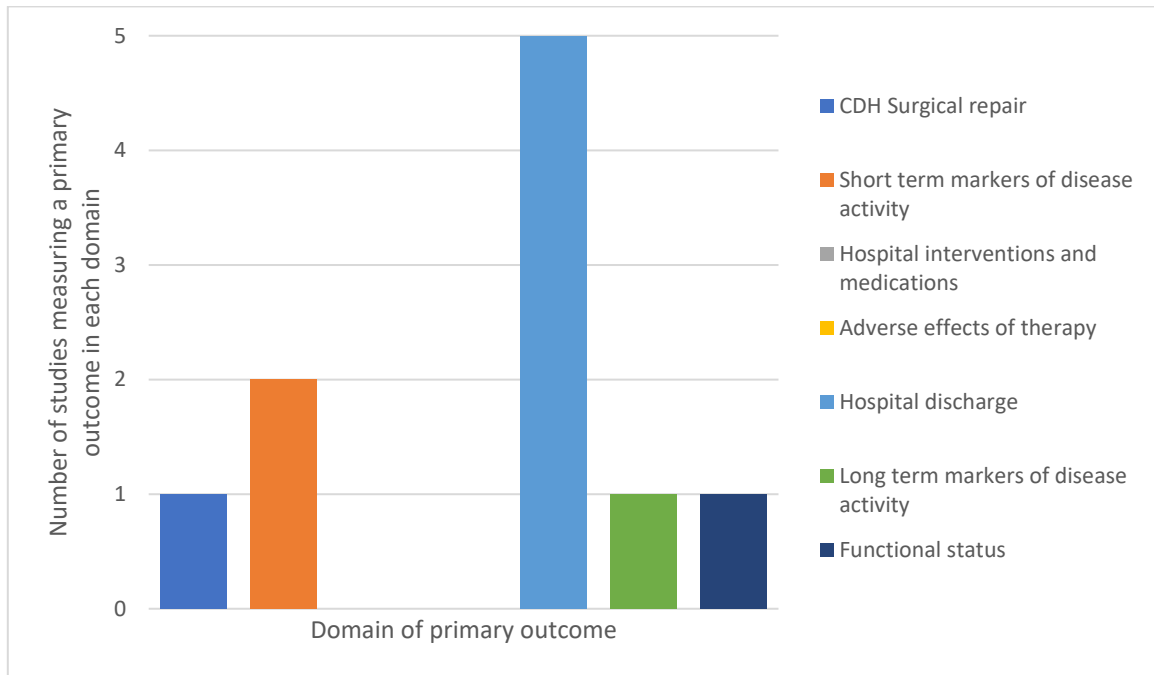
Trends in Outcome reporting based on study quality

As shown in **Figure 10**, there was little difference in domain popularity amongst high and lower quality RCTs (study quality was assessed by the Cochrane Risk of Bias For Randomised Trials).

Trends In CDH Outcome Reporting During 2000 - 2020

Due to the small numbers of papers included we could not draw any valid conclusions on trends in outcome reporting over time.

The average number of outcome metrics reported by each published study was 6. There were no particular trends observed in the number of outcomes reported by each publication over time.

Trends In Outcome Reporting By Age Category And Study type

As the age of patients with CDH advanced short-term outcome metrics decreased in popularity and long-term outcomes correspondingly increased – See **Figure 11** and **Figure 12**.

There was some difference in domain popularity amongst the RCTs and observational CDH studies, the greatest disparity here was for 'hospital interventions and medications' followed by 'short-term markers of disease activity' which were both more popular amongst randomised studies. See **Figure 13**.

Figure 10: Domain popularity in high vs low quality RCTs
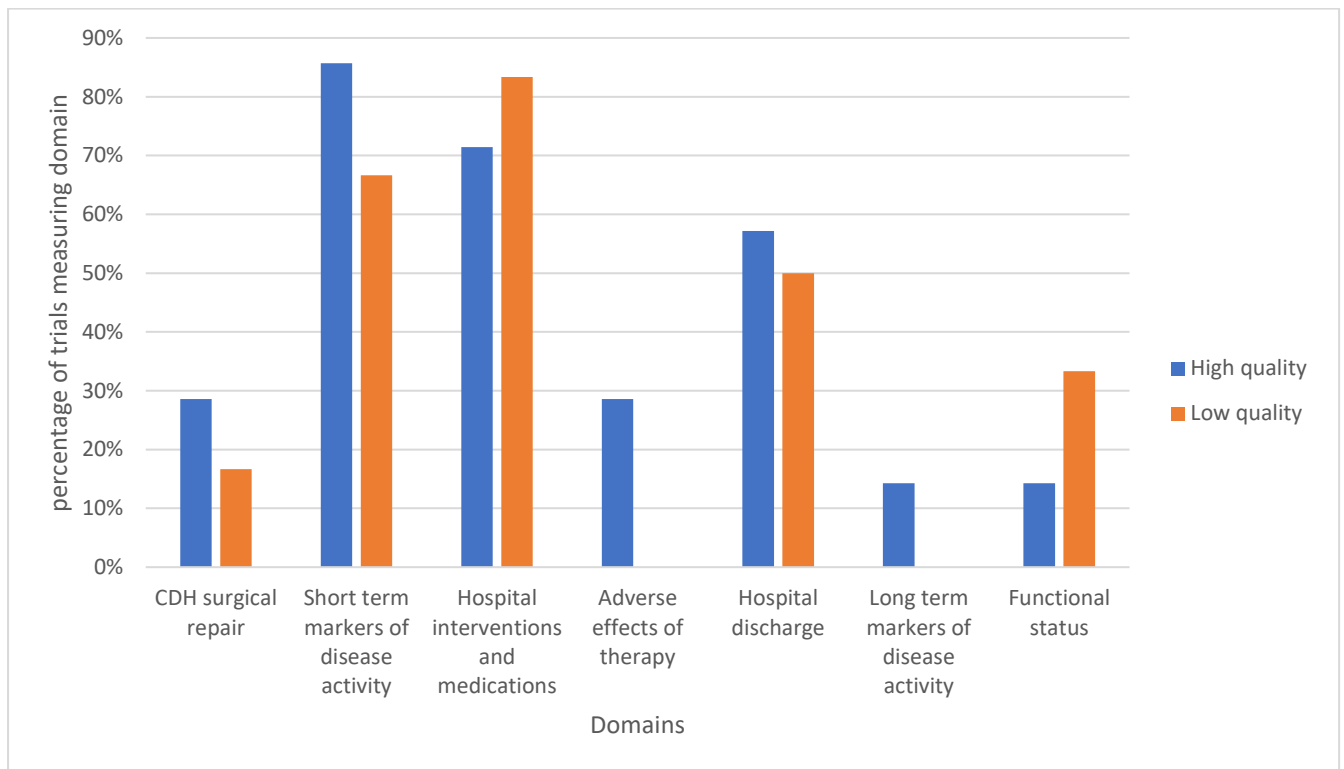
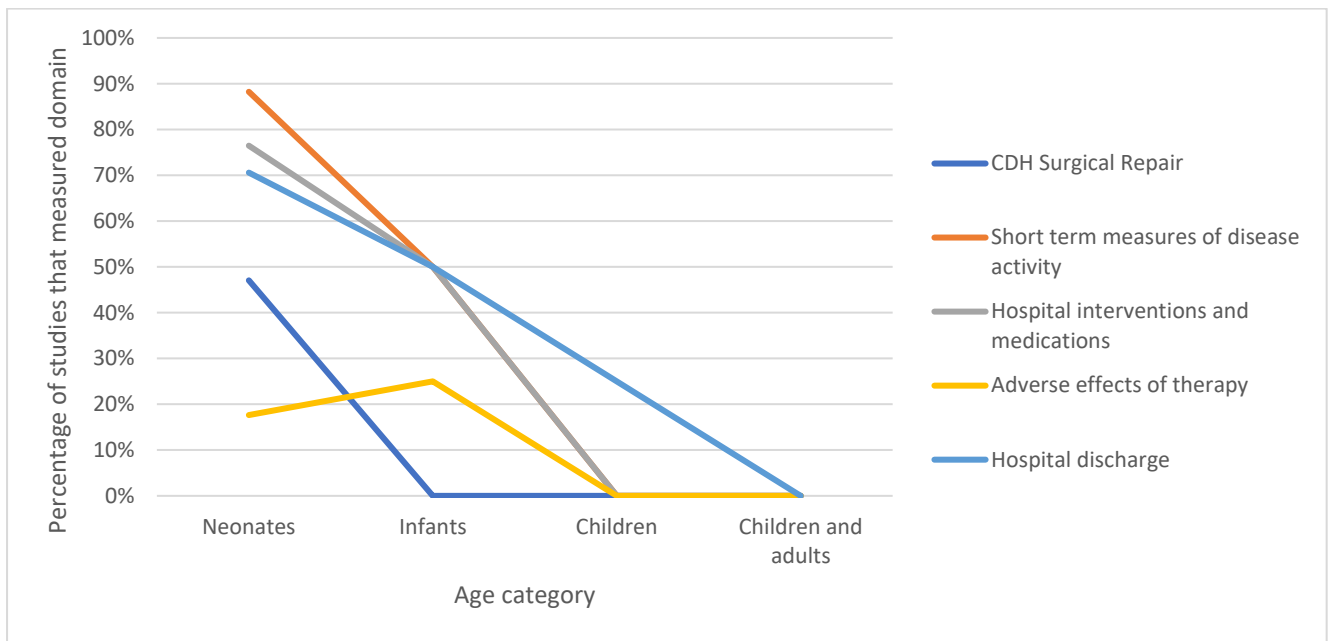*Figure 11: Trends in short-term domain popularity by age category*

