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Title: Trends, Correlates, and Survival of Infants with Congenital Diaphragmatic Hernia and its Subtypes

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Abstract

OBJECTIVE

To identify the live-birth prevalence, trends, correlates, and neonatal and one-year survival rates of congenital diaphragmatic hernia.

METHODS

Using a population-based, retrospective cohort study design, we examined 1,025 cases of congenital diaphragmatic hernia from the 1998–2012 Florida Birth Defects Registry. We used Poisson and joinpoint regression models to compute prevalence ratios and temporal trends, respectively. Kaplan-Meier survival curves and Cox proportional hazards regression were used to describe neonatal and one-year survival and estimate hazard ratios representing the predictors of infant survival.

RESULTS

The birth prevalence of congenital diaphragmatic hernia was 3.19 per 10,000 live births (95% Confidence Interval [CI]:3.00-3.39); there was a 4.2% yearly increase among multiple cases only. Among all cases, maternal education less than high school (prevalence ratio: 1.25, 95% CI:1.02-1.53), high school/associate degree/GED (prevalence ratio: 1.15, 95% CI:1.01-1.32), multiple birth (prevalence ratio: 1.38, 95% CI:1.05-1.81), and male sex (prevalence ratio: 1.18, 95% CI: 1.05-1.32) were associated with increased risk for congenital diaphragmatic hernia. The 24-hour, neonatal, and one-year survival rates were 93.6%, 79.8%, and 71.2%, respectively. The highest hazard ratio of 17.87 (95% CI:1.49-213.82) was observed for neonatal mortality among cases associated with chromosomal anomalies and born <37 weeks at <1,500 grams. Among isolated cases, multiple birth (hazard ratio: 0.41, 95% CI:0.20-0.86) was associated with decreased one-year mortality.

CONCLUSION

Low maternal education and multiple birth may be linked to congenital diaphragmatic hernia. The trends in prevalence, epidemiologic correlates, and predictors of early survival can differ between congenital diaphragmatic hernia subtypes– isolated, multiple, and chromosomal.

KEYWORDS

Congenital diaphragmatic hernia; survival; epidemiology

INTRODUCTION

Congenital diaphragmatic hernia, a rare birth defect of the diaphragm, has an estimated prevalence of 2.61 per 10,000 live births in the United States (Parker et al., 2010) and health care costs of over \$250 million per year (Raval, Wang, Reynolds, & Fischer, 2011). The 24-hour mortality is 21%-31% (Aly, Bianco-Batlles, Mohamed, & Hammad, 2010; Balayla & Abenhaim, 2014), whereas the one-year mortality can be as high as 46% (Balayla & Abenhaim, 2014). In recent years, prenatal diagnosis and advanced neonatal care have decreased mortality; however, survivors face complex morbidities that may require long-term medical support (Crankson, Al Jadaan, Namshan, Al-Rabeeah, & Oda, 2006; Keijzer & Puri, 2010; Tracy & Chen, 2014).

About 50%–64% of congenital diaphragmatic hernia cases are isolated (B. R. Pober, 2007; Shanmugam, Brunelli, Botto, Krikov, & Feldkamp, 2017), while the remainder co-occur with additional birth defects. The risk factors for this defect include maternal smoking during pregnancy (Balayla & Abenhaim, 2014), periconceptional alcohol consumption (Felix et al., 2008), advanced maternal age (Balayla & Abenhaim, 2014; Yang, Carmichael, Harris, & Shaw, 2006), Caucasian race (Balayla & Abenhaim, 2014), prepregnancy obesity (Blomberg & Källén, 2010), nulliparity (Yang et al., 2006), male sex (Balayla & Abenhaim, 2014; Dott, Wong, & Rasmussen, 2003), and increased paternal age (Green et al., 2010). Fetuses with congenital diaphragmatic hernia are at risk for preterm birth and are often small for their gestational age (Dott et al., 2003). Prior research has either used birth certificate data that has low sensitivity (33%) and positive predictive value (64%) for congenital diaphragmatic hernia compared to birth defects registry data (Watkins et al., 1996), examined a single risk factor (Green et al., 2010), have few cases (Blomberg & Källén, 2010; Felix et al., 2008), or are not recent (Dott et al., 2003; Yang et al., 2006). Though there is extensive research on clinical and anatomic predictors

of survival among these infants (Badillo & Gingalewski, 2014; Dott et al., 2003; B. R. Pober, Russell, M.K., Ackerman, K.G., 2006), there is a dearth of current epidemiologic studies.

Using data from a large population-based registry, we investigated the prevalence, temporal trends, and correlates of congenital diaphragmatic hernia among live-born infants during a 15-year period (1998–2012) in the State of Florida. We also investigated the association between sociodemographic and perinatal characteristics and early survival among infants with congenital diaphragmatic hernia and its subtypes.

MATERIALS AND METHODS

We conducted a population-based, retrospective cohort study using 1998–2012 data from the Florida Birth Defects Registry (FBDR). The FBDR is a passive, statewide birth defects surveillance system that includes data on infants born alive to Florida resident mothers on or after January 1, 1998 and who have been diagnosed with one or more structural, genetic, or other specified birth outcomes, primarily identified using diagnostic codes present in clinical and administrative databases. The FBDR contains linked data from the Florida Vital Statistics birth and infant death certificate records, the Agency for Health Care Administration hospital inpatient, ambulatory, and emergency department discharge databases, Regional Perinatal Intensive Care Centers data, Children's Medical Services (CMS) case management records, and CMS Early Steps data (Salemi et al., 2012). The Institutional Review Boards at the University of South Florida and the Florida Department of Health have reviewed and approved the study.

Congenital diaphragmatic hernia cases were ascertained using the International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) code 756.6, or 10th Edition (ICD-10) code Q79.0. Cases were then classified as isolated, multiple, or chromosomal.

