Received: 26 October 2021 | Revised: 15 April 2022 | Accepted: 6 May 2022

DOI: 10.1002/bdr2.2059

RESEARCH ARTICLE

Birth Defects Research | Society for Birth Defects Research & Prevention | WILEY

Maternal cigarette smoking and alcohol consumption and congenital diaphragmatic hernia

Julia Finn[1] | **Jonathan Suhl**[2] | **Vijaya Kancherla**[1] | **Kristin M. Conway**[2] | **Jacob Oleson**[3] | **Alpa Sidhu**[4] | **Eirini Nestoridi**[5] | **Sarah C. Fisher**[6] | **Sonja A. Rasmussen**[7] | **Wei Yang**[8] | **Paul A. Romitti**[2,3] | **the National Birth Defects Prevention Study**

[1]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

[2]Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, Iowa

[3]Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, Iowa

[4]Division of Medical Genetics and Genomics, Stead Family Department of Pediatrics, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA

[5]Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health, Boston, Massachusetts, USA

[6]Birth Defects Registry, New York State Department of Health, Albany, New York, USA

[7]Departments of Pediatrics, Obstetrics and Gynecology, and Epidemiology, College of Public Health and Health Professions, University of Florida College of Medicine, Gainesville, Florida, USA

[8]Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA

Correspondence
Paul A. Romitti, Department of Epidemiology, College of Public Health, University of Iowa, 145 N Riverside Dr, S416 CPHB, Iowa City, IA 52242, USA.
Email: paul-romitti@uiowa.edu

Funding information
Iowa Center for Birth Defects Research and Prevention, Grant/Award Numbers: U01 DD001223, U01 DD001035; Centers for Disease Control and Prevention, Grant/Award Numbers: NOFO #DD18-001, FOA #DD13-003, FOA #DD09-001, PA #02081, PA #96043

Abstract

Background: Congenital diaphragmatic hernia (CDH) occurs when abnormal diaphragm development allows herniation of abdominal organs into the thoracic cavity. Its etiopathogenesis is not well understood, but cigarette smoking and alcohol exposure may impact diaphragm development. Using data from a large, population-based case–control study, we examined associations between maternal cigarette smoking and alcohol consumption and CDH in offspring.

Methods: We analyzed maternal interview reports of cigarette smoking and alcohol consumption during early pregnancy for 831 children with CDH and 11,416 children without birth defects with estimated dates of delivery during 1997–2011. Generalized linear mixed effects models with a random intercept for study site were used to estimate associations between measures of exposure to smoking (any, type, frequency, duration) and alcohol (any, quantity, frequency, variability, type) for all CDH combined and selected subtypes (Bochdalek and Morgagni).

Results: Mothers of 280 (34.0%) case and 3,451 (30.3%) control children reported early pregnancy exposure to cigarette smoking. Adjusted odds ratios

Julia Finn and Jonathan Suhl contributed equally to this study.

for all CDH were increased for any (1.3; 95% confidence interval 1.1–1.5), active (1.3, 1.0–1.7), and passive (1.4, 1.1–1.7) smoking. Early pregnancy alcohol consumption was reported by mothers of 286 (34.9%) case and 4,200 (37.0%) control children; odds were near the null for any consumption (0.9, 0.8–1.1) and consumption with (0.9, 0.7, 1.1) or without (0.9, 0.8, 1.1) binging. Estimates for smoking and alcohol tended to be higher for Bochdalek CDH and Morgagni CDH than those for all CDH.

Conclusions: Findings suggest that maternal early pregnancy exposure to cigarette smoking, but less so to alcohol consumption, contributes to CDH. These findings need to be replicated in additional large studies that use systematic case ascertainment and classification, detailed exposure assessment, and examine subtype-specific associations.

KEYWORDS

alcohol, case–control, congenital diaphragmatic hernia, population-based, pregnancy, smoking

1 | INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a rare, severe birth defect in which abnormal closure of the diaphragm allows herniation of abdominal organs into the thoracic cavity, disrupting normal development of the lungs and heart (Kardon et al., 2017). CDH can present as a small opening of the posterior muscle rim or be as extensive as a complete absence of the diaphragm (reviewed in Chandrasekharan, Rawat, Madappa, Rothstein, & Lakshminrusimha, 2017). There are several subtypes of CDH, with the posterolateral Bochdalek hernia being the most common; others include the anterior Morgagni and central hernias (reviewed in Chandrasekharan et al., 2017). The estimated prevalence of CDH in the United States during 2010–2014 was 2.9 per 10,000 live births (Mai et al., 2019).

CDH may present with several health complications, including pulmonary hypoplasia and hypertension and cardiac dysfunction (reviewed in Chandrasekharan et al., 2017). Despite improvements in survival over the last several decades (Dott, Wong, & Rasmussen, 2003; Yang, Carmichael, Harris, & Shaw, 2006), CDH remains a highly fatal condition, with infant mortality estimates ranging from 30% to 50% (Balayla & Abenhaim, 2014; Dott et al., 2003; Ramakrishnan et al., 2018; Shanmugam, Brunelli, Botto, Krikov, & Feldkamp, 2017; Wang et al., 2015; Yang et al., 2006). Surviving children with CDH may require long-term care (Crankson, Al Jadaan, Namshan, Al-Rabeeah, & Oda, 2006), including pharmacotherapy, respiratory support, and multiple surgical interventions (Hollinger & Buchmiller, 2019).

Although variants in several genes have been associated with CDH (reviewed in Longoni, Pober, & High, 2019), its etiopathogenesis remains largely unknown. Associations observed between environmental (noninherited) exposures and CDH have been inconsistent, although the importance of retinol signaling in the development of the diaphragm (Clugston, Zhang, Alvarez, de Lera, & Greer, 2010; Goumy et al., 2010) suggests the potential for some exposures to influence hernia development. Specifically, cigarette smoking and alcohol consumption, two rather common exposures during pregnancy (England et al., 2020; Kondracki, 2019), have been shown to influence retinol signaling (Kardon et al., 2017; Limpach, Dalton, Miles, & Gadson, 2000; Manoli et al., 2012; Ozerol, Ozerol, Gokdeniz, Temel, & Akyol, 2004; Refsum, 2001). Most previous studies examining these exposures and CDH in offspring had several limitations, including lacking examination of associations for quantity, frequency, or duration of these exposures and associations of these exposures withCDH subtypes (Balayla & Abenhaim, 2014; Felix et al., 2008; García, Machicado, Gracia, & Zarante, 2016; Honein, Paulozzi, & Watkins, 2001; McAteer, Hecht, De Roos, & Goldin, 2014; Mesas Burgos, Ehrén, Conner, & Frenckner, 2019; Ramakrishnan et al., 2018; Schulz et al., 2021).

A previous analysis using data from the National Birth Defects Prevention Study (NBDPS) for children with estimated dates of delivery during 1997–2005 examined maternal exposure to cigarette smoking and alcohol consumption, including quantity, frequency, duration of exposure, during early pregnancy (defined as 1 month

before pregnancy [B1] through the third month of pregnancy [M3]), and CDH in offspring (Caspers et al., 2010). Several positive associations were observed for cigarette smoking and all children with CDH and specific CDH subtypes, whereas most associations for alcohol consumption were near the null. An additional NBDPS study examined exposure to passive cigarette smoking and a spectrum of birth defects among children delivered during 1997–2009 and reported positive associations for all CDH (Hoyt et al., 2016). Our current analyses takes advantage of the full NBDPS dataset (1997–2011), which adds several additional years of data for case and control children, to examine associations between maternal early pregnancy exposure to cigarette smoking and early pregnancy alcohol consumption for all CDH combined and selected CDH subtypes.