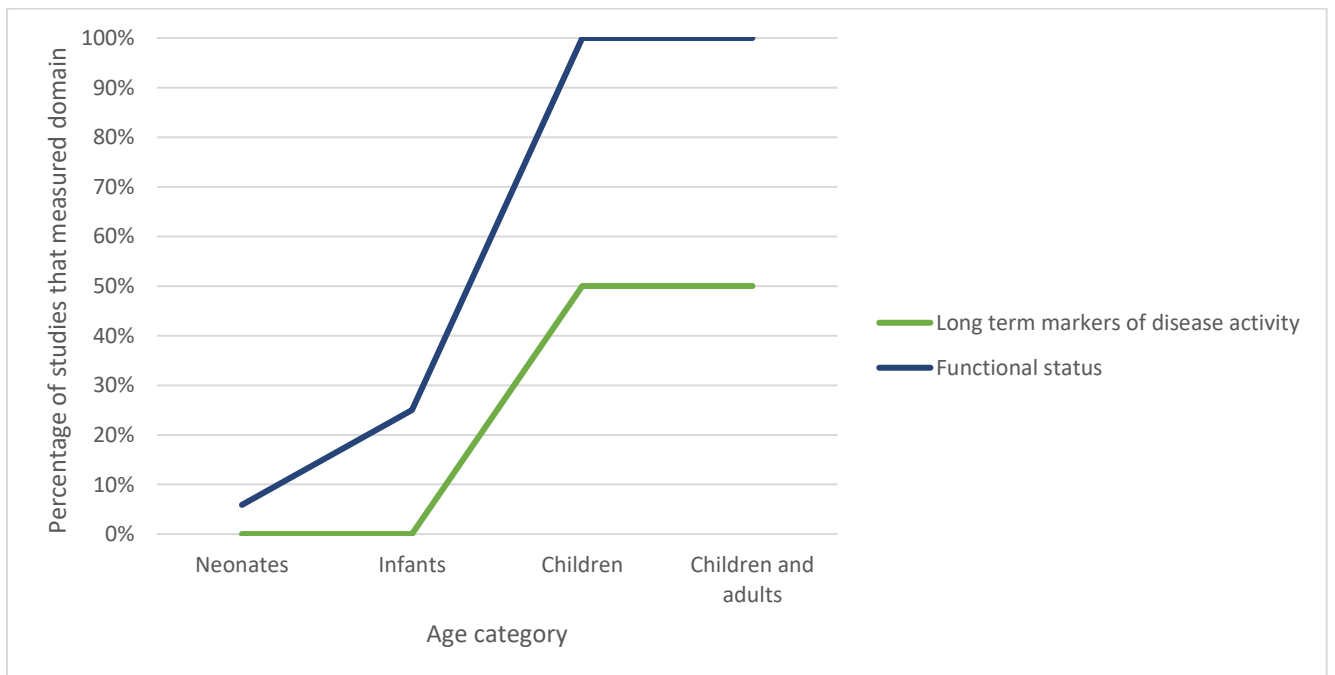*Figure 12: Trends in long-term domain popularity by age category*

Figure 13: Domain popularity by study type
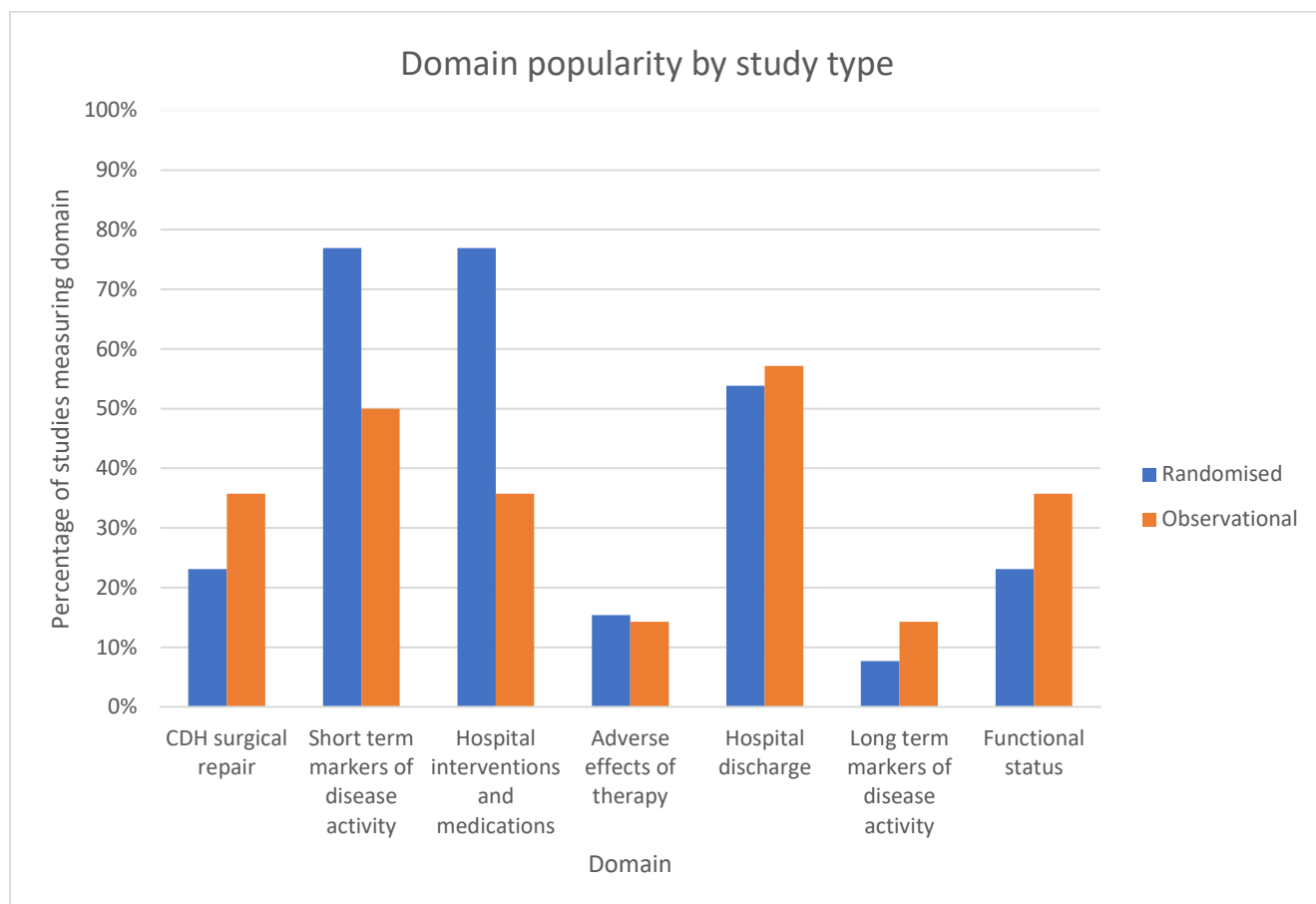

Domain popularity by study type

2.4 Discussion

Our first aim was to review studies of post-natal interventions in CDH to see which outcomes are measured, and if there are any gaps in outcome reporting or non-uniformity between studies. The second aim was to examine trends over time. The third aim was to determine any associations between outcomes with regard to study quality, study type, or patient age group.

In RCTs and observational studies, short-term severity of CDH and outcomes related to hospital discharge are the most frequently reported outcome domains. There was wide variability in the choice of outcomes selected and reported. Only 77% (10/13) of RCTs clearly specified a primary outcome and there was variability in the choice of outcome. The other 33% (3/13) of RCTs reported multiple outcomes but did not specify which was considered their primary outcome. The primary outcome is one of greatest importance to researchers. Sample size calculations are usually performed using the primary outcome and this reduces the risk of false negative findings. Having several primary outcomes can be problematic as this risks false positive errors from statistical testing of too many outcomes, so is not recommended (200).

Surprisingly, markers of functional health status, including HRQoL and education, were rarely measured. These findings are noteworthy and have been cited in other systematic reviews such as those examining paediatric asthma (173). Functional outcomes are important in the day to day lives of individuals with CDH. The lack of functional outcome reporting highlights the need for strong networking with patients and families.

Long-term outcomes were less frequently reported. When reported, we noted they were often one-off measurements rather than part of a well-defined follow up plan. For example, in one trial which measured lung spirometry and cardiopulmonary exercise testing in those aged 5-20 years, participants were only tested on one single occasion (189). These observations further highlight the necessity to develop robust consensus policies on CDH follow-up, the importance of which have been alluded to

before (116, 201, 202). Ijsselstijn *et al* have recently proposed a follow up programme for individuals born with congenital anomalies throughout childhood and into early adulthood (203).

In this study we also documented that CDH outcomes were often measured by different methods and at diverse time points. For example, pulmonary hypertension was estimated in three different ways - echocardiography, electrocardiography (ECG), and by clinical examination. Varied data outcome reporting likely means that these individual papers cannot be adequately compared and that their usefulness is therefore limited.

We have shown with the heterogeneity observed between study outcomes, a clear need for patients with CDH to have well-defined a COS. Core outcome sets have been developed for paediatric asthma (204), neonatology (205), and prenatal foetal interventions in CDH (206). We are currently planning to work with CDH UK and the COMET initiative to develop a bespoke core outcome set for postnatal interventions in CDH. This will require the active participation and engagement of stakeholder groups notably health care professional experts, clinicians, researchers, CDH patients, and their families. Other potential groups to support this include Congenital Diaphragmatic Hernia International (CDHi) (77) and the CDH EURO Consortium, a network of health professionals, set up to standardise CDH research, and which has produced multicentre trials such as the 'VICI' ventilation trial (97).

To the best of our knowledge this is the first study to comprehensively investigate health care outcome reporting and the quality of studies of post-natal interventions in CDH.

Although we did not formally investigate selective reporting bias, this could have had important implications. When reading the many publications and comparing outcomes that were measured to those reported we did uncover some evidence of selective reporting bias. For example, various RCTs did not report measurements on clinical vital signs despite specifying these as an outcome measure (110, 187).

The main limitation of our study was that critical analysis of outcomes was hindered by the relatively small number of studies available in CDH. As study authors we believe this is most likely linked to the rarity of the disease, and possibly lack of super-centralisation of care. Centralisation of care may allow high volume centres to become more specialised in treating CDH thereby facilitating robust trials involving larger numbers of CDH patients.

2.5 Conclusion

In complex disease such as CDH there is a need for management strategies to be assessed in robust clinical trials. One key aspect of RCTs are the outcomes which are measured. This paper demonstrated heterogeneity in outcome reporting amongst published trials, meaning comparisons of studies are limited. We also noted a significant lack of reporting of long-term outcomes, including HRQoL. The benefits of long-term follow up in specialist multidisciplinary clinics have been reported (116, 201-203). This study highlights the pressing need for international consensus on outcome reporting, and particularly those related to long-term follow up. We plan to work actively with CDH UK, the COMET initiative, and a stakeholder group of healthcare professionals to develop a robust COS for postnatal interventions in CDH.

One of the key findings from this review was the lack of reporting of outcomes once the infant leaves hospital. A significant contributor to morbidity and mortality during infancy is the risk of RSV bronchiolitis. In Chapter 3 we conduct a systematic review of the risk of RSV bronchiolitis and whether palivizumab (RSV prophylaxis) mitigates this risk.

