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Maternal Periconceptional Alcohol Consumption and Congenital Heart Defects

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Abstract

Background: Congenital heart defects (CHDs) are the leading cause of infant death from birth defects. Animal studies suggest in utero alcohol exposure is a teratogen for cardiogenesis; however, results from epidemiologic studies are mixed.

Methods: Data from the National Birth Defects Prevention Study were used to estimate associations between CHDs and case (n = 7076) and control (n = 7972) mother reports of periconceptional (1 month before pregnancy through the first trimester) alcohol consumption with expected delivery dates during 1997 to 2007. CHDs were examined by category (conotruncal, septal, left ventricular outflow tract obstruction, and right ventricular outflow tract obstruction, heterotaxy with CHD) and subtype (e.g., tetralogy of Fallot [TOF]). Alcohol measures examined were any consumption, maximum average drinks per month, binge drinking, and alcohol type. Adjusted odds ratios and 95% confidence intervals were estimated using unconditional logistic regression analysis.

Results: Increased risks, albeit marginally statistically significant, were observed for TOF and each maternal alcohol measure examined and for right ventricular outflow tract obstruction and heterotaxy with CHD and consumption of distilled spirits. Significantly reduced risks were observed for several CHD categories (septal defects, left ventricular outflow tract obstruction, and right ventricular outflow tract obstruction) and some corresponding subtypes with different alcohol measures. Significant risks were not observed for the other CHDs examined.

Conclusion: Analysis of this large, well-defined study sample did not show statistically significant increased risks between measures of maternal alcohol consumption and most CHDs examined. These findings may reflect, in part, limitations with retrospective exposure assessment

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or unmeasured confounders. Additional studies with continued improvement in measurement of alcohol consumption are recommended.

Keywords

congenital heart defects; alcohol; pregnancy; epidemiology; birth defects

Introduction

Human cardiogenesis begins at approximately the second week of gestation, progresses to form the heart chambers and valves, and continues with chamber septation at approximately seven weeks of gestation (Bruneau, 2003; Dhanantwari et al., 2009). Disturbances in this developmental cascade can lead to one or more congenital heart defects (CHDs). Collectively, CHDs are estimated to occur in 4 to 9 per 1000 live births in the United States (US) (Ferencz et al., 1985; Botto et al., 2001; Hoffman and Kaplan, 2002; Bjornard et al., 2013), and are the leading cause of infant death from birth defects (Boneva et al., 2001; Lee et al., 2001). Even with the many previous epidemiologic studies conducted, identification of major non-inherited risk factors for CHDs has been elusive (Jenkins et al., 2007; Patel and Burns, 2013).

The relation between maternal alcohol consumption during pregnancy and risk for CHDs has been examined in several epidemiologic studies, but results have been mixed. Specifically, one study reported a significantly increased risk with any maternal alcohol consumption (yes/no) for all CHDs combined (Tikkanen and Heinonen, 1990); however, this finding was not supported in several other studies (Tikkanen and Heinonen, 1991a; Cedergren et al., 2002; Mateja et al., 2012; Fung et al., 2013). Also, any maternal alcohol consumption was not found to be significantly associated with some common CHD subtypes, such as conotruncal defects (Adams et al., 1989; Tikkanen and Heinonen, 1990, 1992a) and ventricular septal defects (VSDs) (Mills and Graubard, 1987; Tikkanen and Heinonen, 1990, 1991a, 1991b), although one study (Tikkanen and Heinonen, 1992b), but not others (Mills and Graubard, 1987; Tikkanen and Heinonen, 1990), reported a significantly increased risk for atrial septal defects (ASDs). Among the studies that examined levels of quantity and frequency of maternal alcohol consumption, many did not identify significantly increased risks for conotruncal defects (Shaw et al., 1992; Carmichael et al., 2003; Grewal et al., 2008), ASDs (Mills and Graubard, 1987; Strandberg-Larsen et al., 2011), or tetralogy of Fallot (TOF) (Carmichael et al., 2003; Grewal et al., 2008); however, results reported for all CHDs combined (Mills and Graubard, 1987; Shaw et al., 1992; Ferencz et al., 1997; Martinez-Frias et al., 2004), VSDs (Mills and Graubard, 1987; Williams et al., 2004; Strandberg-Larsen et al., 2011), and dextro-transposition of the great arteries (d-TGA) (Carmichael et al., 2003; Grewal et al., 2008) were mixed. Similarly, binge drinking was not associated with significantly increased risks for conotruncal defects (Adams et al., 1989; Carmichael et al., 2003; Grewal et al., 2008), TOF (Carmichael et al., 2003; Grewal et al., 2008), ASDs (Strandberg-Larsen et al., 2011), or VSDs (Williams et al., 2004; Strandberg-Larsen et al., 2011), but mixed results were reported for all CHDs combined (Adams et al., 1989; Mateja et al., 2012) and d-TGA (Carmichael et al., 2003; Grewal et al., 2008).

