Virtual follow-up of long-term physical, mental and educational outcomes for children with congenital diaphragmatic hernia

by

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Abstract

Problem

Improved survival of babies born with congenital diaphragmatic hernia (CDH) has predisposed these children to long-term morbidities. There is currently limited long-term outcome data that can be used to counsel parents and provide evidence-informed long-term care. The aim of this study was to determine if children born with CDH have different long-term physical health, mental health and educational outcomes compared to age-matched controls.

Methods

We performed a retrospective cohort study of CDH children born between 1992-2017. CDH cases were identified from Winnipeg's Surgical Database of Outcomes and Management (WiSDOM), and a 10:1 date-of-birth matched control population was selected using the Manitoba Centre for Health Policy (MCHP) data repository. International Classification of Disease (ICD) codes, Drug Program Information Network (DPIN), special education funding, Early Development Instrument (EDI), Grade 3, 7, 8 assessments, grade 9 completion and high-school graduation were used to assess outcomes.

Results

A total of 90 CDH children and 896 controls were identified. We found that CDH children 0-5 years-of-age have a higher risk of chronic airway obstruction, pneumonia, other diseases of the lung (e.g. chronic respiratory failure), other diseases of the respiratory system (e.g. bronchospasms), chronic pulmonary heart disease, symptoms concerning nutrition and development (e.g. failure-to-thrive), diseases of the esophagus (e.g. esophageal reflux), intestinal obstruction, deformities of curvature of spine (e.g. scoliosis), developmental disorders, specific delays in development and hearing loss. CDH Children 6-12 years-of-age were found to have a higher prevalence of asthma, diseases of the esophagus and hearing loss. No difference in physical health outcomes was found for children 13-19 years-of-age. Mental health outcomes and educational outcomes were found to be similar between CDH cases and controls.

Conclusion

The results from our study suggest that children born with CDH have worse physical health outcomes compared to age-matched controls, primarily in the first five years-of-life. No difference was found for mental health or educational outcomes in the first 19 years-of-life.

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The output of data used for this paper was generated using SAS software, Version 9.4 of the SAS system for Unix. Copyright © 2016 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

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Chapter I: Introduction

Congenital diaphragmatic hernia (CDH) is a birth defect caused by incomplete closure of the diaphragm – a muscle that separates the chest from the abdomen - during prenatal development. The resulting hole in the diaphragm allows abdominal organs to migrate up into the chest cavity resulting in limited space for the lungs to develop. There are three basic types of CDH - based on the location of the defect - including: Bochdalek-hernia (posterolateral), Morgani hernia (anterolateral) and central hernia. Bochdalek-hernias are the most common type, encompassing approximately 80-90% of cases, Morgani hernias encompass approximately 2% of cases and central hernias are extremely rare. This study is looking specifically at Bochdalek-type CDH due to the rarity and differences in management associated with the other types of CDH.

Upon delivery, these babies face pulmonary hypoplasia (small lungs) and pulmonary hypertension (high blood pressure in the pulmonary circulation). Consequently, the neonatal period can be comprised of serious respiratory distress. While the majority – approximately 70% - of CDH cases are diagnosed prenatally, the remaining 30% remain undetected until after delivery (Burgos et al., 2019). Postnatal management of CDH includes 'gentle ventilation' (permissive hypercapnia) – to reduce iatrogenic lung injury from barotrauma - and high-frequency ventilation as a rescue therapy. Extracorporeal membrane oxygenation (ECMO) is used in some centers to treat respiratory failure and pulmonary hypertensive crisis when conventional therapies fail. Additional therapies to treat pulmonary hypertension include inhaled nitric oxide (iNO) and sildenafil (a phospho-diesterase inhibitor). Once the neonate in stabilized – following optimization of respiratory and cardiac status – surgery is performed to correct the defect.

The cause of CDH is currently unknown, however, researchers believe that it is multifactorial, including both genetic and environmental factors. A genetic etiology has been found in approximately 30% of non-isolated CDH cases (Enns et al., 1998; Garne et al., 2002; Longoni et al., 2019; Qi et al., 2018; Yu et al., 2015). Additionally, approximately 10–22% of CDH patients have a *de novo* sequence variant that is a major contributing factor to CDH (Enns et al., 1998; Langoni et al., 2019; Qi et al., 2018). Numerous environmental exposures have been suggested as a potential risk factor for the development of CDH, including: maternal exposure to tobacco,

alcohol and vitamin A; presence of pre-gestational diabetes or pre-gestational hypertension; low maternal body weight, high maternal age (>35 yrs), or low socioeconomic status (Balayla & Abenhaim, 2014; Bronberg et al., 2020; Burgos et al., 2019; Caspers et al., 2010; Dingermann et al., 2019; Greer & Thebaud 2003; McAteer et al., 2014; Michikawa et al., 2019; Ramakrishnan et al., 2019; Vrijheid et al., 2000; Waller et al., 2003; Yang et al., 2006). CDH has also been found to be more common in males than females (Balayla & Abenhaim, 2014; Shanmugan et al., 2017).

The prevalence of CDH worldwide is estimated at 2.3-3.6/10,000 live births, with Canada having a prevalence of 3.38/10,000 (Burgos & Frenckner, 2017; Gallot et al., 2007; International Clearinghouse for Birth Defects Surveillance and Research, 2014; McGivern et al., 2015; Shanmugan et al., 2017; Woodbury et al., 2019; Yang et al., 2006). Therefore, approximately 1 in every 3,000 live birth infants will have CDH in Canada. While rare, CDH occurs more often than cystic fibrosis (1 in 3500) (Cystic Fibrosis Canada, 2020). The survival rate is approximately 70-80% for CDH neonates with no associated anomalies (Burgos & Frenckner, 2017; Carmichael et al., 2020; Colvin et al., 2005; Gallot et al., 2007; McGivern et al., 2015; Shanmugan et al., 2017; Stege et al., 2003; Takayasu et al., 2017; Wang et al., 2011; Woodbury et al., 2019; Wright et al., 2011; Yang et al., 2006). Improvements in antenatal diagnosis, neonatal management and surgical techniques have led researchers to believe that the survival rate of CDH has improved (Burgos & Frenckner, 2017; Gallot et al., 2007; Yang et al., 2006). However, due to case selection bias, it is believed that this trend should be interpreted with caution (Azarow et al., 1997; Colvin et al., 2005; Stege et al., 2003; Vanamo et al.,1996a). While improving survival is of continued importance, CDH research has shifted its focus to optimizing the long-term outcomes of survivors. Research has shown that infants born with CDH face long-term pulmonary, gastrointestinal, musculoskeletal and neurodevelopmental morbidities (Bojanic et al., 2017; Haliburton et al., 2015; Jancelewicz et al., 2013; Leeuwen et al., 2017; Montalva et al., 2019; Putnam et al., 2016; Rocha et al, 2012; Russel et al., 2014; Tan et al., 2019; Wynn et al., 2013) as a result of either the etiology, pathophysiology or treatment of CDH. Specifically, respiratory function may be impaired as a result of abnormal lung development (pulmonary hypoplasia and pulmonary hypertension) or ventilator induced lung injury. Disease severity and

factors such as prolonged NICU stay, prolonged intubation, tracheostomy placement and pulmonary hypertension have been found to be associated with worse outcomes.

Pulmonary morbidities include: chronic lung disease, airflow obstruction, asthma, decrease exercise tolerance, recurrent respiratory tract infections and recurrent pneumonia (Bojanic et al., 2016; Davis et al., 2004; EI & Weiss, 2018; Koziarkiewicz et al., 2014; Levesque et al., 2020; Panitch et al., 2015; Peetsold et al., 2009a; Spoel et al., 2013; Trachsel et al., 2005; Vanamo et al., 1996b). Gastrointestinal morbidities include: gastroesophageal reflux, failure to thrive (FTT), oral aversion (OA), and small bowel occlusion (SBO) (Bojanic et al., 2017; Caruso et al., 2013; Haliburton et al., 2015; Jaillard et al., 2003; Jancelewicz et al., 2013; Koivusalo et al., 2008; Leeuwen et al., 2014b; Leeuwen et al., 2017; Peetsold et al., 2010). Musculoskeletal morbidities include pectus deformities and scoliosis, particularly in patients with large defects requiring patch or muscle flap closure (Antiel et al., 2016; Aydin et al., 2019; Jaillard et al., 2003; Kuklová et al., 2011; Russel et al., 2014; Takayasu et al., 2016). Lastly, neurodevelopmental impairment has been found to be a significant morbidity among CDH survivors, with an approximate incidence of 23% (Montalya et al., 2019). Neurodevelopmental impairment has been found to range from motor and sensory (hearing, visual) deficits to cognitive, language and behavioral impairment (Amoils et al., 2015; Danzer et al., 2013; Danzer et al., 2017; Friedman et al., 2008; Leeuwen et al., 2014a; Madderom et al., 2013; Montalya et al., 2019; Wynn et al., 2013). According to a systematic review published in 2019, the most common deficits reported in literature are neuromuscular hypotonia (42%), learning difficulties (31%), neurobehavioral issues (20%), hearing impairment (13%) impairment and visual impairment (8%) (Montalya et al., 2019).

Long-term outcome data for patients with CDH are essential to counsel parents and provide evidence-informed long-term care. Further research into long-term outcomes would allow for optimization of medical care, reliable family counseling, the allocation of healthcare resources and the adaptation of health policies; enabling this growing population of children to achieve optimal potential in all areas of well-being.

Previous research on long-term outcomes of CDH survivors was limited, not population-based, had small sample sizes, looked at outcomes within the first couple years-of-life and lacked a control group. Additionally, many outcome studies used self- or proxy-reported surveys, and while many surveys were validated, they suffer from recall bias, lack of anonymous objectivity and incomplete response rates.

Our study is the first of its kind looking at virtual long-term outcomes of CDH survivors. Our study is unique because it is population-based with a large sample size for both the CDH cohort and date-of-birth matched controls (10:1). Our date-of-birth matched control cohort allows us to control for the confounding influence of age, thereby increasing the validity of our findings. In addition, we generated a large, longitudinal population-based control group without the issues normally associated with longitudinal cohort studies, such as expense, time investment and loss to follow-up. Lastly, we used a large comprehensive repository of population level administrative data which has been validated and extensively used to study physical, phycological and educational outcomes (Jutte et al., 2011; Kozyrskyj & Mustard, 1998; Mustard et al., 1999; Roos et al., 1993; Roos et al., 2005; Roos et al., 2008; Smith et al., 2018)

Based on what is known about CDH, we hypothesize these children will have worse long-term outcomes compared to the general population. To test this, the specific objectives of this study are as follows:

1. To link our CDH cohort to an age-matched control population
2. To compare the long-term physical health outcomes of our CDH cohort to that of age-matched controls
3. To compare the long-term mental health outcomes of our CDH cohort to that of age-matched controls
4. To compare the educational outcomes of our CDH cohort to that of age-matched controls

Chapter II: Methods

Creation of case cohort in the WiSDOM database

The Winnipeg Surgical Database of Outcomes and Management (WiSDOM) contains patient information for children treated for one of eight congenital anomalies between 1992 and 2017; the anomalies include congenital lung lesion, congenital diaphragmatic hernia, gastroschisis, omphalocele, Hirschsprung disease, anorectal malformations, esophageal atresia/trachea-esophageal fistula and intestinal atresia. WiSDOM was created by searching electronic records at Health Sciences Center and St. Boniface Hospital in Winnipeg, MB., using International Classification of Disease (ICD) codes (ninth and tenth revisions). CDH patients were identified using the ICD-9 code 756.6 or the ICD-10 code Q79.0. Once these patients were identified, their medical records were screened to confirm the diagnosis and data was extracted into a Research Electronic Data Capture (REDCap) database. Ethics approval was granted by the University of Manitoba (H2016:014). WiSDOM contains general information, birth characteristics, maternal history, surgical management and disease specific information. General information included: identifiers, confounding diseases, and 1-year survival rates. Birth characteristics included: birthweight, gestational age, and Apgar scores. Maternal history included: medical history, medication use, self-reported substance use during pregnancy, and method of delivery. Surgical management included: the date and type of surgery used to close the defect. Disease specific information for CDH included: defect type, defect side, defect size, presence of a hernia sac, liver herniation, and pulmonary hypertension severity. Pulmonary hypertension severity was determined as mild or severe by echocardiogram. The criteria for severe PPHN included the presence of: (1) either bidirectional or right to left shunt through the PDA, and/or (2) septal flattening. Defect size was determined at the time or repair and categorized into the A-D sizing scale (Tsao & Lally, 2008). Categories A and B were classified as small, and categories C and D were classified as large.

Creation of control cohort using the MCHP

The CDH data was exported from WiSDOM and submitted to Manitoba Health with identifiers such as name and personal health identification number (PHIN) - a unique identifier assigned by Manitoba Health to every person registered for health insurance in Manitoba, and to non-residents who are treated in Manitoba at facilities which submit claims electronically. The CDH

WiSDOM data was then linked (using PHIN's) to the Manitoba Centre for Health Policy (MCHP) – a large comprehensive repository of population level administrative data. The data was then anonymized by scrambling each patient's PHIN and removing other identifiers. Once the linkage was complete, the control group was generated using the Manitoba Health Insurance registry. For each CDH case, 10 date-of-birth matched controls were anonymously identified. The controls were randomly selected from the general population and were not confirmed to be medically healthy (i.e. no controls were excluded from the analysis). The cohort was created using SAS® statistical software.

Baseline characteristics

The first step of our analysis was to compare the baseline characteristics of children with CDH to date-of-birth matched controls. The baseline characteristics were obtained from the *Hospital Abstracts dataset* - a dataset that summarizes demographic and clinical information completed at the point of discharge from the hospital and includes 4 digit ICD-9 codes (April 1, 1979- March 31, 2004) and ICD-10 codes (April 1, 2004 – present) – and the *Registered Postal Code* dataset within the MCHP (Manitoba Centre for Health Policy, Hospital Abstracts, 2020). Baseline characteristics included: sex, birthweight, gestational age, 1-minute Apgar score, 5-minute Apgar score, length of hospital stay at birth, 30-day mortality, small-for-gestational-age. Small-for-gestational-age was determined based on three variables: sex, gestational age (pre-term, post-term or term) and birthweight (small, acceptable (appropriate) or large) (Manitoba Centre for Health Policy. Concept: Size for Gestational Age, 2020). Small-for-gestational-age was determined if the infant was determined to be small for pre-term, small for term, or small for post-term.

