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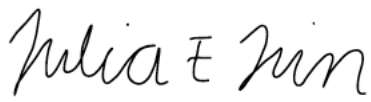

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December 9, 2020

Maternal Exposures to Cigarette Smoking and Alcohol and Congenital Diaphragmatic Hernia

By

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Degree to be awarded: Master of Public Health

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Maternal Exposures to Cigarette Smoking and Alcohol and Congenital Diaphragmatic Hernia

By

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Bachelor of Science
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2018

Faculty Thesis Advisors: Vijaya Kancherla, PhD, MS and Paul Romitti, PhD, MS

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ABSTRACT

Maternal Exposures to Cigarette Smoking and Alcohol and Congenital Diaphragmatic Hernia

By Julia Finn

BACKGROUND: Congenital diaphragmatic hernia (CDH) is a major birth of the diaphragm in which abdominal organs herniate into the thoracic cavity. CDH contributes substantially to infant mortality and disability. CDH has both genetic and environmental risk factors. Previous studies suggest maternal smoking and alcohol exposures during pregnancy may be associated with CDH, but more comprehensive studies are needed. Using data from the National Birth Defects Prevention Study, we examined associations between maternal early pregnancy (one month prior through three months following conception) smoking and alcohol exposures and CDH.

METHODS: CDH cases and unaffected live born singleton controls, delivered from 1997 through 2011, were included. Interview reports of smoking (quantity, frequency, variability) and alcohol consumption (quantity, frequency, variability, type) were obtained from 883 case mothers and 11,829 control mothers. Two analyses were conducted: the main analysis examined deliveries from 2006-2011 and the second, a pooled analysis of all deliveries from 1997 through 2011. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated for each smoking and alcohol exposure variable and all CDH and CDH subtypes using multivariable logistic regression analysis.

RESULTS: In the main analysis, positive associations were observed for any smoking, active and/or passive smoking, smoking a minimum of 15 cigarettes per day, and smoking for any duration during early pregnancy and all CDH. Findings were similar for CDH subtypes. Positive associations were also observed for drinking 30 or more drinks/month and 4 or more binge episodes and all CDH. Findings were generally similar for CDH subtypes, with additional positive association observed for 1 binge episode and drinking for 2 months during early pregnancy and CDH Bochdalek. The results of the pooled analyses were generally similar to those for 2006-2011.

CONCLUSIONS: Several positive associations were observed between maternal smoking and all CDH and CDH subtypes. Whereas few positive associations were observed for maternal early pregnancy alcohol consumption and all CDH or CDH subtypes. Future studies should aim to improve exposure assessment and should examine potential mechanisms accounting for unexpected effects of maternal periconceptional cigarette smoking and alcohol observed in this study.

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THESIS STATEMENT

The aim of the current study was to expand on the work previously published by Caspers et al. (2010). This study included pregnancies from the National Birth Defects Prevention Study with estimated dates of delivery (EDD)s from 1997-2011 and examined the association between maternal periconceptional smoking and alcohol consumption and congenital diaphragmatic hernia (CDH). The current project expanded on this work by including data from NBDPS CDH cases and control with EDDs from 2006-2011 to the previous study years, with a focus on maternal smoking and alcohol consumption during the period one month before conception through the first month following conception and CDH and its subtypes.

KEYWORDS AND ABBREVIATIONS

Keywords: smoking; alcohol; birth defects; case-control study; epidemiology; congenital diaphragmatic hernia

Abbreviations:

aOR	adjusted odds ratio
aPR	adjusted prevalence ratio
BPA	British Pediatric Association Classification of Diseases
BMI	body mass index
CATI	computer-assisted telephone interview
CI	confidence interval
CDC	Centers for Disease Control and Prevention
CDH	congenital diaphragmatic hernia
cOR	crude odds ratio
ECMO	extracorporeal membrane oxygenation
EDD	estimated date of delivery
MACDP	Metropolitan Atlanta Congenital Defects Program
NBDPS	National Birth Defects Prevention Study
NOS	not otherwise specified
OR	odds ratio
RA	retinoic acid
US	United States

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CHAPTER I

PUBLIC HEALTH SIGNIFICANCE

Congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) is a rare, severe birth defect in which abnormal development of the diaphragm leads to herniation of abdominal organs into the thoracic cavity, disrupting normal development of the lungs and heart. CDH can present as a small opening of the posterior muscle rim or be as extensive as a complete absence of the diaphragm (Chandrasekharan et al., 2017). There are four well-described subtypes of CDH – Bochdalek, Morgagni, pars sternalis, and anterolateral hernias. The most common of these subtypes is Bochdalek, a posterolateral hernia that occurs in approximately 70-75% of CDH case infants, with most occurring on the left side of the diaphragm, which can cause the small and large intestines to herniate into the thoracic cavity (Chandrasekharan et al., 2017).

CDH most often presents as an isolated defect, with studies in the US reporting between 58-76% of cases being isolated (Ramakrishnan et al., 2018; Shanmugam et al., 2017; Yang et al., 2006). Several co-occurring defects have been reported among non-isolated cases, with congenital heart defects being the most common (Ramakrishnan et al., 2018; Shanmugam et al., 2017; Yang et al., 2006). CDH is often associated with pulmonary hypoplasia and hypertension, as well as cardiac dysfunction, which are often fatal (Chandrasekharan et al., 2017).

Prevalence

A recent study, using population based surveillance data from 14 active case finding population based registries, estimated the prevalence of CDH in the US as 2.9 per 10,000 live births during 2010-2014 (Mai et al., 2019), with stable prevalence from 1999-2014 (Canfield et

al., 2006; Mai et al., 2019; Parker et al., 2010). Prevalence estimates were generally similar across race/ethnicity categories (Mai et al., 2019). Also, previous state-based studies in California during 1989 - 1997 (Yang et al., 2006), Utah during 1999 - 2011 (Shanmugam et al., 2017), Florida during 1998 – 2012 (Ramakrishnan et al., 2018), and Hawaii during 1987 - 1996 (Forrester & Merz, 1998) reported similar and stable prevalence estimates during their respective study periods.

Survival in CDH

CDH is a highly fatal condition, with previous US studies reporting 1-year mortality estimates ranging from 30-50% (Balayla & Abenhaim, 2014; Dott et al., 2003; Ramakrishnan et al., 2018; Shanmugam et al., 2017; Wang et al., 2015; Yang et al., 2006). The main causes of mortality associated with CDH are pulmonary hypoplasia and treatment resistant pulmonary hypertension (Balayla & Abenhaim, 2014). The size of CDH defect is also correlated with mortality rate, possibly due to increased prevalence of liver in the chest, leading to pulmonary hypoplasia, and increased prevalence of additional defects and abnormal organ systems (Morini et al., 2013). Some studies have found that race other than white was associated with increased risk of death (Dott et al., 2003; Ramakrishnan et al., 2018; Wang et al., 2011).

Reports of survival are consistently higher for infants with isolated CDH than for those with CDH and additional defects or chromosomal/syndromic cases, with mortality increasing with clinical complexity (Ramakrishnan et al., 2018; Shanmugam et al., 2017; Yang et al., 2006). Reported estimates of CDH mortality in the US have decreased over time, with 1-year survival being as low as 19% in 1968 and increasing to 72% in 1997 (Dott et al., 2003; Yang et al., 2006). Additionally, in the Atlanta area, long-term survival (28 years) increased from 1979 to 2006 from 40.5% to 61.9% (Hinton et al., 2017).

Clinical care and costs

Given the severity of the defect, infants with CDH often require long-term care (Crankson et al., 2006). Treatment for CDH often requires surgery, with 80% of infants with CDH receiving surgery (Aly et al., 2010). Additionally, surviving infants may require long-term medications, home respiratory support, vasoactive medications, and multiple surgical interventions (Hollinger & Buchmiller, 2019). National health care expenditures have been estimated to be in excess of $250 million per year in the US (Raval et al., 2011). With its prevalence in the US, as well its considerable cost of care, CDH represents a significant public health burden.

Goal and significance

Despite the clinical severity and reduced survival associated with CDH, little is known about the contribution of modifiable risk factors to CDH risk. The continued exploration of modifiable risk factors is necessary to reduce the public health burden of CDH. Two common, modifiable risk factors in pregnancy are maternal exposure to cigarette smoking and alcohol consumption. In 2016, 7.2% of woman smoked at any time during pregnancy in the US (Drake et al., 2018). Additionally, maternal alcohol exposure during pregnancy, defined as at least 1 drink in the past 30 days, increased from 9.2% in 2011 to 11.3% in 2018 (Denny et al., 2020). To date, a limited number of studies have examined the relationships between CDH and maternal smoking (Balayla & Abenhaim, 2014; Caspers et al., 2010; Felix et al., 2008; García et al., 2016; Honein et al., 2001; Hoyt et al., 2016; McAteer et al., 2014; Ramakrishnan et al., 2018) or alcohol (Balayla & Abenhaim, 2014; Caspers et al., 2010; Felix et al., 2008; García et al., 2016; McAteer et al., 2014). By furthering our understanding of these common, modifiable risk factors in CDH etiology, improvements in future public health interventions to reduce CDH occurrence

and subsequent outcomes can be developed. To this end, we updated an analysis of a previous study which used data on pregnancies from 1997-2005 in the National Birth Defects Prevention Study (NBDPS). Specifically, we examined NBDPS data that became available after the completion of the previous study. Using these data from 2006-2011, as well as the entire cohort from 1997-2011, we examined maternal early pregnancy (1 month before [B1] through the third month [P3] of pregnancy) smoking exposure or alcohol consumption and CDH in the offspring. This study will improve upon previous studies by increasing the sample size of CDH cases. The larger sample size will allow for the analysis of CDH subtypes that were limited in previous studies. The specific aims of this study are as follows:

1) To examine the association between maternal early pregnancy smoking exposure and risk of CDH
2) To examine the association between maternal early pregnancy alcohol exposure and risk of CDH

For both aims, we hypothesize that mothers exposed to early pregnancy smoking or alcohol would have an increased risk of having a infant with CDH. Examining the recent data collected in the NBDPS provide an excellent opportunity to further investigate the association between early pregnancy exposures to smoking and alcohol consumption and CDH.

CHAPTER II

BACKGROUND AND LITERATURE REVIEW

Diaphragm development

Genetic, cellular and morphogenetic mechanisms regulating diaphragm development play a crucial role in congenital diaphragmatic hernia (CDH) (Merrell & Kardon, 2013). Development of the diaphragm begins around day 22 of gestation, and completion of the seal on the left side occurs by week 9 of gestation (Kosinski & Wielgos, 2017). Development of the diaphragm starts when the septum transversum fuses with the pleuroperitoneal folds to form the diaphragm's muscle connective tissue and central tendon (Merrell & Kardon, 2013). Somites give rise to the diaphragm's muscle (Merrell et al., 2015).

Mechanisms of CDH development

Multiple mechanisms have been proposed in the development of CDH. One theory suggests that visceral herniation into the thoracic cavity occurs due to failure of the pleuroperitoneal folds to properly close or due to environmental triggers which affect the differentiation of mesenchymal cells during diaphragm development (Kosinski & Wielgos, 2017). Mechanisms that have been implicated in failure of the pleuroperitoneal folds to close properly include decreased proliferation, increased apoptosis, migration failure, and alteration in differentiation of the pleuroperitoneal folds fibroblasts (Kardon et al., 2017). Environmental triggers – including retinol deficiency and medications, such as thalidomide or anticonvulsant use during pregnancy – may affect mesenchymal cells differentiation during diaphragm development by modifying gene (*GATA4* or *FOG2*) expression in mesenchymal cells (Doi et al., 2009; Kosinski & Wielgos, 2017).

Diagnosis and management of CDH

More than one-half of infants affected with CDH are diagnosed prenatally by ultrasound (Chandrasekharan et al., 2017). CDH is usually detected from 22 to 24 weeks gestation during routine anomaly scan (Benachi et al., 2014), but may be diagnosed during the first trimester if the size of the defect is large and co-occurring defects are present (Daskalakis et al., 2007). Early diagnosis has been associated with decreased survival rates as earlier diagnosis is usually due to co-occurring defects and severe lung hypoplasia (Daskalakis et al., 2007; Metkus et al., 1996).

Surgical intervention is the most common method of clinical management for CDH with 80% of cases requiring surgery (Aly et al., 2010). Extracorporeal membrane oxygenation (ECMO) is used in many CDH cases (30%) to treat pulmonary hypoplasia and pulmonary hypertension, common complications of CDH, and provide cardiopulmonary support for the most severe presentation in 30% of cases (Dao et al., 2019; Rafat & Schaible, 2019; van den Hout et al., 2011). Post-surgical survival is approximately 85%, survival on ECMO was 40.3%, and survival for surgical repair and ECMO was 50.1% (Aly et al., 2010). Infant survival decreased when surgical repair occurred >7 days after birth (Aly et al., 2010).

Genetic risk factors

Identification of genetic syndromes associated with CDH suggests that genetic factors play a role in the development of CDH (Dott et al., 2003; Graham & Devine, 2005; Holder et al., 2007; Kardon et al., 2017; Kosinski & Wielgos, 2017; Longoni et al., 2019; McGivern et al., 2015; Shanmugam et al., 2017; Yang et al., 2006). Although CDH usually occurs as an isolated defect, 10-30% of cases are associated with chromosomal defects like trisomy 18 or tetrasomy 12p (Graham & Devine, 2005). As examples, two population-based studies estimated that about 4% of CHD case infants were diagnosed with trisomy 18 (McGivern et al., 2015; Yang et al.,

2006). Two other population-based studies reported that trisomy 18 was the most common chromosomal anomaly among infants with CDH (Dott et al., 2003; Shanmugam et al., 2017). In addition to trisomy 18, 70 syndromes report CDH as a clinical feature (Kardon et al., 2017). Additional chromosomal aberrations and single gene mutations associated with CDH (Kosinski & Wielgos, 2017) include single gene mutations such as Donnai-Barrow syndrome, *LTBP4*-related cutis laxa, cardiac-urogenital syndrome, microphthalmia and Tonne-Kalscheuer syndrome (Longoni et al., 2019). Chromosome aberrations, such as gene deletions, have been reported in 10% individuals with CDH (Kosinski & Wielgos, 2017; Longoni et al., 2019). Genes encoding for transcription factors, *GATA4* and *NR2F2*, have been implicated in CDH (Kardon et al., 2017). Currently, no major gene for CDH has been identified in humans.

Non-genetic risk factors

A male excess of CDH has been frequently reported (Balayla & Abenhaim, 2014; Dott et al., 2003; García et al., 2016; Grizelj et al., 2016; McGivern et al., 2015; Mohamed & Aly, 2012; Ramakrishnan et al., 2018; Shanmugam et al., 2017; Woodbury et al., 2019; Yang et al., 2006), and some (Ramakrishnan et al., 2018; Yang et al., 2006), but not all (Balayla & Abenhaim, 2014; Dott et al., 2003) studies have reported increased risk of CDH among multiple births.

