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ORIGINAL ARTICLE

Incidence, predictors and outcomes of congenital diaphragmatic hernia: a population-based study of 32 million births in the United States

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Abstract

Objectives: To evaluate the incidence, risk factors and neonatal outcomes associated with a congenital diaphragmatic hernia (CDH).

Study design: We conducted a population-based cohort study using the CDC's Linked Birth-Infant Death and Fetal Death data files on all births and foetal deaths in USA between 1995 and 2002. We estimated the yearly incidence of CDH and measured its adjusted effect on various outcomes using unconditional logistic regression analysis.

Results: About 32 145 448 births during the 8-year study period met the study's inclusion criteria. The incidence of CDH was 1.93/10 000 births. Risk factors for the development of CDH included foetal male gender [OR 1.12, 95% CI: 1.06, 1.17], maternal age beyond 40 [OR 1.51, 95% CI: 1.26, 1.80], Caucasian ethnicity [OR 1.15, 95% CI: 1.10, 1.21], smoking [OR 1.34, 95% CI: 1.22, 1.46] and alcohol use during pregnancy [OR 1.37, 95% CI: 1.05, 1.79]. As compared to foetuses with no CDH, foetuses with CDH were at an increased risk of preterm birth [OR 2.90, 95% CI: 2.72, 3.11], intrauterine growth restriction [OR 3.84, 95% CI: 3.51, 4.18], stillbirth [OR 9.65, 95% CI: 8.20, 11.37] and overall infant death [OR: 94.80, 95% CI: 88.78, 101.23]. The 1-year mortality was 45.89%.

Conclusion: Congenital diaphragmatic hernia is strongly associated with an increased risk of adverse pregnancy, foetal and neonatal outcomes. These findings may be helpful in counselling pregnancies affected by CDH, and may aid in the understanding of the burden of this condition at the public health level.

Keywords

Congenital diaphragmatic hernia, incidence, mortality, predictors

History

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Introduction

Congenital diaphragmatic hernia (CDH) is a congenital anomaly characterized by a discontinuity of the diaphragm, which allows the abdominal viscera to herniate into the chest during embryonic and foetal development. CDH is a significant cause of neonatal morbidity and mortality that is often seen as a purely paediatric and surgical problem [1]. The main culprits for the high index of mortality are pulmonary hypoplasia, and treatment-resistant pulmonary hypertension, likely mechanical consequences of the defect involved [2]. Among survivors, predictors of mortality include lung-to-head ratio, hepatic herniation and the presence of other associated anomalies [3,4]. A high incidence of co-morbidities, most notably bronchopulmonary dysplasia, is of concern [5,6].

The incidence of CDH varies from 1.7 to 5.7 per 10 000 pregnancies, depending on the population studied [5]. The pathogenesis of this condition is still poorly understood. In humans, three different types of hernia can be distinguished: a posterolateral, Bochdalek-type (~70% of the cases); an anterior, Morgagni-type (~27% of the cases) and a central hernia, septum transversum-type (~2–3% of the cases) [6]. Irrespective of type, all CDHs confer poor prognosis, with overall survival rates determined in some studies to be as low as 61% at birth, and 32% by the first year of life [7].

Despite advances in the understanding of the underlying pathophysiology, and the development of new available therapies, the death rate from CDH remains substantial, highlighting the need to identify mechanisms for its primary prevention [8]. As patients with prenatally-diagnosed CDH have been found to be a higher risk group [4], we infer that prenatal care providers may play an important role with regards to this condition's diagnosis and prognosis. Indeed, the key to survival lies in prompt diagnosis [9–12], and studies have shown that prenatal evaluation and multidisciplinary perinatal management allows for improved outcome in these patients [4]. Yet, despite advances in foetal therapy, the role for antenatal care providers is understudied, and often limited to ultrasound detection and elective

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termination. Using a sufficiently large database, the primary objective of this study was 2-fold: to establish the incidence rate while evaluating the maternal and gestational risk factors associated with the development of a CDH and secondly, to quantify specific outcome risks associated with this condition.