Socioeconomic status was determined using the Socioeconomic Factor Index (SEFI). "The SEFI is a factor score derived from Canadian Census data that reflects non-medical social determinants of health and is used as a proxy measure of socioeconomic status (SES)" (Manitoba Centre for Health Policy, Concept: Socioeconomic Factor Index (SEFI), 2020). The SEFI score is based on four variables: unemployment rate for individuals more than 15 years-of-age, average household income for individuals more than 15 years-of-age, proportion of single parent households, and proportion of population more than 15 years-of-age without a high school

diploma. We used SEFI scores calculated using the SEFI-2 methodology (Manitoba Centre for Health Policy, Concept: Socioeconomic Factor Index (SEFI), 2020). The final score is standardized to have a mean of 0 and a variance of 1, with a negative value indicating a more favorable socioeconomic status. Using the *Registered Postal Code* dataset within the MCHP we determined each individual's postal code and the corresponding SEFI at birth; this is reflective of the socioeconomic status of the neighborhood into which the neonate was born.

Two-tailed t-tests, chi-squared tests and Fisher's exact tests were used to compare continuous and categorical baseline characteristics. The statistical analysis was performed using R® version 3.6.1.

Physical health outcomes

The second step of our analysis was to compare the physical health outcomes of children with CDH to date-of-birth matched controls. Physical health outcomes were obtained from the *Medical Claims/Medical Service (MC/MS)* dataset*, Hospital abstracts* dataset, *Drug Program Information Network (DPIN)* dataset and the *Manitoba Education & Youth (MEY) Special Needs* data file (within the *Enrollment, Marks & Assessments* dataset).

The MC/MS dataset is an administrative health dataset available through the MCHP that contains information about all compensatory claims for medical services rendered in Manitoba (Manitoba Centre for Health Policy, Medical Claims/Medical Services, 2020). The MC/MS dataset contains three-digit ICD-9 codes for data entered since March 31, 1979. The MEY Special Needs dataset identifies children receiving special (categorical) funding for special needs and the DPIN is a point-of-sale prescription drug database (Manitoba Centre for Health Policy, Enrollment, Marks and Assessments, 2020; Manitoba Centre for Health Policy, Drug Program Information Network, 2020).The cohort was subdivided for three analyses based on the age at which the physical health outcome occurred: birth through 5 years-of-age, 5 years-of-age to 12 years-of-age and 12 years-of-age to 19 years-of-age. Each analysis included all individuals who had follow-up data for the entire age range. Follow-up data is available for each individual from birth until the end of their coverage as defined by the *Manitoba Health Insurance Registry*; coverage ended at either the date of most recent update (Nov 30, 2019), date of death, or date of

relocation out of province (Manitoba Centre for Health Policy, Manitoba Health Insurance Registry, 2020). For example, the 0-5 years-of-age group contained individuals who were at least 5 years-old and who had health coverage for at least 5 years; the physical health outcomes of these children were then analyzed from birth to five years-of-age. This method was done to insure each child had an equal probability of acquiring the specific outcome.

Risk of physical health diagnoses

Four categories of physical health outcomes were examined: pulmonary, gastrointestinal, musculoskeletal and neurodevelopmental. The specific physical health outcomes examined were selected based on previous research and their availability within the datasets provided by the MCHP. The pulmonary diagnoses were obtained from the *MC/MS* dataset using the following ICD codes: chronic obstructive pulmonary disease (emphysema (ICD-9: 492) or chronic bronchitis (ICD-9: 491)), chronic airway obstruction (ICD-9: 496) asthma (ICD-9: 493), pneumonia (ICD-9: 480-486), acute respiratory infections (ICD-9: 460-466), influenza (ICD-9: 487-488), pneumonitis due to solids and liquids (ICD-9: 507), other diseases of the lung (e.g. chronic respiratory failure and pulmonary insufficiency)(ICD-9: 518), other disease of the respiratory system (e.g. bronchospasms) (ICD-9: 519), and chronic pulmonary heart disease (ICD-9: 416). The outcome of asthma was further examined by using the DPIN to identify prescriptions for inhaled bronchodilators and inhaled steroids based on the Anatomical Therapeutic Chemical classification code – a code that exists for every medication and organized based on the organ system and mechanisms of action. We defined bronchodilators as any medication that fell under the "inhaled adrenergic" (R03A) or "inhaled anticholinergic" (R03BB) categories, and steroids as any medication that fell under the "inhaled glucocorticoids" (R03BA) category.

The gastrointestinal and musculoskeletal outcomes were also obtained from *the MC/MS dataset* using the following ICD codes: symptoms concerning nutrition metabolism and development (e.g. failure to thrive)(ICD-9: 783), diseases of the esophagus (ICD-9: 530), intestinal obstruction without mention of hernia (ICD-9: 560), deformity of curvature of spine (e.g. scoliosis) (ICD-9: 737) and other acquired musculoskeletal deformity (e.g. acquired deformity of the chest and rib)(ICD-9: 738).

Neurodevelopmental outcomes were obtained from the *MC/MS dataset*, *hospital abstracts dataset* and *MEY Special Needs datafile*. Developmental disorders – a term used by the MCHP to cover a broad spectrum of conditions – was obtained from the *MC/MS dataset*, *hospital abstracts dataset* and the *MEY Special Needs datafile*. Developmental disorders were identified using the following modified algorithm (Chartier et al., 2016; Manitoba Centre for Health Policy, Concept: Intellectual Disability (ID) (Mental Retardation)/Developmental Disability (DD)/Developmental Disorders, 2019):

- one or more hospitalizations with diagnoses for intellectual disabilities, pervasive developmental disorders, Down's syndrome, autosomal deletion syndromes, Prader-Willi syndrome, other specified congenital anomalies, or FASD using: ICD-9 codes: 317, 318, 319, 299, 758.0, 758.3, 759.81, 759.89, 760.71; OR ICD-10 codes: : F70.0, F70.1, F70.8, F70.9, F71.0, F71.1, F71.8, F71.9, F72.0, F72.1, F72.8, F72.9, F73.0, F73.1, F73.8, F73.9, F78.0, F78.1, F78.8, F78.9, F79.0, F79.1, F79.8, F79.9, F84.0, F84.1, F84.3, F84.4, F84.5, F84.8, F84.9, P04.3, Q86.0, Q86.1, Q86.2, Q86.8, Q87.0, Q87.1, Q87.2, Q87.3, Q87.5, Q87.8, Q89.8, Q90.0, Q90.1, Q90.2, Q90.9, Q91.0, Q91.1, Q91.2, Q91.3, Q91.4, Q91.5, Q91.6, Q91.7, Q93.0, Q93.1, Q93.2, Q93.3, Q93.4, Q93.5, Q93.6, Q93.7, Q93.8, Q93.9, Q99.2; OR
- one or more physician claims with diagnoses for intellectual disabilities, pervasive developmental disorders: ICD-9 codes: 317, 318, 319, 299

Autism spectrum disorder (ASD) was also identified through the *MC/MS dataset, hospital abstracts dataset* and the *MEY Special Needs datafile* using the following algorithm (Chartier et al., 2016; Manitoba Centre for Health Policy, Concept: Autism Spectrum Disorder (ASD), 2011):

- one or more hospitalizations with any one of the following ICD-9 codes: 299.0, 299.1, 299.8, or 299.9; ICD-10: F84.0-F84.5, F84.8, or F84.9
- one or more physician visits with the diagnosis ICD-9 code: 299
- identified as "ASD" within the variable *CATEORGYN* of the Manitoba Education Special Needs data file.

Attention-Deficit Hyperactivity Disorder (ADHD) was restricted to children 6-19 years of age, as done by Chartier et al. (2016) and identified using the following modified MCHP algorithm (Chartier et al., 2016; Manitoba Centre for Health Policy, Concept: Attention-Deficit Hyperactivity Disorder (ADHD), 2016):

- one or more hospitalizations with a diagnosis of hyperkinetic syndrome (ICD-9: 314 or ICD-10: F90); or
- one or more physician visits with a diagnosis of hyperkinetic syndrome (ICD-9: 314); or
- two or more prescriptions for ADHD drugs (ATC code: N06BA01, N06BA02, N06BA04, N06BA05, N06BA07, N06BA09, N06BA12) without a diagnosis of:
    - conduct disorder (ICD-9: 312 or ICD-10: F63, F91, F92); or
    - disturbance of emotions (ICD-9: 313 or ICD-10: F93, F94); or
    - cataplexy/narcolepsy (ICD-9: 347 or ICD-10: G47.4); or
- One prescription for ADHD drugs in one year AND a diagnosis of hyperkinetic syndrome

The algorithms used for developmental disorder, ASD and ADHD were adopted from a large population-based report conducted by the MCHP examining the mental health of Manitoba's children (Chartier et al., 2016).

The remaining neurodevelopmental outcomes were obtained from the MC/MS using ICD-9 codes, including: specific delays in development (ICD-9: 315), epilepsy and recurrent seizures (ICD-9: 345), cerebral palsy (ICD-9: 343), myoneuronal disorders (ICD-9: 358), hearing loss (389) and visual impairment (ICD-9: 368-369).

For descriptive summaries, we report both the risk ratio (RR) and odds ratio (OR) associated with each physical health diagnoses. An observed p-value less than 0.05 was considered significant. The analysis was performed using R® version 3.6.1.

Rate of common respiratory infections

The relative rate of common respiratory infections was examined to identify if children with CDH are diagnosed with these infections more often than controls. The respiratory infections

and their corresponding ICD codes are as follows: acute respiratory infection (ICD-9:460-466), pneumonia (ICD-9: 480-486) and influenza (ICD-9: 487-488). We modelled the rates of common respiratory diagnoses using a proportional intensity model for recurrent events, an extension of the Cox proportional hazards regression model that can be fit using the coxph function in the survival package in R® (Andersen & Gill, 1982; Therneau, 2015). The proportional intensity model assumes that the rate of diagnoses remains constant for the specific time period, even as the baseline rate varies over time. This assumption was explored by looking at the plot of Schoenfeld residuals versus age and testing the Pearson's correlation between the residuals and age using the cox.zph function of the survival package in R® (Grambsch & Therneau, 1994).

Mental health outcomes

The third step of our analysis was to compare the mental health outcomes of children with CDH to date-of-birth matched controls. Mental health outcomes were obtained from the *Hospital abstracts* dataset, *MC/MS dataset*, and the *Drug Program Information Network (DPIN)*.

The cohort was subdivided into two groups based on the age at which the mental health outcome occurred: 6-12 years-of-age and 13-19 years-of-age. Similar to the physical health outcomes, each group contained individuals who had follow-up data for the entire age range. The 0-5 years-of-age group (as seen in the physical health outcomes) was not included in this analysis because of the age-restrictions surrounding mental health diagnoses (Chartier et al., 2016). The specific mental health outcomes were chosen for two reasons: 1. they are some of the most common childhood mental illnesses; and 2. they have been previously examined using similar methodology in the general population (Chartier et at., 2016).

A diagnosis of conduct disorder was restricted to children 6 – 19 years of age and identified using the following algorithm (Chartier et al., 2016; Manitoba Centre for Health Policy, Concept: Conduct Disorder, 2016):

- one or more hospitalization with a diagnosis of conduct disorder (ICD-9:312 or ICD-10: F91, F91.0, F91.1, F91.2, F91.8, F91.9) or
- one or more physician visits with a diagnosis of conduct disorder (ICD-9: 312).

The MCHP combines depression and anxiety into one condition, Mood and Anxiety Disorders - a broad spectrum of conditions ranging from poor adjustment reactions and anxiety state to anxiety disorders, phobic disorder, obsessive-compulsive disorders, depressive disorders, affective psychoses, and neurotic depression. Mood and Anxiety Disorders were restricted to children aged 6-19 years and identified using the following algorithm (Chartier et al., 2016; Manitoba Centre for Health Policy, Concept: Mood & Anxiety Disorders, 2015):

- one or more hospitalizations with one of the following diagnosis codes: ICD-9: 296.1-296.8, 300.0, 300.2, 300.3, 300.4, 300.7, 309 or 311; ICD-10: F31-F33, F34.1, F38.0, F38.1, F40, F41.0, F41.1, F41.2, F41.3, F41.8, F41.9, F42, F43.1, F43.2, F43.8, F53.0, or F93.0; OR
- one or more hospitalizations with one of the following diagnosis codes: ICD-9: 300; ICD-10: F32, F34.1, F40, F41, F42, F44, F45.0, F45.1, F45.2, F48, F68.0 or F99 AND one or more prescriptions for an antidepressant or mood stabilizer: ATC codes N05AN01, N05BA, N06A, N05BE01; OR
- one or more physician visits with one of the following diagnosis codes: ICD-9: 296, 311; OR
- one or more physician visits with the following diagnosis code: ICD-9: 300 AND one or more prescriptions for an antidepressant or mood stabilizer: ATC codes N05AN01, N05BA, N06A, N05BE01; OR
- three or more physician visits with one of the following diagnosis codes: ICD-9: 300, 309.

Substance use disorders was restricted to individuals 13-19 years-of-age and identified using the following algorithm (Chartier et al., 2016: Manitoba Centre for Health Policy, Concept: Substance Use Disorders/Substance Abuse, 2016):

- one or more hospitalization with a diagnosis for alcohol or drug psychoses, alcohol or drug dependence, nondependent abuse of drugs, and alcohol and drug rehabilitation using the following codes: ICD-9-CM codes: 291, 292, 303, 304, or 305; ICD-10 codes: F10-F19, F55, Z50.2, Z50.3 OR

- one or more physician visits with a diagnosis for alcohol or drug psychoses, alcohol or drug dependence, or nondependent abuse of drugs using ICD codes 291, 292, 303, 304 or 305.