2 | METHODS

2.1 | NBDPS

The NBDPS was a multisite, population-based, case–control study conducted in the United States to examine genetic and environmental factors for more than 30 major structural birth defects as detailed elsewhere (Reefhuis et al., 2015). Briefly, the 10 NBDPS sites covered an annual birth population ranging from 35,000 to 80,000 births per year and included those with estimated dates of delivery (EDDs) during October 1, 1997 through December 31, 2011. Eligible case children were live births (all sites), fetal deaths at 20 weeks gestation or greater (six sites), and elective terminations (five sites). Control children were a random sample of unaffected live births randomly selected from hospital delivery logs or birth certificate files of deliveries that occurred during the same timeframe and within the same geographic catchment areas as case children. Approximately 100 control children were selected per year at each site.

A structured, computer-assisted telephone interview was conducted with birth mothers of case and control children from 6 weeks to 24 months following their EDDs to collect sociodemographic, medical and prenatal care, and environmental and lifestyle information, including information on cigarette smoking and alcohol consumption 3 months before and during pregnancy. The average time to interview was 11.7 months for case and 9.5 months for control mothers (Tinker et al., 2013). A case or control child not in the legal custody of or residing with their birth mother, whose mother did not speak English or Spanish, or whose mother participated in the NBDPS with a previous child was excluded. The NBDPS protocol was approved by the institutional review board at the US Centers for Disease Control and Prevention and each NBDPS site.

2.2 | Case ascertainment and classification

All NBDPS study sites contributed children diagnosed with CDH (British Pediatric Association codes: 756600, 756601, 756602, 756603, 756604, 756605, 756610, 756611, 756612, 756614, 756615, 756616, 756617, 756618, 756619). Clinical geneticists at each site followed standard case definitions in reviewing information abstracted from medical records to classify case children as isolated (no additional major, unrelated defects), multiple (one or more major, unrelated defects), or complex sequence (e.g., Pentalogy of Cantrell) (Rasmussen et al., 2003); those classified with monogenic or chromosomal etiologies were not eligible for the NBDPS. When sufficient diagnostic information was available, case children were further classified by CDH subtype (Bochdalek, Morgagni), laterality (unilateral, bilateral, unknown), and sidedness (left, right, unknown) of the hernia.

2.3 | Exposure assessment

2.3.1 | Cigarette smoking

Mothers were asked to report any exposure to cigarette smoking (active or passive) during the period 3 months before through the end of pregnancy. Mothers who reported any active smoking were asked to report the prepregnancy and pregnancy month(s) actively smoked (duration) and the number of cigarettes smoked/day (frequency categories: <1, 1, 2–4, 5–14 [one-half pack], 15–24 [one pack], 25–34 [one and one-half packs], 35–44 [two packs], and >45) in each month. Mothers who reported any exposure to passive smoking in the home or workplace were asked to report the prepregnancy and pregnancy month(s) during which exposure occurred.

In the current analysis, any (yes, no), type (no exposure, active exposure only, passive exposure only, active + passive exposure), frequency, and duration of smoking exposure were evaluated. Mothers were classified as exposed if maternal active and/or passive smoking was reported during B1-M3; exposures during the month before pregnancy may carry into pregnancy, and the first trimester is the critical developmental period for the diaphragm. Frequency of active smoking exposure was evaluated as no exposure, 1–14, and ≥15 cigarettes/day. To evaluate variability in the frequency of daily number of cigarettes smoked among active smokers,

minimum and maximum number of cigarettes smoked/day during B1-M3 were analyzed. Additionally, duration (no exposure, 1, 2, 3, or 4 months) of smoking exposure was evaluated as the maximum duration of reported active or passive smoking exposure.

2.3.2 | Alcohol consumption

Mothers were asked to report any alcohol consumption from 3 months before through the end of pregnancy. Mothers who reported alcohol consumption were asked to provide the average number of days/month that they drank alcoholic beverages, the average number of drinks consumed/day, and the greatest number of drinks consumed in each drinking month.

Maternal alcohol consumption was classified as any (yes, no) and in terms of quantity (average number of drinks per month), frequency, duration, variability of exposure, and type of exposure, using previously described methods (Romitti et al., 2007). Briefly, mothers were classified as exposed to alcohol if any consumption was reported during B1-M3. Quantity of alcohol consumption was calculated by dividing the reported number of drinks in each drinking month (B1, M1, M2, M3) by the duration of reported drinking months (1–4) The highest reported number of drinks was used to calculate maximum average. Duration of alcohol consumption was evaluated as no alcohol consumption, 1, 2, 3, or 4 months. Alcohol consumption with binge drinking was evaluated using the female-specific criteria of ≥4 drinks per day on average or on one occasion (Wechsler, Dowdall, Davenport, & Rimm, 1995) and classified as no alcohol consumption, alcohol consumption without a binge episode, and alcohol consumption with ≥1 binge episodes. Additionally, the number of binge drinking episodes was evaluated as no alcohol consumption, 1 binge episode, 2–3 binge episodes, ≥4 binge episodes during B1-M3. Mothers were also classified by the type of alcohol consumed (beer only, wine only, distilled spirits [mixed drink, shot liquor] only, or any combination of ≥2 types of alcohol).

2.4 | Covariates

Several child and maternal characteristics and exposures shown in previous studies to be positively associated with major birth defects were evaluated as covariates. Child characteristics were sex (male, female), family history of first-degree relative with CDH (yes, no), and plurality (1, >1). Maternal characteristics were age (<21, 21–25, 26–30, 31–35, >35 years) and education (<12, 12, 13–15, ≥16 years) at delivery, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), gravidity (0, 1, ≥2), prepregnancy body mass index (underweight: <18.5, normal weight: 18.5–24.9, overweight: 25–29.9, obese: ≥30 kg/m^2), prepregnancy dietary folate equivalents (<600, ≥600 μg/day), use of folic acid supplements (yes, no) or vitamin A supplements (yes, no) during B1-M3, and study site (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, CDC Atlanta, North Carolina, Utah).

2.5 | Analytical sample

Mothers of 883 CDH case and 11,829 control children participated in the NBDPS. Among CDH case children, 10 children with complex sequence (Pentalogy of Cantrell), 2 classified with both Bochdalek and Morgagni CDH, and 2 classified with a paraesophageal hernia were excluded from analyses. Among case and control children, 16 case and 87 control mothers were excluded due to reporting pregestational diabetes, as diabetes is associated with several birth defects (Correa et al., 2008; Tinker et al., 2020). Additionally, mothers of 22 CDH case and 326 control children did not respond to interview gateway questions about active smoking ("From 3 months before you became pregnant to the end of your pregnancy, did you smoke cigarettes?"), household ("Did anyone in your household smoke cigarettes in your home between 3 months before you became pregnant to the end of your pregnancy?") and workplace ("Did anyone smoke cigarettes near you at a workplace or school you may have attended during that year?") passive smoking, and alcohol consumption ("From 3 months before you became pregnant to the end of your pregnancy, did you drink any wine, beer, mixed drinks or shots of liquor?") and were excluded. Following exclusions, 831 case and 11,416 control children with EDDs during 1997–2011 were eligible for analysis.