With regard to maternal risk factors, most (Balayla & Abenhaim, 2014; Dott et al., 2003; García et al., 2016; Mesas Burgos et al., 2019; Yang et al., 2006), but not all (McGivern et al., 2015; Ramakrishnan et al., 2018) reported mothers aged 35 years and older at delivery were more likely to have offspring affected by CDH compared to younger mothers. Similarly, evidence is mixed for maternal race/ethnicity with some (Balayla & Abenhaim, 2014; Canfield et al., 2006; Mohamed & Aly, 2012), but not all (Dott et al., 2003; Ramakrishnan et al., 2018; Yang et al., 2006) reporting non-Hispanic white women having an increased risk of delivering a infant

with CDH compared to other race/ethnic groups. Other suggested maternal risk factors include low maternal education (García et al., 2016; Ramakrishnan et al., 2018; Yang et al., 2006), nulliparity (Mesas Burgos et al., 2019; Yang et al., 2006), obesity (body mass index (BMI) (kg/m^2) ≥ 30.0) (Block et al., 2013; Blomberg & Kallen, 2010; McAteer et al., 2014; Mesas Burgos et al., 2019; Waller et al., 2007), underweight (BMI <18) (García et al., 2016; Mesas Burgos et al., 2019), hypertension (McAteer et al., 2014; Mesas Burgos et al., 2019), pregestational diabetes (McAteer et al., 2014; Mesas Burgos et al., 2019), and use of certain medications during pregnancy, including sulfonamides (Ailes et al., 2016; Crider et al., 2009), antifungals (Carter et al., 2008), immunosuppressants, and lithium (Slavotinek, 2014). Additionally, several maternal dietary exposures were reported to be positively associated with CDH, including lower intake of choline, cysteine, and methionine; higher intake of alanine and fat; and both higher and lower intake of protein (Yang et al., 2008). Positive associations have also been reported for low intake of retinol, vitamin B12, vitamin E, selenium, and calcium, among women who did not take vitamin supplements periconceptionally (Yang et al., 2008). Positive association were observed for high intake B vitamins, magnesium, calcium, iron, and zinc among mothers who did who took vitamin supplements during the periconceptional period (Yang et al., 2008).

Maternal smoking and alcohol exposure

Disruption of the retinoic acid (RA) signaling pathways has been implicated in the pathogenesis of CDH (Goumy et al., 2010), as deficiency or excess of retinol can affect embryonic development (Zachman & Grummer, 1998). Cigarette smoking exposure and alcohol exposure may each impact RA signaling. Specifically, maternal exposure to tobacco toxins has been shown to decrease expression of the RA pathway and retinoic acid regulated genes (Manoli

et al., 2012). Also, production of RA requires metabolization by retinol dehydrogenase (Kardon et al., 2017). Alcohol consumption has an effect on retinol metabolism by interacting with retinol dehydrogenase thereby affecting retinoid levels and RA synthesis (Zachman & Grummer, 1998).

Using a retrospective cohort design and dichotomous exposure data (yes, no) from US birth certificates for all births from 1995-2002, including live births, infant deaths, and stillbirths, Balayla and Abenhaim (2014) reported maternal smoking exposure had a 1.34-times increased risk of CDH (95% confidence interval (CI) = 1.19, 1.42); these authors did not examine risk among CDH phenotypes (isolated, multiple, syndromic) nor subtypes. McAteer et al. (2014) used birth certificate data linked to the Washington State Comprehensive Hospital Abstract Reporting System and also observed a positive association between any smoking (yes, no) and all CDH combined (adjusted odds ratio (aOR) = 1.16; 95% CI = 0.65, 2.06) and isolated CDH (aOR = 1.25; 95% CI = 0.64, 2.44). Focusing on nonsyndromic Bockdalek hernia and using retrospective data on parental early pregnancy smoking (active or passive; yes, no) from a small sample of parents in the Netherlands, Felix et al. (2008) observed maternal passive smoking increased the risk of Bochdalek hernia (crude odds ratio (cOR) = 1.5; 95% CI = 0.8, 2.9), but no increase was observed for maternal active smoking (cOR = 0.6, CI = 0.2, 1.4). Using data from the Bogota Birth Defects Surveillance and Follow-up Program, García et al. (2016) observed no association between any maternal smoking (yes, no) and CDH (cOR = 1.02; 95% CI = 0.33, 6.52). Using data from the Swedish Medical Birth Registry and National Patient Registry, Mesas Burgos et al. (2019) observed no association for maternal smoking of 1-9 cigarettes per day and CDH (cOR = 0.97; 95% CI = 0.67, 1.41), and an inverse association for >10 cigarettes per day and CDH (cOR = 0.86; 95% CI = 0.58, 1.29).

Several other studies that examined maternal early pregnancy smoking exposure did not examine smoking exposure individually but rather among a spectrum of exposures. Honein et al. (2001) examined public-use natality data tapes and reported increased prevalence of CDH associated with any active maternal smoking (yes, no) from 1997-1998 (adjusted prevalence ratio (aPR) = 1.13; 95% CI = 0.93, 1.39). Examination by number of cigarettes smoked per day (6-10, 11-20, ≥21) showed similar prevalence estimates (aPR = 1.16; 95% CI = 0.86, 1.56; aPR = 1.23; 95% CI = 0.87, 1.73; aPR = 1.19; 95% CI = 0.49, 2.88, respectively). Ramakrishnan et al. (2018) used data from the Florida Birth Defects Registry and reported no association between any maternal smoking during pregnancy and prevalence of CDH. Hoyt et al. (2016) used maternal interview data from the NBDPS to examine associations between second-hand smoke exposure in the household and workplace/school and CDH. They reported positive associations for any second-hand smoke exposure (aOR = 1.31; 95% CI = 0.97, 1.76), as well as household exposure only (aOR = 1.25; 95% CI = 0.80, 1.96) and workplace/school only (aOR = 1.19; 95% CI = 0.75, 1.89).

Several of the aforementioned studies have also examined associations between any early pregnancy alcohol consumption and CDH. Positive associations for any alcohol consumption were reported by Balayla and Abenhaim (2014) (aOR = 1.37; 95% CI = 1.05, 1.78), García et al. (2016) (cOR = 1.14; 95% CI = 0.36, 3.58), and McAteer et al. (2014) for all CDH (aOR = 3.65; 95% CI = 1.36, 9.83), and for isolated CDH (aOR = 4.02; 95% CI = 1.35, 11.94). Positive associations for CDH Bochdalek by Felix et al. (2008) (cOR = 2.9; 95% CI = 1.6, 5.2). Felix et al. (2008) also examined frequency of alcohol consumption during early pregnancy and reported consumption of alcohol 1-3 times during the periconceptional period showed a 3 times increased odds of all CDH (95% CI = 1.6, 5.6), 1-3 times per month 2 times increased odds of all CDH

(95% CI = 0.7, 6.3), and multiple times per week 3.4 times increased odds of all CDH (95% CI = 1.2, 9.6).

A previous NBPDS study examined early pregnancy smoking and alcohol exposures and CDH representing the most comprehensive examination of these exposures to date (Caspers et al., 2010). Using CDH case and control infants with EDDs from 1997-2005, this study examined associations for early pregnancy smoking exposure (assessed as any active/passive smoking, cigarettes smoked per day, smoking duration) and alcohol consumption (assessed as any alcohol consumption, drinks per month, binge drinking, type of alcohol consumed, and drinking duration). Additionally, CDH subtypes (not otherwise specified (NOS), Bochdalek, Morgani, Isolated, Multiple) were examined. Several increased associations were observed for each smoking exposure metric, although all 95% CIs included the null; positive associations were reported for Isolated Bochdalek and any smoking and smoking during the entire first trimester. Associations for alcohol consumption were mostly near unity, with some modest positive associations for consumption of beer or distilled spirits and consumption during the entire first trimester and CDH Bochdalek, although all CIs included the null (Caspers et al., 2010).

Building on the time period analyzed using NBDPS data by Caspers et al. (2010), the current study examined associations between maternal periconceptional smoking and alcohol exposures and CDH for deliveries from January 1, 2006 - December 31, 2011 and also a pooled analysis using deliveries during October 1, 1997 - December 31, 2011.

CHAPTER III

METHODS

National Birth Defects Prevention Study (NBDPS)

The National Birth Defects Prevention Study (NBDPS) is a multicenter, population-based, case-control study conducted in the United States (US) that examined genetic and environmental factors for more than 30 major structural birth defects among deliveries from October 1, 1997 - December 31, 2011. The NBDPS covered an annual birth population of 482,000 and included case and control deliveries identified by 10 birth defect surveillance programs (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, Utah, and metropolitan Atlanta [Georgia]) (Reefhuis et al., 2015). A brief description of study methods follows.

Subject Selection

All NBDPS study centers contributed live births diagnosed with CDH (BPA codes 756600, 756601, 756602, 756603, 756604, 756605, 756610, 756611, 756612, 756614, 756615, 756616, 756617, 756618, 756619). Study centers (Arkansas, California, metropolitan Atlanta [Georgia], Iowa, Massachusetts, New York, Texas since 2000) also contributed fetal deaths and elective terminations. Control infants were unaffected live births with an estimated dates of delivery (EDD) from October 1, 1997 - December 31, 2011 and were randomly selected from the hospital delivery logs of birth certificate files. A case or control infant not in custody of or residing with their birth mother, and whose mother did not speak English or Spanish were excluded. All case infants with EDDs from October 1, 1997 - December 31, 2011 and a complete NBDPS maternal interview were included in our analytic dataset. Due to previously reported

associations between pregestational diabetes and several birth defects (Correa et al., 2008), cases and controls whose mother with reported pregestational diabetes were excluded from analyses.

Case Classification

Clinical geneticists at each center determined case eligibility using standard case definitions by reviewing clinical information (Rasmussen et al., 2003). Abstracted medical records were reviewed to classify cases as isolated (no additional major, unrelated defects), multiple (one or more major, unrelated defects), or complex sequence (Pentalogy of Cantrell and limb-body wall complex). Case infants were classified by type of hernia (Bochdalek, Morgagni, or not otherwise specified (NOS) when sufficient diagnostic information was unavailable), by laterality (unilateral, bilateral, unknown), and by sidedness (left, right, unknown). Cases diagnosed with Pentalogy of Cantrell, limb-body wall complex, non-Bochdalek, non-NOS types or non-Morgani were excluded. Case infants with known genetic defects were excluded.

Exposure Assessment

Computer assisted telephone interviews were conducted with birth mothers of cases and controls between six weeks and 24 months following the EDD (Reefhuis et al., 2015). The EDD was used to ensure a similar time period between conception and contact of mothers of live births and fetal deaths or elective termination. The interview collected data on several maternal factors, including demographic, environmental, nutritional, and behavioral factors. Detailed questions about maternal cigarette smoking and alcohol consumption from 3 months before conception through delivery date were asked; these questions are included in the Appendix 1 and 2. Information on maternal cigarette smoking and alcohol consumption was collected monthly for the 3 months before pregnancy (labeled B3, B2, B1) and the first 3 months of pregnancy (labeled P1, P2, P3) and by trimester for months 4-6 and 7-9 of pregnancy (labeled T2, T3).

Smoking exposure

Mothers were classified as exposed to smoking in their respective analyses if maternal smoking exposure was reported during B1-P3. Maternal cigarette smoking exposure was classified as active and/or passive (exposure to cigarette smoking in the household or workplace or no exposure). If maternal active smoking was reported, information on the number of cigarettes smoked per day (frequency categories: no exposure, 1-14, ≥15) and month(s) of exposure were collected. If maternal passive smoking exposure was reported, information was collected on location of exposure (household or workplace) and the pregnancy month(s) during which exposure occurred. To evaluate variability in number of cigarettes smoked across months for mothers reporting active smoking, minimum and maximum monthly smoking was calculated. Maximum cigarettes smoked per day was the maximum reported number of cigarettes smoked per day during each month of the early pregnancy period (no exposure, <1 per day, 1 per day, 2-4 per day, ½ pack (5-14) per day, 1 pack (15-24) per day, 1 ½ pack (25-34) per day, 2 packs (35-44) per day, >2 packs per day). Responses were categorized as no exposure, 1-14 cigarettes per day, and ≥15 cigarettes per day for the current analyses. Minimum number of cigarettes smoked per day was the minimum reported number of cigarettes smoked per day during each month of the early pregnancy period. To evaluate duration of periconceptional cigarette smoking exposure, mothers were classified by number of early pregnancy months with reported active smoking exposure (0-4). Case and control mothers with an unknown or missing response to the question regarding smoking during the period 3 months before through the end of pregnancy were excluded from smoking analyses.

Alcohol exposure

Mothers were classified as exposed to alcohol in their respective analyses if maternal alcohol consumption was reported in one or more months during early pregnancy (B1-P3). Maternal pregnancy alcohol consumption was assessed by responses to questions regarding alcoholic beverages using methods described previously (Romitti et al., 2007). Alcohol exposure was classified as any drinking (yes, no) and by quantity (maximum and average number of drinks per drinking day), frequency (maximum and average number of drinking days per month), variability (maximum number of drinks on one occasion per drinking month), and alcohol type (beer only, wine only, distilled spirits only, beer and wine, beer and distilled spirits, wine and distilled spirits, beer and wine and distilled spirits). Average number of drinks per month was calculated by dividing the average number of drinks per month (B1, P1, P2, P3) by the number of months (B1, P1, P2, P3) the mother reported drinking. The maximum average number of drinks per month was calculated using the highest reported average number of drinks per month divided by the number of months a mother drank during early pregnancy. Binge drinking was evaluated using sex-specific criteria (Wechsler et al., 1995). Sex-specific norms for females define binge drinking as 4 or more drinks per day on average, on one occasion, or both. Binge drinking was categorized as: no consumption,1 binge episode, 2-3 binge episodes, 4 or more binge episodes during early pregnancy. Case and control mothers with an unknown or missing response to the question regarding alcohol consumption during the early pregnancy period and those with an average monthly consumption of ≥120 drinks were excluded from analyses.

Covariates

Infant covariates evaluated in this analysis were sex (male, female), family history of diaphragmatic hernia (yes, no), and plurality (1, >1). Maternal covariates evaluated were age at

delivery (<21, 21-25, 26-30, 31-35, ≥35 years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), education at delivery (less than high school, high school graduate, college or higher), gravidity (0, 1-2, ≥3), pre-pregnancy body-mass index (BMI) (<18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2), early pregnancy use of folic acid supplements (yes, no), early pregnancy supplemental vitamin A use (yes, no) pre-pregnancy dietary folate equivalents (<600, ≥600 μg/day), and study site (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, CDC/Atlanta, North Carolina, Utah).