A diagnosis of psychotic disorders was restricted to individuals 13-19 years-of-age and identified using the following algorithm (Chartier et al., 2016; Manitoba Centre for Health Policy, Concept: Psychotic Disorders, 2016):

- one or more hospitalizations with a diagnosis of psychotic disorders, using either: ICD-9 codes: 295 (schizophrenic disorders) or 297 (delusional disorders) or 298 (other nonorganic psychoses); OR ICD-10 codes: F11.5, F12.5, F13.5, F14.5, F15.5, F16.5, F17.5, F18.5, F19.5 (psychotic disorders due to opioids, cannabinoids…etc.), F20 (schizophrenia), F22 (delusional disorder), F23 (acute and transient psychotic disorders), F24 (induced delusional disorder), F25 (schizoaffective disorders), F28 (other nonorganic psychotic disorders), F29 (unspecified nonorganic psychosis); OR
- one or more physician visits with a diagnosis of psychotic disorders using ICD-9 codes: 295 (schizophrenic disorders) or 297 (delusional disorders) or 298 (other nonorganic psychoses)

Lastly, a diagnosis of schizophrenia was restricted to individuals 13-19 years-of-age and identified using the following algorithm (Chartier et al., 2016; Manitoba Centre for Health Policy, Concept: Schizophrenia, 2016):

- one or more hospitalization with a diagnosis for schizophrenia: ICD-9-CM code: 295 (schizophrenic disorders); OR ICD-10-CA codes: F20 (schizophrenia), F21 (schizotypal disorder), F23.2 (acute schizophrenia-like psychotic disorder), F25 (schizoaffective disorders); OR
- one or more physician visits with a diagnosis for schizophrenia using ICD-9-CM code 295.

For descriptive summaries, we report both the risk ratio (RR) and odds ratio (OR) associated with each mental health diagnoses. An observed p-value less than 0.05 was considered significant. The analysis was performed using R® version 3.6.1.

Educational outcomes

The fourth step of our analysis was to compare the educational outcomes of children born with CDH to date-of-birth matched controls. Education outcomes were obtained from the *Early Development Instrument (EDI) dataset* and the *Enrollment, Marks & Assessments dataset*. Education outcomes included the following measures: EDI, grade 3, 7 and 8 assessments, grade 9 completion, grade 9 performance and high-school graduation. Educational outcomes were analyzed for each individual from birth until the end of their coverage as defined by the *Manitoba Health Insurance Registry*. The educational outcomes examined were selected based on their availability within the datasets provided by the MCHP.

The EDI is a questionnaire completed by kindergarten teachers that measures a child's "school readiness" by analyzing their ability to meet age-appropriate developmental expectations. The questionnaire measures the following domains: physical health and well-being, social competence, emotional maturity, language and cognitive development, and communication skills and general knowledge; children are deemed "Not Ready", "Ready", or "Very Ready" for grade 1 (Offord Centre for Child Studies, 2020; Manitoba Centre for Health Policy, Early Development Instrument Outcomes, 2020). EDI data is collected for all kindergarten students (unless participation is withdrawn by parents) at all public-school divisions in Manitoba and some independent and First Nations schools; data is collected once every two years and is available since the 2005/2006 school year. The primary outcome measure was being deemed "Not Ready" for grade 1.

The Manitoba Education policy related to grade level assessments applies to all students in Grade 3, 7 and Grade 8 in provincially funded schools; non-funded and band-operated schools are also invited to participate (Manitoba Centre for Health Policy, Concept: Grade Level Assessments, 2019). Data for the Grade 3 Assessment is available starting with the 2009/2010 school year and includes competency measures in reading and numeracy; the grade 7 assessment is available starting with the 2007/2008 school year and includes competency measures in number sense and number skills and student engagement; the grade 8 assessment is available starting with the 2007/2008 school year and includes competency measures in reading comprehension and expository writing. The outcome of all assessments is categorized as 'not

meeting expectations', 'approaching expectations', or 'meeting expectations'. For the purpose of this study we grouped approaching expectations and meeting expectations to allow for a binary comparison using odds ratios and logistic regression; the outcome measure was the failure to meet expectations for a written standardized assessment.

In order to complete grade 9 in Manitoba, students are required to complete eight or more credits in the first year of grade 9. We also looked at the average mark - a measure of performance - for the students who completed grade 9. Grade 9 completion and average marks were obtained from the *Manitoba Health Insurance Registry dataset* and the *Enrollment, Marks and Assessments dataset*. The MCHP categorizes grade 9 performance into 16 outcomes; taking into account all possible average marks in all classes and the number of credits earned during the grade 9 school year. For the purposes of this study, we focused on the average mark of students who completed grade 9 (had 8+ credits), which includes 8 categories (based on average marks): 50-60%, 60-65%, 65-70%, 70-75%, 75-80%, 80-85%, 85-90%, 90-100%. In order to create a binary comparison, we grouped children who had a 'poor performance' (50-75% average marks) and those who had a 'good performance' (75-100% average marks). For this analysis, our outcome measure was a poor performance in grade 9.

For descriptive summaries, we report both the risk ratio (RR) and odds ratio (OR) associated with a poor education outcome; this was defined as "not ready" for kindergarten, failing to meet expectations on the grade assessments, failure to complete grade 9, a poor performance in grade 9, or failure to graduate high-school. An observed p-value less than 0.05 was considered significant. The analysis was performed using R® version 3.6.1.

Sensitivity analysis to account for excluded population

Sensitivity analyses were conducted to help understand how the excluded population impacted the physical health outcomes, mental health outcomes and two of the educational outcomes (failure to complete grade 9 and failure to graduate high-school). Sensitivity analyses could not be conducted on the EDI, grade 3, 7 and 8 assessments and grade 9 performance because these measures included only children for whom data was available; therefore, no children were excluded. We conducted two sensitivity analyses to account for individuals who were excluded

from the base-model due to loss of coverage (died or moved out of province). The first analysis was a "best-case scenario" (from the CDH patient perspective) - the cases who lost coverage were included as having obtained a good outcome and the controls who lost coverage were included as having obtained a poor outcome. The second analysis was a "worst-case scenario" (from the CDH patient perspective); the cases who lost coverage were included as having obtained a poor outcome and the controls who lost coverage were included as having obtain a good outcome. The best and worst-case scenarios were chosen to demonstrate both ends of the spectrum, allowing us to compare the relative location of our base-model along this spectrum; this provided a better understanding of what impact the excluded population may have had on our conclusions.

Propensity analysis

We used propensity score methods to help examine the effect of CDH on the outcomes while controlling for the possible confounding effects of maternal substance-use, maternal pre-gestational diabetes, maternal pre-gestational hypertension, socioeconomic status (using SEFI) and sex of the baby. With a larger sample size, we could have included these variables in a multiple predictor logistic regression. However, multiple regression models with many covariates can be very unstable, characterized by large standard errors for the coefficient estimates; in the extreme, the model-fitting procedure may even fail to find a solution. However, the estimated propensity score for the exposure summarizes the major differences in those covariates between the exposed and unexposed. Using a propensity score model for the probability that a child would be born with CDH allowed us to use the linear predictor for that probability as a single variable summary of how the several confounders influenced CDH. Using these estimated propensity scores to form a stratification variable in a model for effect of CDH on the outcome allowed us to effectively reduce the confounding effect of the covariates on the effect of the main predictor of interest (D'Agostino, 1998).

Maternal data was obtained through the MCHP by linking our cases and controls to their mothers using PHIN's. Maternal substance use (alcohol, smoking or drug use during pregnancy) was identified through the *Families First Screen dataset* within the MCHP (Manitoba Centre for Health Policy, Families First Screen, 2020). Maternal pre-gestational diabetes and pre-

gestational hypertension were identified through the *Hospital abstracts dataset* and *MC/MS dataset*.

Maternal pre-gestational diabetes was determined if at any time prior to 21 weeks' gestation the mother had (Manitoba Centre for Health Policy, Concept: Diabetes in Pregnancy, 2015):

- One or more hospitalizations with a diagnosis of diabetes: ICD-9: 250, 648.0, 648.8; ICD-10: E10-E14, O24, P70.0, P70.1, R73.0 or
- Two or more physician visits with a diagnosis of diabetes: ICD-9: 250

Pre-gestational hypertension was determined if at any time prior to 21 week's gestation the mother had (Manitoba Centre for Health Policy, Concept: Diabetes in Pregnancy, 2015; Manitoba Centre for Health Policy, Concept: Hypertension, 2015; Martens et al., 2015):

- One or more hospitalizations with a diagnosis of hypertension, ICD-9-CM codes 401-405; ICD-10-CA codes I10-I13, I15; or
- Two or more physician visits with a diagnosis of hypertension: ICD-9-CM: 401-405

We calculated a propensity score that included maternal pre-gestational diabetes, maternal pre-gestational hypertension, SEFI, and sex of the baby. Maternal substance use was not included in the propensity score due to insufficient numbers. The cases and controls were then stratified into five groups by splitting at the quintiles of the estimated propensity scores. We then added this 5-level propensity score stratification variable to the baseline model, utilizing the balancing property of the propensity score to adjust for multiple confounding variables simultaneously (Austin, 2011); only variables with adequate sample sizes ($N \geq 10$ for both outcome possibilities) in the baseline model were used in the propensity analysis.

Chapter III: Results

Baseline characteristics

A total of 110 neonates with CDH were born in Manitoba between 1992-2017; including 93 (84.5%) Bochdalek hernias, 11 (10.0%) Morgagni hernias, and 6 (5.5%) other hernias (Pentalogy of Cantrell and Esophageal Hiatus). Three of the 93 patients with Bochdalek hernias did not have a recorded PHIN, preventing the identification of these patients by the MCHP. Therefore, the case-cohort was comprised of 90 CDH patients. We found that left-sided Bochdalek defects occurred in 72 (80.0%) patients, large defects were present in 25 (27.8%) patients, a hernia sac was present in 19 (21.1%) patients, liver herniation occurred in 34 (37.8%) patients, and severe pulmonary hypertension (systemic or supra-systemic) was diagnosed in 43 (47.8%) patients.

A total of 896 date-of-birth matched controls were randomly selected for the 90 CDH cases; for 4 cases only 9 controls were matched (only 9 children with the same birthdate could be identified within the MCHP). We found a significant difference in baseline characteristics between our cases and controls; neonates with CDH were found to have lower birthweights ($p=0.001$), lower gestational age ($p<0.001$), lower 1-minute Apgar scores ($p<0.001$), lower 5-minute Apgar scores ($p<0.001$), longer hospital stay at birth ($p<0.001$), and a higher 30-day mortality rate ($p<0.001$). No difference was found for sex ($p=0.162$), SEFI ($p=0.162$) or the number of neonates who were classified as small-for-gestational age ($p=1$) (Table 1).

Table 1. Baseline characteristics for CDH cases and controls

Characteristic	CDH (n=90)	Controls (n=896)	P
Sex = Male	52 (57.8%)	443 (49.4%)	0.162
Birthweight (grams)	3226.38 (±789.04)	3465.14 (±596.68)	0.001
Gestational age (weeks)	37.80 (±3.52)	39.10 (±1.92)	<0.001
1-minute Apgar	5.12 (±2.74)	7.88 (±1.66)	<0.001
5-minute Apgar	6.38 (±2.51)	8.34 (±2.02)	<0.001
Length of stay (days)	31.37 (±49.91)	2.86 (±4.46)	<0.001
30-day mortality	14 (15.6%)	8 (0.9%)	<0.001
Small-for-gestational age	8 (8.89%)	78 (8.71%)	1
SEFI	0.18 (±1.15)	0.29 (±1.10)	0.38

Physical health outcomes

Risk of physical health diagnoses

For the 0-5 years-of-age group there were 54 cases and 741 controls. We found that cases and controls had a significant difference in the risk ratio (RR) of chronic airway obstruction (RR=13.72, 95%CI: 3.63-53.36, p=0.001), pneumonia (RR=2.41, 95% CI: 1.64-3.54, p<0.001), other diseases of the lung (RR=20.58, 95%CI: 3.51-120.57, p=0.003), other diseases of the respiratory system (RR=2.42, 95% CI: 1.51-3.89, p=0.002) and chronic pulmonary heart disease (RR= ∞ , 95%CI : 0- ∞, p<0.001) and asthma associated prescription drugs: inhaled bronchodilators (RR=1.73, 95%CI:1.27-2.36, p=0.004) and inhaled steroids (RR=1.76, 95%CI:1.11-2.79, p=0.035). A significant difference was also found for symptoms concerning nutrition and development (RR=5.31, 95%CI: 4.21-6.69, p<0.001), diseases of the esophagus (RR=5.88, 95%CI: 2.83-12.21, p<0.001), intestinal obstruction (RR=45.74, 95%CI: 12.97-161.30, p<0.001), deformities of curvature of spine (RR=41.17, 95%CI: 4.36-389.12, p=0.001), developmental disorders (RR=4.47, 95%CI: 1.53-13.70, p=0.019), specific delays in development (RR=3.35, 95%CI: 1.84-6.10, p<0.001) and hearing loss (RR=4.57, 95%CI: 2.36-8.85, p<0.001). Tables 2, 3, 4 and 5 summarize these results.