2.6 | Statistical analysis

Prior to conducting our primary analyses, we compared child and maternal characteristics for all CDH case and control children in the datasets available (EDDs during 1997–2005) and not available (EDDs during 2006–2011) for the previous NBDPS analysis of cigarette smoking and alcohol consumption and CDH (Caspers et al., 2010) using a noninferiority design. We established a priori that a 5% difference between the two datasets as a meaningful difference in proportions. For each category of a child or maternal characteristic, a 95% one-sided confidence interval (CI) was computed for the absolute value of the

difference in proportions between the two time periods; if the lower bound of a CI exceeded 5% for any category of a characteristic, that characteristic was forced into all multivariable models using the entire NBDPS dataset. Our analyses suggested that only the difference in distribution for study site between the two datasets exceeded our threshold (data not shown); thus, we used a random intercept for study site in all multivariable models.

2.6.1 | Primary analyses

Using the full NBDPS dataset (EDDs during 1997–2011), we estimated frequencies and proportions for selected child and maternal characteristics and smoking exposure and alcohol consumption. Adjusted odds ratios (aORs) and 95% CIs were estimated for each smoking and alcohol variable and all CDH and CDH subtypes using a generalized linear mixed effects model, including a random intercept for study site to account for potential clustering. aORs were estimated for each smoking or alcohol variable when at least five case mothers were classified as exposed. Multivariable models were constructed using a change-in-estimate procedure. Each covariate was entered individually into a model containing the exposure of interest, and those that altered the main effect by >10% were retained in the final model for that exposure-outcome pair. Additionally, for all smoking analyses, an alcohol exposure variable (no alcohol consumption, alcohol consumption without a binge episode, alcohol consumption with ≥1 binge episodes) was included as a covariate in the final model. Similarly, for all alcohol analyses, a smoking variable (no smoking, active smoking only, passive smoking only, active + passive smoking) was included in the final model. Children or mothers with missing data for one or more covariates were removed from adjusted analysis.

2.6.2 | Secondary analyses

Our secondary analyses examined associations for children with isolated CDH only, as those with co-occurring major birth defects may exhibit developmental heterogeneity. We also examined interaction on an additive scale between any smoking exposure and any alcohol consumption as well as type of smoking exposure (no smoking, active smoking only, passive smoking only, active + passive smoking) and alcohol consumption (no alcohol consumption, alcohol consumption without a binge episode, alcohol consumption with ≥1 binge episodes). To assess interaction, we estimated relative excess risk due to interaction (RERI) and corresponding 95% CIs (Knol, van der Tweel, Grobbee, Numans, & Geerlings, 2007). An RERI estimate of 0 indicates no excess risk due to interaction; a 95% CI which excluded 0 was considered to support interaction between smoking and alcohol exposures. All analyses were conducted using SAS Software (version 9.4, SAS Institute Inc.).

3 | RESULTS

Table 1 lists the distribution of selected characteristics of CDH case and control children and their mothers. For all CDH combined, case children most often presented with an isolated defect and were male; case and control distributions for other child characteristics were similar. Mothers of all CDH children combined and control children tended to: be between 21 and 35 years of age and had at least 13 years of education at delivery; identify as non-Hispanic White; and report a gravidity ≥2, a normal prepregnancy weight, and folic acid supplementation during early pregnancy. Case and control mothers infrequently reported prepregnancy intake of 600 μg/day or greater of dietary folate equivalents or vitamin A supplementation during early pregnancy. A similar pattern of child and maternal characteristics was observed for each CDH subtype. Overall, percentages of missing data for child and maternal covariates ranged from 0.0% to 4.1% for controls and 0.0%–4.7% for cases.

Mothers of 280 (34.0%) CDH case children and 3,451 (30.3%) control children reported early pregnancy exposure to any cigarette smoking, producing an aOR of 1.3 (95% CI: 1.1–1.5) for all CDH combined (Table 2). Positive associations (aORs ≥1.2) were also observed for active smoking only and passive smoking only with the CI for passive smoking excluding the null. Additionally, positive associations were observed for reports of smoking 1–14 cigarettes/day or selected durations of exposure (1, 3, or 4 months) with some 95% CIs that excluded the null; however, we did not observe patterns that would suggest a dose–response relationship. Most estimates for Bochdalek CDH were increased compared to all CDH; 95% CIs for any cigarette smoking and durations of exposure of 1 or 4 months excluded the null. The small number of associations estimated for Morgagni CDH were positive but imprecise.

Early pregnancy alcohol consumption was reported by mothers of 286 (34.9%) CDH case children and 4,200 (37.0%) control children, producing an aOR of 0.9 (95% CI: 0.8–1.1) for all CDH combined (Table 3). Associations for drinks per month, duration, and type of consumption or alcohol were near ($0.9 \leq$ aOR ≥ 1.1) or below (aOR < 0.9) unity with 95% CIs that included the null. Those for number of binge drinking episodes increased

TABLE 1 Distribution of selected characteristics of congenital diaphragmatic hernia case and control children and mothers, National Birth Defects Prevention Study, 1997–2011

	Controls	All CDH	Bochdalek CDH	Morgagni CDH
	(*N* = 11,416)	(*N* = 831)	(*N* = 203)	(*N* = 35)
Characteristics	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Child				
Phenotype				
Isolated	—	644 (77.5)	167 (82.3)	25 (71.4)
Multiple	—	187 (22.5)	36 (17.7)	10 (28.6)
Sex				
Female	5,594 (49.0)	339 (40.8)	81 (39.9)	8 (22.9)
Male	5,812 (51.0)	491(59.1)	122 (60.1)	27 (77.1)
Missing	10	1	0	0
First degree family history of CDH				
Yes	3 (0.0)	6 (0.7)	3 (1.5)	0 (0.0)
No	11,413 (100.0)	825 (99.3)	200 (98.5)	35 (100.0)
Missing	0	0	0	0
Plurality				
1	11,075 (97.0)	791 (95.2)	197 (97.0)	30 (85.7)
>1	341 (3.0)	40 (4.8)	6 (3.0)	5 (14.3)
Missing	0	0	0	0
Mother				
Age at delivery (years)				
<21	1,554 (13.6)	101 (12.2)	21 (10.3)	4 (11.4)
21–25	2,714 (23.8)	218 (26.2)	58 (28.6)	7 (20.0)
26–30	3,258 (28.5)	217 (26.1)	52 (25.6)	6 (17.1)
31–35	2,699 (23.6)	195 (23.5)	45 (22.2)	11 (31.4)
>35	1,191 (10.4)	100 (12.0)	27 (13.3)	7 (20.0)
Missing	0	0	0	0
Education (years)				
<12	1,882 (16.6)	140 (17.0)	30 (14.9)	5 (14.3)
12	2,697 (23.7)	184 (22.3)	47 (23.4)	5 (14.3)
13–15	3,045 (26.8)	226 (27.4)	66 (32.8)	9 (25.7)
≥16	3,748 (33.0)	279 (33.4)	58 (28.9)	16 (45.7)
Missing	44	5	2	0
Race and ethnicity				
Non-Hispanic white	6,669 (58.4)	486 (58.5)	132 (65.0)	21 (60.0)
Non-Hispanic black	1,240 (10.9)	66 (7.9)	12 (5.9)	4 (11.4)
Hispanic	2,759 (24.2)	211 (25.4)	43 (21.2)	6 (17.1)
Other	746 (6.5)	68 (8.2)	16 (7.9)	4 (11.4)
Missing	2	0	0	0
Gravidity				
0	3,378 (29.6)	275 (33.1)	63 (31.0)	10 (28.6)
1	3,266 (28.6)	207 (24.9)	52 (25.6)	12 (34.3)
≥2	4,770 (41.8)	349 (42.0)	88 (43.4)	13 (37.1)
Missing	2	0	0	0