Chapter 3: Short Term Outcomes In CDH: Respiratory Syncytial Virus Bronchiolitis

3.1 Background

RSV is a cause of Bronchiolitis. This is a common paediatric respiratory infection affecting almost 1/3 of children in their first year of life (207), most commonly those between 3-6 months (208), and often during the winter (209). Bronchiolitis occurs due to 'inflammation of the lining of the epithelial cells of the small airways in the lungs causing mucus production, inflammation and cellular necrosis of those cells' (210).

However, during 2020 and 2021, the usual seasonal pandemics of RSV Bronchiolitis were disrupted (211-214). Like Covid-19, RSV can spread through viral droplet transmission (209, 215). With less social contact due to Covid-19, lower rates of respiratory infection than expected have been described (211-213, 216). A study of 4 Latin American countries showed a 92% reduction in RSV hospital admissions from January to August 2020 (the majority of the respiratory viral season), as compared to 2018/19 (212). A further study showed over a 99% reduction in recorded RSV cases in Belgium between September and December 2020, as compared to the previous three years (211). Another study subsequently showed an 85.9% reduction in RSV admissions between April-June 2020 as compared to 2015-2019 in Sydney, Australia, even with the number of viral tests doubling (213). There may perhaps be a rebound effect here with some Australian states showing higher Bronchiolitis admission rates in the Spring, than are usually seen in Winter (214). With wider human socialisation coming inevitably after Covid-19, it is unclear what will then happen with regards to RSV seasonality and infectivity.

Certain vulnerable infants can be considered 'at risk' of severe Bronchiolitis, requiring hospitalisation. The most 'at-risk' infants may be given palivizumab (RSV prophylaxis), a monoclonal antibody, administered by monthly intramuscular injection. With the potential for a spike in RSV cases once society reopens, there is ongoing controversial debate about whether to extend palivizumab administration to more at-risk infants.

In the UK and Canada palivizumab is currently recommended in children who are born preterm and are <9 months of age in the UK and <12 months in Canada with chronic lung disease, those <6 months of age in the UK and <12 months in Canada with haemodynamically significant acyanotic congenital heart disease, those with severe combined immunodeficiency syndromes, or infants and toddlers requiring long term ventilation up to the age of 2 years, as well as infants living in remote rural communities in Canada (25, 217).

Recent systematic reviews and meta-analyses have highlighted that infants with Down's syndrome (Trisomy 21), a group not previously thought to be at particular risk of RSV bronchiolitis, may be more prone to repeated hospitalisation (218-222). This however does not necessarily imply that palivizumab administration is an effective or cost-effective prophylaxis intervention. That said it may not be immunodeficiency per se that puts Down's babies at high risk of RSV bronchiolitis so firm conclusions on the efficacy of palivizumab administration can only be drawn from robust RCTs.

It is plausible that infants with CDH would also be at potential risk of severe Bronchiolitis. As we discussed in Chapter 1, newborns with CDH have co-associated lung hypoplasia and pulmonary hypertension. It is further estimated that roughly up to 50% of CDH survivors will be still recovering from the adverse effects of aggressive ventilation in the neonatal period (63).

A Spanish two-round Delphi study (223) of 48 expert panellists sought to reach a consensus for palivizumab use in a number of chronic paediatric conditions, including those patients who had undergone surgery for CDH. The study group considered that infants with CDH, for their first two years of life, should receive palivizumab prophylaxis, but this was not based on any systematic review of health care evidence. Given the burden for infants and their families of having five injections in the first RSV season and the health cost implications of doing so, we investigated if any current clinical evidence could reinforce this recommendation. In this study we aimed to systematically explore all the available literature to determine whether infants born with CDH represent an 'at risk' group for severe RSV Bronchiolitis and evaluate the potential benefit of palivizumab prophylaxis.

3.1.1 Aims

(1) To evaluate if CDH infants have a higher risk of hospital admission with RSV Bronchiolitis than infants in the general population

(2) if palivizumab prophylaxis reduces the risk of hospital admission from RSV Bronchiolitis in CDH infants.

3.2 Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (224). A protocol was developed which defined - (I) study objectives, (II) selection criteria, (III) assessment of study quality, (IV) data extraction and (V) analysis.

3.2.1 Search strategy

We searched PubMed and Scopus (a platform for searching multiple databases including EMBASE) from inception to March 2021 using the strategy [('CDH' OR 'Diaphragmatic Hernia') AND ('Bronchiolitis' or 'Respiratory Syncytial Virus')]. The database was last searched on 21/05/2021. Clinicaltrials.gov was searched for ongoing and unpublished studies, as we were concerned about the risk of publication bias, particularly from industry funded studies.

We included observational studies with active or historical controls that investigated the rates of hospital admission with RSV proven bronchiolitis in CDH infants under two years of age, with or without the use of palivizumab. RCTs of palivizumab prophylaxis administration for infants with CDH were also considered eligible for analysis. We excluded studies where bronchiolitis was not caused by RSV pathogens as well as publications where RSV caused a primary infection that was not deemed to be bronchiolitis.

Two authors (LL and IS) screened potential studies based on their title and abstract.

3.2.2 Data extraction, quality assessment and data synthesis

Two authors (LL and IS) extracted data from all eligible studies, including study characteristics and results. Study characteristics comprised of; (a) year of publication, (b) study type, (c) country of publication, (d) single or multi-centre, (e) number and years of RSV bronchiolitis seasons covered, (f) number of CDH index cases.

Study quality was assessed using the Cochrane Risk of Bias Tool for RCTs (225), and the Critical Appraisal Skills Programme (CASP) checklist for cohort studies (226).

Results were reported descriptively and included in meta-analysis where appropriate. The only outcome was the risk of hospitalisation with RSV proven bronchiolitis within 2 years of birth.

We aimed to report studies descriptively and undertook meta-analysis using Forest Plots to synthesise results of studies that were comparable in methodology, inclusion criteria, and outcome. Plans for meta-analysis of RCT findings would be conducted according to Cochrane methods (225).

3.3. Results

3.3.1 Study search and selection

The search of PubMed yielded 35 papers, and SCOPUS yielded 30 papers. A further 4 papers were found through cross-referencing. The search of clinicaltrials.gov found no ongoing trials. There were 30 duplicates, leaving a total of 39 potentially eligible papers. Titles and abstracts of selected papers were assessed in full for eligibility, excluding 29 papers. Ten publications (227-236) remained, from which 7 more papers (227-233) were excluded (see **Table 7** for reasons for exclusion).

We included 3 studies (234-236), all of which were retrospective cohorts. **Figure 14** shows the PRISMA flowchart.

Table 7: List of excluded studies and reasons for exclusion

Reference	Reason for Exclusion
Manzoni *et al* (227)	Incorrect study design (literature review)
Muratore *et al* (228)	Incorrect population (bronchiolitis in those under 3 years) and unclear definition of bronchiolitis
Paes *et al* (229)	Incorrect population (looked at increased rates of RSV, but not in CDH infants)
Cortes *et al* (230)	Incorrect outcome (did not look at RSV bronchiolitis)
Kim *et al* (231)	No appropriate control group
Teo *et al* (232)	No control group and unclear definition of bronchiolitis
Masumoto *et al* (233)	No control group and unclear RSV prophylaxis status

Figure 14: PRISMA flow diagram
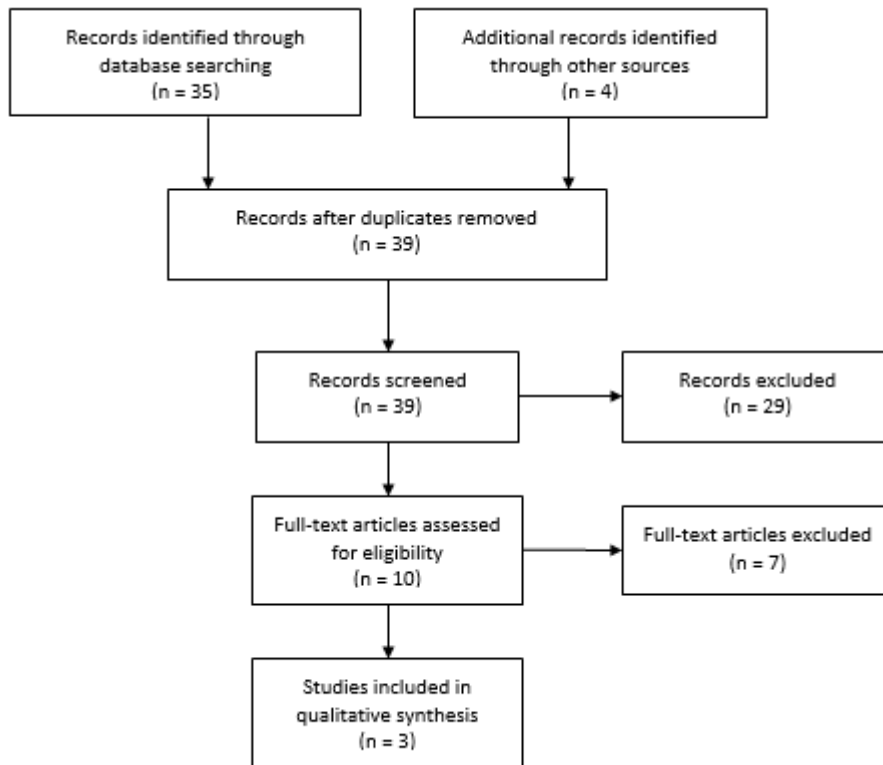
3.3.2 Study characteristics and quality

Study characteristics are shown in **Table 8**. All three papers meeting eligibility criteria were retrospective cohort studies. There were no RCTs comparing evaluating use of palivizumab. Two (234, 236) of the three papers reviewed were multi-centre studies. Studies were published from France and Austria. Papers covered eras of between four and twenty-one complete RSV bronchiolitis seasons. Due to their age at the time of inclusion, some patients were included in multiple seasons.

Assessments of study quality for each included paper are included in **Table 9**. In short, studies were of poor quality. Definitions of control groups, including comorbidity status, were unclear (234). The indications for administration of palivizumab prophylaxis was indeterminant (235, 236). One study was pharmaceutical industry funded (234).