Table 2. Pulmonary outcome for the 0-5 years-of-age group

Pulmonary outcome	Risk ratio	95% CI	Odds ratio	95%CI	P	Odds ratio (PS-adj)	95%CI	P
Chronic obstructive pulmonary disease								
Base model	3.43	0.39-30.16	3.47	0.07-35.86	0.297	-	-	-
Best-case scenario model	0.13	0.02-0.89	0.12	0-0.68	0.007	-	-	-
Worst-case scenario model	72.14	26.00-200.16	109.43	36.57-441.73	<0.001	-	-	-
Chronic airway obstruction								
Base model	13.72	3.53-53.36	14.61	2.64-80.85	0.001	-	-	-
Best-case scenario model	0.5	0.19-1.34	0.48	0.12-1.33	0.227	-	-	-
Worst-case scenario model	79.61	28.87-219.52	127.85	43.01-552.34	<0.001	-	-	-
Asthma								
Base model	1.45	0.96-2.20	1.65	0.85-3.11	0.126	1.63	0.86-2.97	0.124
Best-case scenario model	0.72	0.46-1.11	0.64	0.35-1.14	0.124	0.64	0.35-1.11	0.128
Worst-case scenario model	2.78	2.19-3.54	4.94	3.01-8.13	<0.001	4.72	2.90-7.73	<0.001
Pneumonia								
Base model	2.41	1.64-3.54	3.23	1.70-6.01	<0.001	3.21	1.73-5.84	<0.001
Best-case scenario model	1.05	0.71-1.57	1.07	0.60-1.85	0.785	1.08	0.61-1.84	0.774
Worst-case scenario model	4.19	3.27-5.38	8.66	5.22-14.52	<0.001	8.34	5.07-13.9	<0.001
Acute respiratory infections								
Base model	1.01	0.90-1.13	1.05	0.47-2.63	1	-	-	-
Best-case scenario model	0.65	0.54-0.79	0.21	0.13-0.35	<0.001	0.2	0.12-0.34	<0.001
Worst-case scenario model	1.17	1.08-1.27	2.79	1.31-6.81	0.005	-	-	-
Influenza								
Base model	0.66	0.22-2.05	0.64	0.13-2.09	0.612	-	-	-
Best-case scenario model	0.22	0.07-0.67	0.19	0.04-0.58	<0.001	-	-	-
Worst-case scenario model	4.98	3.45-7.18	7.36	4.23-12.71	<0.001	-	-	-
Pneumonitis								
Base model	∞	0-∞	∞	0.35-∞	0.068	-	-	-
Best-case scenario model	0.13	0.02-0.94	0.12	0-0.72	0.011	-	-	-
Worst-case scenario model	∞	Na-∞	∞	107.93-∞	<0.001	-	-	-
Other diseases of the lung								
Base model	20.58	3.51-120.57	21.5	2.41-261.81	0.003	-	-	-
Best-case scenario model	0.39	0.13-1.20	0.36	0.07-1.15	0.101	-	-	-
Worst-case scenario model	154.24	37.59-632.90	243.26	59.19-2209.62	<0.001	-	-	-
Other diseases of the respiratory system								
Base model	2.42	1.51-3.89	2.96	1.45-5.78	0.002	3.01	1.51-5.71	0.001
Best-case scenario model	0.93	0.58-1.50	0.92	0.47-1.68	0.884	0.92	0.49-1.65	0.798
Worst-case scenario model	5.03	3.77-6.71	9.44	5.64-15.89	<0.001	9.03	5.45-15.0	<0.001

Chronic pulmonary heart disease								
Base model	∞	0-∞	∞	17.38-∞	<0.001	-	-	-
Best-case scenario model	0.8	0.36-1.77	0.78	0.27-1.86	0.689	-	-	-
Worst-case scenario model	∞	Na-∞	∞	139.80-∞	<0.001	-	-	-

Table 3. Prescriptions for inhaled bronchodilators and inhaled steroids

	0-5 years-of-age			6-12 years-of-age			13-19 years-of-age		
Asthma prescriptions	**Risk ratio**	**95% CI**	**P**	**Risk ratio**	**95% CI**	**P**	**Risk ratio**	**95%CI**	**P**
Inhaled bronchodilators	1.73	1.27-2.36	0.004	1.41	0.85-2.35	0.209	1.3	0.46-3.65	0.705
Inhaled steroids	1.76	1.11-2.79	0.035	1.44	0.72-2.88	0.315	2.17	0.74-6.33	0.176

Table 4. Gastrointestinal and musculoskeletal outcomes for the 0-5 years-of-age group

Gastrointestinal outcome	Risk ratio	95% CI	Odds ratio	95%CI	P	Odds ratio (PS-adj)	95%CI	P
Symptoms concerning nutrition and development								
Base model	5.31	4.21-6.69	18.78	9.49-39.50	<0.001	22.2	11.3-47.1	<0.001
Best-case scenario model	2.25	1.75-2.90	3.5	2.14-5.72	<0.001	3.95	2.44-6.43	<0.001
Worst-case scenario model	6.48	5.30-7.92	35.28	18.56-72.03	<0.001	40.5	21.4-83.8	<0.001
Diseases of the esophagus								
Base model	5.88	2.83-12.21	6.82	2.60-16.67	<0.001	-	-	-
Best-case scenario model	0.93	0.49-1.78	0.92	0.39-1.93	1	-	-	-
Worst-case scenario model	17.53	10.80-28.48	30.78	16.12-60.39	<0.001	31.5	16.70-61.20	<0.001
Intestinal obstruction								
Base model	45.74	12.97-161.30	54.99	13.54-319.47	<0.001	-	-	-
Best-case scenario model	1.28	0.69-2.37	1.31	0.58-2.69	0.436	1.44	0.67-2.81	0.309
Worst-case scenario model	126.05	39.78-399.39	229.53	68.84-1180.24	<0.001	-	-	-
Musculoskeletal outcome								
Deformities of curvature of spine								
Base model	41.17	4.36-389.12	42.91	3.38-2251.18	0.001	-	-	-
Best-case scenario model	0.39	0.13-1.22	0.37	0.07-1.17	0.101	-	-	-
Worst-case scenario model	308.49	42.66-2230.59	486.36	77.81-16384	<0.001	-	-	-
Other acquired musculoskeletal deformities								
Base model	∞	0-∞	∞	0.35-∞	0.068	-	-	-
Best-case scenario model	0.13	0.02-0.94	0.12	0-0.72	0.011	-	-	-
Worst-case scenario model	∞	Na-∞	∞	107.93-∞	<0.001	-	-	-

Table 5. Neurodevelopmental outcomes for the 0-5 years-of-age group

Neurodevelopmental outcomes	Risk ratio	95% CI	P	Odds ratio	95%CI	P	Odds ratio (PS-adj)	95%CI	P
Developmental disorders									
Base model	4.47	1.53-13.70	0.019	4.84	1.10-16.74	0.019	-	-	-
Best-case scenario model	0.46	0.17-1.21	0.123	0.43	0.11-1.19	0.123	-	-	-
Worst-case scenario model	26.54	14.23-49.50	<0.001	42.37	19.84-96.36	<0.001	42	20.40-91.70	<0.001
Specific delays in development									
Base model	3.35	1.84-6.10	<0.001	3.95	1.72-8.46	<0.001	3.83	1.70-8.00	<0.001
Best-case scenario model	0.91	0.51-1.62	0.87	0.9	0.42-1.77	0.87	0.87	0.41-1.67	0.687
Worst-case scenario model	8.62	6.0-12.41	<0.001	15.44	8.83-27.16	<0.001	15.7	8.96-28.0	<0.001
Autism									
Base model	3.92	0.83-18.42	0.12	4.02	0.40-21.84	0.12	-	-	-
Best-case scenario model	0.24	0.06-0.97	0.026	0.22	0.03-0.86	0.026	-	-	-
Worst-case scenario model	42.65	19.34-94.04	<0.001	65.75	26.73-186.26	<0.001	-	-	-
Attention-Deficit Hyperactivity Disorder									
Base-model	-	-	-	-	-	-	-	-	-
Best-case scenario model	-	-	-	-	-	-	-	-	-
Worst-case scenario model	-	-	-	-	-	-	-	-	-
Epilepsy									
Base model	5.49	1.09-27.64	0.076	5.64	0.52-35.43	0.076	-	-	-
Best-case scenario model	0.25	0.06-0.99	0.025	0.23	0.03-0.89	0.025	-	-	-
Worst-case scenario model	59.71	23.82-149.69	<0.001	92.28	33.59-317.12	<0.001	-	-	-
Cerebral palsy									
Base model	3.43	0.39-30.16	0.297	3.47	0.07-35.86	0.297	-	-	-
Best-case scenario model	0.13	0.02-0.89	0.007	0.12	0-0.68	0.007	-	-	-
Worst-case scenario model	72.15	26.00-200.16	<0.001	109.43	36.57-441.73	<0.001	-	-	-
Myoneuronal disorders									
Base model	Na	Na	Na	Na	Na	Na	-	-	-
Best-case scenario model	0	0-Na	0.001	0	0-0.47	0.001	-	-	-
Worst-case scenario model	∞	Na-∞	<0.001	∞	101.86-∞	<0.001	-	-	-
Hearing loss							-	-	-

Base model	4.57	2.36-8.85	<0.001	5.36	2.20-12.20	<0.001	4.9	2.06-10.8	<0.001
Best-case scenario model	0.95	0.52-1.74	1	0.94	0.42-1.91	1	0.93	0.42-1.82	0.833
Worst-case scenario model	12.6	8.27-19.21	<0.001	22.43	12.31-41.42	<0.001	22.7	12.60-41.90	<0.001
Visual impairment									
Base model	0	0-Na	1	0	0-15.20	1	-	-	-
Best-case scenario model	0	0-Na	<0.001	0	0-0.43	<0.001	-	-	-
Worst-case scenario model	278.63	38.41-2021.491	<0.001	415.33	66.11-15237.05	<0.001	-	-	-

For the 6-12 years-of-age group we had 32 cases and 394 controls; a significant difference was found for the risk ratio of asthma (RR=1.89, 95%CI: 1.16-3.09, p=0.024), diseases of the esophagus (RR=12.31, 95%CI: 1.79-84.54, p=0.03), and hearing loss (RR=6.16, 95%CI:2.47-15.31, p=0.001). Tables 6, 7 and 8 summarize these results.

Table 6. Pulmonary outcomes for 6-12 years-of-age group

Pulmonary outcomes	Risk ratio	95% CI	Odds ratio	95%CI	P	Odds ratio (PS-adj)	95%CI	P
Chronic obstructive pulmonary disease								
Base model	4.1	0.44-38.33	4.18	0.08-53.84	0.269	-	-	-
Best-case scenario model	0.1	0.01-0.71	0.08	0-0.50	<0.001	-	-	-
Worst-case scenario model	60	18.32-196.53	92.02	25.0-512.35	<0.001	-	-	-
Chronic airway obstruction								
Base model	0	Na	0	0-476.62	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.32	<0.001	-	-	-
Worst-case scenario model	170	23.12-1250.24	252.65	37.38-10056.01	<0.001	-	-	-
Asthma								
Base model	1.89	1.16-3.09	2.42	1.03-5.47	0.024	2.97	1.32-6.50	0.007
Best-case scenario model	0.69	0.42-1.14	0.59	0.27-1.19	0.156	0.63	0.30-1.23	0.191
Worst-case scenario model	3.72	2.73-5.06	7.62	3.94-14.99	<0.001	7.75	4.07-15.1	<0.001
Pneumonia								
Base model	2.24	0.82-6.10	2.41	0.56-7.81	0.121	-	-	-
Best-case scenario model	0.34	0.13-0.88	0.28	0.07-0.79	0.011	-	-	-
Worst-case scenario model	9.55	5.67-16.07	15.77	7.33-34.28	<0.001	15.6	7.41-33.30	<0.001
Acute respiratory infections								
Base model	1.17	0.94-1.44	1.67	0.70-4.42	0.252	-	-	-
Best-case scenario model	0.69	0.51-0.92	0.38	0.20-0.73	0.002	0.37	0.20-0.69	0.002
Worst-case scenario model	1.61	1.39-1.88	4.75	2.14-11.98	<0.001	-	-	-
Influenza								
Base model	0.49	0.07-3.52	0.48	0.01-3.12	0.709	-	-	-
Best-case scenario model	0.08	0.01-0.58	0.06	0-0.38	<0.001	-	-	-
Worst-case scenario model	7.2	4.24-12.23	10.7	4.95-23.03	<0.001	11.1	5.19-23.50	<0.001
Pneumonitis								
Base model	Na	Na	Na	Na	Na	-	-	-
Best-case scenario model	0	0-Na	0	0-0.33	<0.001	-	-	-
Worst-case scenario model	∞	Na-∞	∞	58.39-∞	<0.001	-	-	-
Other diseases of the lung								
Base model	0	Na	0	0-476.62	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.32	<0.001	-	-	-
Worst-case scenario model	170	23.12-1250.24	252.65	37.38-10056.01	<0.001	-	-	-

Other diseases of the respiratory system								
Base model	0	Na	0	0-5.02	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.29	<0.001	-	-	-
Worst-case scenario model	15.45	7.68-31.10	22.79	9.21-58.87	<0.001	-	-	-
Chronic pulmonary heart disease								
Base model	Na	Na	Na	Na	Na	-	-	-
Best-case scenario model	0	0-Na	0	0-0.33	<0.001	-	-	-
Worst-case scenario model	∞	Na-∞	∞	58.39-∞	<0.001	-	-	-

Table 7. Gastrointestinal and musculoskeletal outcomes for 6-12 years-of-age group

Gastrointestional outcomes	Risk ratio	95% CI	Odds ratio	95%CI	P	Odds ratio (PS-adj)	95%CI	P
Symptoms concerning nutrition and development								
Base model	1.23	0.12-9.32	1.24	0.03-9.23	0.581	-	-	-
Best-case scenario model	0.09	0.01-0.66	0.08	0-0.45	<0.001	-	-	-
Worst-case scenario model	18	8.80-36.80	21.42	10.95-72.84	<0.001	-	-	-
Diseases of the esophagus								
Base model	12.31	1.79-84.54	12.87	0.90-183.21	0.03	-	-	-
Best-case scenario model	0.2	0.05-0.80	0.17	0.02-0.67	0.003	-	-	-
Worst-case scenario model	95	22.80-395.84	150.3	33.86-1397.21	<0.001	-	-	-
Intestinal obstruction								
Base model	0	Na	0	0-476.62	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.32	<0.001	-	-	-
Worst-case scenario model	170	23.12-1250.24	252.65	37.38-10056.01	<0.001	-	-	-
Musculoskeletal outcomes								
Deformities of curvature of spine						-	-	-
Base model	0	Na	0	0-30.40	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.32	<0.001	-	-	-
Worst-case scenario model	56.67	17.21-186.59	84.28	22.73-470.67	<0.001			
Other acquired musculoskeletal deformities								
Base model	Na	Na	Na	Na	Na	-	-	-
Best-case scenario model	0	0-Na	0	0-0.33	<0.001	-	-	-
Worst-case scenario model	∞	Na	∞	58.39-∞	<0.001	-	-	-