(Continues)

TABLE 1 (Continued)

	Controls (*N* = 11,416)	All CDH (*N* = 831)	Bochdalek CDH (*N* = 203)	Morgagni CDH (*N* = 35)
Pre-pregnancy BMI (kg/m^2)				
Underweight (<18.5)	587 (5.4)	33 (4.2)	11 (5.6)	2 (6.3)
Normal weight (18.5–24.9)	5,890 (53.8)	431 (54.4)	107 (54.3)	19 (59.4)
Overweight (25.0–29.9)	2,486 (22.7)	175 (22.1)	45 (22.8)	7 (21.9)
Obese (>30)	1,984 (18.1)	153 (19.3)	34 (17.3)	4 (12.5)
Missing	469	39	6	3
Pre-pregnancy dietary folate equivalents (μg/day)				
<600	7,993 (70.1)	614 (73.9)	152 (74.9)	25 (71.4)
≥600	3,414 (29.9)	217 (26.1)	51 (25.1)	10 (28.6)
Missing	9	0	0	0
Folic acid supplementation[a]				
Yes	9,898 (87.8)	727 (88.9)	177 (87.6)	30 (88.2)
No	1,377 (12.2)	91 (11.1)	25 (12.4)	4 (11.8)
Missing	141	13	1	1
Vitamin A supplementation[a]				
Yes	5,272 (47.3)	365 (44.8)	87 (43.7)	19 (55.9)
No	5,875 (52.7)	450 (55.2)	112 (56.3)	15 (44.1)
Missing	269	16	4	1
Study site				
Arkansas	1,436 (12.6)	96 (11.6)	43 (21.2)	3 (8.3)
California	1,228 (10.8)	117 (14.1)	22 (10.8)	5 (14.3)
Iowa	1,269 (11.1)	70 (8.4)	20 (9.9)	3 (8.6)
Massachusetts	1,380 (12.1)	112 (13.5)	18 (8.9)	12 (34.3)
New Jersey	571 (5.0)	40 (4.8)	1 (0.5)	1 (2.9)
New York	953 (8.4)	52 (6.3)	12 (5.9)	3 (8.6)
Texas	1,298 (11.4)	88 (10.6)	21 (10.3)	0 (0.0)
CDC Atlanta	1,221 (10.7)	110 (13.2)	18 (8.9)	4 (11.4)
North Carolina	960 (8.4)	58 (7.0)	17 (8.4)	2 (5.7)
Utah	1,100 (9.6)	88 (10.6)	31 (15.3)	2 (5.7)

Note: Due to rounding, percentages may not total 100.

Abbreviations: BMI, body mass index; CDC, US Centers for Disease Control and Prevention; CDH, congenital diaphragmatic hernia.

[a]During early pregnancy (1 month before through the third month of pregnancy).

with increasing number of episodes, although only the association for the highest number of episodes (4 or more) was positive, and all 95% CIs included the null. Compared to the associations for all CDH combined, those for Bochdalek CDH tended to be similar or increased, with the associations for number of binge drinking episodes not increasing with an increasing number of episodes. Where data were available, associations for Morgani CDH were similar or increased compared to those for all CDH combined.

Findings for maternal early pregnancy exposure to cigarette smoking or early pregnancy alcohol consumption restricted to children with isolated CDH tended to be similar to those that included children with isolated and multiple CDH (Tables S1, S2). Interaction analyses did not support the presence of additive interaction between any smoking exposure and any alcohol consumption (RERI: 0.1, 95% CI: −0.3, 0.4) or between type of smoking exposure and alcohol consumption (Table S3).

TABLE 2 Adjusted odds ratio estimates and 95% confidence intervals for associations between maternal early pregnancy exposure to cigarette smoking and congenital diaphragmatic hernia, National Birth Defects Prevention Study, 1997-2011

	Controls (N=11,416)	All CDH (N = 831)		Bochdalek CDH (N = 203)		Morgagni CDH (N = 35)	
Cigarette Smoking	**N (%)**	**N (%)**	**aOR (95% CI)**	**N (%)**	**aOR (95% CI)**	**N (%)**	**aOR (95% CI)**
Any exposure[a,b]							
No	7,930 (69.7)	543 (66.0)	Ref.	120 (59.7)	Ref.	24 (70.6)	Ref.
Yes	3,451 (30.3)	280 (34.0)	1.3 (1.1, 1.5)	81 (40.3)	1.5 (1.1, 2.1)	10 (29.4)	1.3 (0.6, 3.1)[c]
Type of exposure[a,d]							
Active only	863 (7.6)	74 (9.0)	1.3 (1.0, 1.7)	22 (11.0)	1.6 (1.0, 2.6)	0 (0.0)	NC
Passive only	1,410 (12.4)	127 (15.4)	1.4 (1.1, 1.7)	31 (15.4)	1.5 (1.0, 2.2)	6 (17.7)	2.2 (0.8, 5.7)[c]
Active + passive	1,174 (10.3)	79 (9.6)	1.0 (0.8, 1.4)	28 (13.9)	1.6 (1.0, 2.5)	4 (11.8)	NC
Active smoking maximum cigarettes/day[a,e,f]							
1-14	1,453 (14.6)	114 (16.4)	1.2 (0.9, 1.5)	33 (19.5)	1.4 (1.0, 2.2)[g]	3 (10.7)	NC
≥15	570 (5.7)	38 (5.5)	1.0 (0.7, 1.5)	16 (9.5)	1.7 (0.9, 2.9)[g]	1 (3.6)	NC
Active smoking minimum cigarettes/day[a,e,f]							
1-14	1,713 (17.2)	132 (19.0)	1.2 (1.0, 1.5)	39 (23.1)	1.5 (1.0, 2.2)[h]	4 (14.3)	NC
≥15	310 (3.1)	20 (2.9)	1.0 (0.6, 1.6)	10 (5.9)	1.6 (0.8, 3.4)[h]	0 (0.0)	NC
Duration of exposure (months)[a,d]							
1	356 (3.1)	36 (4.4)	1.6 (1.1, 2.2)	11 (5.5)	2.0 (1.1, 3.9)[i]	1 (2.9)	NC
2	409 (3.6)	28 (3.4)	1.0 (0.7, 1.5)	6 (3.0)	1.0 (0.4, 2.3)[i]	0 (0.0)	NC
3	227 (2.0)	23 (2.8)	1.6 (1.1, 2.6)	5 (2.5)	1.2 (0.4, 3.2)[i]	1 (2.9)	NC
4	2,455 (21.6)	193 (23.5)	1.2 (1.0, 1.4)	59 (29.4)	1.6 (1.2, 2.3)[i]	8 (23.5)	1.5 (0.6, 4.0)[c]