A multiple congenital diaphragmatic hernia case was defined as having documentation of one or more structural concomitant defects listed on the National Birth Defects Prevention Network (NBDPN) list of major structural defects, which are reported by surveillance programs in the US annually (Mai et al., 2014). Furthermore, a case associated with chromosomal anomalies listed on this list was classified as chromosomal congenital diaphragmatic hernia. The sociodemographic and perinatal characteristics included in the study were obtained from the Florida Bureau of Vital Statistics and classified into risk factors and birth outcomes. Risk factors included maternal age, race/ethnicity, education, marital status, smoking during pregnancy, adequacy of prenatal care, parity, plurality, and infant sex. Birth outcomes included method of delivery, gestational age, and birth weight. Maternal age was categorized in years as <20, 20-24, 25-29, 30-34, or ≥ 35 ; maternal race/ethnicity was classified as white non-Hispanic, black non-Hispanic, Hispanic, or other; and maternal education was categorized into <high school, high school equivalent, or >high school. Maternal marital status was dichotomized as married or not married, and method of delivery as vaginal or cesarean. Maternal smoking during pregnancy was dichotomized into 'no' or 'yes'. Adequacy of prenatal care was dichotomized into 'adequate' or 'not adequate' based on the Kotelchuck index (Kotelchuck, 1994). Parity was classified into nulliparous or multiparous; plurality into singleton or multiple (twins, triplets, and higher-order); and birth weight into <1,500g (very low birth weight, VLBW), 1,500-2,499g (LBW), or $\geq 2,500$ g (normal weight). Gestational age was assessed from the clinical estimate of gestation; implausible birth weight/gestational age combinations were excluded from the analytic sample (Alexander, Himes, Kaufman, Mor, & Kogan, 1996). Data were then classified based on completed weeks as <33, 33-36, or ≥ 37 . After cross-tabulation of frequencies of gestational age and weight at birth, a five-category combined variable was created: ≥ 37 weeks and $\geq 2,500$ g, ≥ 37

weeks and <2,500g, <37 weeks and <1,500g, <37 weeks and 1,500-2,499g, or <37 weeks and $\geq 2,500$ g. Prepregnancy body mass index (BMI) was categorized into underweight, normal weight, overweight, or obese. Dates of birth and death obtained from the Florida Bureau of Vital Statistics were used to calculate time-to-death in days.

Birth prevalence per 10,000 was computed as the number of congenital diaphragmatic hernia cases divided by the total number of live births during the entire study period, for each year, and then separately for isolated, multiple, and chromosomal subgroups. In addition to overall and annual rates, prevalence was calculated for each level of selected sociodemographic and perinatal characteristics. Using a Poisson distribution, 95% confidence intervals (CIs) were computed around each prevalence estimate. Temporal trends in prevalence of overall, isolated, and multiple cases, specifically annual percent changes, were then estimated with joinpoint regression, which uses a Monte Carlo permutation test to assess whether there are statistically significant changes in trends over time (Kim, Fay, Feuer, & Midthune, 2000). Trends for chromosomal subtype could not be calculated due to the small sample size for this group. Modified Poisson regression models (Zou, 2004) were used to calculate crude and adjusted prevalence ratios of congenital diaphragmatic hernia (overall and stratified by its subtypes, isolated, and multiple) for each sociodemographic and perinatal characteristic. Two sets of multivariable models were run for overall, isolated, and multiple cases, resulting in a total of six models. The first set of models included all risk factors; the second consisted of birth outcomes and risk factors. We then used Kaplan-Meier curves to describe survival among cases (overall and stratified by its subtypes, isolated, multiple, and chromosomal). Cox proportional hazard regression models were then used to calculate crude and adjusted hazard ratios that represent the association between sociodemographic and perinatal characteristics and neonatal and one-year

survival among infants with congenital diaphragmatic hernia (overall and stratified by its subtypes, isolated, multiple, and chromosomal). The proportional hazards assumption was assessed using log (-log) survival plots, Schoenfeld residuals, and covariate-by-time interaction terms. Missing data ranged from zero percent for plurality to 7.8% for prenatal care. Multiple imputation with ten imputed datasets was applied for all six models. Prepregnancy BMI was available only for 2004–2012. Therefore, the above models were rerun after the addition of prepregnancy BMI to each one them. Survival estimates could not be computed for chromosomal congenital diaphragmatic hernia by prepregnancy BMI status due to too few observations and poor model fit. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) except the joinpoint analyses for which the Joinpoint Regression Program Version 4.5.0.0 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute; 2017) was used.

RESULTS

Data from 1,025 live-born infants diagnosed with congenital diaphragmatic hernia resulted in a prevalence of 3.19 per 10,000 live births (95% CI: 3.00-3.39) in Florida for 1998-2012. Of these, 782 (76.3%) were isolated, 209 (20.4%) multiple, and 34 (3.3%) chromosomal. Multiple CDH was associated mostly with congenital heart defects (80%), but also with genitourinary defects (9.8%), central nervous system defects (4.5%), limb defects (2.8%) and other birth defects (21.5%). Analysis of 15 years of prevalence data for overall and isolated congenital diaphragmatic hernia found no significant temporal trend; however, among multiple cases, the annual percent change during this period was 4.2% (95% CI: 1.3-7.2) (Figure 1).