Materials and methods

We conducted a retrospective cohort study using data from the ''Birth Cohort Linked Birth-Infant Death'' and the ''Fetal Death'' data files from the National Center for Health Statistics (Centers for Disease Control and Prevention). The birth cohort file contains information on ~4 million annual live births of residents and non-residents in USA. This information is obtained from the birth certificate and is available for all births. The infant death file contains information on all infant deaths in USA and can be linked to its corresponding birth record in the birth cohort through a unique identifier. The foetal death cohort file contains the record on all stillbirths and can be readily appended to the live birth cohort file to obtain a final cohort containing all deliveries, whether born dead or alive.

For this study, we assembled an 8-year cohort using data for the years 1995–2002. We selected from this database all records for the contiguous USA, Hawaii and Alaska. The territories Puerto Rico, Guam and the Virgin Islands were excluded from our final aggregate file. Furthermore, births of US citizens outside of USA did not take part in our analysis.

Our exposure was defined as either having a CDH or not, as stated on the reported ''congenital anomalies'' input from the database. This information is based on the recorded status on the birth certificate. Our outcomes included stillbirths and infant deaths. We defined a stillbirth as any death before expulsion from the mother beyond 24-week gestation. Neonatal deaths were defined as any infant death that occurred from birth to 28 days (early neonatal were within the first 7 days and late neonatal death were between day 7 and day 28). Finally, we defined infant death as any postnatal fatality taking place between birth and the first year of life.

Our analysis was conducted in four steps. First, we carried out descriptive statistics to summarize the characteristics of our population stratified according to CDH status (Table 1). We then calculated the incidence of CDH and its changes in time during the study period (Figure 1). To examine the relationship between CDH and specific perinatal outcomes which include prematurity, intrauterine growth restriction (IUGR), small for gestational age [13], large for gestational age [14], stillbirth and, infant death, we used unconditional logistic regression models to estimate the relative risk (RR), along with the 95% confidence intervals (CI). We examined the adjusted effects of CDH on the aforementioned outcomes through a model which adjusted for maternal race, maternal age, marital status, maternal education, prior live births, maternal smoking, maternal alcohol intake during pregnancy and other congenital anomalies. Third, in order to identify predictors of foetal and infant death, we examined the effect of specific baseline characteristics on foetal and infant death in an analysis restricted to women who bore a foetus with a CDH. Finally, a survival curve was plotted, comparing survival rates between male newborns and female newborns at 1 year of life (Figure 2). All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC). This protocol was approved by the Medical Research Ethics Department of the Jewish General Hospital, Montreal, Quebec.

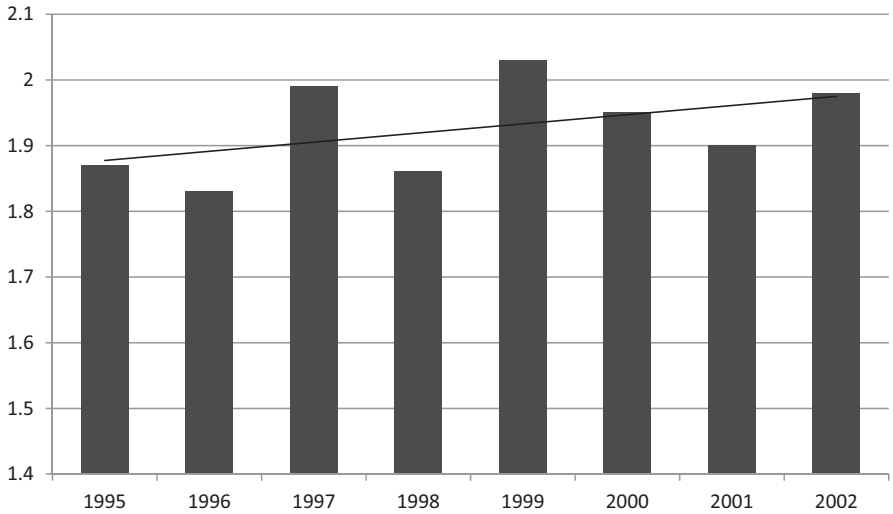
Table 1. Maternal and neonatal baseline characteristics according to congenital diaphragmatic hernia (CDH) status.