aOR, adjusted odds ratio; CDH, congenital diaphragmatic hernia; CI, confidence interval; NC, not calculated; Ref, reference.
Early pregnancy refers to one month before pregnancy through the third month of pregnancy.
[a]All estimates are adjusted for early pregnancy alcohol consumption, and study site is entered as a random intercept.
[b]Missing: controls = 35, all CDH = 8, Bochdalek CDH = 2, Morgagni CDH = 1.
[c]Also adjusted for maternal age and education at delivery, and pre-pregnancy body mass index.
[d]Missing: controls = 39, all CDH = 8, Bochdalek CDH = 2, Morgagni CDH = 1.
[e]Missing among mothers with active or active + passive smoking exposure: controls = 16, all CDH = 1, Bochdalek CDH = 1, Morgagni CDH = 0.
[f]Mothers who reported passive smoking only are not included in cigarettes/day analyses; thus, proportions for the referent category differ from those presented in the table: controls = 7,930 (79.7%), all CDH = 543 (78.1%), Bochdalek CDH = 120 (71.0%), Morgagni CDH = 24 (85.7%).
[g]Also adjusted for maternal race/ethnicity.
[h]Also adjusted for 1st degree family history of CDH and maternal race/ethnicity.
[i]Also adjusted for pre-pregnancy body mass index.

4 | DISCUSSION

Our study updated a previous NBDPS analysis of maternal early pregnancy exposure to cigarette smoking and early pregnancy alcohol consumption and CDH (Caspers et al., 2010) by including data from several additional study years. Positive associations were observed for any, type, frequency, and duration of exposure to cigarette smoking and all CDH combined or CDH subtypes, with several 95% CIs excluding the null. Associations for

TABLE 3 Adjusted odds ratio estimates for associations between maternal early pregnancy alcohol consumption and congenital diaphragmatic hernia, National Birth Defects Prevention Study, 1997-2011

	Controls (N=11,416)	All CDH (N = 831)		Bochdalek CDH (N = 203)		Morgagni CDH (N = 35)	
Alcohol Consumption	**N (%)**	**N (%)**	**aOR (95% CI)**	**N (%)**	**aOR (95% CI)**	**N (%)**	**aOR (95% CI)**
Any consumption[a,b]							
No	7,142 (63.0)	533 (65.1)	Ref.	123 (61.5)	Ref.	20 (58.8)	Ref.
Yes	4,200 (37.0)	286 (34.9)	0.9 (0.8, 1.1)	77 (38.5)	1.1 (0.8, 1.5)	14 (41.2)	1.2 (0.6, 2.4)
Average drinks/month[a,c]							
1-15	3,326 (29.5)	232 (28.4)	0.9 (0.8, 1.1)	64 (32.0)	1.1 (0.8, 1.6)[d]	10 (29.4)	1.0 (0.5, 2.3)
16-30	550 (4.9)	35 (4.3)	0.8 (0.6, 1.2)	8 (4.0)	0.8 (0.4, 1.6)[d]	2 (5.9)	NC
>30	253 (2.2)	18 (2.2)	0.9 (0.6, 1.5)	5 (2.5)	0.9 (0.3, 2.3)[d]	2 (5.9)	NC
Maximum average drinks/month[a,c]							
1-15	3,219 (28.6)	218 (26.7)	0.9 (0.8, 1.1)	59 (29.5)	1.1 (0.8, 1.5)[d]	9 (26.5)	1.1 (0.5, 2.5)[e]
16-30	598 (5.3)	47 (5.8)	1.0 (0.7, 1.4)	13 (6.5)	1.2 (0.7, 2.2)[d]	3 (8.8)	NC
>30	312 (2.8)	20 (2.4)	0.8 (0.5, 1.4)	5 (2.5)	0.7 (0.3, 1.9)[d]	2 (5.9)	NC
Duration of consumption (months)[a,b]							
1	2,368 (20.9)	149 (18.2)	0.8 (0.7, 1.0)	41 (20.5)	1.0 (0.7, 1.5)	8 (23.5)	1.3 (0.5, 3.2)[f]
2	1,260 (11.1)	97 (11.8)	1.0 (0.8, 1.3)	26 (13.0)	1.2 (0.8, 1.9)	5 (14.7)	1.5 (0.6, 4.7)[f]
3	260 (2.3)	21 (2.6)	1.1 (0.7, 1.7)	5 (2.5)	1.1 (0.4, 2.7)	0 (0.0)	NC
4	312 (2.8)	19 (2.3)	0.8 (0.5, 1.3)	5 (2.5)	1.0 (0.4, 2.4)	1 (2.9)	NC
Type of consumption[a,g]							
Consumption without a binge episode	2,761 (24.5)	194 (23.7)	0.9 (0.8, 1.1)	50 (25.0)	1.1 (0.8, 1.6)	11 (32.4)	1.2 (0.6, 2.8)
Consumption with ≥1 binge episodes	1,388 (12.3)	91 (11.1)	0.9 (0.7, 1.1)	27 (13.5)	1.0 (0.7, 1.6)	3 (8.8)	NC
Number of binge drinking episodes[a,h,i]							
1	565 (6.6)	26 (4.2)	0.6 (0.4, 0.9)[j]	11 (7.3)	1.1 (0.6, 2.0)[k]	0 (0.0)	NC
2-3	366 (4.3)	25 (4.0)	0.8 (0.5, 1.3)[j]	5 (3.3)	0.4 (0.1, 1.4)[k]	0 (0.0)	NC
≥4	442 (5.2)	40 (6.4)	1.3 (0.9, 1.8)[j]	11 (7.3)	1.2 (0.6, 2.3)[k]	3 (13.0)	NC
Type(s) of alcohol[a,l]							
Beer only	793 (7.0)	56 (6.9)	0.9 (0.7, 1.3)	17 (8.5)	1.2 (0.7, 2.1)	0 (0.0)	NC
Wine only	1,182 (10.4)	77 (9.4)	0.9 (0.7, 1.1)	17 (8.5)	0.9 (0.6, 1.6)	3 (8.8)	NC

TABLE 3 (Continued)