Statistical Analysis

We conducted two analyses. The main analysis included CDH cases and controls with EDDs during January 1, 2006-December 31, 2011 and a second analysis pooling CDH cases and control with EDDs during October 1, 1997-December 31, 2011. We conducted descriptive analyses to compare characteristics of CDH cases and controls using chi-square test of independence or Fisher's exact tests, when needed, on infant sex and family history of CDH, and maternal age at EDD, race/ethnicity, education, gravidity, pre-pregnancy BMI, folic acid intake from vitamins, vitamin A supplementation, dietary folate intake, and NBDPS center. Unadjusted and multivariable logistic regression models were used to estimate crude and adjusted odds ratios (cORs and aORs, respectively) and 95% confidence intervals (CIs) between each smoking and alcohol exposure variable and CDH. Multivariable models were constructed using a change-in-estimate procedure. For each exposure-outcome pairing, individual covariates that were associated with both the CDH outcome and relevant covariate were entered into a model containing the exposure of interest. Those that altered the main effect by >10% were retained in the final model for that exposure-outcome pair. For all smoking analyses, an alcohol consumption variable (no drinking, drinking with no binge events, drinking with ≥1 binge event)

was included in the final model. Similarly, for all alcohol analyses, a smoking variable (no smoking, active smoking only, passive smoking only, active and passive smoking) was included in the final model. We examined associations for each smoking and alcohol exposure variable and all CDH types and selected CDH phenotypes (NOS, Bochdalek). Analyses were also restricted to controls and isolated CDH cases. Analyses of specific CDH phenotypes were restricted to those with at least five case infants. All analyses were conducted using SAS Software (version 9.4, SAS Institute Inc., Cary, NC, USA).

CHAPTER IV

RESULTS

Findings from the analytic period January 1, 2006 - December 31, 2011

Overall, 883 congenital diaphragmatic hernia (CDH) case mothers and 11,829 control mothers were enrolled in the National Birth Defects Prevention Study (NBDPS) from October 1, 1997-December 31, 2011. Of these, 362 case and 5,008 control mothers had expected dates of delivery (EDDs) during January 1, 2006 - December 31, 2011. We excluded mothers of three case children classified as complex. We also excluded nine case and 43 control mothers due to reported pregestational diabetes and an additional 13 case and 197 control mothers who did not respond to the smoking or alcohol sections of the NBDPS interview, leaving data for 337 CDH case and 4,768 control mothers available for analysis.

Among the 337 CDH case children, 244 (72.4%) were classified as isolated and 93 (27.6%) as multiple (Table 1). Most case children were classified as Not Otherwise Specified (NOS) (n = 213), with fewer children classified with Bochdalek (n = 103) or Morgagni (n = 22) hernias (one CDH case was classified as both Bochdalek and Morgagni subtype). Case children classified as isolated or multiple were predominantly unilateral (isolated = 94.7%; multiple = 91.4%) and left sided (isolated = 84.8%; multiple = 72.9%). Statistical differences were observed between case and control children for sex and family history of CDH and between case and control mothers for race/ethnicity, early pregnancy vitamin A supplementation, and NBDPS site ($p < 0.05$). Statistical differences were not observed for the remaining child or maternal characteristics or maternal exposures.

Reported early pregnancy smoking exposure was higher among all case (30.6%) than control (25.4%) mothers (Table 2). Exposure proportions for mothers of children with NOS and

Bochdalek subtypes were similar to those for all case mothers. Among all mothers, smoking exposure most commonly reported was passive smoking only (cases = 14.9%, controls = 9.5%) with smaller proportions reporting active smoking only (cases = 7.7%, controls = 7.4%) or both active + passive smoking (cases = 8.0%, controls = 8.4%). Smoking exposure was elevated for mothers and those of children with NOS (31.6%) and Bochdalek (30.1%) subtype compared to control mothers. Compared to controls, mothers of children with Bochdalek subtype were more likely to report active smoking only (9.7%) and active + passive smoking exposure (10.7%) (Table 3).

Similar proportions of all case and control mothers were observed for maximum average of 1-14 cigarettes per day (cases = 10.9%; controls = 11.6%) or minimum average of 1-14 cigarettes per day (cases = 12.6%; controls = 13.7%) (Table 2). Smaller proportions of case and control mothers were observed for maximum or minimum totals of ≥15 cigarettes per day. Among all case and control mothers that reported early pregnancy smoking, more mothers smoked each month during B1-M3 (cases=6.9%, controls = 7.7%) than three or fewer months. Proportions of maximum and minimum average smoking totals were near unity for all case mothers and those of children with NOS or Bochdalek subtypes, although larger proportions of mothers of children with Bochdalek subtype were observed to have greater proportions of maximum or minimum average values for smoking ≥15 cigarettes per day. No differences were observed for reports of number of months smoked for all cases or either subtype.

Proportions of all case (33.4%) and control (35.7%) mothers reported any early pregnancy alcohol consumption were near unity; a smaller proportion of case mothers of children with NOS subtype (29.8%), and a larger proportion of those with Bochdalek subtype (39.8%) reported any alcohol consumption (Table 2). Of the case and control mothers who

reported alcohol consumption during early pregnancy, most reported consuming an average of 1-15 drinks per month (cases = 25.4%, controls = 26.8%) with comparable proportions observed for mothers of children with NOS or Bochdalek subtypes. A similar pattern was observed for maximum average drinks per months. For binge episodes, somewhat smaller proportions of all case mothers than control mothers reported 1 (2.9% vs. 4.9%) or 2-3 binge episodes (2.0% vs. 3.2%), with the opposite observed for 4 or more binge episodes (5.1% vs. 3.7%). The respective proportions differed by case subtype for mothers of children with NOS subtype (1.8%, 2.2%, 4.4%) and with Bochdalek subtype (5.8%, 1.9%, 5.8%). For type of alcohol consumption, a similar proportion of all case mothers and control mothers reported drinking beer only (5.4% vs. 5.8%) and liquor only (6.4% vs 6.9%). A somewhat smaller proportion of all case mothers than control mothers reported drinking wine only (9.4% vs. 10.2%) and 2 or more types of alcohol (11.7% vs. 13.1%). The respective proportions differed by case subtype for mothers of children with NOS subtype (6.2%, 6.2%, 8.0%, 9.3%) and with Bochdalek subtype (4.9%, 7.8%, 11.7%, 15.5%).

A crude positive association, defined as an estimate ≥1.1, was observed for maternal exposure to any smoking during early pregnancy and all CDH (crude odds ratio [cOR] = 1.3; 95% C I= 1.0, 1.7) (Table 3). Positive associations were also observed for maternal active smoking only (cOR = 1.2; 95% CI= 0.8, 1.7), passive smoking only (cOR = 1.7; 95% CI = 1.3, 2.4), maximum average of ≥15 cigarettes per day (cOR = 1.2; 95% CI = 0.9, 3.2), and minimum average of ≥15 cigarettes per day (cOR = 1.2; 95% CI = 0.8, 2.1) and all CDH. Additional positive associations were observed for smoking for 1 month (cOR = 1.2; 95% CI = 0.7, 2.2) or 3 months (cOR = 1.1; 95% CI = 0.5, 2.7) during early pregnancy and all CDH. All other associations were near unity. Associations for NOS subtype were generally similar to those for

all CDH. Some differences were observed for Bochdalek subtype with positive associations observed for any smoking exposure, active smoking (cOR = 1.4; 95% CI = 0.7, 2.6), active + passive smoking (cOR = 1.3; 95% CI = 0.7, 2.5), and smoking for 2 (cOR = 1.6; 95% CI = 0.7, 3.7) or 4 (cOR = 1.1; 95% CI = 0.6, 2.3) months during early pregnancy, only results for 2 and 4 months were calculated (Table 3).

In multivariable analyses, a positive association was observed for maternal exposure to any smoking during early pregnancy and all CDH (aOR = 1.4; 95% CI = 1.1, 1.8) (Table 3). Positive associations persisted in adjusted analysis for maternal active smoking only (aOR = 1.3; 95% CI = 0.8, 1.9) and passive smoking only (aOR = 1.9; 95% CI = 1.3, 2.6) exposures, among all CDH. A positive association was also observed for active + passive smoking (aOR = 1.3, 95% CI = 0.9, 2.0). The positive crude association for maximum (aOR = 1.6; 95% CI = 0.9, 2.7) and minimum (aOR = 2.1, 95% CI = 1.1, 4.1) average of ≥15 cigarettes per day remained positive in adjusted analysis. Additionally, smoking durations of 1 month (aOR = 1.3, 95% CI: 0.7, 2.4) and 3 months (aOR = 1.3, 95% CI = 0.6, 3.0) persisted in adjusted analysis. All other estimates for all CDH were near unity. Estimates for CDH subtypes in adjusted analyses were generally in a similar direction to those observed in crude analyses with most CIs including the null value. Positive associations with a CI that excluded the null were observed for any maternal smoking and passive smoking only and NOS subtype, and minimum average of ≥15 cigarettes per day and Bochdalek subtype.

In crude analyses of maternal early pregnancy alcohol consumption, positive associations were observed for average consumption of >30 drinks per month (cOR = 1.1; 95% CI = 0.5, 2.4) and 4 or more binge episodes (cOR = 1.4; 95% CI = 0.8, 2.3) and all CDH (Table 4). All other associations for maternal alcohol consumption and all CDH were inverse or near

unity. Crude estimates for NOS subtype were not materially different than those for all CDH. Several positive estimates were observed for Bochdalek subtype, including any alcohol consumption (cOR = 1.2; 95% CI = 0.8, 1.7); average consumption of 1-15 drinks per month (cOR = 1.2; 95% CI = 0.8, 1.8); maximum average drinks of 16-30 drinks per month (cOR = 1.6; 95% CI = 0.7, 3.3); 1 (cOR = 1.3; 95% CI = 0.5, 2.9) or 4 or more binge episodes (cOR = 1.7; 95% CI = 0.7, 3.9), only associations for 1 and 4 binge episodes were calculated; consumption of wine only (cOR = 1.2; 95% CI = 0.6, 2.2), liquor only (cOR = 1.3; 95% CI = 0.6, 2.7), or combination of alcohol types (cOR = 1.2; 95% CI = 0.7, 2.2); and alcohol duration for 2 months of early pregnancy (cOR = 1.4, 95% CI = 0.8, 2.6). Confidence intervals for all crude estimates included the null value (Table 4).

Most adjusted estimates for maternal alcohol consumption and all CDH were near or below unity, with most associations in a similar direction as the unadjusted associations and all CIs included the null (Table 4). Positive associations for average consumption of >30 drinks per month (aOR = 1.2; 95% CI = 0.5, 2.5) and 4 or more binge episodes (aOR = 1.1; 95% CI = 0.5, 2.5) and all CDH persisted in adjusted analyses. Additionally, a positive association was observed for alcohol consumption duration of 4 months (aOR = 1.1; 95% CI = 0.5, 2.5) among all CDH. Adjusted estimates for NOS subtype were generally similar to crude estimates, and all CIs included the null value. For Bochdalek subtype, although attenuated, positive associations persisted in adjusted analyses for maximum average consumption of 16-30 drinks per month (aOR = 1.3; 95% CI = 0.6, 2.8); 1 (aOR = 1.2; 95% CI = 0.5, 2.8) or 4 or more binge episodes (aOR = 1.5; 95% CI = 0.6, 3.7); and 2 months of alcohol consumption (aOR = 1.4; 95% CI = 0.8, 2.4) (Table 4).

In general, results of smoking analyses restricted to only isolated CDH were similar to

those including all CDH (Table 5). However, adjusted estimates were increased for maximum average of ≥15 cigarettes per day (aOR = 1.8; 95% CI = 1.0, 3.2), minimum average of ≥15 cigarettes per day (aOR = 2.5; 95% CI = 1.2, 5.1), and smoking for 1 month during early pregnancy (aOR = 1.7; 95% CI = 0.9, 3.3) and all CDH; smoking for 1 month during early pregnancy (aOR = 1.9; 95% CI = 0.8, 4.1) and NOS subtype; and active smoking only (aOR = 1.8; 95% CI = 0.9, 3.7), maximum average of ≥15 cigarettes per day (aOR = 2.5; 95% CI = 1.1, 5.4), minimum average of ≥15 cigarettes per day (aOR = 4.0; 95% CI = 1.6, 9.7), and smoking for 2 months during early pregnancy (aOR = 2.1; 95% CI = 0.9, 5.2) and Bochdalek subtype (Table 5). Analyses of all isolated CDH and control children for alcohol exposure produced estimates mostly in the same direction as those of the main analyses. However, most estimates were reduced and positive association were only observed for 4 or more binge episodes and all isolated CDH (aOR = 1.2; 95% CI = 0.6, 2.5) and isolated Bochdalek subtype (aOR = 1.4; 95% CI = 0.5, 3.9); and 1 binge episode and isolated Bochdalek subtype (aOR = 1.2; 95% CI =0.5, 3.1) (Table 6).

Findings from the analytic period October 1, 1997 - December 31, 2011

Overall, a total of 883 case mothers and 11,829 control mothers were enrolled in the National Birth Defects Prevention Study (NBDPS) from October 1, 1997 – December 31, 2011. We excluded mothers of 10 case children classified as complex. We also excluded 16 case and 87 control mothers due to reported pregestational diabetes and an additional 13 case and 198 control mothers who did not respond to the smoking or alcohol portions of the NBDPS, leaving 844 CDH cases and 11,544 controls available for analysis.

Tables 7-10 present the analysis for case and control mothers with EDDs from October 1, 1997 to December 31, 2011. During this study period, positive associations were observed for

maternal exposure to any smoking (aOR = 1.2; 95% CI=1.1, 1.4); active smoking only (aOR = 1.3; 95% CI = 1.0, 1.7); passive smoking only (aOR = 1.3; 95% CI = 1.1, 1.6); smoking a maximum average of 1-14 cigarettes per day (aOR = 1.1; 95% CI: 0.9, 1.4); a minimum average of 1-14 cigarettes per day (aOR = 1.1; 95% CI: 0.9, 1.3); and 1 (aOR = 1.2; 95% CI = 0.8, 1.8), 2 (aOR = 1.3; 95% CI: 0.9, 1.8) or 3 (aOR = 1.5; 95% CI = 1.0, 2.4) months of smoking during early pregnancy and all case children (Table 7). Estimates for NOS subtype were generally similar to those of all CDH. Although estimates for Bochdalek subtype were generally in a similar direction as those for all CDH, they were increased for any smoking (aOR = 1.6; 95% CI = 1.2, 2.2); active smoking only (aOR = 1.7; 95% CI = 1.0, 2.7); passive smoking only (aOR = 1.5; 95% CI = 1.0, 2.3); active + passive smoking (aOR = 1.6; 95% CI = 1.1, 2.5); minimum average of 1-14 cigarettes per day (aOR = 1.5; 95% CI = 0.8, 2.9); and smoking for 4 months (aOR = 1.6; 95% CI = 1.0, 2.4) during early pregnancy; remaining estimates were positive and included the null. All other estimates were near or slightly below unity (Table 7).