The distribution of most of the sociodemographic and perinatal characteristics including maternal race/ethnicity were similar between cases and noncases. However, cases had higher rates of cesarean delivery (49.0% versus 33.0%), male sex (56.3% versus 51.2%), and were less likely to be born ≥ 37 weeks and $\geq 2,500$ g (63.0% versus 87.0%) (Table 1). Among risk factors, the highest prevalence was among multiple birth (4.71 per 10,000 live births). For birth outcomes, infants born ≥ 37 weeks and $\geq 2,500$ g had the lowest prevalence at 2.31 per 10,000 live births. In the adjusted model, compared to mothers with more than high school education, mothers with less than high school and high school/associate degree/GED education had prevalence ratios of 1.25 (95% CI:1.02-1.53) and 1.15 (95% CI:1.01-1.32), respectively. Additionally, the prevalence ratio was 1.38 (95% CI: 1.05-1.81) for twins/higher order multiples compared to singletons and 1.18 (95% CI: 1.05-1.32) for male infants compared to female infants. For the combined effect of gestational age and birth weight, the highest prevalence ratio of 5.23 (95% CI: 4.13-6.62) was observed for the category, <37 weeks and $<1,500$ g compared to ≥ 37 weeks and $\geq 2,500$ g. For cesarean births, the prevalence ratio was 1.55 (95% CI: 1.39-1.74) compared to a vaginal birth (Table 1).

When stratified by the type of defect, isolated and multiple, we found the risk of isolated congenital diaphragmatic hernia to be 22% higher among male infants than for female infants (Table 2). However, we did not find any of the variables to be risk factors for multiple congenital diaphragmatic hernia. For the combined effect of gestational age and birth weight, all categories had prevalence ratios higher than 1.0 when compared with ≥ 37 weeks and $\geq 2,500$ g. The highest prevalence ratio was for the category, <37 weeks and $<2,500$ g (prevalence ratio: 4.40, 95% CI: 3.35-5.80) among isolated cases. As for overall cases, we observed a higher prevalence ratio for

cesarean than for vaginal births among both isolated (prevalence ratio: 1.46, 95% CI: 1.29, 1.65) and multiple (prevalence ratio: 1.40, 95% CI: 1.16, 1.68) cases.

The 24-hour, neonatal, and one-year survival rates were 93.6%, 79.8%, and 71.2%, respectively. Isolated cases had better neonatal and one-year survival rates and chromosomal cases the worst (Figure 2). The highest risk for neonatal and one-year mortality was for infants who were born <37 weeks and had a birth weight <1,500g. Cases associated with chromosomal anomalies had nearly 18-fold higher risk for neonatal mortality; isolated cases had nearly 8-fold and 6-fold higher risk for neonatal and one-year mortality, respectively (Tables 3 and 4). Besides gestational age and birth weight, the only risk factor for neonatal mortality was younger maternal age among multiple cases; mothers aged 20-24 years had nearly 2.5 times higher risk of neonatal mortality compared to mothers aged 25-29 years. Additionally, among chromosomal cases receipt of adequate prenatal care was associated with 84% reduced risk for neonatal mortality compared to receipt of inadequate prenatal care (Table 3). For one-year mortality, among overall and isolated cases, we found 50% lower risk among multiple births compared to singletons. Among infants with multiple congenital diaphragmatic hernia, the other racial category had almost 3-fold higher risk for one-year mortality compared to white non-Hispanic category. The only risk factor for one-year mortality among cases associated with chromosomal anomalies was, maternal age > 35 years compared to 25-29 years (Table 4).

For the prepregnancy BMI analyses based on data for March 2004–December 2012, the highest crude prevalence of congenital diaphragmatic hernia (3.94 per 10,000) was among infants born to obese mothers. However, in the adjusted model, we found that mothers who were obese before pregnancy were 22% (Appendix 1) and 23% (Appendix 2) less likely to have an infant with overall and isolated congenital diaphragmatic hernia, respectively, compared to

mothers who had a normal prepregnancy BMI. We also found 54% and 50% lower risk of neonatal mortality for overall and isolated cases, respectively, among mothers who were underweight before pregnancy compared to who had a normal prepregnancy BMI. For one-year mortality, similar associations were observed for overall and isolated cases only (Appendix 3).

DISCUSSION

In this population-based study of 3,209,775 Florida live-born infants, we identified high school or less maternal education, multiple birth, and male sex as risk factors for congenital diaphragmatic hernia. We found gestational age and birth weight combined to be risk factors for increased neonatal and one-year mortality among overall, isolated, and multiple cases. Being a twin or higher order multiple was protective of one-year mortality among overall and isolated cases. Advanced maternal age and other racial category were risk factors for increased one-year mortality among chromosomal and multiple cases, respectively. Besides gestational age and birth weight, the only risk factor for neonatal mortality among all subtypes was maternal age 20-24 years, whereas receipt of adequate prenatal care was protective of chromosomal congenital diaphragmatic hernia.

The congenital diaphragmatic hernia prevalence in this study based on a passive surveillance system was 23% higher than the national estimate (3.19 vs 2.61 per 10,000 live births) (Parker et al., 2010), but similar to a study from the Utah Birth Defect Network during a similar timeframe (1999–2011) that relies on active case ascertainment (Shanmugam et al., 2017). We detected a significant trend in prevalence for multiple congenital diaphragmatic hernia only. Additionally, 76.3% of the cases were isolated; a finding higher than what has been reported in the literature (Dott et al., 2003; Shanmugam et al., 2017). This may be due, in part, to

our study's reliance on a non-specific ICD-9-CM code that includes both CDH and eventration of the diaphragm; therefore, we cannot rule out the possibility that our higher proportion of isolated congenital diaphragmatic hernia may, in fact, be isolated congenital eventration of the diaphragm. Clinically, however, the prevalence of diaphragmatic eventration is rare and is unlikely to significantly contribute to the estimate of diaphragmatic hernia (B. R. Pober, 2007). Another explanation for these results is the changing FBDR case ascertainment data sources (Rutkowski et al., 2015; Salemi et al., 2011), potentially resulting in the reduced ability to capture some birth defects, not only congenital diaphragmatic hernia, but also others like Trisomy 21 and spina bifida that may impact the classification of subtypes of congenital diaphragmatic hernia (Rutkowski et al., 2015; Salemi et al., 2011). Yet another reason could be a different group of birth defects constituting the definition of multiple congenital diaphragmatic hernia. Our use of NBDPN defects includes major anomalies diagnosed within the first year of life, of public health importance, and with adequate diagnostic accuracy (Mai et al., 2014).