	Controls (N=11,416)	All CDH (N = 831)		Bochdalek CDH (N = 203)		Morgagni CDH (N = 35)	
Alcohol Consumption	N (%)	N (%)	aOR (95% CI)	N (%)	aOR (95% CI)	N (%)	aOR (95% CI)
Liquor only	743 (6.6)	48 (5.9)	0.9 (0.6, 1.2)	19 (9.6)	1.4 (0.8, 2.3)	3 (8.8)	NC
2 or more	1,469 (13.0)	103 (12.6)	0.9 (0.7, 1.2)	23 (11.6)	0.9 (0.6, 1.5)	8 (23.5)	1.8 (0.8, 4.4)[m]

aOR, adjusted odds ratio; CDH, congenital diaphragmatic hernia; CI, confidence interval; NC, not calculated; Ref, reference.
Early pregnancy refers to one month before pregnancy through the third month of pregnancy.
[a]All estimates are adjusted for maternal early pregnancy smoking exposure, and study site is entered as a random intercept.
[b]Missing: controls = 74, all CDH = 12, Bochdalek CDH = 3, Morgagni CDH = 1.
[c]Missing: controls = 145, all CDH = 13, Bochdalek CDH = 3, Morgagni CDH = 1.
[d]Also adjusted for 1st degree history of CDH.
[e]Also adjusted for pre-pregnancy body mass index.
[f]Also adjusted for pre-pregnancy body mass index and early pregnancy vitamin a supplementation.
[g]Missing: controls = 125, all CDH = 13, Bochdalek CDH = 3, Morgagni CDH = 1.
[h]Mothers with no reported binge episodes are not included in number of binge episode analyses; thus, proportions for the referent category differ from those presented in the table: controls = 7,142 (83.9%), all CDH = 533 (85.4%), Bochdalek CDH = 123 (82.0%), Morgagni CDH = 20 (87.0%).
[i]Missing: controls = 2901, all CDH = 207, Bochdalek CDH = 53, Morgagni CDH = 12.
[j]Also adjusted for maternal early pregnancy folic acid supplementation.
[k]Also adjusted for pre-pregnancy body mass index, and early pregnancy folic acid supplementation and vitamin a supplementation.
[l]Missing: controls = 87, all CDH = 14, Bochdalek CDH = 4, Morgagni CDH = 1.
[m]Also adjusted for maternal race/ethnicity and maternal education at delivery.

alcohol consumption were most often near the null with 95% CIs that included the null. The results of secondary analyses examining isolated cases only tended to support the results of the main analyses. Our findings using the full NBDPS dataset (1997–2011) tended to support those reported using the earlier version of the dataset (1997–2005) (Caspers et al., 2010).

The positive associations that we observed for any maternal early pregnancy exposure to cigarette smoking and all CDH were similar to some (Balayla & Abenhaim, 2014; Honein et al., 2001; McAteer et al., 2014), but not other (García et al., 2016; Ramakrishnan et al., 2018; Schulz et al., 2021) previous studies. Although frequency categories of number of cigarettes smoked were not directly comparable, our observation of a decreasing association with increasing number of cigarettes smoked per day for all CDH combined differed from the positive associations reported for smoking 6–10, 11–20, and ≥21 cigarettes/day (Honein et al., 2001) and associations near the null for smoking 1–9 or ≥10 cigarettes/day (Mesas Burgos et al., 2019). Our observation of a positive association between maternal exposure to passive cigarette smoking was consistent with that reported in a previous NBDPS analysis of passive smoking and a spectrum of birth defects that used an earlier version of the NBDPS dataset (1997–2009) (Hoyt et al., 2016). With regard to CDH subtypes, the positive associations that we observed for active smoking only and passive smoking only and Bochdalek CDH differed from an inverse association reported for active smoking, but was consistent with a positive association reported for passive smoking in the lone previous study that examined Bochdalek CDH (Felix et al., 2008); associations that we observed for Morgani CDH were not directly comparable to previous studies.

Associations near or below the null observed between maternal early pregnancy alcohol consumption and CDH in our study differed from the positive associations reported with any alcohol exposure in several previous studies (Balayla & Abenhaim, 2014; Felix et al., 2008; García et al., 2016; McAteer et al., 2014; Schulz et al., 2021). Only one of these studies examined Bochdalek CDH and reported strong positive associations (OR ≥ 2) for any consumption and frequency of consumption (Felix et al., 2008), which differed from our findings of no association for any alcohol consumption and only positive associations for average or maximum consumption of 1–15 drinks/month and maximum consumption of 16–30 drinks/month. No previous studies examined associations between early pregnancy alcohol consumption and other CDH subtypes. Differences in associations between our study and previous non-NBDPS studies may be due to a threshold effect for alcohol exposure, as few mothers reported high levels of alcohol consumption in our study.

Our study has several limitations. The NBDPS included live births, fetal deaths, and elective terminations diagnosed with CDH, but early spontaneous pregnancy losses (prior to 20 weeks gestation) with CDH were not included. Also, subtype analysis was limited

due to lack of clinical certainty in data available for clinical classification. The detailed information on maternal cigarette smoking and alcohol consumption collected in NBDPS allowed for the most comprehensive assessment of these exposures and CDH to date but was based on maternal retrospective self-reports; however, a previous study observed no significant differences in prospective and retrospective reports of smoking and alcohol exposure between case and control mothers (Verkerk, Buitendijk, & Verloove-Vanhorick, 1994). Also, a study from one NBDPS site (2003–2007) that compared maternal interview responses for maternal smoking with birth certificate data and medical record data observed that smoking reported from interview data was of higher quality with less misclassification compared to data obtained from medical records or birth certificates (Srisukhumbowornchai, Krikov, & Feldkamp, 2012). The social stigma that may be associated with reporting cigarette smoking and alcohol consumption during pregnancy may have produced underreporting of these exposures, although we believe that this limitation was minimized given that the proportion of mothers who reported any early pregnancy exposure to cigarette smoking or alcohol consumption in our study exceeded some national estimates (Denny, Acero, Naimi, & Kim, 2019; Drake, Driscoll, & Mathews, 2018). Another limitation of our study was that NBDPS interview questions about drink volume were not defined in terms of standard drinks, but rather as a "glass" of alcohol, which may result in inaccurate estimates of actual amount consumed. In addition to the limitations with data collected for cigarette smoking and alcohol consumption, there remains the possibility of unmeasured confounding that may have impacted our results. Lastly, small case numbers for some exposure measures and for Morgagni CDH produced imprecise associations.

Despite these limitations, our study was strengthened by using the large, multisite population-based sample provided by the NBDPS. A previous analysis showed that several characteristics of NBDPS control mothers were similar to those of mothers of all live births delivered in the NBDPS catchment areas, helping to reduce selection bias (Cogswell et al., 2009). Also, inclusion of live births, fetal deaths, and elective terminations diagnosed with CDH and identified from the population-based birth defect surveillance program at each NBDPS site, along with standardized case review by site clinical geneticists, decreased the likelihood of underreporting of case children. Furthermore, the large NBDPS sample, case ascertainment and classification approaches, and detailed NBDPS interview allowed us to examine more homogeneous groups of CDH case children, including subtypes and isolated case children, as well as to examine cigarette smoking and alcohol consumption in the absence of other teratogenic exposures, such as excluding mothers with prepregnancy diabetes.

In conclusion, our study examined associations between maternal early pregnancy exposure to cigarette smoking and early pregnancy alcohol consumption and CDH. Several positive associations were observed for smoking and all CDH combined and the CDH subtypes examined, although most CIs included the null. Many associations estimated for alcohol consumption were near the null. Although our study represents the most comprehensive examination of maternal smoking and alcohol consumption and CDH to date, the results need to be replicated in additional large studies that use systematic case ascertainment and classification, detailed exposure assessment, and examine subtype-specific associations. Additional efforts should also examine pathways that contribute to the effect of smoking on CDH.