Estimated associations for any maternal early pregnancy alcohol consumption were mostly near unity for all CDH; a positive association was observed for 4 or more binge episodes (aOR = 1.2; 95% CI = 0.9, 1.7); and 3 months of alcohol consumption (aOR = 1.1; 95% CI = 0.7, 1.7) (Table 8). Associations for NOS subtype were mostly similar to those for mothers of all CDH. However, several positive associations were observed for Bochdalek subtype. Positive associations were observed for any alcohol consumption (aOR = 1.2; 95% CI = 0.9, 1.6); average of 1-15 drinks per month (aOR = 1.2; 95% CI = 0.9, 1.7); maximum average of 1-15 (aOR = 1.2; 95% CI = 0.9, 1.65) or 16-30 (aOR = 1.3; 95% CI = 0.7, 2.3) drinks per month; 1 (aOR = 1.1; 95% CI = 0.6, 2.1), and 4 or more binge episodes (aOR = 1.3; 95% CI = 0.7, 2.7); consumption of beer only (aOR = 1.4; 95% CI = 0.8, 2.2) and liquor only (aOR = 1.5; 95% CI = 0.9, 2.4); and

1 months (aOR = 1.1; 95% CI = 0.8, 1.6), 2 months (aOR = 1.3; 95% CI = 0.8, 2.0) or 3 months of early pregnancy alcohol consumption (aOR = 1.1; 95% CI = 0.5, 2.8).

Results of analyses restricted to isolated cases only were similar to the main analyses for both maternal early pregnancy smoking (Table 9) and alcohol consumption (Table 10).

CHAPTER V

DISCUSSION

Using data from the National Birth Defects Prevention Study (NBDPS) – a multisite, population-based, case-control study – we updated a previous analysis of early pregnancy maternal smoking and alcohol exposures and congenital diaphragmatic hernia (CDH), examining data that became available after completion of the previous study. Using data from deliveries with estimated dates of delivery (EDDs) from 2006-2011, several positive associations were observed for maternal early pregnancy smoking exposure and all CDH and CDH subtypes; most confidence intervals (CIs) included the null value. Although some positive associations were observed for early pregnancy alcohol exposure and all CDH and CDH subtypes, most estimates were near or below unity and all CIs included the null value. The results examining all CDH case and control deliveries with EDDs from 1997-2011 were generally similar to those from analyses examining only EDDs from 2006-2011.

Maternal Smoking

Our findings of positive associations for any maternal early pregnancy smoking and all CDH were similar to most (Balayla & Abenhaim, 2014; Caspers et al., 2010; Honein et al., 2001; McAteer et al., 2014), but not all (García et al., 2016; Ramakrishnan et al., 2018) previous studies. The positive association observed for passive smoking and all CDH is similar to that of a previous study Hoyt et al. (2016); however, this is not an independent sample, as this study used data from the NBDPS and included pregnancies with EDDs from 1997-2009. Additionally, Honein et al. (2001) examined the number of cigarettes smoked per day and CDH reported positive associations for smoking 6-10, 11-20, and ≥21 cigarettes. Mesas Burgos et al. (2019) observed associations near unity for smoking 1-9 and >10 cigarettes per day. We observed

associations mostly near unity for minimum or maximum cigarettes smoked per day and all CDH, with the exception of that for smoking a minimum of ≥15 cigarettes per day, which was positive. Results of our analyses of CDH subtypes are not directly comparable with most previous studies, as most did not report results for individual CDH subtypes. However, our findings of a positive association with active smoking and an association consistent with the null for passive smoking and Bochdalek CDH differed from Felix et al. (2008), which reported inverse and positive associations for active smoking and passive smoking exposure, respectively, and CDH Bochdalek. The results for our analyses examining all EDDs from 1997-2011 generally paralleled those for 2006-2011. As such, the comparisons to previous literature are generally similar, with the exception of the association for smoking a minimum ≥15 cigarettes per day, which was near unity and differed from the results reported by Honein et al. (2001).

Several associations reported in the previous NBDPS analysis of CDH cases and controls with EDDs from 1997-2005 were consistent with those from the present analyses. The positive associations reported by Caspers et al. (2010) for any smoking, type of smoking, and smoking duration and all CDH were also observed in the present analyses; although a somewhat stronger effect for passive smoking was observed in our study. Our positive association contrasted with the previously reported null association for combined active and passive smoking and all CDH. The observed association for smoking 1-14 cigarettes per day was also similar to the previous study, however, the positive effect observed for smoking ≥15 cigarettes per day was not observed in the previous study. No results for CDH subtypes including isolated and multiple cases were included in the previous published study, as such, our results for CDH subtypes are not directly comparable. However, comparing results of our analyses of isolated cases only, the consistently increased associations for all smoking exposures and all isolated CDH and isolated

CDH NOS differed from the previous study, which reported associations mostly near unity for all isolated CDH and isolated CDH NOS. The results for isolated Bochdalek were generally similar between the two studies.

The differences between the previous and current studies could be attributed to several factors. There may have been differences in the characteristics of mothers that participated in the NBDPS during 1997-2005 and 2006-2011 study periods. For example, we observed larger proportion of Hispanic mothers than was previously observed among 1997-2005 EDDs Caspers et al. (2010). Additionally, there were differences in the way cigarettes smoked per day was defined between the two. Caspers et al. (2010) categorized smoking exposure as 1-14 and ≥15 cigarettes per day while our study categorized smoking exposure as maximum and minimum averages of 1-14 and ≥15 cigarettes per day. Additionally, Caspers et al. (2010) used *a priori* criteria to adjust all models for infant sex, family history, maternal age, race and ethnicity, periconceptional alcohol consumption, and study center, whereas our study used a 10% change-in-estimate approach to select covariates for adjustment. The different methods for adjusted analysis coupled with the changes in number of cases and controls could account for some of the differences observed between our study and study by Caspers et al. (2010).

Despite the consistency of positive associations from our study and most previous studies examining maternal early pregnancy smoking exposure and CDH (Balayla & Abenhaim, 2014; Caspers et al., 2010; Felix et al., 2008; Honein et al., 2001; Hoyt et al., 2016; McAteer et al., 2014), the biological mechanisms and pathways by which smoking may impact CDH development are not fully understood. However, it is hypothesized that alterations to retinoic acid activity during early pregnancy by smoking exposures may influence diaphragm development. Maternal exposure to tobacco toxins has been implicated in decreasing expression

of retinoic acid pathways and retinoic acid regulated genes (Manoli et al., 2012). Retinoic acid has been shown to regulate expression of *GATA4* and *FOG2* – both of which have been implicated in the pathogenesis of CDH (Doi et al., 2009; Kardon et al., 2017) and that may affect the differentiation of mesenchymal cells during diaphragm development (Doi et al., 2009; Kosinski & Wielgos, 2017). It has also been reported that homocysteine levels were elevated among pregnant women who smoked (Ozerol et al., 2004); alterations to homocysteine levels may interfere with retinol metabolism to retinoic acid (Limpach et al., 2000; Refsum, 2001).

Maternal Alcohol

Associations between maternal early pregnancy alcohol exposures and CDH and CDH subtypes found our study mostly differed in comparison with previous studies. The null association for any alcohol exposure and all CHD was not consistent with previous studies, all of which reported a positive association (Balayla & Abenhaim, 2014; García et al., 2016; McAteer et al., 2014). No other studies have examined additional alcohol exposures, so our results for other analyses are not directly comparable. One previous study examined CDH Bochdalek (Felix et al., 2008). The positive associations we observed for any alcohol exposure and frequency of alcohol use and CDH Bochdalek was also observed in Felix et al. (2008). The results for our analyses examining all EDDs from 1997-2011 were generally similar those for 2006-2011. Comparisons of our results for 1997-2011 to previous studies generally parallel those comparisons for 2006-2011.

Consistent with the present study, Caspers et al. (2010) reported similar associations for drinks per month, for 1 or more binge episodes, types of alcohol exposures, and duration of alcohol consumption and all CDH. Although Caspers et al. (2010) calculated drinks per month, and our study calculated maximum average and average drinks per month, the associations for

maximum drinks per month in the current study and drinks per month in Caspers et al. (2010) were similar. Some differences in associations for binge drinking and all CDH in the current study and previous study by Caspers et al. (2010) could have been due to the different categorization of binge drinking variables, which categorized binge drinking as drinking but no binge episodes and 1 or more binge episodes. Our study categorized binge drinking as 1, 2-3, or 4 or more binge episodes. Consistent with current study, Caspers et al. (2010) observed similar associations for drinks per month, 1 or more binge episodes, types of alcohol, and duration of alcohol consumption and Isolated CDH, Isolated NOS CDH; similar associations for drinks per month, types of alcohol, and duration of alcohol consumption and Isolated Bochdalek CDH.

It is hypothesized that disruption of the retinoic acid (RA) signaling pathways may influence the development of CDH (Kardon et al., 2017). Additionally, previous studies suggest that alcohol exposures may influence RA levels. As such, we had hypothesized that maternal early alcohol exposure would be positively associated with CDH. The general lack of positive association between alcohol and CDH in our study may be in part due to the reported drinking patterns of the mothers, notably the lack of mothers with high levels of alcohol consumption. This could be due to the association between heavy alcohol use during early pregnancy and increased risk of miscarriage (Henriksen et al., 2004), leading to survival bias (Khoury et al., 1992). The NBDPS is not able to comprehensively identify early pregnancy loss (prior to 20 weeks gestation), suggesting a possible under-representation of these possible early pregnancy losses. Similarly, a small proportion of mother reported heavy drinking and there could be a threshold for the effects of maternal early pregnancy alcohol exposure, which may contribute to the null findings. Of the women who drank during the early pregnancy period, the majority reported drinking 1 month before conception or 1 month before conception through 1 month

after conception, which may not have overlapped with diaphragm development which begins around day 22 of gestation and is completed around week 9 of gestation (Kosinski & Wielgos, 2017). Our study found binge drinking of 4 or more episodes was associated with increased adjusted odds of all CDH. Binge drinking is particularly harmful to fetal development due to peak blood alcohol concentration and the prolonged period of alcohol exposure (Maier & West, 2001), which may explain this pattern of association. Finally, the consistent null associations observed in this study may be due to there being no association between alcohol and CDH.

Strengths and Limitations

The extensive detail of cigarette smoking and alcohol exposure measurement available in NBDPS is unique; however, it should be noted that these are retrospective assessments of exposures with a degree of social stigma, which can result in recall and reporting bias. Both smoking and alcohol exposures for case mothers may have been underreported compared to control mothers. However, percentages of mothers reporting any early pregnancy smoking or alcohol exposure in this study exceed national estimates (Denny et al., 2019; Drake et al., 2018), suggesting minimal potential of underreporting in our study. There is also a potential for differential recall of exposures between case and control mothers leading to recall bias. However, Verkerk et al. (1994) found no significant differences in prospective and retrospective reports of cigarette smoking and alcohol consumption between case and control mothers, suggesting minimal recall bias. Furthermore, no differences were observed between case and control mothers for duration of cigarette smoking exposure and alcohol consumption duration during early pregnancy.

NBDPS collected detailed information on smoking and alcohol consumption during early pregnancy, allowing for the most comprehensive examination of smoking and alcohol exposures and CDH to date. Detailed information about the source of passive smoking, and location of exposure (workplace or household) were collected, although frequency or duration were not. This resulted in varying degrees of passive smoking exposure for mothers who reported active and passive smoking, as they had greater exposure than mothers who reported active only smoking due to multiple sources of passive smoke exposure in the active and passive group. Binge drinking episodes were calculated from maternal reports of average number of drinking days, average number of drinks per drinking day, and largest number of drinks on one occasion during early pregnancy, potentially leading to underestimation of the actual number of episodes, especially among women with infrequent and/or low monthly averages (i.e., <5 drinks on average). Questions about drink volume were not defined in terms of standard drinks but rather as a 'glass' of alcohol, possibly resulting in inaccurate estimates of actual amount consumed. In addition to limitations to exposure assessment, there were some limitations related to outcome status. A large proportion of case infants were classified as 'not otherwise specified' (NOS) indicating a lack of clinical certainty for a large number of cases children. Examination of heterogeneous case groups may mask subtype specific effects. Additionally, small case numbers precluded the analysis of several exposures or CDH subtypes (i.e. CDH Morgagni).

Although some exposures may lack detail, this is the most comprehensive study of smoking and alcohol and CDH to date. The NBDPS is a large, multisite population-based sample, minimizing potential for selection bias; several characteristics of control mothers in NBDPS were found to be similar to mothers of all delivered live births in the US (Cogswell et al., 2009). NBDPS further reduces selection bias by only including live births (all centers), fetal

deaths of 20 weeks gestation or greater (6 centers), and elective terminations (5 centers) (Yoon et al., 2001). CDH cases were reviewed and confirmed by clinical geneticists decreasing likelihood of case misclassification. Exposure data was obtained from detailed NBDPS maternal interviews conducted by trained study staff using computer-assisted telephone interviews. The stringent protocol to ensure consistency in NBDPS study methods, with respect to inclusion criteria and interview practices, across all 10 study centers, allowed NBDPS to be a large data source on a relatively rare birth defect such as CDH, and to be internally consistent (Reefhuis et al., 2015). The current study evaluated associations between maternal alcohol consumption and smoking and CDH subtypes, which is important as examination of all CDH may mask possible subtype-specific effects. Additionally, mothers who reported risk factors that are known to be strongly associated with the development of infant CDH, such as pre-pregnancy diabetes were excluded from analyses.

In conclusion, our study examined associations between maternal early pregnancy cigarette smoking and alcohol consumption and CDH in their offspring. Positive associations were observed for any cigarette smoking, active only smoking, passive only smoking, and all CDH, which persisted among the majority of the subtypes, both in the 2006-2011 study period, and in the pooled 1997-2011 study period. During both study periods, there was a positive association observed between 4 or more binge episodes and all CDH which persisted among the majority of the subtypes. These associations should be further examined based on the biological mechanisms and pathways as they are clarified in the future. Even though our study has a large sample of cases and controls recruited over a long time span compared to previous studies, our results should be interpreted cautiously, considering the limitations in the way exposures were assessed. Future studies should aim to improve exposure assessment and should examine

potential mechanisms accounting for unexpected effects of maternal periconceptional cigarette smoking and alcohol observed in this study.