	Total births ($n = 30\,878\,893$)	
	CDH ($n = 5958$) (%)	Ø CDH ($n = 30\,872\,935$) (%)
Maternal age		
<15	0.75	0.89
15–19	11.48	11.38
20–24	24.73	24.83
25–29	25.78	27.06
30–34	21.89	23.08
35–39	12.09	10.62
40–44	3.08	2.04
≥45	0.19	0.10
Maternal race		
White	69.27	59.76
African–American	12.69	14.89
Hispanic	14.30	20.15
Other	3.74	5.20
Marital status		
Married	65.87	67.16
Plurality		
Singleton	96.60	97.05
Twin	3.25	2.78
Triplet or higher	0.14	0.16
Infant gender		
Male	57.21	51.06
Female	42.79	48.94
Maternal education		
0–8 years	4.88	5.94
9–11 years	14.22	15.82
12 years	35.15	32.13
13–15 years	21.24	21.60
>16 years	21.21	22.98
Alcohol use		
Yes	1.36	0.99
No	92.77	84.22
Unknown	5.87	14.79
Smoking		
Yes	13.86	10.59
No	77.35	71.20
Unknown	8.79	18.21
Prior births		
0	40.19	40.28
1	31.47	32.19
≥2	37.34	27.53

Results

Our cohort consisted of 32 145 448 births and foetal deaths, of which 30 878 893 met the study criteria. A total of 30 872 935 births were compared with 5968 births with confirmed cases of CDH. The average incidence of CDH was thus 1.93/10 000 births, and did not change on a yearly basis (Figure 1). Table 1 summarizes the prevalence of selected sociodemographic characteristics for each group during the study period. Foetuses with CDH appear to be from older mothers, from singleton pregnancies, and did not seem to be affected by maternal parity. With regards to our main outcomes, foetuses with CDH were at an increased risk of preterm birth, IUGR,

Figure 1. Annual incidence and yearly trend of CDH per 10 000 births.