Table 8: Study characteristics

	Fauroux (234)	**Resch (235)**	**Benoist (236)**
Year of publication	2020	2017	2016
Study type	Retrospective cohort	Retrospective cohort	Retrospective cohort
Country	France	Austria	France
Single or multi-centre	Multi	Single	Multi
Number of complete Bronchiolitis seasons	4	21	4
Years covered	2009-2013	1993-2014	2009-2013
Number of infants with CDH	Mean of 267 per season	29	86

Table 9: Quality assessment using CASP checklist for cohort studies

	Fauroux *et al* (234)	Resch *et al* (235)	Benoist *et al* (236)
Did the study address a clearly focused issue?	Yes	Yes	Yes
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes
Was the exposure accurately measured to minimise bias?	Can't tell (no definition for CDH)	No (indication for prophylaxis was indeterminant)	No (indication for prophylaxis was indeterminant)
Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes
Have the authors identified all important confounding factors?	Can't tell (unclear comorbidity status of control group)	Can't tell	Can't tell
Have they taken account of the confounding factors in the design and/or analysis?	Yes	Can't tell	Can't tell
Was the follow up of subjects complete enough?	Yes	Yes	Yes
Was the follow up of subjects long enough?	Yes	Yes	Yes
How precise are the results?	Precise (95% CI's given)	Precise (95% CI's given)	Precise (95% CI's given)
Do you believe the results?	Can't tell (study population not clearly defined)	Can't tell	Can't tell
Can the results be applied to the local population?	Can't tell	Can't tell	Can't tell
Do the results of this study fit with other available evidence?	Can't tell	Yes	Yes
Does the study have implications for practice?	Yes	Yes	Yes

3.3.3 Study results

Rates of RSV Bronchiolitis in infants with CDH compared with the general population

Only one analysis, which was a retrospective cohort study (234), compared the rates of RSV bronchiolitis in CDH with those in the general population. The study authors found that CDH was an independent risk factor for hospitalisation with RSV bronchiolitis (Adjusted Odds Ratio [OR] 2.99, 95% CI 2.01-4.44, p<0.0001; CDH vs non-CDH for RSV hospitalisation).

Two further papers (232, 233) investigated rates of bronchiolitis in CDH infants at their individual centres but neither included a comparison cohort group, so are not included in subsequent analysis. Teo *et al* (232), from Singapore, found the rates of bronchiolitis hospitalisation (not RSV proven) to be 33% (8/24). Masumoto *et al* (233), conducting a study from Japan found the rates of RSV bronchiolitis hospitalisation to be 14% (3/21).

Use of palivizumab in infants with CDH

Two papers (235, 236) examined use of palivizumab prophylaxis in CDH. In these two retrospective cohort studies, the rates of RSV bronchiolitis were compared between CDH infants with and without palivizumab prophylaxis. Resch *et al* (235) found that 2/20 (10%) of infants with prophylaxis and 0/9 (0%) of infants without had proven RSV hospitalisation over two seasons. Benoist *et al* (236) noted 2/33 (6%) of infants with prophylaxis and 5/53 (9%) of cases without prophylaxis were hospitalised with RSV. The pooled RR was 1.11 (95% CI 0.29-4.23, p=0.88) (**Figure 15**).

Figure 15: Forest plot from two cohort studies showing risk of RSV bronchiolitis in CDH infants with and without palivizumab prophylaxis.
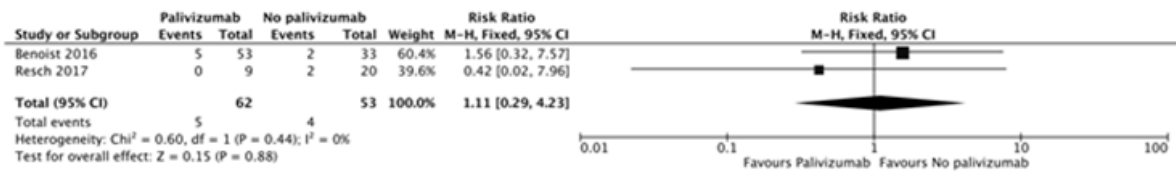
CDH: Congenital Diaphragmatic Hernia, CI: Confidence interval

3.4 Discussion

This study shows that there is limited quality evidence available with regards to the rate of RSV bronchiolitis and use of palivizumab prophylaxis in CDH. Only a single paper directly compared rates of RSV hospitalisation to that of the general population, for which comorbidity status was unclear (234). The study authors (industry funded) found that CDH was an independent risk factor for RSV hospital admission.

Two papers compared the rates of RSV hospitalisation in infants with CDH with and without prophylaxis (235, 236). On the basis of very low-quality evidence, there is no indicator currently that palivizumab is beneficial for infants with CDH.

The publications included were limited by their study design. The fact the studies were observational, rather than RCTs, left the studies open to bias (237). Various RCTs have not confirmed the efficacy of treatment when compared to corresponding observational studies (238, 239). In particular, the presence of confounding variables brought difficulty here. The infants were not treated at random, yet the studies gave no indication as to why individual infants were administered palivizumab. The definitions of control groups was also vague. In particular study authors did not specify the comorbid status of controls, and again why they had received palivizumab. We excluded a number of papers on the basis of their population and definition of bronchiolitis. If outcomes had been measured in a standardised way, we may have been able to draw firmer conclusions from the literature. A bronchiolitis core outcome set would greatly help to standardise outcome reporting in any future trials.

This, to our knowledge, is the first systematic review addressing whether infants with CDH are at higher risk of acquiring severe RSV bronchiolitis, and whether palivizumab administration may mitigate this risk. The findings from this systematic review were somewhat limited by the poor quality of included published studies. We identified no eligible RCTs – either completed or in progress – addressing this question.

As previously mentioned, a Spanish Delphi study (223) of 48 expert panellists made effort to reach a consensus on the recommendations for palivizumab prophylaxis in CDH infants. They did however stress the need for further clinical trials. Such trials, as well as varied meta-analyses, have found infants with Down's syndrome (Trisomy 21), a group not previously considered to have an increased probability of acquiring RSV infection (218-222).

We elected *a priori* to measure only one outcome i.e. hospitalisation with RSV bronchiolitis, as this is the key focus of much discussion around the benefits and cost-effectiveness of palivizumab administration. Future research should therefore focus on outcomes that are of high relevance to children, families, clinicians, and policymakers. Decisions around palivizumab prophylaxis should be made in an informed and shared process. Currently, we can only advise parents of babies born with CDH that there is an absence of meaningful evidence with regard to palivizumab prophylaxis. Infants with CDH who require home supplemental oxygen therapy, those born prematurely, and survivors with significant pulmonary hypertension may in theory represent a subgroup of high-risk patients at particular risk of severe RSV bronchiolitis.

Larger cohort studies scrutinizing bronchiolitis risk in CDH survivors are needed. Well-designed multicentre RCTs should seek to address the effectiveness and cost value of palivizumab. Outcomes from future trials if undertaken should be standardised and relevant to parents. Furthermore, a bronchiolitis core outcome set would be helpful.

To this end, it is large scale RCTs that have demonstrated palivizumab is effective and protective in preterm babies (240). CDH patients and families require the same RCTs to be rigorously designed to reach valid conclusions on the potential health benefits of RSV prophylaxis.

3.5 Conclusions

On the basis of current evidence, it is uncertain whether CDH infants are at particular risk of severe

RSV bronchiolitis. At time of writing there is no compelling data available that CDH patients should

routinely receive palivizumab.

In this chapter we examined evidence around one short-term outcome in CDH. In the next chapter

we look at the evidence for other outcomes that are important to children with CDH and their

families. Chapter 4 focuses on cardiopulmonary outcomes and HRQoL, as discussed in Chapter 1,

these may present long-term problems for individuals with CDH.

Chapter 4: Long Term Outcomes in CDH: Cardiopulmonary Outcomes and Health Related Quality of Life

4.1 Background

Improvements in management over the past two decades have led to an increase in the number of survivors with CDH. Infants that do survive to hospital discharge may be left with complex health problems affecting many aspects of their HRQoL. These complications can be cardiopulmonary, neurological, or gastrointestinal in nature. It is well reported that CDH is linked with developmental insults including lung hypoplasia and pulmonary hypertension (63, 241), and is also associated with extrapulmonary cardiac anomalies (62, 242, 243). There is, however, less research into long-term complications in childhood and adulthood caused by CDH. This would be important to know and understand, so that parents of CDH survivors can take measures to better recognise and/or prevent sequelae. Healthcare professionals should be increasingly aware of CDH co-morbidities, and surveillance follow-up programmes in bespoke speciality centres should incorporate elements of multispecialty care.

To the best of our knowledge, there are currently no systematic reviews focusing specifically on long-term cardiopulmonary outcomes in CDH. Therefore, we aimed to study and comprehensively review the prevalence of long-term cardiopulmonary outcomes in CDH survivors over 2 years of age.

4.1.1 Aims

1) To investigate the prevalence of adverse cardiopulmonary outcomes in survivors with CDH over 2 years of age

2) To determine risk factors for cardiopulmonary morbidity and poor HRQoL in survivors with CDH

4.2 Methods

As with the reviews in Chapters 2 and 3, this systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (175). A PROSPERO protocol was developed and published (PROSPERO ID CRD42021254998) which defined – (I) study objectives, (II) search strategy, (III) assessment of study quality, (IV) data extraction and (V) analysis.

4.2.1 Search strategy

We searched Pubmed and SCOPUS, a platform for searching multiple databases, using the search '(congenital diaphragmatic hernia OR CDH) AND (Outcome* OR Sequelae OR follow-up OR long-term OR survivors) AND (Cardio* OR Pulmonary OR Respiratory OR Exercise OR Quality of life)'. CENTRAL was also searched using the heading term 'congenital diaphragmatic hernia'. Databases were last searched on 14/05/2021.

We examined potential studies based on title and abstract. The selected studies were then read in full to screen for eligibility.

Studies were included if they were published in the last 30 years and specifically investigated long term cardiopulmonary outcomes in CDH patients over 2 years of age. We chose not to review papers before the last 30 years due to a shift towards 'gentle' ventilation and delayed surgery at that time. We included large cohort studies of individuals with pulmonary hypertension or those on ECMO for various indications if CDH patients were evaluated as a separate group.

We excluded studies not in the English language.

4.2.2 Data extraction, quality assessment and data synthesis

Data from selected eligible studies were extracted by the study authors. Extracted data included study characteristics and results.

From each study we extracted the following characteristics: (a) study design, (b) single or multi-centre study, (c) country of study, (d) number of patients, and € age of patients.