Table 1
Selected Characteristics of Case and Control Infants and Birth Mothers, National Birth Defects Prevention Study, 2006–2011

Characteristics	Controls (N= 4768) n (%)	All CDH[a] (N = 337) n (%)	p value	CDH NOS (N = 213) n (%)	p value	CDH[a] Bochdalek (N = 103) n (%)	p value	CDH Morgagni (N = 22) n (%)	p value
Infant									
Isolated Defect Status	--	244 (72.4)		146 (68.5)		82 (79.6)		17 (77.3)	
Laterality									
Unilateral	--	231 (94.7)		140 (95.9)		80 (97.6)		11 (64.7)	
Bilateral	--	3 (1.2)		0 (0)		1 (1.2)		2 (11.8)	
Unknown Laterality	--	11 (4.5)		6 (4.1)		1 (1.2)		4 (23.5)	
Sidedness	--								
Left	--	196 (84.8)		116 (82.9)		71 (88.8)		9 (81.8)	
Right	--	33 (14.3)		23 (16.4)		9 (11.3)		1 (9.1)	
Unknown Side	--	2 (0.9)		1 (0.7)		0 (0.0)		1 (9.1)	
Multiple Defect Status	--	93 (27.6)		67 (31.5)		21 (20.4)		5 (22.7)	
Laterality									
Unilateral	--	85 (91.4)		61 (91.0)		20 (95.2)		4 (80.0)	
Bilateral	--	3 (3.2)		2 (3.0)		1 (4.8)		0 (0.0)	
Unknown Laterality	--	5 (5.4)		4 (6.0)		0 (0.0)		1 (20.0)	
Sidedness									
Left	--	62 (72.9)		44 (72.1)		16 (80.0)		2 (50.0)	
Right	--	22 (25.9)		16 (26.2)		4 (20.0)		2 (50.0)	
Unknown Side	--	1 (1.1)		1 (1.6)		0 (0.0)		0 (0.0)	
Sex			0.010		0.167		0.052		0.047
Female	2310 (48.5)	139 (48.5)		93 (43.7)		40 (38.8)		6 (27.3)	
Male	2453 (51.5)	198 (58.8)		120 (56.3)		63 (61.2)		16 (72.7)	
Missing	5 (0.1)	0 (0)		0 (0.0)		0 (0.0)		0 (0.0)	
Family History			<0.001[a]		0.123[a]		<0.001[a]		1.000[a]
Yes	2 (0.0)	4 (1.2)		1 (0.5)		3 (2.9)		0 (0.0)	
No	4766(100.0)	333 (98.8)		212 (99.5)		100 (97.1)		22(100.0)	
Missing	0 (0.0)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
Plurality			0.070		0.070		0.552[a]		0.487[a]
1	4626 (97.0)	321 (95.3)		202 (94.8)		99 (96.1)		21 (95.5)	
>1	142 (3.0)	16 (4.8)		11 (5.2)		4 (3.9)		1 (4.6)	
Missing	1 (0.0)	0 (0)		0 (0.0)		0 (0.0)		0 (0.0)	
Mother									
Age at delivery (years)			0.139		0.543		0.025		0.838
<21	578 (12.1)	38 (11.3)		29 (13.6)		6 (5.8)		3 (13.6)	
21-25	1127 (23.6)	96 (28.5)		58 (27.2)		33 (32.0)		5 (22.7)	
26-30	1446 (30.3)	86 (25.5)		58 (27.2)		23 (22.3)		6 (27.3)	
31-35	1127 (23.6)	76 (22.6)		44 (20.7)		25 (24.3)		7 (31.8)	
>35	490 (10.3)	41 (12.2)		24 (11.3)		16 (15.5)		1 (4.6)	
Missing	0 (0)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0)	
Race and ethnicity			0.043		0.008		0.013		0.247[a]
Non-Hispanic white	2683 (56.3)	178 (52.8)		99 (46.5)		69 (67.0)		11 (50)	
Non-Hispanic black	479 (10.1)	25 (7.4)		18 (8.5)		3 (2.9)		4 (18.2)	
Hispanic	1260 (26.4)	99 (29.4)		75 (35.2)		20 (19.4)		4 (18.2)	
Other	344 (7.2)	35 (10.4)		21 (9.9)		11 (10.7)		3 (13.6)	
Missing	2 (0.0)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
Education (years)			0.291		0.107		0.141		0.412[a]
<12	755 (15.8)	61 (18.1)		45 (21.1)		11 (10.78)		5 (22.7)	
12	1060 (22.2)	64 (19.0)		45 (21.1)		17 (16.5)		2 (9.1)	
13-15	1267 (26.6)	99 (29.4)		60 (28.2)		34 (33.0)		6 (27.3)	
≥16	1658 (34.8)	111 (32.9)		61 (28.6)		41 (39.8)		9 (40.9)	
Missing	28 (0.6)	2 (0.6)		2 (0.9)		0 (0.0)		0 (0.0)	
Gravidity			0.087		0.094		0.865		0.293
0	1437 (30.1)	117 (34.7)		75 (35.2)		33 (32.0)		10 (45.5)	
1	1305 (27.4)	76 (22.6)		45 (21.1)		26 (25.2)		5 (22.7)	
>1	2025 (42.5)	144 (42.7)		93 (43.7)		44 (42.7)		7 (31.8)	
Missing	1 (0.02)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
Pre-pregnancy BMI (kg/m^2)			0.626		0.762		0.878		0.846[a]
Underweight (<18.5)	233 (4.9)	12 (3.6)		7 (3.3)		4 (3.9)		1 (4.6)	
Normal weight (18.5-24.9)	2319 (48.6)	162 (48.1)		100 (47.0)		53 (51.5)		9 (40.9)	
Overweight (25.0-29.9)	1053 (22.1)	80 (23.7)		49 (23.0)		25 (24.3)		6 (27.3)	
Obese (>30)	964 (20.2)	64 (19.0)		42 (19.7)		19 (18.5)		4 (18.2)	
Missing/out of range	199 (4.2)	19 (5.6)		15 (7.0)		2 (1.9)		2 (9.1)	
Folic Acid intake			0.462		0.449		0.855		1.000[a]
Yes	4187 (87.8)	299 (88.7)		189 (88.7)		92 (89.3)		19 (86.3	
No	531 (11.1)	333 (9.8)		20 (9.4)		11 (10.7)		2 (9.1)	
Missing	50 (1.1)	5 (1.5)		4 (1.9)		0 (0.0)		1 (4.6)	

Tale 1 – *Continued.*	Controls (N= 4768)	All CDH (N = 337)		CDH NOS (N = 213)		CDH Bochdalek (N = 103)		CDH Morgagni (N = 22)	
Characteristics	n (%)	n (%)	p value	n (%)	p value	n (%)	p value	n (%)	p value
Vitamin A Supplementation			0.015		0.012		0.153		0.315
Yes	2088 (43.8)	127 (37.7)		76 (35.7)		39 (37.9)		12 (54.6)	
No	2432 (51.0)	197 (58.5)		128 (60.1)		61 (59.2)		9 (40.9)	
Missing	248 (5.2)	13 (3.9)		9 (4.2)		3 (2.9)		1 (4.6)	
Dietary folate intake			0.260		0.878		0.069		0.811
<600 µg/day	3351 (70.3)	247 (73.3)		151 (70.9)		81 (78.6)		17 (73.9)	
≥600 µg/day	1409 (29.6)	90 (26.7)		62 (29.1)		22 (21.4)		6 (26.1)	
Missing	8 (0.2)	0 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
Study center			<0.001		<0.001		0.256		0.131
Arkansas	612 (12.8)	40 (11.9)		22 (10.3)		14 (13.6)		4 (18.2)	
California	358 (7.5)	48 (14.2)		37 (17.4)		8 (7.8)		3 (13.6)	
Iowa	530 (11.1)	18 (5.3)		9 (4.2)		8 (7.8)		1 (4.6)	
Massachusetts	532 (11.2)	47 (14.0)		31 (14.6)		11 (10.7)		5 (22.7)	
New York	367 (7.7)	17 (5.0)		8 (3.8)		7 (6.8)		2 (9.1)	
Texas	550 (11.5)	33 (9.8)		28 (13.2)		5 (4.9)		0 (0.0)	
CDC / Atlanta	505 (10.6)	41 (12.2)		28 (13.2)		10 (9.7)		4 (18.2)	
North Carolina	573 (12.0)	37 (11.0)		19 (8.9)		16 (15.5)		2 (9.1)	
Utah	741 (15.5)	56 (16.6)		31 (14.6)		24 (23.3)		1 (4.6)	

BMI, body mass index; CDC, US Centers for Disease Control and Prevention; CDH, congenital diaphragmatic hernia; NOS, not otherwise specified. Numbers vary because of incomplete or missing data. Due to rounding, percentages may not total 100.
[a]Fisher's exact test used

Table 2
Reported Pattern of Periconceptional Exposure for Cigarette Smoking and Alcohol for Case and Control Mothers, National Birth Defects Prevention Study, 2006-2011

	Controls		CDH	
Exposure	n	%	n	%
Cigarette smoking				
Any periconceptional exposure				
No	3479	70.1	223	63.7
Yes	1259	25.4	107	30.6
Missing	227	4.6	20	5.7
Type of exposure				
Active + passive smoking	416	8.4	28	8.0
Active smoking only	368	7.4	27	7.7
Passive smoking only	471	9.5	52	14.9
Missing	231	4.7	20	5.7
Duration of active smoking				
1 month	145	2.9	12	3.4
2 months	182	3.7	13	3.7
3 months	75	1.5	6	1.7
4 months	384	7.7	24	6.9
Missing	212	4.3	17	4.9
Maximum Cigarettes / day				
1-14	578	11.6	38	10.9
≥ 15	195	3.9	17	4.9
Missing	225	4.5	17	4.9
Minimum Cigarettes / day				
1-14	679	13.7	44	12.6
≥ 15	94	1.9	11	3.1
Missing	225	4.5	17	4.9
Alcohol				
Any periconceptional exposure				
No	2956	59.5	211	60.3
Yes	1770	35.6	117	33.4
Missing	239	4.8	22	6.3
Average number of drinks / month				
1-15	1373	27.7	96	27.4
16-30	247	5.0	13	3.7
>30	99	2.0	8	2.3
Missing	290	5.8	22	6.3
Maximum average number of drinks / month				
1-15	1329	26.8	89	25.4
16-30	258	5.2	18	5.1
>30	132	2.7	10	2.9
Missing	290	5.8	22	6.3
Number of binges				
1 Binge episode	241	4.9	10	2.9
2-3 Binge episodes	161	3.2	7	2.0
4 or more binge episodes	183	3.7	18	5.1
Missing	1424	28.7	104	29.7
Type(s) of alcohol				
Beer only	290	5.8	19	5.4
Wine only	505	10.2	33	9.4
Distilled spirits only	319	6.4	24	6.9
Beer + wine	213	4.3	10	2.9
Beer + distilled spirits	136	2.7	10	2.9
Wine + distilled spirits	189	3.8	14	4.0
Beer + wine + distilled spirits	110	2.2	7	2.0
Missing	248	5.0	22	6.3
Duration of alcohol consumption				
1 month	1072	21.6	70	20.0
2 months	522	10.5	37	10.6
3 months	86	1.7	3	0.9
4 months	90	1.8	7	2.0
Missing	239	4.8	22	6.3

CDH, Congenital diaphragmatic hernia.

Table 3
Adjusted Odds Ratio Estimates for Infant Phenotype Associated with Maternal Reports of Cigarette Smoking, National Birth Defects Prevention Study, 2006-2011

	Controls	All CDH (N = 350)			CDH NOS (N = 225)			CDH Bochdalek (N = 103)		
Exposure	N (%)	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)
Any smoking exposure										
No	3479 (70.1)		Ref.	Ref.	138 (61.3)	Ref.	Ref.	70 (68.0)	Ref.	Ref.
Yes	1259 (25.4)	107 (30.6)	1.3 (1.0, 1.7)	1.4 (1.1, 1.8)[a]	71 (31.6)	1.4 (1.1, 1.9)	1.7 (1.3, 2.4)[a,b]	31 (30.1)	1.2 (0.9, 1.9)	1.2 (0.8, 1.9)[a]
Active and/or passive smoking										
Active only	416 (8.4)	27 (7.7)	1.2 (0.8, 1.7)	1.3 (0.8, 1.9)[a,b]	17 (7.6)	1.2 (0.7, 2.0)	1.3 (0.8, 2.3)[a,b]	10 (9.7)	1.4 (0.7, 2.6)	1.4 (0.7, 2.7)[a]
Passive only	368 (7.4)	52 (14.9)	1.7 (1.3, 2.4)	1.9 (1.3, 2.6)[a,b]	39 (17.3)	2.1(1.5, 3.0)	2.3 (1.6, 3.4)[a,b]	10 (9.7)	1.1 (0.5, 2.1)	1.1 (0.6, 2.1)[a]
Active + passive	471 (9.5)	28 (8.0)	1.1 (0.7, 1.6)	1.3 (0.9, 2.0)[a,b]	15 (6.7)	0.9 (0.5, 1.6)	1.3 (0.7, 2.3)[a,b]	11 (10.7)	1.3 (0.7, 2.5)	1.3 (0.7, 2.6)[a]
Maximum cigarettes / day										
1-14 / day	578 (11.6)	38 (10.9)	0.9 (0.7, 1.3)	1.1 (0.7, 1.5)[a,b]	23 (10.2)	0.9 (0.6, 1.4)	1.1 (0.7, 1.7)[a,b]	13 (12.6)	1.1 (0.6, 2.0)	1.1 (0.6, 2.0)[a,c]
≥15 / day	195 (3.9)	17 (4.9)	1.2 (0.8, 2.1)	1.6 (0.9, 2.7)[a,b]	9 (4.0)	1.0 (0.5, 2.1)	1.5 (0.7, 2.9)[a,b]	8 (7.8)	2.0 (1.0, 4.2)	1.8 (0.9, 3.9)[a,c]
Minimum cigarettes / day										
1-14 / day	679 (13.7)	44 (12.6)	0.9 (0.7, 1.3)	1.1 (0.8, 1.5)[a,b]	27 (12.0)	0.9 (0.6, 1.4)	1.1 (0.7, 1.7)[a,b]	15 (14.6)	1.1 (0.6, 1.9)	1.0 (0.6, 1.9)[a,c]
≥15 / day	94 (1.9)	11 (3.1)	1.7 (0.9, 3.2)	2.1 (1.1, 4.1)[a,b]	5 (2.2)	1.2 (0.5, 3.0)	1.6 (0.6, 4.1)[a,b]	6 (5.8)	3.1 (1.3, 7.3)	3.0 (1.2, 7.1)[a,c]
Duration										
1 month	145 (2.9)	12 (3.4)	1.2 (0.7, 2.2)	1.3 (0.7, 2.4)[a,b]	8 (3.6)	1.2 (0.6, 2.6)	1.4 (0.7, 2.9)[a,b]	4 (3.9)	NC	NC
2 months	182 (3.7)	13 (3.7)	1.0 (0.7, 1.8)	1.1 (0.6, 2.1)[a,b]	6 (2.7)	0.7 (0.3, 1.7)	0.9 (0.4, 2.1) [a.b]	6 (5.8)	1.6 (0.7, 3.7)	1.5 (0.6, 3.7)[a,c]
3 months	75 (1.5)	6 (1.7)	1.1 (0.5, 2.7)	1.3(0.6, 3.0)[a,b]	4 (1.8)	NC	NC	2 (1.9)	NC	NC
4 months	384 (7.7)	24 (6.9)	0.9 (0.6, 1.4)	1.1 (0.7, 1.7)[a,b]	14 (6.2)	0.8 (0.5, 1.4)	1.1 (0.6, 1.9)[a,b]	9 (8.7)	1.1 (0.6, 2.3)	1.1 (0.5, 2.2)[a,c]

aOR, adjusted odds ratio; CDH, Congenital diaphragmatic hernia; CI, confidence interval; cOR, crude odds ratio, NOS, not otherwise stated.
[a] Adjusted for calculated binge drinking 1 month before pregnancy through month 3 of pregnancy (≥4 drinks)
[b] Adjusted for NBDPS site
[c] Adjusted for maternal race