ACKNOWLEDGMENT

Open access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

This work was funded by the Centers for Disease Control and Prevention cooperative agreements under PA #96043, PA #02081, FOA #DD09-001, FOA #DD13-003, and NOFO #DD18-001 to the Centers for Birth Defects Research and Prevention participating in the NBDPS and/or the Birth Defects Study To Evaluate Pregnancy exposureS (BD-STEPS), and grants (U01 DD001035 and U01 DD001223) awarded to the Iowa Center for Birth Defects Research and Prevention.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Vijaya Kancherla https://orcid.org/0000-0002-2803-8030
Kristin M. Conway https://orcid.org/0000-0001-8633-966X
Sarah C. Fisher https://orcid.org/0000-0002-4702-1007
Sonja A. Rasmussen https://orcid.org/0000-0002-0574-4928
Paul A. Romitti https://orcid.org/0000-0001-5393-9984

REFERENCES

Balayla, J., & Abenhaim, H. A. (2014). Incidence, predictors and outcomes of congenital diaphragmatic hernia: a population-based study of 32 million births in the United States. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *27*(14), 1438–1444. https://doi.org/10.3109/14767058.2013.858691

Caspers, K. M., Oltean, C., Romitti, P. A., Sun, L., Pober, B. R., Rasmussen, S. A., ... Druschel, C. (2010). Maternal periconceptional exposure to cigarette smoking and alcohol consumption and congenital diaphragmatic hernia. *Birth Defects Research Part A: Clinical and Molecular Teratology*, *88*(12), 1040–1049. https://doi.org/10.1002/bdra.20716

Chandrasekharan, P. K., Rawat, M., Madappa, R., Rothstein, D. H., & Lakshminrusimha, S. (2017). Congenital Diaphragmatic hernia - A review. *Maternal Health, Neonatology and Perinatology*, *3*, 6. https://doi.org/10.1186/s40748-017-0045-1

Clugston, R. D., Zhang, W., Alvarez, S., de Lera, A. R., & Greer, J. J. (2010). Understanding abnormal retinoid signaling as a causative mechanism in congenital diaphragmatic hernia. *American Journal of Respiratory Cell and Molecular Biology*, *42*(3), 276–285. https://doi.org/10.1165/rcmb.2009-0076OC

Cogswell, M. E., Bitsko, R. H., Anderka, M., Caton, A. R., Feldkamp, M. L., Hockett Sherlock, S. M., ... National Birth Defects Prevention Study. (2009). Control selection and participation in an ongoing, population-based, case-control study of birth defects: the National Birth Defects Prevention Study. *American Journal of Epidemiology*, *170*(8), 975–985. https://doi.org/10.1093/aje/kwp226

Correa, A., Gilboa, S. M., Besser, L. M., Botto, L. D., Moore, C. A., Hobbs, C. A., ... Reece, E. A. (2008). Diabetes mellitus and birth defects. *American Journal of Obstetrics and Gynecology*, *199*(3), 237.e231–237.e239. https://doi.org/10.1016/j.ajog.2008.06.028

Crankson, S. J., Al Jadaan, S. A., Namshan, M. A., Al-Rabeeah, A. A., & Oda, O. (2006). The immediate and long-term outcomes of newborns with congenital diaphragmatic hernia. *Pediatric Surgery International*, *22*(4), 335–340. https://doi.org/10.1007/s00383-006-1643-6

Denny, C. H., Acero, C. S., Naimi, T. S., & Kim, S. Y. (2019). Consumption of alcohol beverages and binge drinking among pregnant women aged 18-44 Years - United States, 2015-2017. *MMWR. Morbidity and Mortality Weekly Report*, *68*(16), 365–368. https://doi.org/10.15585/mmwr.mm6816a1

Dott, M. M., Wong, L.-Y. C., & Rasmussen, S. A. (2003). Population-based study of congenital diaphragmatic hernia: risk factors and survival in Metropolitan Atlanta, 1968-1999. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *67*(4), 261–267. https://doi.org/10.1002/bdra.10039

Drake, P., Driscoll, A. K., & Mathews, T. J. (2018). Cigarette smoking during pregnancy: United States, 2016. *NCHS Data Brief*, (305), 1–8.

England, L. J., Bennett, C., Denny, C. H., Honein, M. A., Gilboa, S. M., Kim, S. Y., ... (2020). Alcohol Use and Co-Use of Other Substances Among Pregnant Females Aged 12–44 Years — United States, 2015–2018. *MMWR. Morbidity and Mortality Weekly Report*, *69*(31), 1009–1014. https://doi.org/10.15585/mmwr.mm6931a1

Felix, J. F., van Dooren, M. F., Klaassens, M., Hop, W. C., Torfs, C. P., & Tibboel, D. (2008). Environmental factors in the etiology of esophageal atresia and congenital diaphragmatic hernia: results of a case-control study. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *82*(2), 98–105. https://doi.org/10.1002/bdra.20423

García, A. M., Machicado, S., Gracia, G., & Zarante, I. M. (2016). Risk factors for congenital diaphragmatic hernia in the Bogota birth defects surveillance and follow-up program, Colombia. *Pediatric Surgery International*, *32*(3), 227–234. https://doi.org/10.1007/s00383-015-3832-7

Goumy, C., Gouas, L., Marceau, G., Coste, K., Veronese, L., Gallot, D., ... Tchirkov, A. (2010). Retinoid pathway and congenital diaphragmatic hernia: Hypothesis from the analysis of chromosomal abnormalities. *Fetal Diagnosis and Therapy*, *28*(3), 129–139. https://doi.org/10.1159/000313331

Hollinger, L. E., & Buchmiller, T. L. (2019). Long term follow-up in congenital diaphragmatic hernia. *Seminars in Perinatology*, *151171*, 151171. https://doi.org/10.1053/j.semperi.2019.07.010

Honein, M. A., Paulozzi, L. J., & Watkins, M. L. (2001). Maternal smoking and birth defects: validity of birth certificate data for effect estimation. *Public Health Reports*, *116*(4), 327–335. https://doi.org/10.1093/phr/116.4.327

Hoyt, A. T., Canfield, M. A., Romitti, P. A., Botto, L. D., Anderka, M. T., Krikov, S. V., ... Feldkamp, M. L. (2016). Associations between maternal periconceptional exposure to secondhand tobacco smoke and major birth defects. *American Journal of Obstetrics and Gynecology*, *215*(5), 613 e611. https://doi.org/10.1016/j.ajog.2016.07.022

Kardon, G., Ackerman, K. G., McCulley, D. J., Shen, Y., Wynn, J., Shang, L., ... Chung, W. K. (2017). Congenital diaphragmatic hernias: from genes to mechanisms to therapies. *Disease Models & Mechanisms*, *10*(8), 955–970. https://doi.org/10.1242/dmm.028365

Knol, M. J., van der Tweel, I., Grobbee, D. E., Numans, M. E., & Geerlings, M. I. (2007). Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *International Journal of Epidemiology*, *36*(5), 1111–1118. https://doi.org/10.1093/ije/dym157

Kondracki, A. J. (2019). Prevalence and patterns of cigarette smoking before and during early and late pregnancy according to maternal characteristics: the first national data based on the 2003 birth certificate revision, United States, 2016. *Reproductive Health*, *16*(1). https://doi.org/10.1186/s12978-019-0807-5