The study results of relevance to this review related to:

(i) Prevalence of adverse cardiopulmonary outcomes in CDH

(ii) Risk factors for adverse cardiopulmonary outcomes and HRQoL in CDH

Adverse cardiopulmonary outcomes

(a) Indices of lung function

Basic spirometry is often used by clinicians, but more complex areas of lung function include plethysmography and exhaled nitric oxide. We extracted absolute measurements e.g. litres or % predicted values, and Z scores (which are a marker of results in comparison to the normal population)

- **Forced Expiratory Volume in the first second (FEV1)** – this is a measure of the size of airways

- **Forced vital capacity (FVC)** – this is a marker of overall lung capacity

- **FEV1/FVC ratio** – this is a marker of airway obstruction

- **Full body plethysmography** – this is a test only used in specialist tertiary centres as a way of evaluating alveolar volume and total lung volume

- **Exhaled nitric oxide** – a marker of airway inflammation

(b) Pulmonary hypertension (PHT)

There are various direct and indirect methods of diagnosing PHT. This may be clinical by ECG monitoring (however this is nonspecific), by echocardiography (which is non-invasive), and catheterisation (an invasive technique undertaken in select patients under general anaesthesia). Right ventricular function gives an indication of the work over time of the right ventricle distributing blood to the pulmonary vasculature.

- **Prevalence of PHT** – either by echocardiogram (Tricuspid Regurgitation>2.8m/s), direct catheter pressure (mean Pulmonary Artery pressure >25mmHg), or ECG)

If PHT was present we looked specifically at:

- **Severity of PHT** – mild/moderate/severe (by echocardiogram or catheter)

- **Right Ventricle function** – normal or mild/ moderate/ severe impairment

- **Use of PHT medications**

- **Death related to pulmonary hypertension**

(c) Risk of asthma, emphysema, COPD

(d) Functional outcomes

- **Exercise tolerance and breathlessness** – including a 6-minute walk test or a cardiopulmonary exercise test

- **Health Related Quality of life (HRQoL)**

(e) Radiological outcomes

- **Chronic changes on Chest X-ray, CT scan, or MRI**

4.2.3 Study quality

The primary author (LL) assessed study quality based primarily on study design and whether the recruitment of study participants was considered adequate. The Newcastle-Ottawa Scale (244) was then used to quality assess case-control studies. Cohort studies were quality assessed using the CASP checklist for cohort studies (226). Any studies with a high risk of bias were excluded.

4.2.4 Result analysis

Results are reported descriptively and where possible we tried to collate results by different age groups (2-4, 5-12, 13-18, over 18 years).

4.3 Results

4.3.1 Study search and selection

The search of PubMed yielded 838 results, Scopus yielded 928, CENTRAL yielded 168 papers, and 7 were found from additional sources, totalling 1941 papers. After removal of 507 duplicates, 1434 papers were further screened. Titles and abstracts were assessed in full for eligibility, excluding 1333 papers. The remaining 101 publications were independently read in full by two authors (LL and IS), and a further 37 papers excluded, see **Table 10** for reasons for exclusion.

64 papers were included, 23 case control studies in the main analysis, as the best level of evidence available. A further 41 cohort studies were included in additional analysis. **Figure 16** shows the PRISMA flowchart for the study review.

Table 10: Reason for study exclusion

Paper	Reason for exclusion
Arena *et al* (245)	Duplicate
Bagolan & Morini (157)	Literature review
Cashen *et al* (246)	CDH not analysed as a separate cohort to ECMO patients
Chiu & Hedrick (247)	Literature review
Cortes *et al* (230)	Patients too young at follow-up (average age <2 years)
Delacourt *et al* (248)	Literature review
Glinianaia *et al* (249)	Systematic review
Hamutchu *et al* (250)	CDH not analysed as a separate cohort
Hollinger & Buchmiller (251)	Literature review
Hollinger *et al* (252)	Literature review
Huddy *et al* (253)	No age at follow up
Iguchi *et al* (254)	CDH not analysed as a separate cohort to ECMO patients
Ijsselstijn & van Heijst (255)	Literature review
Ijsselstijn *et al* (256)	Literature review
Kassner *et al* (257)	Incorrect outcomes analysed (not cardiorespiratory)
Kattan (258)	Literature review
Lally & Engle (259)	Literature review
Leeuwen & Fitzgerald (260)	Literature review
Lund *et al* (261)	Incorrect outcomes analysed (not cardiorespiratory)
Mansell (262)	Literature review
Matina *et al* (263)	Literature review
Matina *et al* (263)	Literature review
Morini *et al* (264)	Literature review
Mota *et al* (265)	CDH not analysed as a separate cohort to pulmonary hypertension patients
Mugford *et al* (101)	Systematic review
Nobuhara *et al* (43)	Incorrect outcomes analysed (not cardiorespiratory) and patients too young at follow-up
Peetsold *et al* (241)	Literature review
Prendergast *et al* (266)	Patients too young at follow-up (average age <2 years)
Safavi *et al* (267)	No age at follow up
Suda *et al* (268)	No age at follow up
Van den Hout *et al* (269)	Literature review
van der Cammen-van Zijp *et al* (270)	Duplicate
van der Cammen-van Zijp *et al* (271)	Duplicate
Vanamo *et al* (272)	CDH not analysed as a separate cohort
West & Wilson (273)	Literature review
Zach & Eber (274)	Literature review
Zollner *et al* (256)	Incorrect outcomes analysed (not cardiorespiratory)

Figure 16: PRISMA flowchart
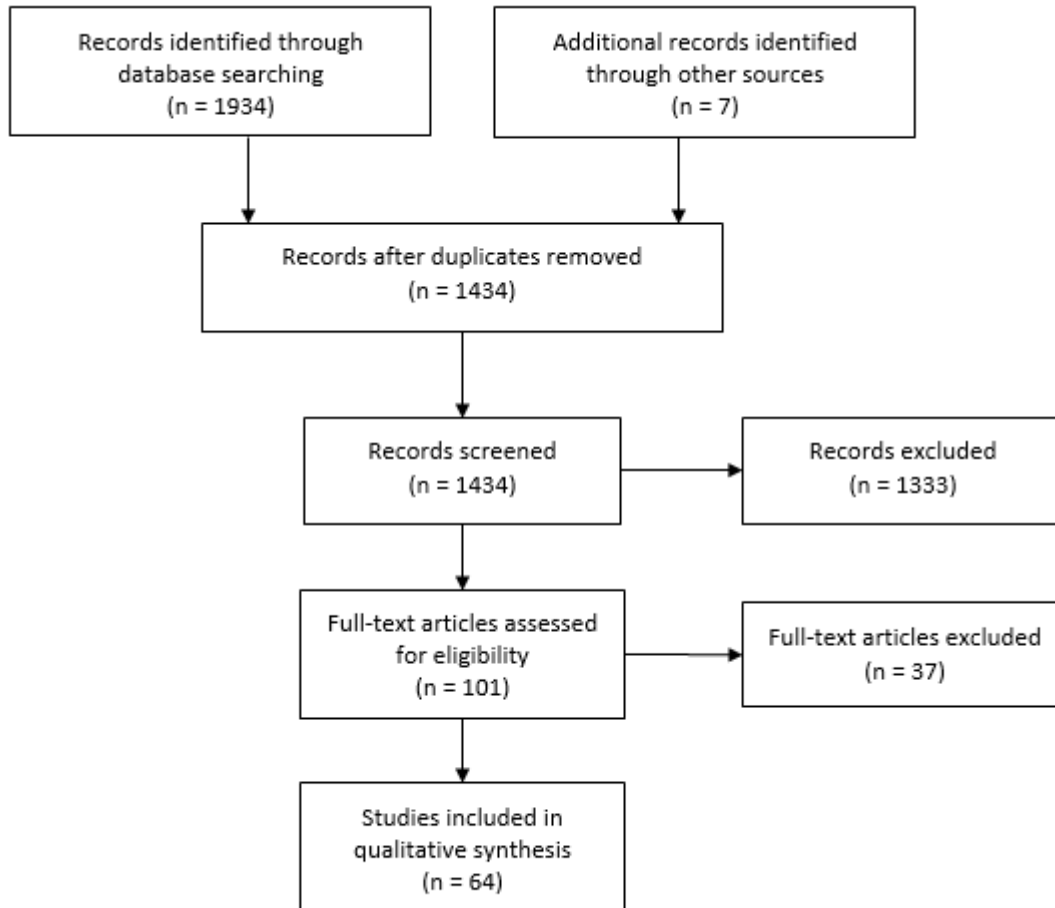
4.3.2 Study characteristics

There were 64 studies, which overall included 3128 individuals with CDH. The mean number of participants with CDH were 49 per publication (range 7-251). All studies were observational (23 case control and 41 cohort). 53 were single-centre studies and 11 were multi-centre. Studies were conducted in various countries including those in the UK, Europe, USA, Canada, Asia, Africa, and Australia. CDH patient age ranged from 0-42 years, though the mean or median age in each study was above 2 years.

4.3.3 Study Quality

Case control study quality (assessed using the Newcastle Ottawa Scale(244)) is shown in **Table 11**. Cohort study quality (assessed using the CASP checklist for cohort studies (226)) is shown in **Table 12**.

Study quality was adequate. Outcomes were often measured accurately, papers investigating spirometry data almost always followed the American Thoracic Society (ATS) or European Respiratory Society (ERS) guidelines, and the majority of papers investigating pulmonary hypertension used echocardiogram for this. However, very few papers reported results with corresponding confidence intervals. 20/64 (31%) studies were retrospective rather than prospective. Retrospective studies are less likely to have predetermined objectives and standardised outcomes and are more susceptible to having confounding variables. Not all relevant confounding factors were considered in these papers. Many papers identified gestational age as a confounding factor, but not exposure to second-hand smoke, family history of cardiorespiratory disease, or socioeconomic factors.

4.3.4 Study results

Indices of lung function

Spirometry results - FEV1, FVC, and FEV1/FVC ratio

Spirometry results are shown in **Table 13**. As also found in study I, outcomes were often reported in different ways. This heterogeneity limited the comparisons we could make between spirometry results.

Figure 17 is a graph showing mean FEV1 (percent predicted) in children over 5 years of age. Due to difficulties in spirometry testing, results were only reported in children over 5 years of age.