The finding that maternal education high school or less is a risk factor for congenital diaphragmatic hernia concurs with the Born in Bradford study that found low maternal education was a risk factor for birth defects in general (Sheridan et al., 2013). Higher risk for this defect among mothers with high school or less education may reflect disparities in access to health care and decisions regarding prenatal diagnostic tests or pregnancy termination. We also found a 38% higher risk of congenital diaphragmatic hernia among multiple births compared to singletons, consistent with a 1996-2000 Florida study that found a 46% increased risk of birth defects among multiple births compared to singletons (Tang et al., 2006). Though obese mothers in our study had the highest prevalence of congenital diaphragmatic hernia, we did not find maternal obesity to be a risk factor for congenital diaphragmatic hernia after adjustment for confounders,

unlike a study based on the 1995–2007 Swedish Medical Birth Registry data (Blomberg & Källén, 2010).

Infants with congenital diaphragmatic hernia are at risk not only for prematurity and/or LBW/VLBW, but these characteristics can also predispose them to increased infant mortality (Levison et al., 2006; Tsao, Allison, Harting, Lally, & Lally, 2010). A possible reason for the increased risk for prematurity is that fetuses diagnosed with congenital diaphragmatic hernia may be delivered earlier by elective cesarean delivery. A study in Brazil found decreased observed-to-expected lung to head ratio, a variable that we couldn't measure in our study, a predictor for increased spontaneous prematurity (Barbosa et al., 2018). Since we found survival rates to be lower in LBW/VLBW infants, irrespective of gestational age, it may suggest a greater role for birth weight rather than gestational age in the prognosis of infants with congenital diaphragmatic hernia. In our study, the 24-hour and one-year survival rates were 93.6% and 71.2%, respectively; those estimates are within the range reported in previous studies (Badillo & Gingalewski, 2014; Balayla & Abenhaim, 2014; Dott et al., 2003). Consistent with what has been found in the literature, our study also found worse survival rates among cases associated with chromosomal anomalies followed by multiple subtype, likely due to the deleterious effects of co-occurring birth defects (B. R. Pober, Russell, M.K., Ackerman, K.G., 2006; Shanmugam et al., 2017). A surprising finding was that, among isolated cases, multiple births had more than 50% lower risk for one-year mortality. This could be due, at least in part, to underascertainment of deaths among multiple births due to the decreased birth-infant death certificate linkage rates among twins or higher order multiples. Another finding was that infants born to underweight mothers had lower risk for neonatal and one-year mortality compared to infants born to mothers with normal BMI. However, these findings should be interpreted with caution due to the small

sample size within this category. Unlike previous studies (Balayla & Abenhaim, 2014; Yang et al., 2006) we did not find advanced maternal age to be a risk factor for congenital diaphragmatic hernia; but it was found to be a risk factor for one-year mortality among chromosomal cases only.

Strengths of this study include its large sample size and assessment of associations among congenital diaphragmatic hernia, overall and stratified by its subtypes, isolated, multiple, and chromosomal. Florida has considerable diversity in its population, both in terms of race/ethnicity and maternal nativity; therefore, the results of this study could be generalized to other diverse populations. The FBDR relies on linkage of discharge data to identify birth defects; 35.9% of live-born infants who die within 24 hours are missed by data linkage compared to infants alive after one year (Salemi, Tanner, Bailey, Mbah, & Salihu, 2013). This could have underestimated early mortality. Our study focused on live-born infants with congenital diaphragmatic hernia; therefore, pregnancies that end in stillbirths and abortions (elective or spontaneous) are missed by the birth defects registry; this likely results in underestimated prevalence rates. The estimates for the categories ≥ 37 weeks and $< 2,500$ g, and < 37 weeks and $< 1,500$ g should be interpreted with caution due to the wide confidence intervals. This study was limited by lack of information on prenatal diagnosis, procedures performed, and details regarding the defect –severity, side, and size of the defect, and liver position– which could have biased survival estimates. Self-reported maternal smoking during pregnancy is likely to be underreported (Northam & Knapp, 2006) among cases and noncases alike, resulting in nondifferential misclassification and bias in measures of association toward the null.

In addition to risk factors found in the literature, this study suggests a role for maternal education and multiple birth in congenital diaphragmatic hernia. Further research into

environmental factors or measures of socioeconomic status besides maternal education may elucidate the role of disparities in the etiology of congenital diaphragmatic hernia. We may need studies to further investigate the role of prepregnancy BMI, multiple births, maternal age, and prenatal care in the survival of infants with congenital diaphragmatic hernia. Additional research and surveillance of the differential correlates and survival outcomes among isolated, multiple, and chromosomal cases is also warranted.

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CONFLICT OF INTEREST

The authors have no potential conflict of interest to report.

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Figure 1. Legend

Fig 1(A):■ Observed

—— 1998–2012 APC = 0.3 (95%CI: -1.1-1.7)

Fig 1(B):■ Observed

—— 1998–2012 APC = -0.9 (95%CI: -2.4-0.7)

Fig 1(C):■ Observed

—— 1998–2012 APC = 4.2 (95%CI: 1.3-7.2)

Figure 2. Legend

—— Isolated congenital diaphragmatic hernia

—— Multiple congenital diaphragmatic hernia

—— Chromosomal congenital diaphragmatic hernia

Table 1. Prevalence Rates/Ratios of Congenital Diaphragmatic Hernia by Sociodemographic and Perinatal**Characteristics in the State of Florida:1998-2012**