Limpach, A., Dalton, M., Miles, R., & Gadson, P. (2000). Homocysteine inhibits retinoic acid synthesis: a mechanism for homocysteine-induced congenital defects. *Experimental Cell Research*, *260*(1), 166–174. https://doi.org/10.1006/excr.2000.5000

Longoni, M., Pober, B. R., & High, F. A. (2019). Congenital diaphragmatic hernia overview. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. Stephens, & A. Amemiya (Eds.), *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle. https://www.ncbi.nlm.nih.gov/pubmed/20301533

Mai, C. T., Isenburg, J. L., Canfield, M. A., Meyer, R. E., Correa, A., Alverson, C. J., ... National Birth Defects Prevention Network. (2019). National population-based estimates for major birth

defects, 2010-2014. *Birth Defects Research*, *111*(18), 1420–1435. https://doi.org/10.1002/bdr2.1589

Manoli, S. E., Smith, L. A., Vyhlidal, C. A., An, C. H., Porrata, Y., Cardoso, W. V., ... Haley, K. J. (2012). Maternal smoking and the retinoid pathway in the developing lung. *Respiratory Research*, *13*, 42. https://doi.org/10.1186/1465-9921-13-42

McAteer, J. P., Hecht, A., De Roos, A. J., & Goldin, A. B. (2014). Maternal medical and behavioral risk factors for congenital diaphragmatic hernia. *Journal of Pediatric Surgery*, *49*(1), 34–38; discussion 38. https://doi.org/10.1016/j.jpedsurg.2013.09.025

Mesas Burgos, C., Ehrén, H., Conner, P., & Frenckner, B. (2019). Maternal risk factors and perinatal characteristics in congenital diaphragmatic hernia: A nationwide population-based study. *Fetal Diagnosis and Therapy*, *1-8*, 385–391. https://doi.org/10.1159/000497619

Ozerol, E., Ozerol, I., Gokdeniz, R., Temel, I., & Akyol, O. (2004). Effect of smoking on serum concentrations of total homocysteine, folate, vitamin B12, and nitric oxide in pregnancy: A preliminary study. *Fetal Diagnosis and Therapy*, *19*(2), 145–148. https://doi.org/10.1159/000075139

Ramakrishnan, R., Salemi, J. L., Stuart, A. L., Chen, H., O'Rourke, K., Obican, S., & Kirby, R. S. (2018). Trends, correlates, and survival of infants with congenital diaphragmatic hernia and its subtypes. *Birth Defects Research*, *110*(14), 1107–1117. https://doi.org/10.1002/bdr2.1357

Rasmussen, S. A., Olney, R. S., Holmes, L. B., Lin, A. E., Keppler-Noreuil, K. M., Moore, C. A., & National Birth Defects Prevention Study. (2003). Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *67*(3), 193–201. https://doi.org/10.1002/bdra.10012

Reefhuis, J., Gilboa, S. M., Anderka, M., Browne, M. L., Feldkamp, M. L., Hobbs, C. A., ... National Birth Defects Prevention Study. (2015). The National Birth Defects Prevention Study: A review of the methods. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *103*(8), 656–669. https://doi.org/10.1002/bdra.23384

Refsum, H. (2001). Folate, vitamin B12 and homocysteine in relation to birth defects and pregnancy outcome. *The British Journal of Nutrition*, *85*(Suppl 2), S109–S113.

Romitti, P. A., Sun, L., Honein, M. A., Reefhuis, J., Correa, A., & Rasmussen, S. A. (2007). Maternal periconceptional alcohol consumption and risk of orofacial clefts. *American Journal of Epidemiology*, *166*(7), 775–785. https://doi.org/10.1093/aje/kwm146

Schulz, F., Jenetzky, E., Zwink, N., Bendixen, C., Kipfmueller, F., Rafat, N., ... Schaible, T. (2021). Parental risk factors for congenital diaphragmatic hernia - A large German case-control study. *BMC Pediatrics*, *21*(1), 278. https://doi.org/10.1186/s12887-021-02748-3

Shanmugam, H., Brunelli, L., Botto, L. D., Krikov, S., & Feldkamp, M. L. (2017). Epidemiology and prognosis of congenital diaphragmatic hernia: A population-based cohort study in Utah. *Birth Defects Research*, *109*(18), 1451–1459. https://doi.org/10.1002/bdr2.1106

Srisukhumbowornchai, S., Krikov, S., & Feldkamp, M. L. (2012). Self-reported maternal smoking during pregnancy by source in Utah, 2003-2007. *Birth Defects Research. Part A, Clinical and Molecular Teratology*, *94*(12), 996–1003. https://doi.org/10.1002/bdra.23058

Tinker, S. C., Gibbs, C., Strickland, M. J., Devine, O. J., Crider, K. S., Werler, M. M., ... National Birth Defects Prevention Study. (2013). Impact of time to maternal interview on interview responses in the National Birth Defects Prevention Study. *American Journal of Epidemiology*, *177*(11), 1225–1235. https://doi.org/10.1093/aje/kws352

Tinker, S. C., Gilboa, S. M., Moore, C. A., Waller, D. K., Simeone, R. M., Kim, S. Y., ... National Birth Defects Prevention Study. (2020). Specific birth defects in pregnancies of women with diabetes: National Birth Defects Prevention Study, 1997–2011. *American Journal of Obstetrics and Gynecology*, *222*(2), 176 e1–176 e11. https://doi.org/10.1016/j.ajog.2019.08.028

Verkerk, P. H., Buitendijk, S. E., & Verloove-Vanhorick, S. P. (1994). Differential misclassification of alcohol and cigarette consumption by pregnancy outcome. *International Journal of Epidemiology*, *23*(6), 1218–1225. https://doi.org/10.1093/ije/23.6.1218

Wang, Y., Liu, G., Canfield, M. A., Mai, C. T., Gilboa, S. M., Meyer, R. E., ... National Birth Defects Prevention Network. (2015). Racial/ethnic differences in survival of United States children with birth defects: A population-based study. *The Journal of Pediatrics*, *166*(4), 819–826 e811-812. https://doi.org/10.1016/j.jpeds.2014.12.025

Wechsler, H., Dowdall, G. W., Davenport, A., & Rimm, E. B. (1995). A gender-specific measure of binge drinking among college students. *American Journal of Public Health*, *85*(7), 982–985. https://doi.org/10.2105/ajph.85.7.982

Yang, W., Carmichael, S. L., Harris, J. A., & Shaw, G. M. (2006). Epidemiologic characteristics of congenital diaphragmatic hernia among 2.5 million california births, 1989–1997. *Birth Defects Research Part A: Clinical and Molecular Teratology*, *76*(3), 170–174. https://doi.org/10.1002/bdra.20230

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Finn, J., Suhl, J., Kancherla, V., Conway, K. M., Oleson, J., Sidhu, A., Nestoridi, E., Fisher, S. C., Rasmussen, S. A., Yang, W., Romitti, P. A., & the National Birth Defects Prevention Study (2022). Maternal cigarette smoking and alcohol consumption and congenital diaphragmatic hernia. *Birth Defects Research*, *114*(13), 746–758. https://doi.org/10.1002/bdr2.2059