Table 8. Neurodevelopmental outcomes for 6-12 years-of-age group

Neurodevelopmental outcomes	Risk ratio	95% CI	Odds ratio	95%CI	P	Odds ratio (PS-adj)	95%CI	P
Developmental disorders								
Base model	2.74	0.62-12.13	2.84	0.29-14.64	0.197	-	-	-
Best-case scenario model	0.29	0.09-0.87	0.24	0.05-0.77	0.008	-	-	-
Worst-case scenario model	15.83	8.18-30.65	24.82	10.38-61.95	<0.001	27.2	11.7-66.1	<0.001
Specific delays in development								
Base model	1.64	0.39-6.87	1.68	0.18-7.79	0.37	-	-	-
Best-case scenario model	0.18	0.05-0.71	0.15	0.02-0.57	0.001	-	-	-
Worst-case scenario model	12.67	6.88-23.31	19.78	8.60-46.62	<0.001	19.9	8.56-43.20	<0.001
Autism								
Base model	3.08	0.35-26.73	3.13	0.06-32.92	0.325	-	-	-
Best-case scenario model	0.1	0.01-0.70	0.08	0-0.49	<0.001	-	-	-
Worst-case scenario model	45	15.86-127.68	68.9	21.05-295.36	<0.001	-	-	-
Attention-Deficit Hyperactivity Disorder								
Base-model	0.36	0.05-2.56	0.34	0-2.19	0.499	-	-	-
Best-case scenario model	0.08	0.01-0.54	0.06	0-0.35	<0.001	-	-	-
Worst-case scenario model	5.29	3.24-8.64	7.73	3.68-16.02	<0.001	7.43	3.57-5.2	<0.001
Epilepsy								
Base model	0	0-Na	0	0-13.79	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.31	<0.001	-	-	-
Worst-case scenario model	34	13.11-88.17	50.43	16.56-186.57	<0.001	-	-	-
Cerebral palsy								
Base model	0	0-Na	0	0-66.30	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.32	<0.001	-	-	-
Worst-case scenario model	85	20.23-357.12	126.32	28.12-1165.68	<0.001	-	-	-
Myoneuronal disorders								
Base model	0	0-Na	0	0-476.62	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.32	<0.001	-	-	-
Worst-case scenario model	170	23.12-1250.24	252.65	37.38-10056.01	<0.001	-	-	-
Hearing loss								

Base model	6.16	2.47-15.31	7.28	2.07-23.09	0.001	-	-	-
Best-case scenario model	0.56	0.26-1.20	0.49	0.17-1.21	0.141	-	-	-
Worst-case scenario model	19.17	10.18-36.10	34.57	14.72-85.50	<0.001	38.1	16.60-92.80	<0.001
Visual impairment								
Base model	0	0-Na	0	0-10.74	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.30	<0.001	-	-	-
Worst-case scenario model	∞	Na-∞	∞	58.39-∞	<0.001	-	-	-

Lastly, for the 13-19 years-of-age group we had 12 cases and 156 controls. No significant difference was found for the risk ratio of any of the physical health outcomes studied (Tables 9, 10 and 11). These results suggest that children born with CDH face numerous physical health morbidities, primarily up to adolescence.

Table 9. Pulmonary outcomes for 13-19 years-of-age group

Pulmonary outcomes	Risk ratio	95% CI	Odds ratio	95%CI	P	Odds ratio (PS-adj)	95%CI	P
Chronic obstructive pulmonary disease								
Base model	0	Na	0	0-71.45	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.55	0.003	-	-	-
Worst-case scenario model	45	10.39-194.75	73.57	13.33-755.52	<0.001	-	-	-
Chronic airway obstruction								
Base model	Na	Na	Na	Na	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.58	0.005	-	-	-
Worst-case scenario model	∞	Na-∞	∞	28.94-∞	<0.001	-	-	-
Asthma								
Base model	1.77	0.62-5.08	2.02	0.33-8.96	0.391	-	-	-
Best-case scenario model	0.39	0.14-1.14	0.3	0.05-1.06	0.053	-	-	-
Worst-case scenario model	5.45	3.17-9.38	11.18	3.85-33.87	<0.001	-	-	-
Pneumonia								
Base model	0	Na	0	0-8.21	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.48	0.001	-	-	-
Worst-case scenario model	11.25	4.86-26.06	18.37	5.29-66.53	<0.001	-	-	-
Acute respiratory infections								
Base model	1.22	0.80-1.87	1.67	0.42-7.88	0.551	-	-	-
Best-case scenario model	0.57	0.33-0.99	0.3	0.10-0.83	0.015	-	-	-
Worst-case scenario model	1.95	1.50-2.54	5.97	1.86-25.21	<0.001	-	-	-
Influenza								
Base model	0	Na	0	0-33.21	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.54	0.003	-	-	-
Worst-case scenario model	30	8.79-102.35	49.2	10.62-317.28	<0.001	-	-	-
Pneumonitis								
Base model	Na	Na	Na	Na	Na	-	-	-
Best-case scenario model	0	0-Na	0	0-0.58	0.005	-	-	-
Worst-case scenario model	∞	Na-∞	∞	28.94-∞	<0.001	-	-	-
Other diseases of the lung								
Base model	0	Na	0	0-71.45	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.55	0.003	-	-	-
Worst-case scenario model	45	10.40-194.75	73.57	13.33-755.52	<0.001	-	-	-
Other diseases of the respiratory system								

Base model	0	Na	0	0-33.21	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.54	0.003	-	-	-
Worst-case scenario model	30	8.79-102.35	49.2	10.62-317.28	<0.001	-	-	-
Chronic pulmonary heart disease								
Base model	Na	Na	Na	Na	Na	-	-	-
Best-case scenario model	0	0-Na	0	0-0.58	0.005	-	-	-
Worst-case scenario model	∞	Na-∞	∞	28.94-∞	<0.001	-	-	-

Table 10. Gastrointestinal and musculoskeletal outcomes for 13-19 years-of-age group

Gastrointestinal outcomes	Risk ratio	95% CI	Odds ratio	95%CI	P	Odds ratio (PS-adj)	95%CI	P
Symptoms concerning nutrition and development								
Base model	0	Na	0	0-21.01	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.53	0.003	-	-	-
Worst-case scenario model	22.5	7.57-66.86	36.92	8.84-189.37	<0.001	-	-	-
Diseases of the esophagus								
Base model	3.25	0.77-13.63	3.65	0.34-22.18	0.153	-	-	-
Best-case scenario model	0.32	0.08-1.23	0.25	0.03-1.10	0.071	-	-	-
Worst-case scenario model	13.75	6.22-30.38	26.75	7.93-97.29	<0.001	-	-	-
Intestinal obstruction								
Base model	Na	Na	Na	Na	Na	-	-	-
Best-case scenario model	0	0-Na	0	0-0.58	0.005	-	-	-
Worst-case scenario model	∞	Na-∞	∞	28.94-∞	<0.001	-	-	-
Musculoskeletal outcomes								
Deformities of curvature of spine								
Base model	0	Na	0	0-71.45	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.55	0.003	-	-	-
Worst-case scenario model	45	10.40-194.75	73.57	13.33-755.52	<0.001	-	-	-
Other aquired musculoskeletal deformities								
Base model	Na	Na	Na	Na	Na	-	-	-
Best-case scenario model	0	0-Na	0	0-0.58	0.005	-	-	-
Worst-case scenario model	∞	Na-∞	∞	28.94-∞	<0.001	-	-	-

Table 11. Neurodevelopmental outcomes for 13-19 years-of-age group

Neurodevelopmental outcomes	Risk ratio	95% CI	Odds ratio	95%CI	P	Odds ratio (PS-adj)	95%CI	P
Developmental disorders								
Base model	1.86	0.25-13.88	1.93	0.04-17.43	0.455	-	-	-
Best-case scenario model	0.33	0.09-1.25	0.26	0.03-1.12	0.071	-	-	-
Worst-case scenario model	12.5	5.54-28.22	22.19	6.51-80.08	<0.001	-	-	-
Specific delays in development								
Base model	0	Na	0	0-503.02	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.57	0.005	-	-	-
Worst-case scenario model	90	11.98-676.21	146.52	18.03-6557.38	<0.001	-	-	-
Autism								
Base model	4.33	0.49-38.55	4.56	0.08-62.62	0.259	-	-	-
Best-case scenario model	0.18	0.03-1.20	0.13	0-0.88	0.031	-	-	-
Worst-case scenario model	33.33	9.94-111.75	59.32	13.02-379.48	<0.001	-	-	-
Attention-Deficit Hyperactivity Disorder								
Base-model	0	Na	0	0-3.80	0.604	-	-	-
Best-case scenario model	0	0-Na	0	0-0.41	<0.001		-	-
Worst-case scenario model	6	3.0-12.01	9.57	3.05-29.70	<0.001	-	-	-
Epilepsy								
Base model	0	0-Na	0	0-33.21	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.54	0.003	-	-	-
Worst-case scenario model	30	8.79-102.35	49.2	10.62-317.29	<0.001	-	-	-
Cerebral palsy								
Base model	0	0-Na	0	0-33.21	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.54	0.003	-	-	-
Worst-case scenario model	30	8.79-102.35	49.2	10.62-317.29	<0.001	-	-	-
Myoneuronal disorders								
Base model	Na	Na	Na	Na	Na	-	-	-
Best-case scenario model	0	0-Na	0	0-0.58	0.005	-	-	-
Worst-case scenario model	∞	Na-∞	∞	28.94-∞	<0.001	-	-	-
Hearing loss								
Base model	0	Na	0	0-503.02	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.57	0.005	-	-	-
Worst-case scenario model	90	11.98-676.21	146.52	18.03-6557.38	<0.001	-	-	-
Visual impairment								
Base model	Na	Na	Na	Na	Na	-	-	-

Best-case scenario model	0	0-Na	0	0-0.58	0.005	-	-	-
Worst-case scenario model	∞	Na-∞	∞	28.94-∞	<0.001	-	-	-

Rate of common respiratory infections

We found that cases 0-5 years-of-age have a relative rate of acute respiratory tract infections 1.14 times that of controls (95%CI: 1.03-1.27, p=0.013) and a relative rate of pneumonia 5.89 times higher than controls (95%CI: 4.80-7.22, p<0.001); with the rates remaining constant from birth to 5 years-of-age. The relative rate of acute respiratory tract infections was found to be higher for cases in the 6-12 years-of-age group (relative rate = 1.32, 95%CI: 1.11-1.58, p<0.001). No difference was found for the relative rate of influenza between 0-5 years-of-age, pneumonia and influenza between 6-12 years-of-age, and for any of the common respiratory infections between 13-19 years-of-age (Table 12, 13 and 14).

Table 12: Relative rate of common respiratory infections for 0-5 years-of-age group

	Proportional Intensity Model			Pearson's correlation	
Pulmonary outcomes	**Relative rate**	**95% CI**	**P**	**chisq**	**P**
Pneumonia	5.89	4.80-7.22	<0.001	3.72	0.053
Acute Respiratory Infections	1.14	1.03-1.27	0.013	0.01	0.91
Influenza	0.62	0.25-1.51	0.292	1.05	0.306

Table 13: Relative rate of common respiratory infections for 6-12 years-of-age group

	Proportional Intensity Model			Pearson's correlation	
Pulmonary outcomes	**Relative rate**	**95% CI**	**P**	**chisq**	**P**
Pneumonia	0.9	0.39-2.05	0.794	2.8	0.094
Acute Respiratory Infections	1.32	1.11-1.58	0.002	1.96	0.162
Influenza	0.98	0.30-3.18	0.976	0.63	0.428

Table 14: Relative rate of common respiratory infections for 13-19 years-of-age group

	Proportional Intensity Model			Pearson's correlation	
Pulmonary outcomes	**Relative rate**	**95% CI**	**P**	**chisq**	**P**
Pneumonia	0	Na	1	0	1
Acute Respiratory Infections	1.9	1.38-2.62	<0.001	0.004	0.947
Influenza	0	Na	1	0	1

Mental health outcomes

We found no significant difference in the relative risk of obtaining a diagnosis of conduct disorder (p=1) or mood and anxiety disorders (p=1) between 6-12 years-of-age (Table 15). Additionally, between 13-19 years-of-age we found no difference in the diagnosis of: conduct disorder (p=0.363, mood and anxiety disorders (p=1), substance use disorders (p=1), psychotic disorders (p=1) or schizophrenia (p=1) (Table 16). These results suggest that cases and controls have similar mental health outcomes.

Table 15: Mental health outcomes for 6-12 years-of-age group

Mental health outcome	Risk ratio	95% CI	Odds ratio	95% CI	P	Odds ratio (PS-adj)	95% CI	P
Conduct Disorder								
Base-model	0	0-Na	0	0-5.02	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.29	<0.001	-	-	-
Worst-case scenario model	15.45	7.68-31.10	22.79	9.21-58.87	<0.001	25.6	10.40-66.00	<0.001
Mood and Anxiety Disorders								
Base-model	0.95	0.13-7.01	0.94	0.02-6.70	1	-	-	-
Best-case scenario model	0.09	0.01-0.64	0.07	0-0.44	<0.001	-	-	-
Worst-case scenario model	13.85	7.23-26.53	21	8.84-51.39	<0.001	23.7	10.20-57.30	<0.001
Substance Use Disorders								
Base-model	-	-	-	-	-	-	-	-
Best-case scenario model		-		-	-		-	-
Worst-case scenario model	-	-	-	-	-	-	-	-
Psychotic Disorders								
Base-model	-	-	-	-	-	-	-	-
Best-case scenario model	-	-		-	-		-	-
Worst-case scenario model	-	-	-	-	-	-	-	-
Schizophrenia								
Base-model	-	-	-	-	-	-	-	-
Best-case scenario model	-	-		-	-		-	-
Worst-case scenario model	-	-	-	-	-	-	-	-

Table 16: Mental health outcomes for 13-19 years-of-age group

Mental health outcome	Risk ratio	95% CI	Odds ratio	95% CI	P	Odds ratio (PS-adj)	95% CI	P
Conduct Disorder								
Base model	2.6	0.33-20.51	2.72	0.05-27.71	0.363	-	-	-
Best-case scenario model	0.16	0.02-1.16	0.13	0-0.84	0.018		-	-
Worst-case scenario model	20	7.54-53.04	35.63	9.31-157.74	<0.001	-	-	-
Mood and Anxiety Disorders								
Base model	0.81	0.22-2.99	0.78	0.08-3.92	1	-	-	-
Best-case scenario model	0.23	0.06-0.88	0.15	0.02-0.66	0.004	-	-	-
Worst-case scenario model	3.44	2.05-5.77	6.05	2.14-17.37	<0.001	6.83	2.50-19.2	<0.001
Substance Use Disorders								
Base model	0	0-Na	0	0-8.21	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.48	0.001		-	-
Worst-case scenario model	11.25	4.86-26.06	18.37	5.29-66.53	<0.001	-	-	-
Psychotic Disorders								
Base model	0	0-Na	0	0-9.73	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.49	0.001		-	-
Worst-case scenario model	12.86	5.33-31.0	21.03	5.88-79.79	<0.001	-	-	-
Schizophrenia								
Base model	0	0-Na	0	0-21.03	1	-	-	-
Best-case scenario model	0	0-Na	0	0-0.53	0.003		-	-
Worst-case scenario model	22.5	7.57-66.86	36.92	8.84-189.37	<0.001	-	-	-

Educational outcomes

A total of 218 children were assessed via the EDI; 18 cases and 200 controls. We found no difference in the risk ratio of being deemed "not ready" for grade 1 (p=1). A total of 317 children completed the grade 3 assessments; 24 cases and 293 controls. We found no difference in failure to meet expectations for the grade 3 reading and numeracy assessments (p=0.189, p=0.445). A total of 329 children completed the grade 7 assessments; 30 cases and 299 controls. We found no difference in the grade 7 student engagement and number sense and numbers skills assessments (p=1, p=0.536). A total of 286 children completed the grade 8 assessment; 21 cases and 265 controls. We found no difference in the grade 8 reading comprehension and expository writing assessment (p=0.725). We had a total of 299 children who were eligible to complete grade 9; 21 cases and 278 controls. We found no difference in the risk ratio of not completing grade 9 (p=0.478); of those who completed grade 9, no difference in performance was found (p=0.764).