Characteristic	CDH	No CDH	Prevalence Rate^a	Adjusted^b
	N (%)	N (%)	(95% CI)	Prevalence Ratio (95% CI)
Risk Factors				
Maternal age (years)				
<20	110 (10.7)	2,502,279 (10.7)	3.20 (2.65-3.85)	0.94 (0.76-1.16)
20-24	257 (25.1)	811,838 (25.3)	3.16 (2.80-3.58)	0.97 (0.83-1.14)
25-29	270 (26.3)	863,903 (26.9)	3.12 (2.77-3.52)	1.00
30-34	230 (22.4)	722,802 (22.5)	3.18 (2.80-3.62)	1.03 (0.88-1.21)
35+	158 (15.4)	466,898 (14.6)	3.38 (2.89-3.95)	1.09 (0.91-1.30)
Maternal Race/Ethnicity				
White Non-Hispanic	502 (49.3)	1,522,144 (47.6)	3.30 (3.02-3.60)	1.00
Black Non-Hispanic	186 (18.3)	597,667 (18.7)	3.11 (2.69-3.59)	0.92 (0.79-1.08)

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Hispanic	295 (29.0)	952,350 (29.8)	3.10 (2.76-3.47)	0.91 (0.80-1.05)
Other	35 (3.4)	126,183 (4.0)	2.77 (1.99-3.86)	0.88 (0.64-1.18)
Maternal Education				
< High School	153 (15.1)	437031 (13.7)	3.50 (2.99-4.10)	1.25 (1.02-1.53)
High School/Associate Degree/GED	524 (51.6)	1589850 (49.7)	3.29 (3.02-3.59)	1.15 (1.01-1.32)
> High School	338 (33.3)	1170698 (36.6)	2.89 (2.59-3.21)	1.00
Marital Status				
Not Married	447 (46.6)	1,371,707 (42.8)	3.26 (2.97-3.57)	1.00
Married	577 (56.4)	1,836,809 (57.2)	3.14 (2.89-3.41)	0.98 (0.86-1.12)
Maternal Smoking during Pregnancy				
No	931 (91.0)	1,836,809 (91.5)	3.18 (2.98-3.39)	1.00
Yes	92 (9.0)	271,551 (8.5)	3.39 (2.76-4.15)	0.97 (0.80-1.19)
Parity				
Nulliparous	671 (65.9)	2,138,807 (66.9)	3.14 (2.95-3.35)	1.00
Multiparous	348 (34.1)	1,058,892 (33.1)	3.29 (2.96-3.64)	1.05 (0.93-1.18)
Receipt of Prenatal Care				
Not Adequate	238 (25.9)	749,752 (25.3)	3.17 (2.79-3.60)	1.00
Adequate	679 (74.1)	2,209,807 (74.7)	3.07 (2.85-3.31)	1.00 (0.88-1.14)

Plurality

Singleton	978 (95.4)	3,109,982 (96.9)	3.14 (2.95-3.35)	1.00
Multiple	47 (4.6)	99,712 (3.1)	4.71 (3.54-6.27)	1.38 (1.05-1.81)

Infant Sex

Female	448 (43.7)	1,566,804 (48.8)	2.86 (2.61-3.14)	1.00
Male	576 (56.3)	1,642,922 (51.2)	3.50 (3.23-3.80)	1.18 (1.05-1.32)

Birth Outcomes

Method of Delivery

Vaginal	520 (51.0)	2,126,549 (67.0)	2.44 (2.24-2.66)	1.00
Cesarean	499 (49.0)	1,047,451 (33.0)	4.76 (4.36-5.20)	1.55 (1.39-1.74)

Gestational Age & Birth Weight

≥37 weeks & ≥2,500g	646 (63.0)	2,792,818 (87.0)	2.31 (2.14-2.50)	1.00
≥37 weeks & <2,500g	82 (8.0)	78,298 (2.4)	10.46 (8.43-12.99)	3.85 (3.09-4.80)
<37 weeks & <1,500g	78 (7.6)	49,598 (1.6)	15.70 (12.58-19.60)	5.23 (4.13-6.62)
<37 weeks & 1,500-2,499g	137 (13.4)	142,908 (4.5)	9.58 (8.10-11.32)	3.56 (2.97-4.27)
<37 weeks & ≥2,500g	82 (8.0)	146,046 (4.6)	5.61 (4.52- 6.97)	2.07 (1.68-2.56)

CDH = Congenital diaphragmatic hernia, CI = confidence interval

Column percentages displayed.

Frequencies may not add to the total due to missing data; percentage may not add to 100% due to rounding.

^aCongenital diaphragmatic hernia cases per 10,000 live births

^bRisk factors adjusted for other risk factors; birth outcomes adjusted for all other variables in the table

Table 2. Prevalence Ratios of Congenital Diaphragmatic Hernia, Isolated and Multiple^a, by Selected Sociodemographic and Perinatal Characteristics in the State of Florida:1998-2012

Characteristic	Isolated CDH			Multiple CDH	
	Total Cases	Cases	Adjusted ^b	Cases	Adjusted ^b Prevalence
		N (%)	Prevalence Ratio (95% CI)	N (%)	Ratio (95% CI)
Total	1,025	782 (76.3)^c		209 (20.4)^c	
Risk Factors					
Maternal age (years)					
<20	110 (10.7)	83 (10.6)	0.93 (0.74-1.18)	25 (12.0)	1.02 (0.73-1.44)
20-24	257 (25.1)	198 (25.3)	0.98 (0.82-1.16)	54 (25.8)	1.02 (0.79-1.31)