Table 4
Odds Ratio Estimates for Infant Phenotype Associated with Maternal Reports of Alcohol Consumption, National Birth Defects Prevention Study, 2006-2011

	Controls	All CDH (N = 350)			CDH NOS (N = 225)			CDH Bochdalek (N = 103)		
Exposure	N (%)	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)
Any alcohol consumption										
No	2956 (59.5)	211 (60.3)	Ref.	Ref.	141 (62.7)	Ref.	Ref.	59 (57.3)	Ref.	Ref.
Yes	1770 (35.6)	117 (33.4)	0.9 (0.7, 1.2)	0.9 (0.8, 1.2)[a]	67 (29.8)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)[a]	41 (39.8)	1.1 (0.8, 1.7)	1.1 (0.7, 1.7)[a]
Average drinks / month										
1-15	1373 (27.7)	96 (27.4)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)[a,b]	57 (25.3)	0.9 (0.6, 1.2)	0.9 (0.6, 1.2)[a,b]	32 (31.1)	1.2 (0.8, 1.8)	1.1 (0.7, 1.7)[a,c]
16-30	247 (5.0)	13 (3.7)	0.7 (0.4, 1.3)	0.7 (0.4, 1.3)[a,b]	7 (3.1)	0.6 (0.3, 1.3)	0.6 (0.3, 1.2)[a,b]	5 (4.9)	1.0 (0.4, 2.6)	0.8 (0.3, 2.2)[a,c]
>30	99 (2.0)	8 (2.3)	1.1 (0.5, 2.4)	1.2 (0.5, 2.5)[a,b]	3 (1.3)	NC	NC	4 (3.9)	NC	NC
Maximum average drinks / month										
1-15	1329 (27.7)	89 (25.4)	0.9 (0.7, 1.2)	1.0 (0.7, 1.3)[a,b]	54 (24.0)	0.9 (0.6, 1.2)	0.9 (0.6, 1.2)[a,b]	29 (28.2)	1.1 (0.7, 1.7)	1.0 (0.6, 1.6)[a,c,e]
16-30	258 (5.2)	18 (5.1)	1.0 (0.6, 1.6)	1.0 (0.6, 1.6)[a,b]	8 (3.6)	0.7 (0.3, 1.3)	0.6 (0.3, 1.3)[a,b]	8 (7.8)	1.6 (0.7, 3.3)	1.3 (0.6, 2.8)[a,c,e]
>30	132 (2.7)	10 (2.9)	1.1 (0.6, 2.1)	1.1 (0.6, 2.2)[a,b]	5 (2.2)	0.8 (0.3, 2.0)	0.8 (0.3, 2.2)[a,b]	4 (3.9)	NC	NC
Number of binges										
1 binge episode	241 (4.9)	10 (2.9)	0.6 (0.3, 1.1)	0.6 (0.3, 1.2)[a,b,c]	4 (1.8)	NC	NC	6 (5.8)	1.3 (0.5, 2.9)	1.2 (0.5, 2.8)[a]
2-3 binge episodes	161 (3.2)	7 (2.0)	0.6 (0.3, 1.3)	0.6 (0.3, 1.4)[a,b,c]	5 (2.2)	0.7 (0.3, 1.6)	0.7 (0.3, 1.8)[a,b]	2 (1.9)	NC	NC
4 or more binge episodes	183 (3.7)	18 (5.1)	1.4 (0.8, 2.3)	1.5 (0.9, 2.7)[a,b,c]	10 (4.4)	1.2 (0.6, 2.2)	1.4 (0.7, 2.8)[a,b]	6 (5.8)	1.7 (0.7, 3.9)	1.5 (0.6, 3.7)[a]
Type(s) of alcohol										
Beer only	290 (5.8)	19 (5.4)	0.9 (0.6, 1.5)	1.0 (0.6, 1.6)[a,b]	14 (6.2)	1.0 (0.6, 1.8)	1.0 (0.5, 1.7)[a,e]	5 (4.9)	0.9 (0.3, 2.2)	0.8 (0.3, 2.0)[a,c,e]
Wine only	505 (10.2)	33 (9.4)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)[a,b]	18 (8.0)	0.8 (0.5, 1.2)	0.8 (0.5, 1.4)[a,e]	12 (11.7)	1.2 (0.6, 2.2)	1.1 (0.6, 2.0)[a,c,e]
Liquor only	319 (6.4)	24 (6.9)	1.1 (0.7, 1.6)	1.1 (0.7, 1.3)[a,b]	14 (6.2)	0.9 (0.5, 1.6)	0.9 (0.5, 1.6)[a,e]	8 (7.8)	1.3 (0.6, 2.7)	1.1 (0.6, 2.0)[a,c,e]
2 or more	648 (13.1)	41 (11.7)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)[a,b]	21 (9.3)	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)[a,e]	16 (15.5)	1.2 (0.7, 2.2)	1.0 (0.6, 1.8)[a,c,e]
Duration of alcohol consumption										
1 month	1072 (21.6)	70 (20.0)	0.9 (0.7, 1.2)	1.0 (0.7, 1.3)[a,b,d]	44 (19.6)	0.9 (0.6, 1.2)	0.9 (0.6, 1.3)[a,b,d,e]	22 (21.4)	1.0 (0.6, 1.7)	1.0 (0.6, 1.6)[a]
2 months	522 (10.5)	37 (10.6)	1.0 (0.7, 1.4)	1.0 (0.7, 1.5)[a,b,d]	17 (7.6)	0.7 (0.4, 1.1)	0.7 (0.4, 1.3)[a,b,d,e]	15 (14.6)	1.4 (0.8, 2.6)	1.4 (0.8, 2.4)[a]
3 months	86 (1.7)	3 (0.9)	NC	NC	2 (0.9)	NC	NC	1 (1.0)	NC	NC
4 months	90 (1.8)	7 (2.0)	1.1 (0.5, 2.4)	1.1 (0.5, 2.5)[a,b,d]	4 (1.8)	NC	NC	3 (2.9)	NC	NC

aOR, adjusted odds ratio; CDH, Congenital diaphragmatic hernia; CI, confidence interval; cOR, crude odds ratio, NC, not calculated; NOS, not otherwise stated.
[a] Adjusted for active and/or passive smoking 1 month before pregnancy through month 3 of pregnancy
[b] Adjusted for NBDPS site
[c] Adjusted for first degree family of diaphragmatic hernia
[d] Adjusted for vitamin A consumption (composite of multivitamins, prenatal vitamins, other vitamins, single vitamin) 1 month before pregnancy through month 3 of pregnancy
[e] Adjusted for maternal race

Table 5
Odds Ratio Estimates for Isolated Infant Phenotype Associated with Maternal Reports of Cigarette Smoking, National Birth Defects Prevention Study, 2006-2011

	Isolated CDH (N = 254)			Isolated CDH NOS (N=156)			Isolated CDH Bochdalek (N=82)		
Exposure	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)
Any smoking exposure									
No	164 (64.6)	Ref.	Ref.	98 (68.1)	Ref.	Ref.	54 (67.5)	Ref.	Ref.
Yes	76 (29.9)	1.3 (1.0, 1.7)	1.4 (1.1, 1.9)[a]	46 (31.9)	1.3 (0.9, 1.9)	1.7 (1.1, 2.4)[a,b]	26 (32.5)	1.3 (0.8, 2.1)	1.4 (0.8, 2.3)[a]
Active and/or passive smoking									
Active only	22 (8.7)	1.3 (0.8, 2.0)	1.5 (0.9, 2.3)[a,b]	12 (8.3)	1.2 (0.6, 2.1)	1.4 (0.8, 2.6)[a,b]	10 (12.5)	1.8 (0.9, 3.5)	1.8 (0.9, 3.7)[a]
Passive only	34 (13.3)	1.5 (1.1, 2.2)	1.7 (1.2, 2.5)[a,b]	24 (16.7)	1.8 (1.2, 2.9)	2.1 (1.3, 3.3)[a,b]	7 (8.8)	1.0 (0.4, 2.1)	1.0 (0.4, 2.2)[a]
Active + passive	20 (7.9)	1.0 (0.6, 1.6)	1.3 (0.8, 2.2)[a,b]	10 (6.9)	0.9 (0.4, 1.7)	1.3 (0.7, 2.6)[a,b]	9 (11.3)	1.4 (0.7, 2.8)	1.5 (0.7, 3.1)[a]
Maximum cigarettes / day									
1-14 / day	29 (11.4)	1.0 (0.7, 1.5)	1.2 (0.8, 1.8)[a,b]	17 (11.8)	1.0 (0.6, 1.6)	1.2 (0.7, 2.1)[a,b]	11 (13.4)	1.2 (0.6, 2.3)	1.3 (0.6, 2.5)[a,c]
≥15 / day	13 (5.1)	1.3 (0.7, 2.4)	1.8 (1.0, 3.2)[a,b]	5 (3.5)	0.8 (0.3, 2.1)	1.3 (0.5, 3.2)[a,b]	8 (9.8)	2.6 (1.2, 5.5)	2.5 (1.1, 5.4)[a,c]
Minimum cigarettes / day									
1-14 / day	33 (13.0)	1.0 (0.7, 1.4)	1.2 (0.8, 1.7)[a,b]	19 (13.2)	0.9 (0.6, 1.5)	1.2 (0.7, 2.0)[a,b]	13 (15.9)	1.2 (0.7, 2.2)	1.2 (0.7, 2.3)[a,c]
≥15 / day	9 (3.5)	1.9 (0.9, 3.8)	2.5 (1.2, 5.1)[a,b]	3 (2.1)	NC	NC	6 (7.3)	4.0 (1.7, 9.5)	4.0 (1.6, 9.7)[a,c]
Duration									
1 month	11 (4.3)	1.5 (0.8, 2.8)	1.7 (0.9, 3.3)[a,b]	7 (4.9)	1.6 (0.7, 3.4)	1.9 (0.8, 4.1)[a,b]	4 (4.9)	NC	NC
2 months	10 (3.9)	1.1 (0.6, 2.1)	1.3 (0.7, 2.6)[a,b]	3 (2.1)	NC	NC	6 (7.3)	2.1 (0.9, 4.9)	2.1 (0.9, 5.2)[a,c]
3 months	4 (1.6)	NC	NC	2 (1.4)	NC	NC	2 (2.4)	NC	NC
4 months	17 (6.7)	0.9 (0.5, 1.5)	1.1 (0.7, 1.9)[a,b]	10 (6.9)	0.9 (0.4, 1.6)	1.2 (0.6, 2.3)[a,b]	7 (8.5)	1.2 (0.5, 2.5)	1.1 (0.5, 2.6)[a,c]

aOR, adjusted odds ratio; CDH, Congenital diaphragmatic hernia; CI, confidence interval; cOR, crude odds ratio, NC, not calculated; NOS, not otherwise stated.
[a] Adjusted for calculated binge drinking 1 month before pregnancy through month 3 of pregnancy (≥4 drinks)
[b] Adjusted for NBDPS site
[c] Adjusted for maternal race

Table 6
Odds Ratio Estimates for Isolated Infant Phenotype Associated with Maternal Reports of Alcohol Consumption, National Birth Defects Prevention Study, 2006-2011

	Isolated CDH (N = 254)			Isolated CDH NOS (N=156)			Isolated CDH Bochdalek (N=82)		
Exposure	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)
Any alcohol consumption									
No	156 (61.4)	Ref.	Ref.	99 (69.2)	Ref.	Ref.	49 (62.0)	Ref.	Ref.
Yes	81 (31.9)	0.9 (0.7, 1.1)	0.8 (0.6, 1.1)[a]	44 (30.8)	0.7 (0.5, 1.1)	0.7 (0.5, 1.0)[a]	30 (38.0)	1.0 (0.7, 1.6)	0.9 (0.6, 1.5)[a]
Average drinks / month									
1-15	63 (24.8)	0.9 (0.6, 1.2)	0.9 (0.6, 1.2)[a,b,c]	36 (25.2)	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)[a,b]	21 (26.6)	0.9 (0.6, 1.6)	0.8 (0.5, 1.4)[a,c,d]
16-30	13 (5.1)	1.0 (0.6, 1.8)	0.9 (0.5, 1.6)[a,b,c]	7 (4.9)	0.9 (0.4, 1.8)	0.8 (0.3, 1.7)[a,b]	5 (6.3)	1.2 (0.5, 3.1)	0.9 (0.3, 2.4)[a,c,d]
>30	5 (2.0)	1.0 (0.4, 2.4)	0.8 (0.3, 2.2)[a,b,c]	1 (0.7)	NC	NC	4 (5.1)	NC	NC
Maximum average drinks / month									
1-15	61 (24.0)	0.9 (0.6, 1.2)	0.9 (0.7, 1.2)[a,b]	35 (24.5)	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)[a,b]	21 (26.6)	1.0 (0.6, 1.6)	0.8 (0.5, 1.4)[a,c,d]
16-30	13 (5.1)	1.0 (0.5, 1.7)	0.9 (0.5, 1.7)[a,b]	6 (4.2)	0.7 (0.3, 1.6)	0.6 (0.3, 1.5)[a,b]	5 (6.3)	1.2 (0.5, 3.0)	0.9 (0.3, 2.3)[a,c,d]
>30	7 (2.8)	1.0 (0.5, 2.2)	1.0 (0.5, 2.3)[a,b]	3 (2.1)	NC	NC	4 (5.1)	NC	NC
Number of binges									
1 binge episode	7 (2.8)	0.6 (0.3, 1.2)	0.5 (0.2, 1.2)[a,b,c]	2 (1.8)	NC	NC	5 (8.3)	1.3 (0.5, 3.2)	1.2 (0.5, 3.1)[a]
2-3 binge episodes	4 (1.6)	NC	NC	3 (2.7)	NC	NC	1 (1.7)	NC	NC
4 or more binge episodes	12 (4.7)	1.2 (0.7, 2.3)	1.2 (0.6, 2.5)[a,b,c]	6 (5.5)	1.0 (0.4, 2.3)	1.0 (0.4, 2.6)[a,b,d]	5 (8.3)	1.7 (0.7, 4.2)	1.4 (0.5, 3.9)[a]
Type(s) of alcohol									
Beer only	11 (4.3)	0.7 (0.4, 1.3)	0.7 (0.4, 1.4)[a,b]	7 (4.9)	0.7 (0.3, 1.6)	0.7 (0.3, 1.5)[a,d]	4 (5.1)	NC	NC
Wine only	21 (8.3)	0.8 (0.5, 1.3)	0.8 (0.5, 1.3)[a,b]	13 (9.1)	0.8 (0.4, 1.4)	0.8 (0.5, 1.5)[a,d]	6 (7.6)	0.7 (0.3, 1.7)	0.6 (0.3, 1.5)[a,c,d]
Liquor only	17 (6.7)	1.0 (0.6, 1.7)	1.0 (0.6 1.7)[a,b]	10 (7.0)	0.9 (0.5, 1.8)	1.0 (0.5, 1.9)[a,d]	6 (7.6)	1.1 (0.5, 2.7)	0.9 (0.4, 2.3)[a,c,d]
2 or more	32 (16.5)	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)[a,b]	14 (9.8)	0.7 (0.4, 1.1)	0.7 (0.4, 1.2)[a,d]	14 (17.7)	1.3 (0.7, 2.4)	1.0 (0.52, 1.9)[a,c,d]
Duration of alcohol consumption									
1 month	52 (20.5)	0.9 (0.7, 1.3)	0.9 (0.6, 1.2)[a]	29 (20.3)	0.8 (0.5, 1.2)	0.8 (0.5, 1.3)[a,d]	20 (25.3)	1.1 (0.7, 1.9)	1.0 (0.6, 1.8)[a]
2 months	24 (9.5)	0.9 (0.6, 1.4)	0.8 (0.5, 1.3)[a]	11 (7.7)	0.6 (0.3, 1.2)	0.7 (0.4, 1.3)[a,d]	9 (11.4)	1.0 (0.5, 2.1)	0.9 (0.4, 1.9)[a]
3 months	1 (0.4)	NC	NC	1 (0.7)	NC	NC	0 (0)	NC	NC
4 months	4 (1.6)	NC	NC	3 (2.1)	NC	NC	1 (1.3)	NC	NC

aOR, adjusted odds ratio; CDH, Congenital diaphragmatic hernia; CI, confidence interval; cOR, crude odds ratio, NC, not calculated; NOS, not otherwise stated.
[a] Adjusted for active and/or passive smoking 1 month before pregnancy through month 3 of pregnancy
[b] Adjusted for NBDPS site
[c] Adjusted for first degree family history of diaphragmatic hernia
[d] Adjusted for maternal race