Lastly, a total of 174 children were eligible to complete grade 12; 12 cases and 162 controls. We found no difference in the number of cases who did not graduate high-school (p=1). The results from the educational outcomes suggest that cases and controls perform similarly in school (Table 17).

Table 17: Educational outcomes

Education measure	Risk ratio	95% CI	Odds ratio	95%CI	P	Odds ratio (PS-adj)	95%CI	P
EDI	1.01	0.46-2.20	1.01	0.27-3.21	1	-	-	-
Grade 3								
Reading assessment	1.66	0.90-3.05	1.98	0.70-5.18	0.189	-	-	-
Numeracy assessment	1.34	0.69-2.58	1.47	0.49-3.94	0.445	-	-	-
Grade 7								
Student engagement assessment	0.95	0.58-1.56	0.93	0.38-2.14	1	1.04	0.46-2.29	0.903
Number sense and number skills assessment	1.2	0.73-1.99	1.32	0.54-3.06	0.536	1.76	0.75-4.02	0.18
Grade 8								
Reading comprehension and expository writing	0.78	0.31-1.92	0.72	0.17-2.33	0.725	-	-	-
Grade 9								
Completion								
Base model	1.25	0.75-2.11	1.44	0.52-3.88	0.478	1.7	0.61-4.60	0.299
Best-case model	0.9	0.55-1.50	0.84	0.33-1.98	0.941	1	0.41-2.35	0.995
Worst-case model	1.73	1.15-2.60	2.45	1.04-5.79	0.031	3.16	1.31-7.61	0.01
Performance	0.78	0.35-1.77	0.67	0.14-2.63	0.764	-	-	-
Grade 12								
High-school graduation								
Base model	0.94	0.34-2.59	0.92	0.15-3.93	1	-	-	-
Best-case model	0.33	0.11-0.95	0.22	0.04-0.78	0.01	-	-	-
Worst-case model	2.79	1.77-4.40	5.13	1.85-14.78	<0.001	-	-	-

Sensitivity analysis to account for excluded population

Physical health outcomes

The physical health outcomes sensitivity analyses for the 0-5 years-of-age group included a total of 898 children; 82 cases and 816 controls. The best-case scenario model produced only one significantly higher risk ratio for the cases compared to controls; specifically, symptoms concerning nutrition and development (RR=2.25, 95%CI:1.75-2.90, p<0.001). As expected, the best-case scenario model revealed higher risk ratios for the controls in multiple outcomes, including: acute respiratory infections, influenza, pneumonitis, other acquired musculoskeletal deformities, autism, epilepsy, cerebral palsy, myoneuronal disorders and visual impairment. The worst-case scenario model demonstrated a higher risk ratio for all of the physical health outcomes, including: chronic obstructive pulmonary disease (RR=72.14, 95%CI:26.00-200.16, p<0.001), chronic airway obstruction (RR=79.61, 95%CI:28.87-219.52, p<0.001), asthma (RR=2.78, 95%CI:2.19-3.54, p<0.001), pneumonia (RR=4.19, 95%CI: 3.27-5.38), acute respiratory infections (RR=1.17, 95%CI:1.08-1.27, p=0.005), influenza (RR=4.98, 95%CI: 3.45-7.18, p<0.001), pneumonitis (RR=∞, 95%CI:Na-∞, p<0.001), other diseases of the lung (RR=154.24, 95%CI:37.59-632.90, p<0.001), other diseases of the respiratory system (RR=5.03, 95%CI:3.77-6.71, p<0.001), chronic pulmonary heart disease (RR=∞, 95%CI:Na-∞, p<0.001), symptoms concerning nutrition and development (RR=6.48, 95%CI:5.30-7.92, p<0.001), diseases of the esophagus (RR=17.53, 95%CI:10.80-28.48, p<0.001), intestinal obstruction (RR=126.05, 95%CI:39.78-399.39, p<0.001), deformities of curvature of spine (RR=308.49, 95%CI:42.66-2230.59, p<0.001), other acquired musculoskeletal deformities (RR=∞, 95%CI:Na-∞, p<0.001), developmental disorders (RR=26.54, 95%CI:14.23-49.50, p<0.001), specific delays in development (RR=8.62, 95%CI:6.0-12.41, p<0.001), autism (RR=42.65, 95%CI:19.34-94.04, p<0.001), epilepsy (RR=59.71, 95%CI:23.82-149.69, p<0.001), cerebral palsy (RR=72.15, 95%CI: 26.0-200.12, p<0.001), myoneuronal disorders (RR= ∞, 95%CI: Na-∞, p<0.001), hearing loss (RR=12.6, 95%CI:8.27-19.21, p<0.001) and visual impairment (RR=278.63, 95%CI: 38.41-2021.49, p<0.001) (Tables 2, 4 and 5).

For the 6-12 years-of-age group, we had a total of 539 children; 49 cases and 490 controls. The best-case scenario model demonstrated that CDH cases have no increased risk of developing any of the physical health outcomes. All but two outcomes – asthma and hearing loss – revealed an

increased risk for the controls; again, this is to be expected based on the nature of the best-case scenario model. For the worst-case scenario model, we found that cases had a higher risk ratio for all of the physical health outcomes, including: chronic obstructive pulmonary disease (RR=60, 95%CI:18.32-196.53, p<0.001), chronic airway obstruction (RR=170, 95%CI:23.12-1250.24, p<0.001), asthma (RR=3.72, 95%CI:2.73-5.06, p<0.001), pneumonia (RR=9.55, 95%CI: 5.67-16.07, p<0.001), acute respiratory infections (RR=1.16, 95%CI:1.39-1.88, p<0.001), influenza (RR=7.2, 95%CI: 4.24-12.23, p<0.001), pneumonitis (RR=∞, 95%CI:Na-∞, p<0.001), other diseases of the lung (RR=170, 95%CI:23.12-1250.24, p<0.001), other diseases of the respiratory system (RR=15.45, 95%CI:7.68-31.10, p<0.001), chronic pulmonary heart disease (RR=∞, 95%CI:Na-∞, p<0.001), symptoms concerning nutrition and development (RR=18, 95%CI:8.80-36.80, p<0.001), diseases of the esophagus (RR=95, 95%CI:22.80-395.84, p<0.001), intestinal obstruction (RR=170, 95%CI:23.12-1250.24, p<0.001), deformities of curvature of spine (RR=56.67, 95%CI:17.21-186.59, p<0.001), other acquired musculoskeletal deformities (RR=∞, 95%CI:Na-∞, p<0.001), developmental disorders (RR=15.83, 95%CI:8.18-30.65, p<0.001), specific delays in development (RR=12.67, 95%CI:6.88-23.31, p<0.001), autism (RR=45, 95%CI:15.86-127.68, p<0.001), ADHD (RR=5.29, 95%CI: 3.24-8.64,p<0.001), epilepsy (RR=34, 95%CI: 13.11-88.17, p<0.001), cerebral palsy (RR=85, 95%CI: 20.23-357.12, p<0.001), myoneuronal disorders (RR=170, 95%CI: 23.12-1250.24, p<0.001), hearing loss (RR=19.17, 95%CI:10.18-36.10, p<0.001) and visual impairment (RR= ∞, 95%CI: Na- ∞, p<0.001) (Tables 6, 7 and 8).

The 13-19 years-of-age group contained a total of 231 children; 21 cases and 210 controls. The best-case scenario model demonstrated no increased risk of cases acquiring any of the physical health outcomes studied; all but one outcome (developmental disorders), revealed an increased risk for controls. For the worst-case scenario model we found that cases had a higher risk for all of the outcomes, including: chronic obstructive pulmonary disease (RR=45, 95%CI:10.39-194.75, p<0.001), chronic airway (RR=∞, 95%CI:Na-∞, p<0.001), asthma (RR=5.45, 95%CI:3.17-9.38, p<0.001), pneumonia (RR=11.25, 95%CI: 4.86-26.06, p<0.001), acute respiratory infections (RR=1.95, 95%CI:1.50-2.54, p<0.001), influenza (RR=30, 95%CI: 48.79-102.2.54, p<0.001), pneumonitis (RR=∞, 95%CI:Na-∞, p<0.001), other diseases of the lung (RR=45, 95%CI:10.40-194.75, p<0.001), other diseases of the respiratory system (RR=30,

95%CI:8.79-102.35, p<0.001), chronic pulmonary heart disease (RR=∞, 95%CI:Na-∞, p<0.001), symptoms concerning nutrition and development (RR=22.5, 95%CI:7.57-66.86, p<0.001), diseases of the esophagus (RR=13.75, 95%CI:6.22-30.38, p<0.001), intestinal obstruction (RR=∞, 95%CI:Na-∞, p<0.001), deformities of curvature of spine (RR=45, 95%CI:10.40-194.75, p<0.001), other acquired musculoskeletal deformities (RR=∞, 95%CI:Na-∞, p<0.001),), developmental disorders (RR=12.5, 95%CI:5.54-28.22 p<0.001), specific delays in development (RR=90, 95%CI:11.98-676.21, p<0.001), autism (RR=33.33, 95%CI:9.94-111.75, p<0.001), ADHD (RR=6, 95%CI: 3.0-12.01, p<0.001), epilepsy (RR=30, 95%CI: 8.79-102.35, p<0.001), cerebral palsy (RR=30, 95%CI: 8.70-102.35, p<0.001), myoneuronal disorders (RR= ∞, 95%CI: Na- ∞, p<0.001), hearing loss (RR=90, 95%CI:11.98-676.21, p<0.001) and visual impairment (RR= ∞, 95%CI: Na- ∞, p<0.001) (Tables 9, 10 and 11).

Mental health outcomes

The mental health outcomes sensitivity analyses for the 6-12 years-of-age group contained a total of 539 children; 49 cases and 490 controls. The best-case scenario model demonstrated that cases have no increased risk of being diagnosed with ADHD, conduct disorder or mood and anxiety disorders; conversely, this model indicated that controls have a risk of these diagnoses. The worst-case scenario model revealed an increased risk of diagnoses for all of the mental health outcomes, including: ADHD (RR=5.29, 95%CI: 3.24-8.64, p<0.001), conduct disorder (RR=15.45, 95%CI: 7.68-31.10, p<0.001) and mood and anxiety disorders (RR=13.85, 95%CI: 7.23-26.53, p<0.001) (Table 15).

The sensitivity analyses for the 13-19 years-of-age group contained a total of 231 children; 21 cases and 210 controls. All of the mental health outcomes – ADHD, conduct disorder, mood and anxiety disorders, substance use disorders, psychotic disorders and schizophrenia – demonstrated an increased risk of diagnosis for the controls in the best-case scenario model. The worst-case scenario model demonstrated an increased risk of diagnoses for the controls, specifically: ADHD (RR=6, 95%CI: 3.0-12.01, p<0.001), conduct disorder (RR=20, 95%CI: 7.54-53.04, p<0.001), mood and anxiety disorders (RR=3.44, 95%CI: 2.05-5.77, p<0.001), substance use disorders (RR=11.25, 95%CI: 4.86-26.06, p<0.001), psychotic disorders (RR=12.86, 95%CI: 5.33-31.0, p<0.001) and schizophrenia (RR=22.5, 95%CI: 7.57-66.86, p<0.001) (Table 16).

Educational outcomes

The sensitivity analyses for grade 9 completion included a total of 364 children; 28 cases and 336 controls. The best-case scenario model demonstrated no difference between cases and controls and the completion of grade 9. The worst-case scenario model indicated that cases have a higher risk of not completing grade 9 (RR=1.73, 95%CI: 1.15-2.60, p=0.031).

The sensitivity analyses for high-school graduation included a total of 210 children; 15 cases and 195 controls. The best-case scenario model and the worst-case scenario model showed no difference in the risk of not graduating high-school (Table 17).

Propensity analysis

Physical health outcomes

The variables eligible for inclusion in the propensity analysis (had adequate sample sizes) for the 0-5 years-of-age group included: asthma: base model, best-case scenario model and worst-case scenario model; pneumonia: base model, best-case scenario model and worst-case scenario model; acute respiratory tract infections best-case scenario model; other diseases of the respiratory system: base model, best-case scenario model and worst-case scenario model; symptoms concerning nutrition and development: base model, best-case scenario model and worst-case scenario model; diseases of the esophagus worst-case scenario model; intestinal obstruction best-case scenario model; hearing loss: base model, best-case scenario model and worst-case scenario model; specific delays in development: base model, best-case scenario model and worst-case scenario model; and developmental disorders worst-case scenario model. Controlling for confounders by use of a propensity score resulted in no change to the significance of any of the physical health outcomes included (Tables 2, 4 and 5).

The variables eligible for inclusion in the propensity analysis for the 6-12 years-of-age group included: asthma: base model, best-case scenario model and worst-case scenario model; pneumonia worst-case scenario model; acute respiratory tract infections best-case scenario model; influenza worst-case scenario model; hearing loss worst-case scenario model; specific delays in development worst-case scenario model; and developmental disorder worst-case

scenario model. No change in significance for any of these outcomes was observed with the inclusion of the propensity score (Tables 6, 7 and 8).

No variables were eligible for inclusion in the propensity analysis for the 13-19 years-of-age group.