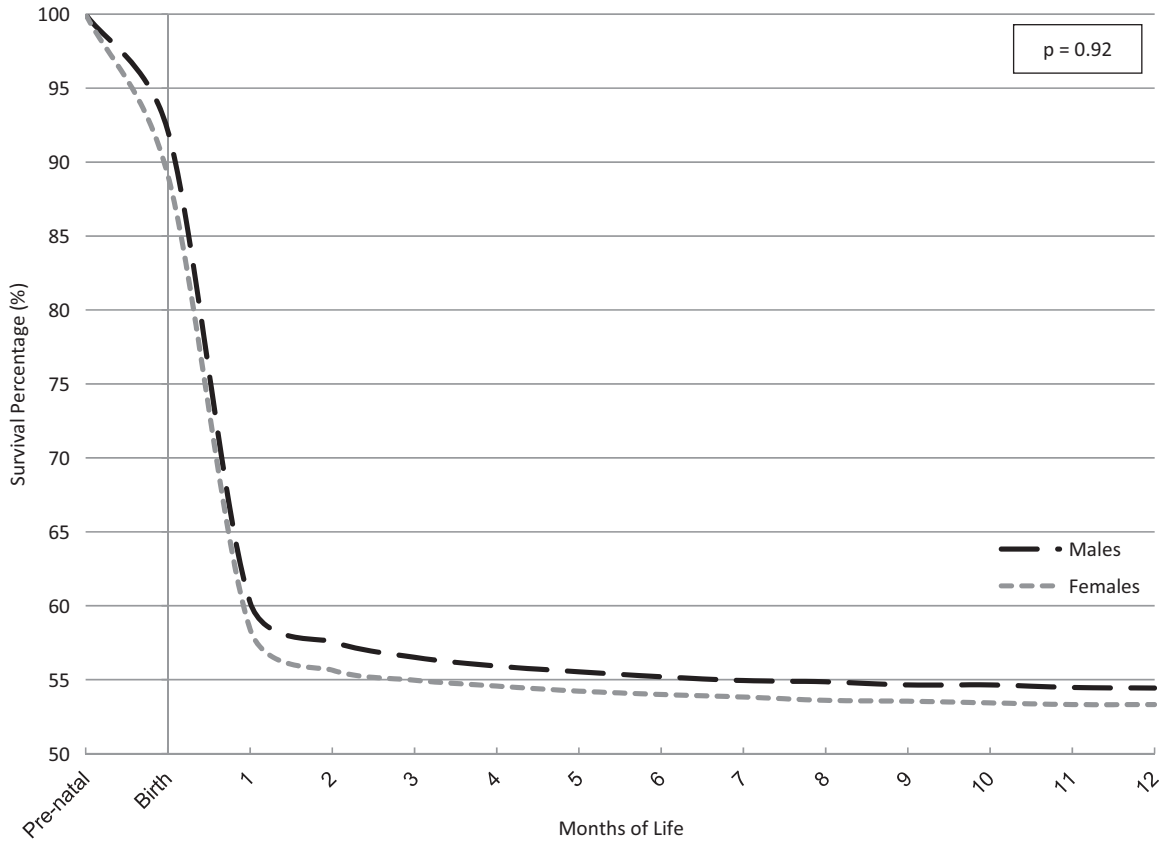


Figure 2. Survival curve at 1 year.

SGA, stillbirth, early neonatal death, late neonatal death and overall infant death at 1 year of life [$****p<0.0001$] (Table 2). There does not appear to be an association between the development of a CDH and being part of a multiple gestation. The 1-year mortality was 45.89% for the study cohort and though male foetuses showed a greater incidence, the difference in gender survival at the first year of life was not statistically significant [$p=0.92$] (Figures 2 and 3). Statistically significant risk factors for the development of CDH included male foetal gender, maternal age beyond age 40 years, maternal Caucasian race, maternal smoking and alcohol use during pregnancy (Table 3).

Discussion

Congenital diaphragmatic hernia is a developmental discontinuity of the diaphragm that allows abdominal viscera to herniate into the chest, resulting in pulmonary hypoplasia and pulmonary hypertension, which are often fatal. Several studies have shown that prenatal evaluation and multidisciplinary perinatal management allows for improved outcome in these patients, thus the primary objective of this study was to evaluate the incidence and maternal risk factors associated with the development of a CDH, and to establish specific outcome risks associated with the development of this

Table 2. Relative risk and frequency of outcomes by congenital diaphragmatic hernia status in 1995–2002.

	CDH ($n = 5958$) (%)	Ø CDH ($n = 30\,872\,935$) (%)	Unadjusted RR (95% CI)	Adjusted RR* (95% CI)	p Value
Preterm birth	31.41	11.88	3.20 [3.00, 3.42]	2.90 [2.72, 3.11]	<0.0001
IUGR†	15.49	4.35	4.03 [3.70, 4.39]	3.84 [3.51, 4.18]	<0.0001
SGA‡	11.58	7.51	1.61 [1.47, 1.78]	1.60 [1.45, 1.76]	<0.0001
LGA¶	8.35	11.89	0.67 [0.60, 0.75]	0.68 [0.61, 0.77]	<0.0001
Stillbirth	9.03	0.84	11.69 [10.50, 13.00]	9.65 [8.20, 11.37]	<0.0001
Early neonatal death	23.67	0.37	84.66 [78.77, 90.98]	90.49 [84.01, 97.47]	<0.0001
Late neonatal death	7.69	0.09	97.05 [86.49, 108.90]	100.15 [89.16, 112.50]	<0.0001
Infant death	36.87	0.68	85.25 [80.01, 90.83]	94.80 [88.78, 101.23]	<0.0001

*Adjusted for maternal race, maternal age, marital status, maternal education, prior live births, maternal smoking, alcohol and other congenital anomalies.
†Intra-uterine growth restriction: having a birthweight under the 3rd percentile.
‡Small for gestational age: having a birthweight between the 3rd and 10th percentile.
¶Large for gestational age: having a birthweight above the 90th percentile.