Table 7
Adjusted Odds Ratio Estimates for Infant Phenotype Associated with Maternal Reports of Cigarette Smoking, National Birth Defects Prevention Study, 1997-2011

	Controls	All CDH			CDH NOS			CDH Bochdalek		
Exposure	N (%)	N (%)	cOR (95%)	aOR (95% CI)	N (%)	cOR (95%)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)
Any smoking exposure										
No	7942 (67.6)	545 (63.6)	Ref.	Ref.	399 (65.3)	Ref.	Ref.	120 (58.3)	Ref.	Ref.
Yes	3462 (29.5)	283 (33.0)	1.2 (1.0, 1.4)	1.2 (1.1, 1.4)[a]	189 (30.9)	1.1 (0.9, 1.3)	1.1 (0.9, 1.4)[a]	83 (40.3)	1.6 (1.2, 2.1)	1.6 (1.2, 2.1)[a]
Active and/or passive smoking										
Active only	865 (7.4)	75 (8.8)	1.3 (1.0, 1.6)	1.3 (1.0, 1.7)[a]	52 (8.5)	1.2 (0.9, 1.6)	1.4 (1.0, 1.8)[a,b]	22 (10.7)	1.7 (1.1, 2.7)	1.7 (1.0, 2.7)[a]
Passive only	1412 (12.0)	128 (14.9)	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)[a]	90 (14.7)	1.3 (1.0, 1.6)	1.3 (1.0, 1.7)[a,b]	32 (15.5)	1.5 (1.0, 2.2)	1.5 (1.0, 2.3)[a]
Active + passive	1177 (10.0)	80 (9.3)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)[a]	47 (7.7)	0.8 (0.6, 1.1)	0.9 (0.7, 1.3)[a,b]	29 (14.1)	1.6 (1.1, 2.5)	1.6 (1.1, 2.5)[a]
Maximum cigarettes / day										
1-14 / day	1459 (12.4)	116 (13.5)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)[a]	78 (12.8)	1.0 (0.8, 1.3)	1.1 (0.9, 0.5)[a,b]	34 (16.5)	1.4 (1.0, 2.1)	1.4 (1.0, 2.1)[a]
≥15 / day	571 (4.9)	38 (4.4)	0.9 (0.7, 1.3)	1.0 (0.7, 1.4)[a]	21 (3.4)	0.7 (0.5, 1.1)	0.8 (0.5, 1.3)[a,b]	16 (7.8)	1.7 (1.0, 2.9)	1.7 (1.0, 3.0)[a]
Minimum cigarettes / day										
1-14 / day	1719 (14.6)	134 (15.6)	1.1 (0.9, 1.3)	1.1 (0.9, 1.4)[a]	89 (14.6)	1.0 (0.8, 1.3)	1.1 (0.9, 1.4)[a,b]	40 (19.4)	1.4 (1.0, 2.0)	1.5 (1.0, 2.1)[a,c]
≥15 / day	311 (2.7)	20 (2.3)	0.9 (0.6, 1.4)	0.9 (0.5, 1.4)[a]	10 (1.6)	0.6 (0.3, 1.2)	0.7 (0.4, 1.4)[a,b]	10 (4.9)	2.0 (1.0, 3.8)	1.7 (0.8, 3.5)[a,c]
Duration										
1 month	318 (2.7)	25 (2.9)	1.1 (0.7, 1.7)	1.2 (0.8, 1.8)[a]	19 (3.1)	1.1 (0.7, 1.8)	1.3 (0.8, 2.0)[a,b]	6 (2.9)	1.2 (0.5, 2.6)	1.2 (0.5, 2.7)[a]
2 months	452 (3.9)	39 (4.6)	1.2 (0.9, 1.7)	1.3 (0.9, 1.8)[a]	26 (4.3)	1.1 (0.7, 1.7)	1.2 (0.8, 1.8)[a,b]	11 (5.3)	1.5 (0.8, 2.8)	1.5 (0.8, 2.9)[a]
3 months	227 (1.9)	23 (2.7)	1.4 (0.9, 2.2)	1.5 (1.0, 2.4)[a]	17 (2.8)	1.4 (0.9, 2.4)	1.7 (1.0, 2.8)[a,b]	6 (2.9)	1.6 (0.7, 3.7)	1.7 (0.7, 3.9)[a]
4 months	1050 (8.9)	68 (7.9)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)[a]	37 (6.1)	0.7 (0.5, 1.0)	0.8 (0.5, 1.1)[a,b]	28 (13.6)	1.6 (1.1, 2.4)	1.6 (1.0, 2.4)[a]

aOR, adjusted odds ratio; CDH, Congenital diaphragmatic hernia; CI, confidence interval; cOR, crude odds ratio, NC, not calculated; NOS, not otherwise stated.
[a] Adjusted for calculated binge drinking 1 month before pregnancy through month 3 of pregnancy (≥4 drinks)
[b] Adjusted for NBDPS site
[c] Adjusted for first degree family history of diaphragmatic hernia

Table 8
Adjusted Odds Ratio Estimates for Infant Phenotype Associated with Maternal Reports of Alcohol Consumption, National Birth Defects Prevention Study, 1997-2011

	Controls	All CDH (N = 350)			CDH NOS (N = 225)			CDH Bochdalek (N = 103)		
Exposure	N (%)	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)
Any alcohol consumption										
No	7148 (60.9)	535 (62.4)	Ref.	Ref.	391 (63.99)	Ref.	Ref	123 (59.7)	Ref.	Ref.
Yes	4203 (35.8)	288 (33.6)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)[a]	195 (31.9)	0.8 (0.7, 1.0)	0.9 (0.7, 1.0)[a]	78 (37.9)	1.1 (0.8, 1.4)	1.2 (0.9, 1.6)[a,b]
Average drinks / month										
1-15	3329 (28.4)	234 (27.3)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)[a]	158 (25.9)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)[a]	65 (31.6)	1.1 (0.8, 1.5)	1.2 (0.9, 1.7)[a,b]
16-30	550 (4.7)	35 (4.1)	0.9 (0.6, 1.2)	0.8 (0.6, 1.2)[a]	25 (4.1)	0.8 (0.6, 1.3)	0.8 (0.6, 1.3)[a]	8 (3.9)	0.9 (0.4, 1.7)	0.8 (0.4, 1.7)[a,b]
>30	253 (2.2)	18 (2.1)	1.0 (0.6, 1.6)	0.9 (0.6, 1.5)[a]	11 (1.8)	0.8 (0.4, 1.5)	0.8 (0.4, 1.5)[a]	5 (2.4)	1.2 (0.5, 2.8)	0.9 (0.4, 2.4)[a,b]
Maximum average drinks / month										
1-15	3221 (27.4)	220 (25.7)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)[a]	150 (24.6)	0.9 (0.7, 1.0)	0.9 (0.7, 1.0)[a]	60 (29.1)	1.1 (0.8, 1.5)	1.2 (0.9, 1.7)[a,b,c]
16-30	550 (4.7)	47 (5.5)	1.1 (0.8, 1.4)	1.0 (0.8, 1.4)[a]	31 (5.1)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)[a]	13 (6.3)	1.3 (0.7, 2.3)	1.3 (0.7, 2.3)[a,b,c]
>30	312 (2.7)	20 (2.3)	0.9 (0.5, 1.4)	0.8 (0.5, 1.3)[a]	13 (2.1)	0.8 (0.4, 1.3)	0.8 (0.4, 1.4)[a]	5 (2.4)	0.9 (0.4, 2.3)	0.9 (0.3, 2.2)[a,b,c]
Number of binges										
1 binge episode	565 (4.8)	26 (3.0)	0.6 (0.4, 0.9)	0.6 (0.4, 0.9)[a]	15 (2.5)	0.5 (0.3, 0.8)	0.5 (0.3, 0.8)[a]	11 (5.3)	1.1 (0.6, 2.1)	1.1 (0.6, 2.1)[a,b]
2-3 binge episodes	366 (3.1)	25 (2.9)	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)[a]	20 (3.3)	1.0 (0.6, 1.6)	1.0 (0.7, 1.7)[a]	5 (2.4)	0.8 (0.3, 2.0)	0.8 (0.3, 2.0)[a,b]
4 or more binge episodes	443 (3.8)	40 (4.7)	1.2 (0.9, 1.7)	1.2 (0.9, 1.7)[a]	26 (4.3)	1.1 (0.7, 1.6)	1.2 (0.8, 1.8)[a]	11 (5.3)	1.4 (0.8, 2.7)	1.3 (0.7, 2.5)[a,b]
Type(s) of alcohol										
Beer only	793 (6.8)	58 (6.8)	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)[a]	39 (6.4)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)[a]	18 (8.7)	1.3 (0.8, 2.2)	1.4 (0.8, 2.3)[a,b]
Wine only	1183 (10.1)	77 (9.0)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)[a]	57 (9.3)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)[a]	17 (8.3)	0.8 (0.5, 1.4)	1.0 (0.6, 1.7)[a,b]
Liquor only	744 (6.3)	48 (5.6)	0.9 (0.6, 1.2)	0.9 (0.6, 1.2)[a]	26 (4.3)	0.6 (0.4, 1.0)	0.6 (0.4, 1.0)[a]	19 (9.2)	1.5 (0.9, 2.4)	1.5 (0.9, 2.4)[a,b]
2 or more	1470 (12.5)	103 (12.0)	0.9 (0.8, 1.2)	0.9 (0.7, 1.2)[a]	72 (11.8)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)[a]	23 (11.2)	0.9 (0.6, 1.4)	1.0 (0.6, 1.6)[a,b]
Duration of alcohol consumption										
1 month	2370 (20.2)	151 (17.6)	0.9 (0.7, 1.0)	0.9 (0.7, 1.0)[a]	100 (16.4)	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)[a]	42 (20.4)	1.0 (0.7, 1.5)	1.1 (0.8, 1.6)[a,b]
2 months	1261 (10.7)	97 (11.3)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)[a]	66 (10.8)	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)[a]	26 12.6)	1.3 (0.8, 1.8)	1.3 (0.8, 2.0)[a,b]
3 months	260 (2.2)	21 (2.5)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)[a]	16 (2.6)	1.1 (0.7, 1.9)	1.1 (0.7, 1.9)[a]	5 (2.4)	1.1 (0.5, 2.8)	1.1 (0.5, 2.8)[a,b]
4 months	312 (2.7)	19 (2.2)	0.8 (0.5, 1.3)	0.8 (0.5, 1.3)[a]	13 (2.1)	0.8 (0.4, 1.3)	0.8 (0.4, 1.4)[a]	5 (2.4)	0.9 (0.4, 2.3)	1.0 (0.4, 2.5)[a,b]

aOR, adjusted odds ratio; CDH, Congenital diaphragmatic hernia; CI, confidence interval; cOR, crude odds ratio, NC, not calculated; NOS, not otherwise stated.
[a] Adjusted for active and/or passive smoking 1 month before pregnancy through month 3 of pregnancy
[b] Adjusted for NBDPS site
[c] Adjusted for first degree family history of diaphragmatic hernia

Table 9
Adjusted Odds Ratio Estimates for Infant Phenotype Associated with Maternal Reports of Cigarette Smoking, National Birth Defects Prevention Study, 1997-2011