Mental health outcomes

The variables eligible for inclusion in the mental health outcomes propensity analysis for the 6-12 years-of-age group included: ADHD worst-case scenario, conduct disorder worst-case scenario and mood and anxiety disorders worst-case scenario. No change in significance was found for any of these variables while controlling for the propensity score (Table 15).

The propensity analysis for the 13-19 years-of-age group included only one outcomes variable – mood and anxiety disorders worst-case scenario; no change in significance was observed (Table 16).

Educational outcomes

The variables eligible for inclusion in the education outcomes propensity analysis included: grade 7: student engagement and number sense and number skills assessment; and grade 9 completion: base model, best-case scenario model and worst-case scenario model. We found no change in significance for any of these variables with the inclusion of the propensity score (Table 17).

Chapter IV: Discussion

We conducted a novel population-based study comparing virtual long-term physical, mental and educational outcomes of CDH survivors to age-matched controls. The results suggest that children born with CDH have a higher risk of numerous physical health morbidities, primarily in the first five years-of-life. We also found that compared to controls, CDH children appear have equivalent mental health and educational outcomes.

Physical health outcomes

Our study found that neonates born with CDH have an increased risk of developing long-term morbidities of the pulmonary, gastrointestinal, musculoskeletal and neurodevelopmental systems compared to children from the general population without CDH.

Our CDH cohort demonstrated an increased risk of being diagnosed with chronic airway obstruction within the first 5 years-of-life. Numerous studies have shown the presence of airway obstruction in CDH cases in infancy, childhood, adolescence and adulthood (Arena et al., 2005; Basek et al.,2008; Ijsselstijn et al., 1997; Panitch et al., 2015; Peetsold et al., 2007; Peetsold et al., 2009a; Spoel et al., 2012; Tan et al., 2019; Trachsel et al., 2005). Spoel et al. (2013) found that airflow obstruction and diffusion capacity deteriorated with age for CDH children compared to age-matched non-CDH patients who underwent similar neonatal intensive care treatment (Spoel et al., 2013). Our study did not find an increased risk of chronic airway obstruction beyond 5 years-of-age, as would be expected based on Spoel et al.'s (2013) findings. Spoel et al. investigated the lung function of 27 CDH adults (mean age of 26.8 years) and 30 date-of-birth matched controls who were previously studied as children (mean age of 11.8 years). While the number of CDH cases were similar when studied as children (32 vs 27), our analysis contained only 12 CDH cases for the 13-19 years-of-age group. Additionally, while the number of controls was much higher in our study (10 date-of-birth matched), Spoel et al. was able to obtain 1 control who was matched by age at follow-up, gestational age, birth weight, duration of mechanical ventilation, supplemental oxygen, and sex; we believe this method provides a more substantiated comparison. Our study examined the risk of diagnosis and not the progression of the disease; CDH children diagnosed with airway obstruction in early childhood may continue to be afflicted by the disease in later childhood but are less clinically diagnosed. In addition, given a

larger sample size for the 13-19 years-of-age group, we believe a difference may have been detected. Asthma - a condition with inherent airflow obstruction – was found in a higher prevalence of CDH children 6-12 years-of-age but not 0-5 years-of-age. While asthma is difficult to diagnose in young children, we did find increased use of asthma related prescription drugs in CDH children 0-5 years-of-age (Asthma Canada, 2020); this suggests that although there is no difference in the risk of diagnosis, children with CDH appear to be having asthma related symptoms in the first five years of life. Additionally, the increased risk of asthma found for children 6-12 years-of-age may suggest that the issue of airflow obstruction (not found to be significant for 6-12 years-of-age) is being identified through the diagnosis of asthma, not chronic airway obstruction. Children 13-19 years-of-age were not found to have an increased risk of an asthma diagnosis or use of asthma related prescription drugs; while this may suggest an improvement in lung function with age, it may also be a result of the reduced sample size for this age group. If the non-significant finding for asthma in the 13-19 years-of-age group were a consequence of an earlier diagnoses and not the absence of disease, we would have seen a significant finding for asthma related prescription drugs; however, this was not the case. Decreased pulmonary function in CDH children is also apparent in the increased risk of a diagnoses of other diseases of the lung, including chronic respiratory failure and pulmonary insufficiency, and other disease of the respiratory system, including bronchospasms. After 5 years-of-age, CDH children were no longer found to be at an increased risk of these diagnoses. Again, while this may suggest an improvement in lung function over time, it may also be a result of disease management and less clinical diagnoses. In addition to the risk of diagnosis, we also examined the rate of diagnosis for common respiratory infections. We found that CDH cases had a higher risk of developing pneumonia in the first five years-of-life. This supports previous reports that in the first year-of -life, pneumonia occurs in at least 7% of CDH infants (Bos et al., 1993; Davis et al., 2004; Vanamo et al., 1996b). Susceptibility to pneumonia, appears to decrease with age, as no increased risk was found beyond the age of 5 years. Similarly, we found that CDH children five years-of-age and under have a higher rate of pneumonia. This suggests that CDH children not only have a higher risk of developing pneumonia, but that they are more susceptible to recurrent bouts of pneumonia. In addition, we found that although CDH cases do not have an increased risk of being diagnosed with a respiratory tract infection, they do have a rate of diagnosis that is significantly greater than controls from birth to 12 years-of-age. This

finding coincides with previous research demonstrating that CDH children are more susceptible to recurrent respiratory tract infections (Gischler et al., 2009; Koziarkiewicz et al., 2014). In summary, our study suggests that the lung function of CDH children is decreased up to 12 years-of-age, but improves with age and some CDH children are more prone to recurrent lung infections.

Our CDH cohort demonstrated an increased risk of being diagnosed with gastrointestinal morbidity, including nutrition and growth dysfunction from birth to 5 years-of-age. This finding is not surprising, as numerous studies have shown that nutritional problems are a significant source of morbidity for CDH survivors (Bojanić et al., 2017; Haliburton et al., 2015; Leeuwen et al., 2017; Muratore et al., 2001). Muratore et al. (2001) found that in the first year-of-life, 24% of their CDH patients had severe oral aversion and, despite aggressive nutritional management, 56% of their CDH population remained below the 25th percentile for weight (Muratore et al., 2001). Similarly, Bojanić et al. (2017) found that at discharge, 23% of their CDH patients had failure-to-thrive (Bojanić et al., 2017). While an increased risk of failure-to-thrive was found for our CDH cohort between 0 and 5 years-of-age, we found no difference in the risk from 6-19 years-of-age. This finding contradicts previous research suggesting that failure-to-thrive extends through childhood and adolescent. Haliburton et al. (2015) found that the prevalence of failure-to-thrive was 7% in children 5-7 years-of-age and 19% in children 10-17 years-of-age (Haliburton et al., 2015). Haliburton et al.'s (2015) study contained a much larger sample size (N=132 for 5-7 years-of-age and N=128 for the 10-17 years-of-age) and used anthropometrics converted to z-score to examine growth failure, a much more in-depth analysis than the 3-digit ICD code used in our analysis. Additionally, Leeuwen et al. (2017) found that poor linear growth persisted to age 12 years, and that early decline of weight gain and linear growth is suggestive of inadequate nutritional intake during infancy (Leeuwen et al., 2017). Leeuwen et al.'s (2017) conducted a prospective study of 172 CDH patients and calculated Z scores of height-for-age, weight-for-height, and distance-to-target height from 6-months to 12 years-of-age. Again, we believe this provides a much better picture than the presence or absence of a diagnoses. Our non-significant finding for children older than 5 years-of-age should not be interpreted as a lack of morbidity but potentially a pre-diagnosed or even undiagnosed condition.

Gastroesophageal reflux and oral aversion are long-term sequela of CDH survivors and said to be the primary cause of growth failure (Bojanić et al., 2017; Jaillard et al., 2003; Muratore et al., 2001; Tan et al., 2019). This coincides with our finding of an increased risk of being diagnosed with diseases of the esophagus, which includes a diagnosis of gastroesophageal reflux. Unlike failure-to-thrive, children with CDH had a higher risk of esophageal disease from birth to 12 years-of-age. While numerous studies report gastroesophageal reflux during infancy and early childhood, Peetsold et al. (2010) demonstrated reflux in late childhood (mean age of 12 ± 3.4 years) (Caruso et al., 2013; Peetsold et al., 2010; Putnam et al., 2016; Tan et al., 2019). The increased risk of esophageal disease from birth to 12 years-of-age may indicate that growth failure – as a consequence of esophageal impairment - continues to be a concern past age 5 but is less diagnosed. Lastly, small bowel obstruction has been found to occur in CDH survivors and said to be a major cause of late death (Bojanić et al., 2017; Burgos & Frenckner, 2017; Jancelewicz et al., 2013; Koziarkiewics et al., 2014). This coincides with our finding that the risk of intestinal obstruction was significantly greater in CDH cases than controls from birth to five years-of-age. Our study found that nutritional, esophageal and intestinal morbidities are present in children born with CDH, primarily in the first five years-of-life.

CDH has been associated with musculoskeletal deformities, such as scoliosis (7-18.6%), chest deformities including pectus excavatum and chest asymmetry (7.5-20%), (Antiel et al., 2016; Aydin et al., 2019, Jancelewicz et al., 2013; Takayasu et al., 2017). Our CDH cohort demonstrated an increased risk of being diagnosed with deformities of curvature of spine, including scoliosis, from birth to 5 years-of-age. The risk of a diagnosis of other acquired musculoskeletal deformities, including acquired deformity of chest and neck, was found to be infinite but not significant; this is a result of a small number of CDH cases who obtained the diagnosis and no controls. The overt nature of these deformities predisposes it to an early diagnosis, therefore the finding that there is no difference in the risk in later childhood is not surprising. Additionally, the majority of these musculoskeletal deformities are said to be mild and do not require surgical intervention (Lally & Engle, 2008). The results of our study suggest that children born with CDH have an increased risk of musculoskeletal deformities.

Neurodevelopmental impairment is a common and potentially disabling outcome of CDH and its treatment, with 49% of CDH survivors demonstrating abnormal postnatal brain imaging (Montalva et al., 2019). Risk factors for neurodevelopmental impairment have been found to include: large diaphragmatic defect size (C or D) or need for patch repair, low lung-to-head-ratio or fetal lung volume, supplemental oxygen at discharge or at day 30 of life, prolonged ventilator time, ECMO treatment, length of hospital stay, and socioeconomic status (Montalva et al., 2019). Previous studies have suggested a direct correlation between the length of mechanical ventilation and the risk of neurodevelopmental delay, with ventilation time being a possible marker for disease severity (Bevilacqua et al., 2015; Bevilacqua et al., 2017; Friedman et al., 2008). However, Madderom et al. (2013) found that CDH children, regardless of neonatal ECMO treatment – another marker for disease severity– are at an increased risk of neurodevelopmental impairment, primarily motor and concentration problems (Madderom et al., 2013).

Our CDH cohort had a greater risk of being diagnosed with developmental disorders and specific delays in development – including speech, language, coordination and reading disorders – within the first five years-of-life. The majority of studies examining neurodevelopmental outcomes in CDH children focus on the first 3 years-of-life and demonstrate abnormal motor, cognitive and language performance (Chen et al., 2007; Danzer et al., 2010; Friedman 2008, Madderom et al., 2013; Wynn et al., 2013). Additionally, studies have suggested that the developmental delay seen in CDH children improves with time. Danzer et al. (2013), found that at 3 years-of-age, developmental delays were found to be more psychomotor than neurocognitive, and that most children demonstrating early delays improved and were functioning in the average range (Danzer et al., 2013). A similar study found that at 5 years-of-age, neurodevelopmental outcomes were in the average range (Danzer et al., 2017). The results from our study demonstrate an increased risk of neurodevelopmental impairment only in the first five years-of-life, supporting the notion that the delay seen in these children improves as they age. Conversely, one study did find that at 8 years-of-age, motor, concentration and behavioural attention problems were significantly greater in CDH children (Madderom et al., 2013). However, this study had a relatively small sample size of 32 CDH children, 16 of which required ECMO treatment – predisposing this group to worse outcomes; our study included 32 CDH children for this age group, all of which were non-ECMO treated.

Autism and ADHD have been found to be present in a large number of CDH children. The incidence of autism is said to be 7-14%, a significantly higher prevalence than the general population (1.5% at school age) (Danzer et al., 2010; Danzer et al., 2017, Danzer et al., 2018; Morsberger et al., 2019). Additionally, ADHD has been reported in 7-39% of CDH children (Danzer et al., 2017; Frisk et al., 2011; Morsberger et al., 2019; Peetsold et al., 2009b). Our study found no difference in the risk of autism or ADHD for CDH cases compared to controls. Autism was found in 0.94% of the control population and 3.70% of the CDH cohort (by age 6); this suggests that our CDH cohort had a lower incidence of autism than what is expected based on previous literature. Additionally, ADHD was found in 8.63% of the control population and 3.13% of the CHD cohort (by age 13). An incidence of 3.13% for ADHD is much lower than the 7-39% that has previously been reported. The non-significant finding for these outcomes may be a result of their lower than expected prevalence in our CDH cohort. Given a larger sample size these results may differ. However, the majority of the studies reporting autism and ADHD incidence fail to compare their CDH cohort to a control population, thereby not representing the true risk of these disorders for CDH survivors.

Neuromuscular hypotonia, - a functionally significant reduction of muscle tone and strength, cerebral palsy, and seizures have been highly reported in children born with CDH (Montalva et al., 2019). Neuromuscular hypotonia has been found in 38%–56% of CDH survivors (Montalva et al., 2019). Our study analyzed the risk of being diagnosed with a myoneural disorder – which includes a diagnosis of neuromuscular hypotonia – and found no increased risk for our CDH cohort. Motor function, including gross and fine motor outcomes, has also been found to be impaired in CDH children (Church et al., 2018; Jakobson et al., 2009; Leeuwen et al., 2014a; Safavi et al., 2012; Snoek et al., 2016; Tureczek et al., 2012; Wynn et al., 2013). Our study was unable to examine motor function specifically. The diagnoses of specific delays in development includes a diagnosis of developmental coordination disorders (including gross and fine motor delay), which was found to be more prevalent in CDH survivors compared to controls. Previous research reports that 4-9% of CDH survivors have epilepsy and 2% have cerebral palsy (Montalva et al., 2019). When we compared our CDH cohort to an age-matched control population, no increased risk of being diagnosed with epilepsy or cerebral palsy was found. According to a systematic review, sensory deficits such as hearing (13%) and visual (8%)

impairment are commonly reported in CDH survivors (Montalva et al., 2019). While our study found no increased risk for a diagnosis of visual impairment – including visual disturbances and blindness or loss vision – we did find that the risk of hearing loss was 4-6 times higher in our CDH cases compared to controls up to age 12. Research is beginning to indicate that not only is there a high prevalence of hearing loss in CDH children, but that CDH is an independent risk factor for the development of hearing loss (Amoils et al., 2015; Fligor et al., 2005). In summary, our study found that CDH survivors have an increased risk of developmental disorders, specific delays in development and hearing loss.