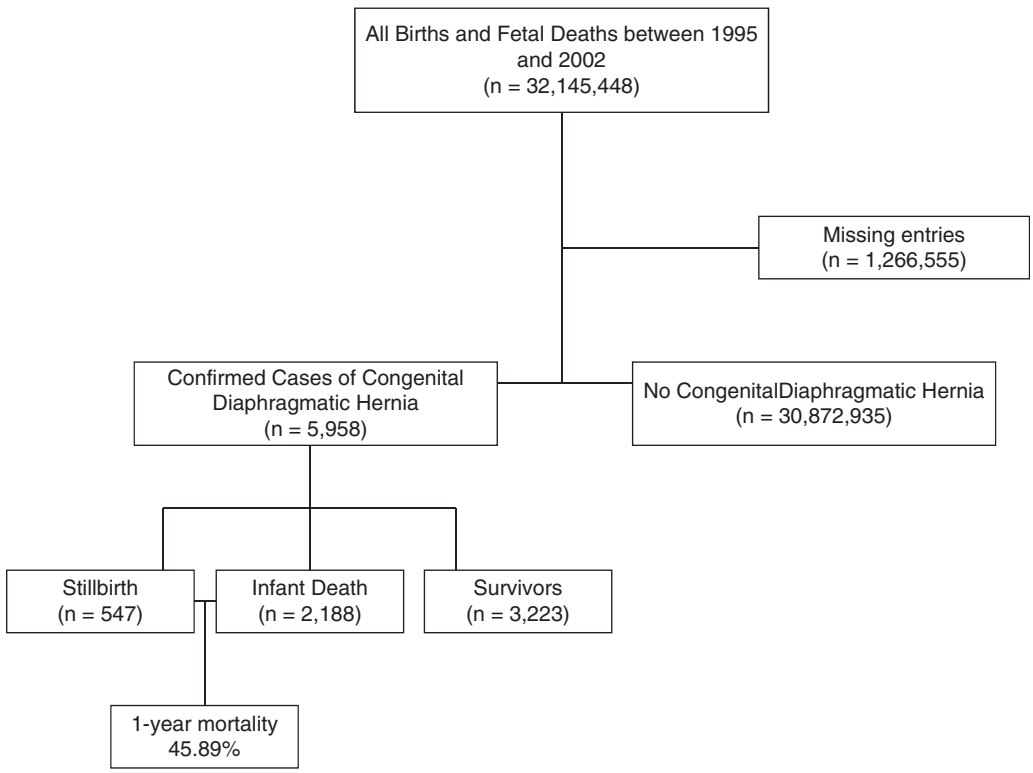


Figure 3. Exclusion flowchart.

condition. Our results suggest that CDH occurs on an average in 1 out of every 5000 pregnancies that goes beyond 24-week gestation, and that it is strongly associated with an increased risk of adverse foetal and neonatal outcomes, ranging from preterm birth, to IUGR, stillbirth and infant death.

Visceral herniation into the thoracic cavity occurs during the critical period of lung development when the bronchi and pulmonary arteries are undergoing branching, from the third week post-fertilization through the 16th week of gestation. This implies that risk factors for developing CDH must precede the gestational period, and that the development of CDH should therefore not be affected by pregnancy-specific pathologies which occur later on, such as hypertensive disorders of pregnancy or gestational diabetes. Though the pathogenesis of CDH is controversial, genetic or environmental triggers early in pregnancy have been proposed as the main culprits. This study sought to determine some of the demographic characteristics of these patients, and found primarily that advanced maternal age, maternal smoking and alcohol intake, as well as Caucasian ethnicity are risk factors for developing CDH. However, maternal parity and multiple pregnancy do not appear to be risk factors.

With regards to our study, there are several aspects that need to be considered in the interpretation and implication of its results. The first pertains to the incidence rate of CDH and whether it is quantified in terms of pregnancies or births. CDHs are detected prenatally in ~54–73% of all cases [4,15,16]. The prenatal detection takes place on average at 26.1 weeks of gestation and leads to a termination rate of up to 59% of cases [17]. Hence, as the database used in this study does not take into account elective terminations, it is likely that the rate found in this study is underestimated. Earlier detection may in fact lead to a greater number of terminations. If terminations do indeed take place for more than half of the

Table 3. Maternal and gestational predictors of congenital diaphragmatic hernia (CDH).