Table 11: Newcastle-Ottowa study quality scale

Study	Total score /9	Selection /4	Comparability/2	Exposure/3
Abolmaali *et al* **(275)**	7	3	2	2
Arena *et al* **(276)**	5	2	1	2
Bojanic *et al* **2016(189)**	7	3	2	2
Bojanic *et al* **2018(277)**	6	3	1	2
Egan *et al* **(278)**	3	1	1	1
Ijjsselstijn *et al* **(279)**	6	2	2	2
Kamata *et al* **(280)**	4	3	0	1
Koh *et al* **(281)**	5	2	2	1
Koivusalo *et al* **(282)**	5	2	2	1
Laviola *et al* **(283)**	6	3	1	2
Levesque *et al* **(284)**	7	4	1	2
Marven *et al* **(285)**	6	4	2	0
Michel *et al* **(286)**	7	4	2	1
Peetsold *et al* **(241)**	7	4	2	1
Poley *et al* **(287)**	3	3	0	0
Schwartz *et al* **(288)**	6	3	1	2
Spoel *et al* **(289)**	6	2	2	2
Stoll-Dannenhauer *et al* **(290)**	5	2	1	2
Tan *et al* **(291)**	6	3	2	1
Trachsel *et al* **2005(292)**	8	4	2	2
Trachsel *et al* **(293)**	8	4	2	2
Zaccara (294)	5	3	1	1

Table 12: Quality assessment using CASP checklist for cohort studies (295)

Paper	Clearly focused issue?	Cohort recruited in an acceptable way?	Exposure accurately measured to minimise bias?	Outcome accurately measured to minimise bias?	Identified all confounding factors?	Taken account of confounding factors in design or analysis?	Follow up complete enough?	Follow up long enough?	Are the results precise?	Do you believe the results?	Can results be applied to local population?	Do the results fit with other available evidence?	Does the study have implications for practice?
Ali *et al* (296)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Amin *et al* (297)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Bojanic *et al* (298)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Cauley *et al* (299)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Chen *et al* (201)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Chiu *et al* (300)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Crankson *et al* (301)	Can't tell	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Dao *et al* (302)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Davis *et al* (99)	Can't tell	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Engle *et al* (303)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Ferrante *et al* (304)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Fritz *et al* (305)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes

Study													
Garcia *et al* (306)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Gischler *et al* (307)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Gray *et al* (308)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Haliburton *et al* (309)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Hayward *et al* (310)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kamata *et al* (311)	Can't tell	Yes	Yes	Yes	No	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Khirani *et al* (312)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
King *et al* (313)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Majaesic *et al* (314)	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Mesas Burgos *et al* (315)	Yes	Yes	Yes	Can't tell	No	No	Yes	Yes	N/A	Yes	Yes	Yes	Yes
Moawd *et al* (181)	Yes	Yes	Yes	Can't tell	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Morsberger *et al* (316)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Muratore *et al* (228)	Yes	Yes	Yes	Can't tell	No	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Ost *et al* (317)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Pal & Gupta (318)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Peetsold *et al* (319)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Peetsold *et al* (320)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes

Rocha *et al* (321)	Yes	Yes	Yes	Can't tell	No	No	Yes	Yes	N/A	Yes	Yes	Yes	Yes
Safavi *et al* (267)	Yes	Yes	Yes	Can't tell	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Sheikh *et al* (322)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shieh *et al* (323)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	N/A	Yes	Yes	Yes	Yes
Spoel *et al* (324)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Spoel *et al* (325)	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Stefanutti *et al* (326)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Toussaint-Duyster *et al* (327)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Turchetta *et al* (199)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Valfre *et al* (328)	Yes	Yes	Yes	Can't tell	No	No	Yes	Yes	N/A	Yes	Yes	Yes	Yes
Van Meurs *et al* (329)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	N/A	Yes	Yes	Yes	Yes
Weber *et al* (330)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	N/A	Yes	Yes	Yes	Yes
Weidner *et al* (331)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Wong *et al* (332)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes

Table 13: Spirometry results in CDH patients before bronchodilation therapy

Study	Age of Patients (years) mean (median) ± SD (range)	Spirometric values /mean ± SD (range)			% predicted /mean ± SD (range)			Z score /mean ± SD (range)			SD score /mean ± SD (range)		
		FEV1	FVC	FEV1/FVC	FEV1	FVC	FEV1/FVC	FEV1	FVC	FEV1/FVC	FEV1	FVC	FEV1/FVC
Children (5-12 years)													
Spoel *et al* (324)	5										-0.71 ± 0.40	-0.69 ± 0.43	0.11 ± 0.35
Gischler *et al* (272)	5				91 (72-122)								
Koh *et al* (281)	6.2 ± 0.2	1.1 ± 0.05	1.2 ± 0.1		90.7 ± 2.7	91.2 ± 2.6	91.1 ± 1.3						
Turchetta *et al* (199)	6.6 ± 2.6				78.7 ± 19.3	75.5 ± 15							
Spoel *et al* (324)	8										-2.27 ± 0.36	-1.48 ± 0.35	-1.47 ± 0.39
Majaesic *et al* (314)	8				63 ± 18	72 ±18	80 ± 14						
Stefanutti *et al* (326)	8.15 ± 2.80				89.77 ± 16.33	88.23 ± 16.11	91.10 ±6.44						
Bojanic *et al* 2016 (189)	8.2 ± 5.7	2.33 ± 1.05	2.66 ± 1.19	0.89 ± 0.09	91.6 ± 20.1	91.2 ± 19.4							
Moawd *et al* (181)	(9-11)				72.3 ± 8.5	78.5 ± 9.8							
Tan *et al* (291)	10 (4-22)							-1.49 ± 1.99	0.26 ± 1.81	-1.92 ±0.87			
Zaccara *et al* (279)	11.25 (6-19)				86 ± 13	90 ± 15							
Haliburton *et al* (309)	11.3 ± 3.4							-2.21 ± 1.68	-1.32 ± 1.39	-1.78 ±0.73			
Marven *et al* (285)	11.5 (7.3-16.9)				78.7 (72.5-84.8)	84.7 (78.8-90.6)							
Ijsselstijn *et al* (279)	(11.7) (7-18)				89 ± 3		77 ± 2						
Peetsold *et al* (333)	11.9 ± 3.5							-1.63 ± 1.78 (-7.14-1.45)	-1.28 ± 1.62 (-6.33-1.93)	-0.84 ± 1.27 (-4.03-1.07)			
Spoel *et al* (324)	12										-2.73 ± 0.61	-1.28 ± 0.98	-2.16 ± 0.30
Spoel *et al* (289)	11.8 ±2.6										-0.8 ± 1.2	-0.4 ± 1.0	-0.6 ± 1.2
Adolescents (13-17 years)													
Trachsel *et al* (292)	13.2 (10.2-16.9)				79 ± 16	85 ± 14	78 ±10						
Adults (>18 years)													
Peetsold *et al* (319)	24.3 ± 4.1							-1.30 ±1.37	-0.84 ± 1.52	-0.80 ±1.34			
Spoe *et al* (289)	26.8 ± 2.9										-1.3 ± 1.4	-0.7 ± 1.2	-0.9 ± 1.2
Spoel *et al* (325)	28.4 (18.1-31.0)										-1.47 ± 0.96		

Figure 17: Mean and standard deviation (where available) of FEV1 percent predicted in children over 5 years with CDH
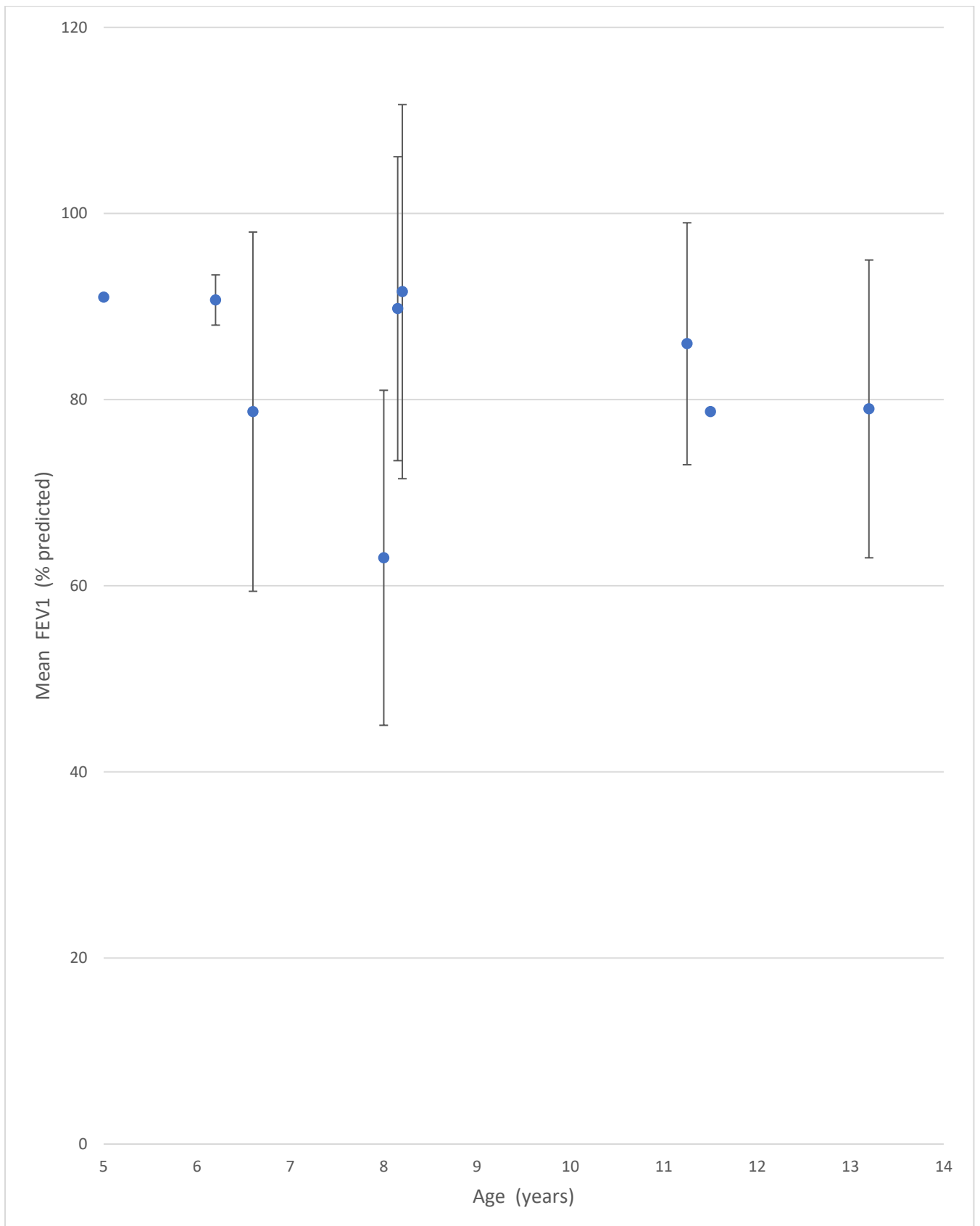
Spirometry results in CDH cases vs controls

Seven papers compared spirometry results between CDH patients and healthy controls (281, 285, 289, 291, 292, 324, 333).