The results from this study suggest that while a number of impairments are present in early childhood, they seem to improve over time. However, this may not be the case. This discrepancy could be attributed to a reduction in sample size as the cohort gets older: 54 CDH children in the 0-5 years-of-age group, 32 in the 6-12 years-of-age group and 12 in the 13-19 years-of-age group. The small sample size for the older cohorts may contribute to the non-significant finding; given a larger sample size, we believe a difference may be observed. The management of CDH has also changed over time; given that this study spans over 25 years, these changes may have affected the long-term outcomes of these children. However, if this were the case, we would expect to see the older cohort have worse outcomes than the youngest cohort. For example, children in the youngest cohort (0-5 years-of-age) were born before 2012, whereas those in the oldest cohort (13-19 years-of-age) were born before 1998. Based on the nature of scientific research and medical advancements, we believe it is safe to assume that any changes that have occurred have been for the good – improving outcomes, not hindering them. Another possibility is that the more severe cases of CDH are now surviving their anomaly. This would result in the youngest cohort containing children who would have otherwise not survived and therefore exhibit more morbidities. The worst-case scenario model– which includes the children who died as having obtained the outcome - helps examine this possibility. This model creates an even playing field, including those severe cases that did not survive in previous years. While on the extreme end of the spectrum, this analysis resulted in a significant difference between cases and controls for all of the outcomes examined.

Mental health outcomes

Research has suggested that children born with CDH have a higher risk of developing mental health problems compared to the general population (Bouman et al., 2000; Danzer et al., 2017, Kubota et al., 2011; Peetsold et al., 2009b). Our study found that CDH survivors do not have an increased risk of mental health disorders, including, conduct disorder, mood and anxiety disorders, substance use disorders, psychotic disorders and schizophrenia. Previous research examining the mental health outcomes of CDH survivors is disparate, limited and contradictory. The majority of research that is available uses the Child Behavior Checklist (CBCL) or health related quality of life (HRQoL) measures. The CBCL is a questionnaire used to obtain parental report of behavior problems across internalizing domains - withdrawn, somatic complaints, anxious/depressed and emotionally reactive subscales - and externalizing domains – social problems, thought problems, attention problems, delinquent behavior and aggressive behavior (Achenbach & Ruffle, 2000; Achenbach System of Empirically Based Assessments, 2020). Thirty-eight percent of CDH children have been found to be in the clinical range (indicating impairment) on the CBCL, compared to the 25% typically seen in the general population; this suggests that children with CDH demonstrate more behavioural problems (Kubota et al., 2011). Danzer et al (2017) found that CDH survivors were at an increased risk of developing emotionally reactive problems compared to the general population; but, they also found no difference for anxious/depressed, aggressive behaviour or oppositional defiant behaviour as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Danzer et al., 2017). A small study of 11 CDH children aged 8 to 12 found that parents and teachers reported more emotional and behavioral problems in CDH children than the general population (Bouman et al., 2000). Additionally, Peetsold et al. (2009) found that approximately one fifth of the mothers and the teachers of CDH survivors reported significant emotional and behavioural problems, especially on the internalizing domain (Peetsold et al., 2009b). Alternatively, one study found no impairment in the anxious/depressed, delinquent or emotional behavior subscales of the CBCL, suggesting no increased risk of mental health problems for CDH children (Frisk et al., 2011).

Health-related quality-of-life measures have also been used to examine the mental health outcomes of CDH children. The majority of these studies have found no increased risk of

behavioral or emotional problems in CDH survivors (Fritz et al., 2019; Morsberger et al., 2019; Öst et al., 2018; Tan et al., 2019). Alternatively, Bojanić et al. (2018) found that their CDH cohort scored significantly lower on the emotional and social subdomains compared to their control participants (Bojanić et al., 2018). Our study used specific mental health diagnoses as opposed to subjective measures of mental health outcomes seen in previous literature. While it could be argued that a mental health diagnosis is more definitive, children may demonstrate less severe symptoms that would fall under the radar of clinical diagnosis. Additionally, mental health in general, and most notably in children, is difficult to assess and diagnose compared to physical morbidities. Therefore, the results of our study – indicating no increased risk of mental health diagnoses – does not warrant the conclusion that children with CDH do not face mental health difficulties. While conduct disorder and mood and anxiety disorder proxy measures have been seen in literature and discussed above, no known information exists on the risk of substance use disorder, psychotic disorders or schizophrenia.

Education outcomes

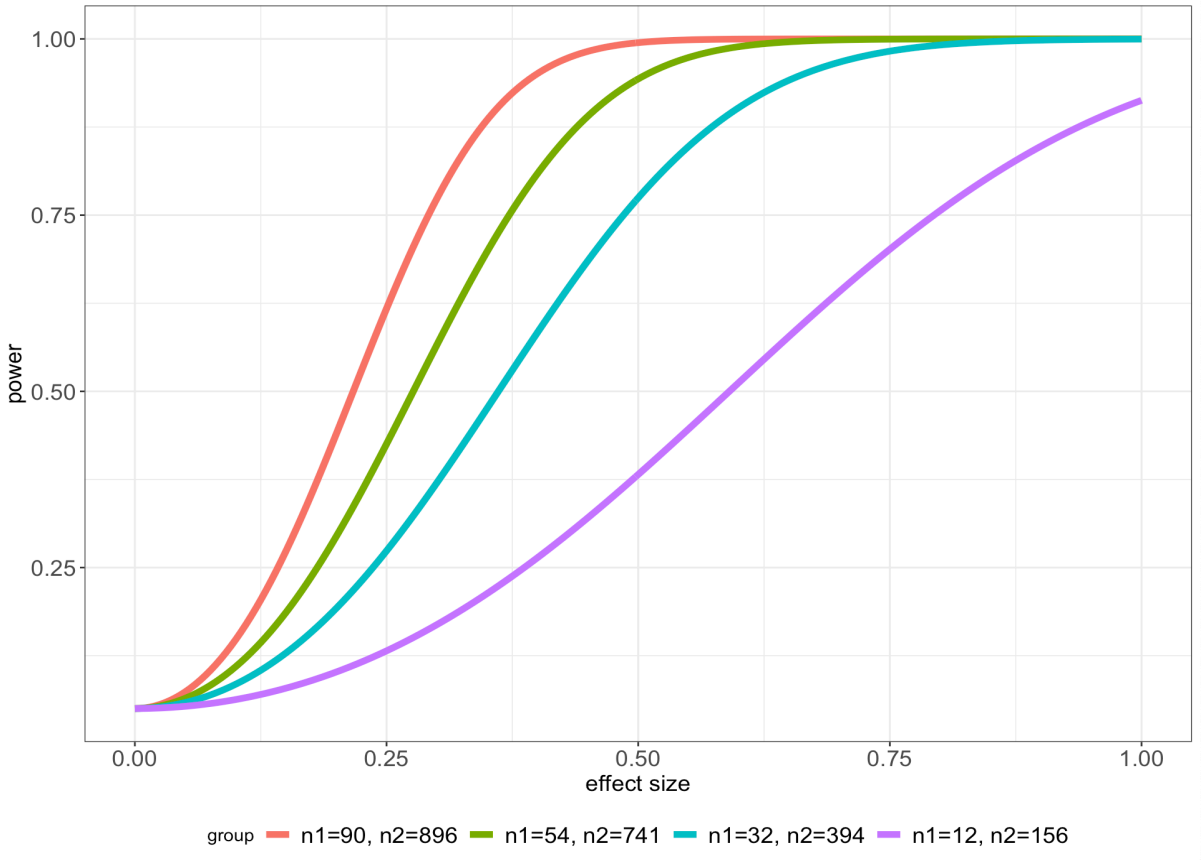
Learning difficulties have been reported in 31% of CDH children (Montalva et al., 2019). Our study comparing CDH children to the general population found no increased risk of a poor educational outcome; suggesting that these children perform similarly in school and do not have more learning difficulties. Research suggests that while overall school performance is similar to that of the general population, these children may suffer subtle cognitive deficits. Danzer et al. (2017) found that at 5 years-of-age the majority of CDH survivors had rates of borderline and extremely low IQ scores that were significantly higher than the general population (Danzer et al., 2017). Similarly, at school age (4 to 7 years), neurocognitive delay - defined as a score < 80 in Verbal Scale IQ, Performance Scale IQ, Expressive Language, or Receptive Language – was present in 44% of CDH survivors (Benjamin et al., 2013). However, it has been stated that intelligence testing alone cannot identify those at risk of academic problems (Schiller et al., 2016). Frisk et al. (2011) reported that CDH children 10-16 years-of-age have high rates of school difficulties, with 56% of their CDH cohort indicating educational concerns (Frisk et al., 2011). Using psychometric testing, they found a significant difference between CDH cases and controls for phonological awareness, written expression, numerical operations, working memory, global executive composite and attention problems (Frisk et al., 2011). Similarly, educational

outcome studies in later childhood report similar IQ's but significantly lower information processing speed and ability to sustain attention (Madderom et al., 2013; Peetsold et al., 2009b). Madderom et al. (2013) found that extra support in regular education was needed for 42% of CDH children, compared to 21% seen in the reference group (Madderom et al., 2013). Regardless of cognitive difficulties and the need for additional support, overall school performance has been found to be similar for CDH survivors and controls, which is congruent with our findings (Madderom et al., 2013; Morsberger 2019).

Power analysis

While we do understand that a power analysis is usually run before a study is conducted, this was a retrospective cohort study with a fixed number of CDH cases - we could not alter our sample size to provide a certain degree of power. However, in order to give some insight regarding how our sample sizes affected the analyses, we conducted retrospective power calculations for our various sample sizes. Assuming a standardized difference of 0.5 (a "medium" effect size per Cohen et al., 1988), we found that for our original sample size of 90 cases and 896 controls, the power of our analysis was 0.99 (using a significance level of 0.05). This indicates that, prior to examining the data, our analysis had a 99% chance to correctly detect a "medium-sized" difference between the cases and controls; equivalently, our analysis had a 1% chance of making a type II error (failing to detect the difference). When we examined the sample sizes used in the 0-5 years-of-age group (54 cases and 741 controls), the 6-12 years-of-age group (32 cases and 394 controls) and the 13-19 years-of-age group (12 cases and 156 controls) we found that the statistical power was 0.94, 0.77 and 0.38, respectively (Figure 1). This demonstrates that as our age group increased and our sample size decreased, the power of the analysis also decreased.

Figure 1. The effect of sample size and effect size on the power of analysis



The statistical power of a case-control study is generally believed to increase up to a ratio of 5 controls to one case, with only slight increase in power seen beyond this ratio. However, Hennesy et al. (1999) observed that when there is a low prevalence of exposure among controls, an increase in power can be found by increasing the control-to-case ratio above 5 (Hennesy et al.,1999). The controls in our study had a low - even negligible - prevalence of exposure to CDH, therefore, by including a control-to-case ratio of 10 we were able to improve the power of our analysis.

Limitations and strengths

There are several limitations to our study. First, while we had a relatively large number of CDH cases (N=90) and controls (N=896), splitting the cohort into age-groups significantly reduced our power of analysis; for example, the 0-5 years-of-age group contained 54 cases and 741 controls. In addition, our cohort size continued to decrease as the age at which the analysis occurred

increased. Second, the retrospective nature of our analysis presents a concern regarding the accuracy and completeness of the data. Third, information was collected from a cohort that was managed over 25 years; advances in the management and treatment of CDH patients over time may have impacted our results. Lastly, we were limited to analyzing outcomes for which data was available from the MCHP. Despite these limitations, our study is unique in that we used a large comprehensive repository of unbiased population level administrative data that has been validated and extensively used to study the outcomes we were interested in. The use of administrative datasets allowed us to perform a virtual follow-up on every individual in our cohort (with the exception of those who died or moved out of province). Previous studies have used in person follow-up to collect data on long-term outcomes, therefore limiting their cohort to patients for whom follow-up data was available, resulting in selection bias. The use of administrative datasets also enabled us to collect data over a long period of time without issues such as expense, time investment and loss-to-follow-up normally associated with longitudinal cohort studies. In addition, we compared the outcomes of children with CDH to their date-of-birth matched peers, from the general population, at a ratio of 1:10; this has not been done in previous studies. This allowed us to quantify differences in physical, mental, and educational outcomes between children with CDH and date-of-birth matched controls. As a final note, some of the discrepancies between our study and the results of long-term follow up clinics might be explained by the fact that some diagnoses might only be found by actively searching for them. In other words, it might be easier for a specialized clinic to diagnose a mental disorder than for a rural General Practitioner following these children.

Recommendation for future research and clinical practice

Future research should examine long-term medical, educational and socio-economic outcomes of CDH survivors using large cohorts of CDH cases and controls, potentially by means of multicenter collaborations. Additionally, the age-group discrepancy observed in this study should be further examined: do these apparent morbidities really improve with age? Long-term outcome data is essential to identify modifiable risks, provide prognostic information for patients and their families and guide evidence informed long-term care. Given the number of morbidities faced by CDH survivors, multidisciplinary follow-up clinics are essential for the allocation of healthcare

resources. Early recognition may mitigate the severity of long-term problems, allowing these children to achieve optimal well-being.

Chapter V: Conclusion

Our study found that CDH survivors have an increased risk of developing long-term pulmonary, gastrointestinal, musculoskeletal and neurodevelopmental morbidities compared to age-matched controls, primarily in the first five years-of-life. We found no increased risk of mental health problems or poor educational outcomes. This study used novel and unique methods for studying the long-term outcomes of CDH survivors. Given the limited nature of previous research, we believe our study provides valuable insight into the long-term quality of life of these children.

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