	CDH ($n = 5958$) (%)	Adjusted RR (95% CI)	p Value
Maternal age			
<15	0.75	0.84 [0.59, 1.20]	0.3517
15–19	11.48	1.00 [0.91, 1.10]	0.8906
20–24	24.73	0.99 [0.92, 1.06]	0.8888
25–29	25.78	1.00 [Reference]	–
30–34	21.89	0.94 [0.88, 1.01]	0.1510
35–39	12.09	1.13 [1.03, 1.24]	0.0064
40–44	3.08	1.51 [1.26, 1.80]	<0.0001
≥45	0.19	1.94 [0.97, 3.88]	0.0608
Maternal race			
Caucasian	69.27	1.15 [1.10, 1.21]	<0.0001
Other	31.73	1.00 [reference]	–
Foetal gender			
Male	57.21	1.12 [1.06, 1.17]	<0.0001
Female	42.79	1.00 [Reference]	–
Plurality			
Singleton	96.60	1.00 [Reference]	–
Twin	3.25	1.03 [0.98, 1.08]	<0.1730
Triplet	0.14	0.97 [0.93, 1.01]	<0.1960
Maternal behaviours			
Smoking	13.86	1.34 [1.19, 1.42]	<0.0001
Alcohol	1.36	1.37 [1.05, 1.78]	0.0185

cases [17], then our incidence should on average double from 1.93 to around 4 per 10 000 pregnancies, thus making it compatible with other estimates that have been described in the literature [5,16]. Therefore, the rate of 1.93/10.000 described in this study refers to a rate per birth, not a rate per pregnancy.

Secondly, gestational factors are important determinants of neonatal outcomes. They are, however, difficult to address from the perspective of an antenatal care provider given that some factors are not modifiable. Of the non-modifiable characteristics, maternal race and foetal gender are identified in this study as risk factors (Table 3). Despite their non-modifiable nature, these may serve as important informative tools for parental counselling, dictate future studies that analyze those particular populations in more depth, as well as influence cases where the pre-natal diagnosis may be equivocal. Of the modifiable risk factors, advanced maternal age, smoking and alcohol intake are all risk factors. Though it is not clear how the modification of these behaviours can affect individual cases, these risk factors may be amenable to pre-conception counselling as well as public health measures which further discourage their practice.

The European Respiratory Society Task Force on Congenital Diaphragmatic Hernia has put forth recommendations for the antenatal management and delivery of CDH infants [5]. Among these, the following guidelines figure: (1) routine antenatal ultrasound scanning for anomalies is essential in industrialized countries; (2) MRI should be used to confirm the diagnosis of CDH in cases of equivocal ultrasound findings; (3) antenatal counselling is essential and should be conducted by a multidisciplinary team; (4) genetic consultation and amniocentesis to screen for chromosomal anomalies is advised; (5) in those with a poor prognosis, termination of pregnancy should be sensitively considered; (7) antenatal surgical intervention should be considered in selected cases after discussion with the parents, but going forward with this should be done in the context of randomized trials and (8) obstetric decisions should guide the mode of delivery. In agreement with these recommendations, obstetrical input in cases of CDH become increasingly relevant, and may even attain prenatal surgical management in the coming years [18].

In keeping with the last recommendation, our study finds that CDH newborns are more likely to exhibit IUGR. This fact may play an important role in deciding whether the most adequate method of delivery for these patients is in fact via caesarean section. On this matter, the Canadian Pediatric Surgery Network finds that there is no benefit to any specific delivery plan or route for prenatally diagnosed CDH, but that conformity to any birth plan was associated with a trend toward improved survival [13]. In this matter too, obstetrical care providers may play a significant role. In addition, Hutcheon et al. [19] find that neonatal and infant mortality for newborns with CDH delivered at 37 weeks of gestation were significantly higher than those delivered at 40 weeks. Yet, we show that foetuses with CDH are at a significantly higher risk of being born prematurely, indicating once again that gestational factors play a large role in the prognosis of these patients.