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25-29	270 (26.3)	209 (26.7)	1.00	51 (24.4)	1.00
30-34	230 (22.4)	175 (22.4)	1.01 (0.85-1.21)	48 (23.0)	1.07 (0.83-1.38)
35+	158 (15.4)	117 (15.0)	1.04 (0.86-1.27)	31 (14.8)	1.08 (0.81-1.45)
Maternal Race/Ethnicity					
White Non-Hispanic	502 (49.3)	395 (50.8)	1.00	91 (43.5)	1.00
Black Non-Hispanic	186 (18.3)	135 (17.4)	0.88 (0.73-1.05)	45 (21.5)	1.08 (0.84-1.40)
Hispanic	295 (29.0)	224 (28.8)	0.90 (0.78-1.05)	62 (29.6)	0.99 (0.80-1.24)
Other	35 (3.4)	24 (3.1)	0.81 (0.57-1.14)	11 (5.3)	1.17 (0.75-1.81)
Maternal Education					
< High School	153 (15.1)	115 (14.9)	1.18 (0.95-1.47)	34 (16.4)	1.22 (0.88-1.68)
High School/Associate Degree/GED	524 (51.6)	392 (50.7)	1.09 (0.94-1.26)	114 (54.8)	1.17 (0.94-1.46)
> High School	338 (33.3)	267 (34.5)	1.00	60 (28.8)	1.00
Marital Status					
Not Married	447 (46.6)	342 (43.8)	1.00	92 (44.0)	1.00
Married	577 (56.4)	439 (56.2)	0.96 (0.83-1.11)	117 (56.0)	1.05 (0.85-1.30)
Maternal Smoking during Pregnancy					
No	931 (91.0)	708 (90.8)	1.00	193 (92.3)	1.00
Yes	92 (9.0)	72 (9.2)	0.99 (0.79-1.23)	16 (7.7)	0.92 (0.66-1.30)

Parity

Nulliparous	671 (65.9)	503 (64.7)	1.00	147 (70.3)	1.00
Multiparous	348 (34.1)	274 (35.3)	1.08 (0.95-1.23)	62 (29.7)	0.95 (0.78-1.15)

Receipt of Prenatal Care

Not Adequate	238 (25.9)	179 (25.4)	1.00	53 (29.6)	1.00
Adequate	679 (74.1)	526 (74.6)	1.01 (0.88-1.17)	126 (70.4)	0.96 (0.78-1.18)

Plurality

Singleton	978 (95.4)	746 (95.4)	1.00	201 (96.2)	1.00
Multiple	47 (4.6)	36 (4.6)	1.36 (1.00-1.84)	8 (3.8)	1.08 (0.66-1.78)

Infant Sex

Female	448 (43.7)	330 (42.3)	1.00	94 (45.0)	1.00
Male	576 (56.3)	451 (57.8)	1.22 (1.08-1.37)	115 (55.0)	0.94 (0.78-1.12)

Birth Outcomes

Method of Delivery

Vaginal	520 (51.0)	410 (52.7)	1.00	96 (46.4)	1.00
Cesarean	499 (49.0)	368 (47.3)	1.46 (1.29-1.65)	111 (53.6)	1.40 (1.16-1.68)

Gestational age & Birth Weight

≥37 weeks & ≥2,500g	646 (63.0)	524 (67.0)	1.00	118 (56.5)	1.00
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≥37 weeks & <2,500g	82 (8.0)	45 (5.8)	2.60 (1.96-3.46)	21 (10.0)	2.89 (1.96-4.27)
<37 weeks & <1,500g	78 (7.6)	56 (7.2)	4.40 (3.35-5.80)	15 (7.2)	2.80 (1.72-4.56)
<37 weeks & 1,500-2,499g	137 (13.4)	97 (12.4)	2.99 (2.42-3.69)	35 (16.7)	2.78 (2.03-3.82)
<37 weeks & ≥2,500g	82 (8.0)	60 (7.8)	1.83 (1.45-2.34)	20 (9.6)	1.79 (1.25-2.55)

CDH = congenital diaphragmatic hernia, CI = confidence interval

Column percentages displayed.

Frequencies may not add to the total due to missing data; percentages may not add to 100% due to rounding.

^aA case that had associated structural and non-chromosomal birth defects listed on the National Birth Defects Prevention Network was classified as multiple (Mai et al., 2014)

^bRisk factors adjusted for other risk factors only; birth outcomes adjusted for all other variables in the table

^cThirty-four (3.3%) cases of chromosomal congenital diaphragmatic hernia were included in the description of all cases of CDH; however, they were not included in the models for estimation of prevalence ratios by subtypes.

Table 3: Neonatal Survival Among Live-born Congenital Diaphragmatic Hernia Cases by Selected

Sociodemographic and Perinatal Characteristics in Florida:1998-2012

	All Cases	Isolated CDH	Multiple ^a CDH	Syndromic ^a CDH
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Characteristics	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Risk Factors				
Maternal age (years)				
<20	0.97 (0.55-1.72)	0.90 (0.45-1.80)	2.22 (0.74-6.66)	—
20-24	1.27 (0.84-1.91)	1.09 (0.66-1.80)	2.44 (1.02-5.84)	
25-29	1.00	1.00	1.00	
30-34	1.25 (0.83-1.87)	1.22 (0.75-2.01)	0.96 (0.37-2.48)	
35+	0.99 (0.63-1.57)	0.76 (0.41-1.42)	1.09 (0.43-2.81)	
Maternal Race/Ethnicity				
White Non-Hispanic	1.00	1.00	1.00	—
Black Non-Hispanic	1.06 (0.72-1.56)	0.96 (0.59-1.56)	1.33 (0.60-2.98)	
Hispanic	0.91 (0.64-1.29)	0.88 (0.57-1.36)	0.96 (0.46-1.99)	
Other	1.08 (0.52-2.25)	0.93 (0.34-2.60)	1.47 (0.43-5.01)	
Maternal Education				
> High School	1.00	1.00	1.00	—
< High School	1.30 (0.80-2.11)	1.59 (0.88-2.88)	0.69 (0.24-2.01)	