5 studies had a mean participant age of between 5 and 12 years (children) and found FEV1 to be reduced in CDH vs controls in 4/5 studies (281, 285, 291, 333), FVC in 3/5 studies 264)(285, 333) and FEV1/FVC in 2/3 studies (291, 333) (p<0.05).

A single paper (292) had a mean participant age between 13 and 18 years (adolescents) and found FVC, FEV1, and FEV1/FVC to all be significantly reduced in CDH vs controls (p<0.05).

One paper (289) found FEV1/FVC to be significantly reduced in adults with CDH vs controls (p<0.05). FEV1 and FVC were not significantly different between CDH and controls (p>0.05).

Full body plethysmography

Ijsselstijn *et al* (279) reported CDH patients to have a significantly higher residual volume and residual volume/total lung capacity vs. control patients (p=0.001 and 0.006) at a mean age of 11.7 (range 7-18) years.

Laviola *et al* (283) found tidal volume was significantly lower in CDH patients compared to healthy controls (p<0.05) both with patch and primary repair. This was however not the case when tidal volume was normalised to weight. Air trapping was not significantly different between CDH vs. controls.

Spoel *et al* (289) found that TLC, Residual Volume (RV), and Functional Residual Capacity (FRC) were not significantly different in CDH vs controls (p=0.977, p=0.071 and p=0.960 respectively).

Spoel *et al* (325) found mean standard deviation (SD) score for total lung capacity (TLC) to be -0.21 (1.61), and RV%TLC to be 25.3 (4.48). This was not compared to a control group.

Spoel *et al* (324) reported that 12/14 (86%) CDH patients had a significant volume of air trapping (FRC plethysmography / spirometry >1.10) on body plethysmography at age 8 and 12 years.

Exhaled nitric oxide

Gischler *et al* (307) reported the median fraction of exhaled Nitric Oxide (FENO) in CDH patients to be in the low range of normative values (median 5.2 (range, 2.8-10.0)).

Risk factors for reduced indices of lung function

Factors associated with reduced PFTs included:

(i) diaphragm defect size - CDH International Study Group - Grades C and D (302)

(ii) smaller head size or abdominal circumference at birth (281)

(iii) a lower BMI (309)

(iv) gastro-oesophageal reflux disease (333)

(v) duration of ventilation (279, 326, 333)

(vi) oxygen use at hospital discharge (302)

(vii) lower total lung volume(s) (281)

(ix) the ventilated volume of the ipsilateral lung to the diaphragmatic defect (325)

Factors not proven to be significantly associated with reduced PFTs:

(a) sedentary vs active patients (189, 199)

(b) gestational age (279)

(c) birth weight (279)

(d) parental smoking (279)

(e) neonatal factors including highest peak inspiratory pressure, highest Partial pressure of carbon dioxide (paCo2), APGAR score at 5 mins (292) maximum fraction inspired oxygen (FiO2) (279)

(f) ECMO use (302)

(g) left sided CDH defect (302)

(h) respiratory muscle training (181)

(I) primary vs patch diaphragm repair (328)

Pulmonary hypertension

Thirteen studies (189, 267, 275, 278, 288, 291, 306, 315, 321, 323, 326, 329, 332) investigated pulmonary hypertension in CDH survivors. Six of which were case control studies, six were retrospective cohort studies, and one was a prospective cohort study. Patient age ranged from 4 months to 26 years.

Prevalence of Pulmonary hypertension

Eleven studies investigated the prevalence of pulmonary hypertension in CDH. Five studies had a mean or median participant age of between 2-5 years (pre-school), five papers had a mean or median participant age of between 5-13 years (children), one paper reported on PHT in both pre-schoolers and children. No papers focused exclusively on adolescents or adults with PHT.

Pulmonary hypertension in pre-schoolers with CDH

Six papers reported prevalence of PHT in participants with CDH where the average age was between 2 and 5 years (preschool). All six papers used echocardiography to diagnose PHT. Rates of pulmonary hypertension ranged from 4.5% to 38% (267, 288, 306, 321, 323, 329).

Pulmonary hypertension in children with CDH

Six papers investigated prevalence of PHT in children with CDH. Four studies used exclusively echocardiography for diagnosis (189, 278, 291, 326), one study used both echocardiogram and ECG (275), and a single study did not specify their method of diagnosis for PHT (321). No studies with an average participant age of over 5 years reported any incidences of PHT, despite one study reporting 33% of CDH neonates having PHT (189) and another reporting 5.1% of preschool aged children having PHT (321).

Pulmonary hypertension in adolescents and adults with CDH

There were no reports of PHT in adolescents or adults with CDH.

Severity of Pulmonary hypertension

A single paper documented PHT as 'severe' in two preschool aged children with CDH, though did not provide a clear definition with regard to severity (267).

Right ventricle function

Pulmonary hypertension can result in varying severity and degrees of right ventricle dysfunction. Five studies investigated right ventricle function.

From Doppler imaging Egan *et al* (278) showed a significant reduction in systolic (s') and early diastolic wave (e') velocities in children with CDH, indicating a degree of right ventricle impairment, compared to controls ($p < 0.01$ and $p = 0.02$ respectively) . Right ventricle strain values were not significantly different between CDH survivors and controls ($p > 0.05$).

Schwartz *et al* (288) and Van Meurs *et al* (329) reported right ventricular hypertrophy and right axis deviation from ECG studies in preschool aged patients. Schwartz *et al* reported 6/21 (29%) of patients had either right axis deviation or right ventricular hypertrophy, 2 of which also had PHT. Van Meurs *et al* reported 6/18 (33%) patients had evidence of right ventricular hypertrophy, four of whom (4/18 22%) also had right axis deviation.

Stefanutti *et al* (326) estimated right ventricle systolic pressure (RVsp) in children with CDH (mean age ± SD, 8.15 years ± 2.80), and found these values to be normal. Values ranged from 20 to 30 mmHg (mean SD 24.43 ± 3.57 mm Hg). These were not compared to systolic blood pressure, but an RVsp of less than 30mmHg was considered normal.

Wong *et al* (332) also deployed echocardiography to monitor right ventricular systolic pressure (RVsp) in preschool aged patients. Mean RVsp was between 25 and 30 mmHg (read from graph) though again this was not compared to mean systolic blood pressure or left ventricular pressure.

Use of pulmonary hypertension medications

Three papers reported pharmacologic use of PHT medications. All three papers reported that all CDH study participants with PHT required pulmonary vasodilator therapies, such as sildenafil (either inhaled or intravenously through a central venous line) (267, 306, 323).

Reports of late death from pulmonary hypertension

A single paper (315) reported a late death from pulmonary hypertension in a child with CDH aged 9 years.

Risk factors for PHT

The only associated factor linked with presence of pulmonary hypertension (defined as raised RVsp) were CDH infants defined as 'high risk' CDH. High risk was defined as O/E LHR ≤ 45%. High risk CDH survivors had persistently higher right ventricular systolic pressures on serial echocardiography at 2-5 years old compared to 'low risk' CDH survivors (p<0.05) (332).

Garcia *et al* (306), however, found LHR not to be associated with presence of PHT (p=0.54).

A further study by Shieh *et al* (323) showed that CDH patients who underwent EXIT to have higher rates of PHT requiring sildenafil, though this was not statistically significant (0/8 vs 2/9 p=0.16).

Asthma, Emphysema, COPD

Asthma

Eight case control papers (277, 278, 282, 284, 285, 289, 291) investigated asthma diagnosis, symptoms, or medication use in CDH survivors. Results were mixed - publications found rates of asthma, symptoms, or medication use to be both significant (282, 284, 289, 291) and not significant (279, 284, 289, 291) when compared to aged matched controls. Often the amount of scattered data reported here was too small to draw firm conclusions (277, 278, 285).

14/15 cohort studies that investigated rates of asthma reported cases of asthma or asthma medication use in CDH survivors (99, 296, 298-301, 303, 307, 311, 316, 318, 321, 323, 328, 330). This was found to be associated with pulmonary support on day 30 of life, lower birthweight, and lower gestational age (284, 299).

Emphysema and COPD

There were no reports of emphysema or COPD documented in CDH survivors or controls though it is likely that patients were too young at point of publication of these studies to accurately reflect these factors.

Cardiopulmonary exercise testing (CPET)

Eight studies described using CPET for CDH survivor follow-up. All four case control studies found CPET to be reduced in CDH survivors compared to controls (p<0.05) (189, 285, 293, 334). A further four cohort studies found abnormal CPET parameters in CDH patients (199, 307, 319, 327). There were significant differences noted in CPET between CDH survivors who were considered athletic and those who were sedentary (p<0.05) (189, 199, 334). Of interest CDH survivors often perceived their own fitness to be worse than their healthy counterparts (285).

Risk factors for reduced CPET results

Predictors for worse CPET results were (i) a reduced FEV1 (293), (ii) a higher residual volume/total lung capacity value (293), (iii) diffusion capacity corrected for alveolar volume (Kco) (327), (iv) ECMO use (327) (v) duration of hospital stay (327), (vi) parent's estimation of their child's exercise capacity (327), and (vii) those CDH index cases who were considered sedentary rather than athletic (189, 285, 294). Duration of neonatal ventilation was not found to be significantly associated with CPET results (189).

Health Related Quality of Life

Four case control studies reported on HRQoL of which, all found HRQoL to be reduced in CDH survivors compared to healthy controls (277, 286, 287, 291). Ten cohort studies also examined HRQoL. Six out of ten found health related quality of life (201, 316, 317, 320, 335, 336) to be reduced in CDH survivors.

Risk factors for reduced HRQoL

Risk factors associated with reduced HRQoL included (i) oxygen dependence on day 30 of life (322), (ii) hospital length of stay (320), (iii) lack of prenatal diagnosis (305), (iv) those with ongoing medical morbidity (201, 287), particularly respiratory symptoms (277, 286), (v) primary diaphragm defect repair, (335) (vi) supplemental feeds (335) and (vii) neonatal ECMO use (317).

Thoracoscopic (MIS) CDH repair was associated with a higher median HRQoL score (316). Patient age was associated with both a better and a worse HRQoL (316, 317).

Risk factors found to be not significantly associated with reduced HRQoL included (a) prematurity (297), (b) prolonged hospital length of stay (297), (c) Oxygen requirement at primary hospital discharge (297), (d) use of neonatal ECMO (201, 322), (e) cardiac problems (201), (f) genetic abnormalities (201), (g) disease severity (322), and (h) prenatal imaging values (322).