	Isolated CDH			Isolated CDH NOS			Isolated CDH Bochdalek		
Exposure	N (%)	cOR (95%)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)
Any smoking exposure									
No	431 (65.0)	Ref.	Ref.	313 (69.7)	Ref.	Ref.	98 (59.0)	Ref.	Ref.
Yes	212 (32.0)	1.1 (1.0, 1.3)	1.2 (1.0, 1.4)[a]	136 (30.3)	1.0 (0.8, 1.22)	1.0 (0.8, 1.3)[a]	68 (41.0)	1.6 (1.2, 2.2)	1.6 (1.2, 2.2)[a]
Active and/or passive smoking									
Active only	58 (8.8)	1.2 (0.9, 1.6)	1.3 (1.0, 1.7)[a]	36 (8.0)	1.1 (0.7, 1.5)	1.2 (0.8, 1.7)[a,b]	21 (12.7)	2.0 (1.2, 3.2)	2.0 (1.2, 3.3)[a]
Passive only	91 (13.7)	1.2 (0.9, 1.5)	1.2 (1.0, 1.5)[a]	62 (13.8)	1.1 (0.8, 1.5)	1.2 (0.9,1.5)[a,b]	24 (14.5)	1.4 (0.9, 2.2)	1.4 (0.9, 2.2)[a]
Active + passive	63 (9.5)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)[a]	38 (8.5)	0.8 (0.6, 1.2)	0.9 (0.7, 1.4)[a,b]	23 (13.9)	1.6 (1.0, 2.5)	1.7 (1.0, 2.7)[a]
Maximum cigarettes / day									
1-14 / day	91 (13.7)	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)[a]	60 (13.3)	1.0 (0.8, 1.4)	1.2 (0.9, 1.6)[a,b]	28 (16.8)	1.5 (1.0, 2.2)	1.5 (1.0, 2.3)[a]
≥15 / day	29 (4.4)	0.9 (0.6, 1.3)	0.9 (0.6, 1.4)[a]	14 (3.1)	0.6 (0.4, 1.1)	0.7 (0.4, 1.2)[a,b]	15 (9.0)	2.0 (1.2, 3.4)	2.1 (1.2, 3.7)[a]
Minimum cigarettes / day									
1-14 / day	105 (15.8)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)[a]	68 (15.1)	1.0 (0.8, 1.3)	1.1 (0.9, 1.5)[a,b]	34 (20.4)	1.5 (1.0, 2.2)	1.6 (1.1, 2.4)[a,c]
≥15 / day	15 (2.3)	0.9 (0.5, 1.5)	0.8 (0.5, 1.5)[a]	6 (1.3)	0.5 (0.2, 1.1)	0.5 (0.2, 1.2)[a,b]	9 (5.4)	2.2 (1.1, 4.4)	1.9 (0.9, 4.1)[a,c]
Duration									
1 month	19 (2.9)	1.1 (0.7, 1.7)	1.1 (0.7, 1.8)[a]	14 (3.1)	1.1 (0.6, 1.9)	1.2 (0.7, 2.1)[a,b]	5 (3.0)	1.2 (0.5, 2.9)	1.3 (0.5, 3.2)[a]
2 months	31 (4.7)	1.2 (0.8, 1.8)	1.3 (0.9, 2.0)[a]	19 (4.2)	1.1 (0.7, 1.7)	1.2 (0.7, 1.9)[a,b]	10 (6.0)	1.7 (0.9, 3.2)	1.9 (1.0, 3.6)[a]
3 months	16 (2.4)	1.3 (0.8, 2.1)	1.4 (0.8, 2.3)[a]	10 (2.2)	1.1 (0.6, 2.1)	1.3 (0.7, 2.5)[a,b]	6 (3.6)	2.0 (0.9, 4.6)	2.2 (1.0, 5.1)[a]
4 months	55 (8.3)	0.9 (0.7, 1.3)	0.9 (0.7, 1.2)[a]	31 (6.9)	0.7 (0.5, 1.1)	0.8 (0.6, 1.2)[a,b]	23 (13.7)	1.7 (1.0, 2.6)	1.7 (1.0, 2.7)[a]

[a] Adjusted for calculated binge drinking 1 month before pregnancy through month 3 of pregnancy (≥4 drinks)
[b] Adjusted for NBDPS site
[c] Adjusted for first degree family history of diaphragmatic hernia

Table 10
Adjusted Odds Ratio Estimates for Infant Phenotype Associated with Maternal Reports of Alcohol Consumption, National Birth Defects Prevention Study, 1997-2011

	Isolated CDH (N = 254)			CDH Isolated NOS (N=156)				CDH Isolated Bochdalek (N=82)	
Exposure	N (%)	cOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)	aOR (95% CI)	aOR (95% CI)	N (%)	cOR (95% CI)
Any alcohol consumption									
No	415 (62.6)	Ref.	Ref.	297 (66.6)	Ref.	Ref.	104 (63.4)	Ref.	Ref.
Yes	221 (33.3)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)[a]	149 (33.4)	0.9 (0.7, 1.0)	0.9 (0.7, 1.1)[a]	60 (36.6)	1.0 (0.7, 1.4)	1.0 (0.8, 1.5)[a,b]
Average drinks / month									
1-15	177 (26.7)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)[a]	119 (26.7)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)[a]	49 (29.9)	1.0 (0.7, 1.4)	1.1 (0.8, 1.6)[a,b,c]
16-30	31 (4.7)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)[a]	22 (4.9)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)[a]	7 (4.3)	0.9 (0.4, 1.9)	0.8 (0.4, 1.1)[a,b,c]
>30	13 (2.0)	0.9 (0.5, 1.6)	0.9 (0.5, 1.5)[a]	8 (1.8)	0.8 (0.4, 1.6)	0.8 (0.4, 1.6)[a]	4 (2.4)	NC	NC
Maximum drinks/ month									
1-15	169 (25.5)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)[a]	114 (25.6)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)[a]	47 (28.7)	1.0 (0.7, 1.4)	1.1 (0.8, 1.5)[a,b,c]
16-30	37 (5.6)	1.1 (0.8, 1.5)	1.0 (0.7, 1.1)[a]	25 (5.6)	1.0 (0.7, 1.5)	1.0 (0.7, 1.6)[a]	9 (5.5)	1.0 (0.5, 2.1)	1.0 (0.5, 2.0)[a,b,c]
>30	15 (2.3)	0.8 (0.5, 1.4)	0.8 (0.5, 1.4)[a]	10 (2.2)	0.8 (0.4, 1.5)	0.8 (0.4, 1.6)[a]	4 (2.4)	NC	NC
Number of binges									
1 binge episode	22 (3.3)	0.7 (0.4, 1.0)	0.7 (0.4, 1.0)[a]	13 (3.8)	0.6 (0.3, 1.0)	0.6 (0.3, 1.0)[a]	9 (7.3)	1.1 (0.6, 2.2)	0.9 (0.5,)[a,b,c]
2-3 binge episodes	17 (2.6)	0.8 (0.5, 1.3)	0.8 (0.5, 1.3)[a]	15 (4.4)	1.0 (0.6, 1.7)	1.0 (0.6, 1.8)[a]	2 (1.6)	NC	NC
4 or more binge episodes	29 (4.4)	1.1 (0.8, 1.7)	1.1 (0.8, 1.7)[a]	18 (5.3)	1.0 (0.6, 1.6)	1.1 (0.6, 1.8)[a]	9 (7.3)	1.4 (0.7, 2.8)	1.13 (0.53, 2.39)[a,b,c]
Type(s) of alcohol									
Beer only	43 (6.5)	0.9 (0.7, 1.3)	0.9 (0.7, 1.3)[a]	27 (6.1)	0.8 (0.6, 1.2)	0.8 (0.6, 1.2)[a]	15 (9.2)	1.3 (0.8, 2.2)	1.32 (0.75, 2.34)[a,b]
Wine only	60 (9.1)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)[a]	47 (10.5)	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)[a]	11 (6.8)	0.6 (0.4, 1.2)	0.77 (0.41, 1.45)[a,b]
Liquor only	37 (5.6)	0.9 (0.6, 1.2)	0.9 (0.6, 1.2)[a]	20 (4.5)	0.7 (0.4, 1.0)	0.7 (0.4, 1.0)[a]	15 (9.2)	1.4 (0.8, 2.4)	1.35 (0.77, 2.36)[a,b]
2 or more	80 (12.1)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)[a]	55 (12.3)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)[a]	18 (11.0)	0.8 (0.5, 1.4)	0.91 (0.54, 1.53)[a,b]
Duration of alcohol consumption									
1 month	120 (18.1)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)[a]	77 (12.3)	0.78 (0.61, 1.01)	0.8 (0.6, 1.0)[a]	36 (22.0)	1.0 (0.7, 1.5)	1.12 (0.75, 1.65)[a,b]
2 months	73 (11.0)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)[a]	51 (11.4)	0.97 (0.72, 1.32)	1.0 (0.7, 1.4)[a]	18 (11.0)	1.0 (0.6, 1.6)	1.05 (0.62, 1.77)[a,b]
3 months	15 (2.3)	1.0 (0.6, 1.7)	1.0 (0.6, 1.7)[a]	11 (2.5)	1.02 (0.55, 1.88)	1.0 (0.6, 1.9)[a]	4 (2.4)	NC	NC
4 months	13 (2.0)	0.7 (0.4, 1.3)	0.7 (0.4, 1.3)[a]	10 (2.2)	0.77 (0.41, 1.46)	0.8 (0.4, 1.5)[a]	2 (1.2)	NC	NC

aOR, adjusted odds ratio; CDH, Congenital diaphragmatic hernia; CI, confidence interval; cOR, crude odds ratio, NC, not calculated; NOS, not otherwise stated.
[a] Adjusted for active and/or passive smoking 1 month before pregnancy through month 3 of pregnancy
[b] Adjusted for NBDPS site
[c] Adjusted for first degree family history of diaphragmatic hernia

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APPENDIX

Appendix 1. Computer assisted telephone interview questions on maternal cigarette smoking

SECTION E: TOBACCO-MOTHER

E1. The next questions are about tobacco use. Did you ever smoke cigarettes?

YES 1
NO ..... (SKIP TO E5) 2
DK ..... (SKIP TO E5) 8

E2. At any time from (-3) to (DOIB), did you smoke cigarettes?

YES 1
NO ..... (SKIP TO E5) 2
DK ..... (SKIP TO E5) 8

E3. During which months did you smoke?
CIRCLE FOR EACH MONTH. DO NOT CODE SHADED AREA.

MO	YES (ASK E4)	NO	DK	E4. During (SPECIFY MONTH) about how many cigarettes did you smoke a day?/Did you continue to smoke that many cigarettes through (LAST MONTH STATED)?
B3	1	2	8	<1/DAY ..... 01 1/DAY ..... 02 2-4/DAY ..... 03 ½ PACK (5-14) ..... 04 1 PACK(15-24) ..... 05 1 ½ PACK (25-34) ..... 06 2 PACK (35-44) ..... 07 >2 PACK ..... 08 DK 98
B2	1	2	8	<1/DAY ..... 01 1/DAY ..... 02 2-4/DAY ..... 03 ½ PACK (5-14) ..... 04 1 PACK(15-24) ..... 05 1 ½ PACK (25-34) ..... 06 2 PACK (35-44) ..... 07 >2 PACK ..... 08 DK 98
B1	1	2	8	<1/DAY ..... 01 1/DAY ..... 02 2-4/DAY ..... 03 ½ PACK (5-14) ..... 04 1 PACK(15-24) ..... 05 1 ½ PACK (25-34) ..... 06 2 PACK (35-44) ..... 07 >2 PACK ..... 08 DK 98
P1	1	2	8	<1/DAY ..... 01 1/DAY ..... 02 2-4/DAY ..... 03 ½ PACK (5-14) ..... 04 1 PACK(15-24) ..... 05 1 ½ PACK (25-34) ..... 06 2 PACK (35-44) ..... 07 >2 PACK ..... 08 DK 98
P2	1	2	8	<1/DAY ..... 01 1/DAY ..... 02 2-4/DAY ..... 03 ½ PACK (5-14) ..... 04 1 PACK(15-24) ..... 05 1 ½ PACK (25-34) ..... 06 2 PACK (35-44) ..... 07 >2 PACK ..... 08 DK 98

MO	YES (ASK E4)	NO	DK	E4. During (SPECIFY MONTH) about how many cigarettes did you smoke a day?/Did you continue to smoke that many cigarettes through (LAST MONTH STATED)?
P3	1	2	8	<1/DAY ..... 01 1/DAY ..... 02 2-4/DAY ..... 03 ½ PACK (5-14) ..... 04 1 PACK(15-24) ..... 05 1 ½ PACK (25-34) ..... 06 2 PACK (35-44) ..... 07 >2 PACK ..... 08 DK 98
T2	1	2	8	<1/DAY ..... 01 1/DAY ..... 02 2-4/DAY ..... 03 ½ PACK (5-14) ..... 04 1 PACK(15-24) ..... 05 1 ½ PACK (25-34) ..... 06 2 PACK (35-44) ..... 07 >2 PACK ..... 08 DK 98
T3	1	2	8	<1/DAY ..... 01 1/DAY ..... 02 2-4/DAY ..... 03 ½ PACK (5-14) ..... 04 1 PACK(15-24) ..... 05 1 ½ PACK (25-34) ..... 06 2 PACK (35-44) ..... 07 >2 PACK ..... 08 DK 98

E5. Did anyone in your household smoke cigarettes in your home between (-3) and (DOIB)?

YES 1
NO ..... (SKIP TO E7) 2
DK ..... (SKIP TO E7) 8

E6. During which months did someone smoke in your home? CIRCLE FOR EACH MONTH. DO NOT CODE SHADED AREA.

MO	YES	NO	DK
B3	1	2	8
B2	1	2	8
B1	1	2	8
P1	1	2	8
P2	1	2	8
P3	1	2	8
T2	1	2	8
T3	1	2	8

TOBACCO-WORKPLACE

E7. Did anyone smoke cigarettes near you at a workplace or school you may have attended during that year?

YES 1
NO ..... (SKIP TO F1) 2
DK ..... (SKIP TO F1) 8

E8. During which months from (-3) to (DOIB) did someone smoke near you at work/school? CIRCLE FOR EACH MONTH. DO NOT CODE SHADED AREA.

MO	YES	NO	DK
B3	1	2	8
B2	1	2	8
B1	1	2	8
P1	1	2	8
P2	1	2	8
P3	1	2	8
T2	1	2	8
T3	1	2	8

Appendix 2. Computer assisted telephone interview questions on maternal alcohol consumption

SECTION F: ALCOHOL

F1. Now I'm going to ask you some questions about drinking alcoholic beverages. We define an alcoholic drink as one beer, one glass of wine, one mixed drink, or one shot of liquor. Between (-3) and (DOIB), did you drink any wine, beer, mixed drinks or shots of liquor?

YES 1
NO ..... (SKIP TO G1) 2
DK ..... (SKIP TO G1) 8
RF ..... (SKIP TO G1) 7

MO	F2. During which months did you drink any alcoholic beverages? **CIRCLE FOR EACH MONTH. DO NOT CODE SHADED AREA.** YES (ASK F3-F5)	NO (NXT)	DK (NXT)	F3. In the (3rd/2nd/1st month before pregnancy, 1st/2nd/3rd...9th month of pregnancy), on average, how many **days** did you drink alcoholic beverages? (DK = 98) (RF = 97) # DAYS	F4. On those days that you drank alcoholic beverages, on average, how many drinks did you have per day? (DK = 98) (RF = 97) # DRINKS	F5. What was the greatest number of drinks you had on one occasion in (MONTH)? (DK = 98) (RF = 97) # DRINKS
B3	1	2	8	⌊⌋⌊⌋	⌊⌋⌊⌋	⌊⌋⌊⌋
B2	1	2	8	⌊⌋⌊⌋	⌊⌋⌊⌋	⌊⌋⌊⌋
B1	1	2	8	⌊⌋⌊⌋	⌊⌋⌊⌋	⌊⌋⌊⌋
P1	1	2	8	⌊⌋⌊⌋	⌊⌋⌊⌋	⌊⌋⌊⌋
P2	1	2	8	⌊⌋⌊⌋	⌊⌋⌊⌋	⌊⌋⌊⌋
P3	1	2	8	⌊⌋⌊⌋	⌊⌋⌊⌋	⌊⌋⌊⌋
T2	1	2	8	⌊⌋⌊⌋	⌊⌋⌊⌋	⌊⌋⌊⌋
T3	1	2	8	⌊⌋⌊⌋	⌊⌋⌊⌋	⌊⌋⌊⌋

F6. On the days that you drank alcohol, what type(s) of alcohol did you usually drink? READ CHOICES.

	YES	NO	RF	DK
a. Beer	1	2	7	8
b. Wine	1	2	7	8
c. Mixed drink	1	2	7	8
d. Shot liquor	1	2	7	8
e. Other alcohol	1	2	7	8

SPECIFY: _____