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High School/ Associate Degree/GED	0.94 (0.67-1.32)	1.11 (0.72-1.70)	0.50 (0.23-1.05)	
Marital Status				
Not Married	1.00	1.00	1.00	1.00
Married	1.08 (0.77-1.51)	0.93 (0.61-1.43)	1.49 (0.74-2.99)	0.92 (0.14-6.08)
Maternal Smoking during Pregnancy				
No	1.00	1.00	1.00	1.00
Yes	1.33 (0.83-2.12)	1.50 (0.86-2.61)	0.47 (0.10-2.13)	6.31 (0.43-93.49)
Parity				
Nulliparous	1.00	1.00	1.00	1.00
Multiparous	1.05 (0.78-1.42)	1.01 (0.70-1.47)	1.23 (0.66-2.30)	0.55 (0.15-1.97)
Receipt of Prenatal Care				
Not Adequate	1.00	1.00	1.00	1.00
Adequate	1.02 (0.71-1.47)	1.41 (0.87-2.26)	0.73 (0.37-1.42)	0.16 (0.04-0.70)
Plurality				
Singleton	1.00	1.00	1.00	1.00
Multiple	0.51 (0.27-0.97)	0.46 (0.21-1.03)	0.38 (0.08-1.73)	1.83 (0.26-12.78)
Infant Sex				

Female	1.00	1.00	1.00	1.00
Male	0.97 (0.73-1.28)	0.97 (0.68-1.39)	1.06 (0.58-1.92)	0.49 (0.08-3.10)
Birth Outcomes				
Delivery Route				
Vaginal	1.00	1.00	1.00	1.00
Cesarean	1.15 (0.86-1.53)	1.20 (0.83-1.73)	0.93 (0.52-1.66)	0.91 (0.23-3.49)
Gestational age & Birth Weight				
≥37 weeks & ≥2,500g	1.00	1.00	1.00	1.00
≥37 weeks & <2,500g	3.80 (2.45-5.89)	3.70 (2.02-6.79)	3.17 (1.31-7.70)	1.39 (0.17-11.13)
<37 weeks & <1,500g	7.00 (4.64-10.55)	7.55 (4.52-12.61)	3.46 (1.40-8.58)	17.87 (1.49-213.82)
<37 weeks & 1,500-2,499g	3.22 (2.19-4.73)	3.81 (2.40-6.06)	1.75 (0.77-3.97)	3.95 (0.41-37.77)
<37 weeks & ≥2,500g	1.89 (1.10-3.26)	1.87 (0.94-3.71)	1.47 (0.52-4.13)	2.83 (0.10-76.52)

CDH = congenital diaphragmatic hernia, HR = hazard ratio, CI = confidence interval

Hyphen = Estimates could not be computed due to few observations and poor model fit when this variable was included.

^aA case that had associated chromosomal anomalies listed on the National Birth Defects Prevention Network was categorized as chromosomal; a case associated with structural birth defects was classified as multiple (Mai et al., 2014)

Each variable adjusted for all other variables in the table. `

Table 4: One-Year Survival Among Live-born Congenital Diaphragmatic Hernia Cases by Selected Sociodemographic and Perinatal Characteristics in Florida:1998-2012

	All Cases	Isolated CDH	Multiple ^a CDH	Syndromic ^a CDH
Characteristics	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Risk Factors				
Maternal age (years)				
<20	1.05 (0.67-1.64)	0.96 (0.54-1.70)	1.59 (0.70-3.65)	0.49 (0.03-7.28)
20-24	1.19 (0.85-1.66)	1.15 (0.76-1.75)	1.70 (0.86-3.36)	0.38 (0.03-4.40)
25-29	1.00	1.00	1.00	1.00
30-34	1.13 (0.80-1.59)	1.16 (0.76-1.78)	0.91 (0.44-1.88)	3.12 (0.55-17.74)
35+	0.97 (0.66-1.42)	0.83 (0.50-1.38)	0.84 (0.39-1.81)	8.90 (1.15-68.65)
Maternal Race/Ethnicity				
White Non-Hispanic	1.00	1.00	1.00	-
Black Non-Hispanic	1.12 (0.82-1.54)	1.03 (0.69-1.54)	1.29 (0.68-2.44)	
Hispanic	0.91 (0.68-1.22)	0.88 (0.61-1.26)	0.90 (0.49-1.66)	

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Other	1.32 (0.74-2.36)	0.83 (0.34-2.07)	2.84 (1.14-7.06)	
Maternal Education				
> High School	1.00	1.00	1.00	1.00
< High School	1.35 (0.91-2.02)	1.41 (0.86-2.31)	1.12 (0.48-2.60)	0.05 (0.00-0.58)
High School/ Associate Degree/GED	0.94 (0.71-1.24)	1.02 (0.71-1.46)	0.56 (0.30-1.02)	0.32 (0.08-1.30)
Marital Status				
Not Married	1.00	1.00	1.00	1.00
Married	0.94 (0.71-1.24)	0.86 (0.60-1.23)	1.05 (0.60-1.82)	0.15 (0.02-1.20)
Maternal Smoking during Pregnancy				
No	1.00	1.00	1.00	1.00
Yes	1.07 (0.71-1.61)	1.25 (0.77-2.03)	0.42 (0.14-1.27)	0.94 (0.09-10.10)
Parity				
Nulliparous	1.00	1.00	1.00	1.00
Multiparous	0.97 (0.76-1.25)	1.00 (0.73-1.36)	0.84 (0.49-1.45)	1.29 (0.35-4.78)
Receipt of Prenatal Care				
Not Adequate	1.00	1.00	1.00	1.00
Adequate	1.13 (0.84-1.51)	1.26 (0.86-1.85)	1.03 (0.58-1.83)	0.25 (0.05-1.42)

Plurality

Singleton	1.00	1.00	1.00	1.00
Multiple	0.45 (0.25-0.80)	0.41 (0.20-0.86)	0.35 (0.08-1.54)	3.40 (0.38-30.32)