Radiological outcomes

Diaphragmatic radiology

Diaphragmatic growth (280) and markers of diaphragmatic strength were reduced in CDH survivors compared to controls (276) (p<0.05). Another study found diaphragmatic dysfunction to be present in CDH survivors (312).

Chest CT Imaging

Three studies examined and reported Chest CT in CDH survivors, two of which showed abnormalities. These imaging findings included 'subpleural triangular opacities, architectural lung distortion, and linear lung opacities' (291) as well as 'flat costo-phrenic angles, peripheral opaque spikes of consolidation, lung hyperlucency, and mediastinal shift' (326).

Lung perfusion

Three studies described measurement of lung perfusion (318, 331, 332) and found this to be reduced in CDH patients. A single study found ipsilateral mean lung density to be reduced compared to controls (p=0.0005) (337). V/Q mismatch or ventilation abnormalities were present in all three CDH studies where investigated (228, 310, 311, 313, 325, 337).

Risk factors for abnormal radiology

Markers of abnormal radiology evident in CDH survivors included: (i) those who had a diaphragm patch repair (310, 311, 318) (ii) ECMO or HFOV use (228, 310, 311), (iii) individuals with frequent respiratory tract infections (311), (iv) index cases with right sided CDH defects (311), and (v) those on pulmonary support at day 30 of life (299). Kamata *et al,* however, found patch repair to not be correlated with abnormal radiology findings (280). Wong *et al* found lung perfusion did not significantly differ between high and low risk patients (332).

4.4 Discussion

Our primary outcome was to investigate risk of adverse cardiopulmonary outcomes and HRQoL.

We noted that indices of lung function were often abnormal. Analysis, however, was hampered due to the varied methods of reporting spirometry results.

The incidence of pulmonary hypertension was highly variable, likely due to non-standardised diagnostic criteria utilised for establishing PHT between the individual studies and variances in diagnostic modalities i.e. ECG/Echocardiogram. Rates of PHT appeared higher in preschool aged children than children over 5 years of age, indicating a possibility that PHT may improve with age. There were eight recorded cases of late death in those <2 years of age, 5 of which were attributed to respiratory causes (99, 301, 315), one of which was due to persistent pulmonary hypertension (315).

Radiological outcomes were often abnormal, and CPET and HRQoL results were frequently reduced. Findings regarding asthma diagnosis or medication use showed mixed results from case-controlled studies, though were well reported by the cohort studies. There were no definitive reports describing emphysema or COPD.

Our secondary outcome was to investigate risk factors for cardiopulmonary morbidity in CDH survivors. It is clear that further prospective multicentre studies on risk factors for cardiorespiratory morbidity in CDH survivors are vital. Additional research into other long-term health sequalae, such as neurological morbidity and failure to thrive, in CDH survivors are also needed.

The main limitation of our study is the small sample size of CDH participants in the included publications, although due to the rare nature of the birth defect this is perhaps to be expected. To the best of our knowledge this is the first systematic review that comprehensively examines long term cardiopulmonary health outcomes in CDH survivors. Various narrative reviews have addressed such outcomes including asthma, respiratory tract infection, bronchopulmonary dysplasia, pulmonary function testing, chest X-rays, health related quality of life, and exercise endurance. A

single paper focused additionally on the impact of CDH on the family (252). All papers shared some themes with our systematic review and stressed the importance of long term follow up (157, 241, 248, 252, 255, 260, 264, 269, 273, 338).

The recommendation for long term follow-up in CDH has been reported elsewhere(63, 76). This study, however, for the first time shows an underscored prevalence of chronic morbidity in CDH, and the 'unmet needs' of vulnerable at-risk patients and their families. There is compelling evidence for CDH multidisciplinary follow up clinics to be more widely available in healthcare systems to cater for the ongoing needs of survivors and families.

4.5 Conclusion

We have found that cardiopulmonary morbidity and a reduced HRQoL are prevalent and underscored amongst CDH survivors. MDT follow-up should be established by clinical teams to support CDH patients and their families into adulthood. Future prospective studies into the risk factors for cardiopulmonary complications, as well as research work addressing other long-term outcomes are crucially needed.

Chapter 5: Discussion

This thesis consisted of three systematic reviews looking at short- and long-term outcomes in CDH of relevance to children with CDH and their families.

Three key themes arose from this thesis. The first was that outcome selection, measurement, and reporting in studies of CDH is variable and hinders appraisal.

The second is that there is minimal research into short term outcomes in CDH, specifically the risk of bronchiolitis.

The third was that survivors of CDH are often left with long term health problems.

5.1 Outcome reporting in CDH

The first theme arose from Study I. Study I was a systematic review of outcome reporting in CDH. There is a high degree of morbidity and mortality associated with CDH (22, 23, 65, 81, 122, 130, 131). This will only be improved by good quality research trials driving advancements in healthcare. It was for this reason we chose to conduct this review.

We found there was heterogeneity amongst outcome selection, measurement, and reporting. Having variability in outcome reporting hinders the comparisons that can be made between studies and reduces their utility. We came across this again in Studies 2 and 3 when we attempted to pool results. Studies were often not comparable. For example, papers included in Study 2, the bronchiolitis systematic review, often had participant populations of different ages or varying definitions of bronchiolitis. In Study 3 we again came into difficulty when trying to compare studies looking at long term cardiopulmonary outcomes in CDH. This limited the useful comparisons that we could make between studies.

There have been a handful of good quality large multicentre RCTs in CDH. The recent FETO RCT (86) for example was across multiple centres and continents. This was adequately powered and produced useful results. There is a clear need for similar quality studies.

From Study I we also noted a lack of reporting of long term and functional outcomes, including health related quality of life. When these were measured they were often 'one off' measurements rather than being part of a strong follow-up plan. As we saw in the CDH MDT clinic at Alder Hey these functional outcomes affect individuals with CDH on a daily basis and so are important to individuals and families. A 2012 trial looking to develop a COS for paediatric asthma found at times there was disparity between the outcomes most relevant to researchers and those relevant to parents (339).

This review demonstrated the need for standardisation of outcome reporting and the need for good quality research. We plan to work with CDH UK and CDH International to develop a COS. These standardised outcomes should be of relevance to clinicians, patients and families. We hope to have the engagement of individuals with CDH of different ages and their families to identify key outcomes of importance. A 2005 trial conducted by OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) was one of the first to identify which outcomes patients felt were most important for designing a COS (340). Ideally, a COS would standardise outcome reporting in CDH, put greater emphasis on functional outcomes and overall aim to improve the quality of CDH research.

5.2 Short term outcomes in CDH

The second key theme from this thesis was focused on illustrating the lack of research into short term outcomes in CDH. Study II reviewed the risk of RSV bronchiolitis hospitalisation, and whether Palivizumab (RSV) prophylaxis modulates this risk. We found there was a lack of evidence about acute short-term illness in babies who go home with CDH. This was again something that came up in the CDH MDT clinic with parents. They felt their babies had been well supported in hospital, though after discharge there was much concern about respiratory winter viruses, particularly in the time of Covid-19.

As found from our first review, there was distinct areas of heterogeneity between studies, and this unfortunately limited pooling of data.

More research into short term outcomes in survivors with CDH is needed. A prospective multicentre cohort study across the UK and other countries should identify those most at risk of bronchiolitis. An evaluation of baseline data at hospital discharge would be useful here.

There is also a need for robust multicentre RCTs to evaluate the effectiveness and cost effectiveness of palivizumab use. Although expensive, palivizumab is currently used in preterm babies. It is the evidence from large scale RCTs that has particularly driven the use of palivizumab in preterm infants (240). CDH infants deserve these same robust research trials. Such RCTs should be adequately powered with standardised outcomes relevant to infants and parents.

5.3 Long term outcomes in CDH

The third theme to emerge from this thesis were the observations that survivors with CDH are often left with long term health problems. This was a subject that often came up in the CDH clinic. Parents and clinicians want survivors with CDH to have a joyful, healthy childhood and transition easily to adulthood. Unfortunately, some children are at risk of long-term sequelae from CDH. We are currently unsure, however, of the natural history of CDH survivorship. It is unknown which babies are more likely to develop long term complications and how this will develop over time with ageing. These long-term complications will inevitably impact upon HRQoL, and yet few studies reported on this.

There is a necessity here for large scale prospective database trials examining the long-term outcomes of individuals with CDH. CDH although much considered a rare disease is as common as CF and yet there is less interest invested in CDH research and allied health services. For example, CF services are intensely scrutinized and benchmarked against each other. In order to receive financial funding for the services they provide, CF care teams in the UK must register patient data with the CF Trust (341). This incentivizes and pushes developments in research. Similar inducements are needed to drive research in CDH.

5.4 Summary

From these overarching themes we concur that there needs to be further collaboration between health service institutions, clinicians, and families. Active collaboration would be the key drivers for benchmarking and setting quality improvement in CDH health outcomes research.

The thesis demonstrates an unmet need for MDT clinics to support CDH survivors through childhood and into adulthood. Many children experience chronic health complications, and this may go unnoticed for many years if the child is not adequately followed up in a supportive MDT clinic.

There is also a compelling need for a smoother transition to adult health services. This thesis showed that adults can have long term problems from CDH, and yet research or indeed support services are not directed towards the adult population. From the CDH clinic we often found this was a real concern for families. Many families struggled to find an adult health service institution equipped with the specialisms needed for long-term follow up.

Other long-term paediatric chronic disorders such as CF have a system of care known as 'hub and spoke' models. This is where tertiary centres, which offer a full array of services (hub), work together with district general hospitals who offer more limited services closer to the patients home (spokes) (342). Travelling a long distance to Alder Hey Children's hospital where we ran clinic was often difficult and disrupting for parents. Ironically, we observed this was greatly helped by the new virtual clinics established with the emergence of the Covid-19 pandemic. A hub-and-spoke model of care would therefore be very beneficial for CDH patients and families.

There is a further crucial need for active network collaboration and standardisation of care pathways linking centres treating CDH. The *James Lind Alliance* sets research priorities (343). We hope to work with them, as well as CDH UK and CDHi to direct research outcomes in a way that is relevant to CDH patients and families.

We would also strongly recommend further large-scale collaborative research trials. Collaborative studies, such as the recently published NEJM 2021 FETO trial (86), have shown how innovation and advances in healthcare may be rigorously interrogated.

5.5 Conclusion

This thesis has sought to highlight the wide diversity of health burden affecting CDH survivors, both in the short- and long- term. These vulnerable patients and their families should be catered for and adequately supported in multidisciplinary long term follow up clinics. There is an enormous need for further research studies particularly those of a robust nature focused on large scale multicentre trials with clear and defined pre-set outcomes.

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