Mortality is perhaps the most important consideration in the prognosis of these patients. The degree of respiratory distress is dependent on the severity of lung hypoplasia and pulmonary hypertension. Though prenatally lung hypoplasia can be estimated using ultrasound by determining if the herniated contents include the liver and by measuring the lung area to head circumference ratio, there is no accurate way to determine the degree of hypoplasia, and thus of respiratory capacity, after delivery. The clinical severity of the respiratory distress and the response of the infant to treatment are the best measure of lung hypoplasia. The postnatal survival rate at tertiary centres has improved with reported rates of 70–92% [20,21]. This increased survival rate appears to be a result of the shift from early surgical intervention to intensive preoperative supportive care aimed at avoiding lung injury, followed by surgical correction. This may be a direct consequence of prenatal detection measures. Not surprisingly, up to 35% of liveborn infants die before reaching a tertiary centre, demonstrating once again that prenatal diagnosis, as well as planned delivery are crucial in increasing survival rates [7]. Our study demonstrates that the death rates from CDH appear to be similar in other developed nations, though rates might be affected by treatment received. In a study from Great Britain, the survival rate of all cases of CDH was estimated to be ~40% [22]. In a population-based study from Eastern Australia, 8% of pregnancies were electively terminated, 10% of infants were stillborn and 82% liveborn. Of the liveborn infants, a 56% survival rate was noted. This results in an overall survival rate of 46%, which slightly rises to 48%, if electively terminated pregnancies are excluded [23]. In a nationwide Japanese retrospective study of 463 infants diagnosed with CDH, the overall survival rate with isolated CDH was 84%. Survival of infants who required post-natal interventions was lower and included the rates of 74%, 68% and 37% for infants treated with high frequency ventilation, inhaled nitric oxide or ECMO, respectively [24].

Despite the unprecedented power that our study provides for the investigation of the question at hand, we must acknowledge several limitations. The databases that we used to perform our study used the newborn as the unit of analysis. Consequently, we often had limited information on maternal factors, which may have acted as potential confounders and could have provided more detailed analysis of the population at risk. Socioeconomic status and income are two particular variables of interest missing from our data. As well, though it is likely that our estimates of infant mortality are correct, as they compare to the rates reported in the literature, we cannot distinguish which newborns received adequate NICU care, and this may have an important impact in prognosis and mortality rate. In addition, the ability to distinguish ante-natal from post-natal detection is lacking from the database, and this data may have in fact provided us with key information about potential intervention strategies in pregnancy management geared towards obstetrical care providers. Moreover, we have no ultrasound or management information on these foetuses. It is evident that there are strict criteria that help with determining prognosis. Given that this database is based on birth certificate reports, that information is not available and thus makes for an important limitation to our study. As with all large databases, we had no way to validate reported diagnoses. Finally, we have no information on the affected cases past the 1 year of life and thus, no way to assess long-term morbidity and mortality.

On the other hand, this study has notable strengths. First, with 32.1 million births, this is the largest study to ever have investigated the perinatal outcomes and risk factors of CDH. In addition, most studies addressing our study question do so for post-natal infant mortality and neonatal surgical and resuscitative outcomes. Our study is unique in that it demonstrates the potentially etiological and modifiable maternal behaviours which take place during gestation, and makes the case that gestational outcomes such as prematurity, IUGR and stillbirth, are likely contributors to the high indices of morbidity and mortality observed in this condition. In addition, as we established that male foetuses are at higher risk of developing CDH (Table 3), we make a gender-specific survival curve at 1 year of life, demonstrating equal mortality risk despite unequal incidence. Furthermore, the data used are population-based, and the information collected is thus unlikely biased with respect to our study question. This study gives important population percentages on the effect of this disease that could not be estimated from case series and single centre experience. This information, while helpful in helping counsel parents on a range of outcomes, can be helpful on a public health level in understanding the burden or effect of this condition in the general population.

In conclusion, CDH is strongly associated with an increased risk of adverse foetal and neonatal outcomes in the context of multiple gestational risk factors. These findings illustrate the increasingly important role played by antenatal care providers, the need for prompt foetal and maternal antenatal screening, the importance of addressing maternal modifiable behaviours, as well as the need for adequate perinatal counselling for parents. Further studies are required to determine the true aetiology of CDH and other potentially modifiable risk factors that may impact its prognosis.

Declaration of interest

The authors report no conflict of interest.

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