Infant Sex

Female	1.00	1.00	1.00	1.00
Male	1.00 (0.79-1.26)	0.99 (0.74-1.33)	1.08 (0.67-1.73)	0.25 (0.04-1.60)

Birth Outcomes

Delivery Route

Vaginal	1.00	1.00	1.00	1.00
Cesarean	1.16 (0.91-1.47)	1.19 (0.88-1.62)	1.03 (0.64-1.65)	1.09 (0.30-4.04)

Gestational age & Birth Weight

≥37 weeks & ≥2,500g	1.00	1.00	1.00	1.00
≥37 weeks & <2,500g	3.65 (2.54-5.25)	3.37 (2.02-5.62)	2.70 (1.27-5.75)	0.72 (0.11-4.79)
<37 weeks & <1,500g	5.37 (3.75-7.71)	5.67 (3.61-8.90)	2.62 (1.16-5.89)	2.92 (0.25-34.67)
<37 weeks & 1,500-2,499g	2.97 (2.17-4.08)	3.29 (2.23-4.87)	1.97 (1.06-3.66)	0.23 (0.02-3.44)
<37 weeks & ≥2,500g	1.86 (1.21-2.87)	2.09 (1.23-3.55)	0.97 (0.41-2.32)	0.94 (0.06-15.18)

CDH = congenital diaphragmatic hernia, HR = Hazard Ratio, CI = confidence interval

Hyphen = Estimates could not be computed due to few observations and poor model fit when this variable was included.

^aA case that had associated chromosomal anomalies listed on the National Birth Defects Prevention Network was categorized as chromosomal; a case associated with structural birth defects was classified as multiple (Mai et al., 2014)

Each variable adjusted for all other variables in the table. `

Appendix 1 Prevalence Ratios of Congenital Diaphragmatic Hernia by Prepregnancy Body Mass Index in the State of Florida: March 2004-December 2012 (N = 1,963,766)

Prepregnancy Body Mass Index	CDH	No CDH	Prevalence Rate ^a	Adjusted ^b Prevalence
	N (%)	N (%)	(95% CI)	Ratio (95% CI)

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Normal weight	278 (43.9)	919797 (46.9)	3.02 (2.66-3.37)	1.00
Underweight	82 (13.0)	219981 (11.2)	3.73 (2.92-4.53)	0.83 (0.64-1.06)
Overweight	126 (19.9)	450316 (22.9)	2.80 (2.31-3.28)	1.09 (0.88-1.34)
Obese	147 (23.2)	373039 (19.0)	3.94 (3.30-4.57)	0.78 (0.64-0.96)

CDH = Congenital diaphragmatic hernia, CI = confidence interval

Column percentages displayed.

^aCongenital diaphragmatic hernia cases per 10,000 live births

^bAdjusted for maternal age, race/ethnicity, education, smoking during pregnancy, marital status, parity, receipt of prenatal care, plurality, and infant sex.

Appendix 2 Prevalence Ratios of Congenital Diaphragmatic Hernia (Isolated and Multiple^a) by Prepregnancy**Body Mass Index in the State of Florida: March 2004-December 2012 (N= 1,963,766)**

Prepregnancy Body Mass Index	Isolated CDH		Multiple^a CDH	
	Cases	Adjusted^b Prevalence	Cases	Adjusted^b Prevalence
	N (%)	Ratio (95% CI)	N (%)	Ratio (95% CI)
Normal weight	208 (44.3)	1.00	61 (41.8)	1.00
Underweight	61 (13.0)	0.90 (0.67-1.21)	23 (15.8)	0.70 (0.43-1.14)
Overweight	91 (19.4)	1.12 (0.87-1.43)	30 (20.6)	1.01 (0.65-1.57)
Obese	110 (23.4)	0.77 (0.64-0.97)	32 (21.9)	0.81 (0.53-1.26)

CDH = Congenital diaphragmatic hernia, CI = confidence interval

^aA case that had associated structural birth defects listed on the National Birth Defects Prevention Network was classified as multiple (Mai et al., 2014)

^bAdjusted for maternal age, race/ethnicity, education, smoking during pregnancy, marital status, parity, receipt of prenatal care, plurality, and infant sex.

Appendix 3. Neonatal and One-Year Survival Among Live-born Congenital Diaphragmatic Hernia Cases by Prepregnancy Body**Mass Index in Florida: March 2004–December 2012 (N= 1,963,766)**

	Neonatal Period			First Year of Life		
	All Cases	Isolated CDH	Multiple ^a CDH	All Cases	Isolated CDH	Multiple ^a CDH
Characteristics	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Normal weight	1.00	1.00	1.00	1.00	1.00	1.00
Underweight	0.46 (0.28-0.78)	0.50 (0.25-0.98)	0.46 (0.17-1.27)	0.50 (0.33-0.76)	0.46 (0.27-0.81)	0.71 (0.32-1.58)
Overweight	1.15 (0.64-1.04)	1.40 (0.64-3.08)	1.95 (0.59-6.42)	1.34 (0.84-2.13)	1.44 (0.76-1.53)	2.06 (0.86-4.93)
Obese	0.90 (0.55-1.46)	0.93 (0.55-1.75)	0.68 (0.26-1.78)	1.01 (0.68-1.52)	0.91 (0.54-2.72)	1.13 (0.51-2.49)

Notes: CDH = congenital diaphragmatic hernia, HR = Hazard Ratio, CI = confidence interval

^aA case that had associated chromosomal anomalies listed on the National Birth Defects Prevention Network was categorized as chromosomal; a case associated with structural birth defects was classified as multiple (Mai et al., 2014).

All models adjusted for maternal age, race/ethnicity, education, smoking during pregnancy, marital status, parity, receipt of prenatal care, plurality, infant sex, delivery route, gestational age and birthweight.

Hazard ratios could not be computed for chromosomal congenital diaphragmatic hernia due to insufficient sample size and poor model fit.