Limitations in some previous epidemiologic studies were the absence of subtype-specific analysis (Cedergren et al., 2002; Martinez-Frias et al., 2004; Mateja et al., 2012; Fung et al., 2013), which made conclusions less generalizable due to the underlying complexity and heterogeneity of CHDs, or the availability of only a modest number of cases for a particular CHD subtype (Mills and Graubard, 1987; Adams et al., 1989; Tikkanen and Heinonen, 1991b, 1992a,b; Shaw et al., 1992; Carmichael et al., 2003; Williams et al., 2004; Grewal et al., 2008; Strandberg-Larsen et al., 2011). Also, some studies only examined any alcohol consumption (Tikkanen and Heinonen, 1990, 1991a,b, 1992a; Cedergren et al., 2002; Fung et al., 2013); others examined quantity and frequency of alcohol consumed or binge drinking, but only for any CHD (Martinez-Frias et al., 2004; Mateja et al., 2012), and no study examined the impact of type(s) of alcohol consumed (e.g., beer, wine, distilled spirits). The type of alcohol consumed may have an impact on folate levels in pregnant women. For example, a previous study observed a positive relationship between beer consumption and red blood cell folate levels in pregnant women (Larroque et al., 1992). Maternal use of folate-containing supplements has been associated with a reduced risk of CHDs in offspring (Botto et al., 2000; van Beynum et al., 2010).

Continued investigation into the risk of CHDs is of great importance because alcohol exposure is common and in principle, modifiable. A US survey of women of childbearing age reported that 51.5% consumed alcohol (Marchetta et al., 2012); at this level of exposure, and with the increasing trend of unintended pregnancies in the US (Finer and Zolna, 2014), even a small increased risk for some severe CHDs can translate in many preventable cases of disease. In addition, alcohol has a demonstrated teratogenic effect on cardiogenesis in animal studies (Randall and Taylor, 1979; Beauchemin et al., 1984; Webster et al., 1984; Daft et al., 1986; Fang et al., 1987; Bruyere and Stith, 1993; Cavieres and Smith, 2000; Sarmah and Marrs, 2013) and heart defects are observed in children with the physical manifestations of fetal alcohol syndrome (Burd et al., 2007). The current study used data from the population-based National Birth Defects Prevention Study (NBDPS) to investigate associations between different measures of maternal periconceptional (1 month before pregnancy through the first trimester) alcohol consumption and CHDs.

Methods

The NBDPS was a population-based case-control study designed to investigate environmental and genetic risk factors for over 30 major birth defects at ten participating sites (Arkansas [AR], California [CA], Iowa [IA], Massachusetts [MA], New Jersey [NJ], New York [NY], North Carolina [NC], Texas [TX], Utah [UT], and the Centers for Disease Control and Prevention/Georgia [CDC/GA]) (Yoon et al., 2001; Rasmussen et al., 2002, 2003). All sites ascertained live births diagnosed with CHDs and all but NJ ascertained fetal deaths (AR, CA, CDC/GA, IA, MA, NC, NY 2000–2011, TX, and UT) or elective terminations (AR, CA, CDC/GA, IA, MA 2011, NC, NY 2000–2011, TX, and UT). Control infants were unaffected live births with an estimated date of delivery (EDD) during the same time frame and randomly selected from hospital delivery logs (AR 1997–2000, CA, CDC/GA 1997–2000, NY, and TX) or birth certificate records (AR 2001–2011, CDC/GA 2001–2011, IA, MA, NC, NJ, and UT). In each site, controls were births in the same catchment areas and birth years as cases. Because of the number of case groups included in

the NBPDS, we chose not to use 1:1 case:control matching. Instead, each NBDPS site attempted to recruit 100 controls per birth year. This number provided, at a minimum, a 1:1 case:control ratio for the largest defect groups (e.g., CHDs) per year included in the NBDPS. This approach, however, did not permit matching for selected variables (e.g., city of residence, water supply, etc.) within a site nor across sites. Each site obtained institutional review board approval for the study.

CASE CLASSIFICATION

Classification of CHDs in the NBDPS was implemented by a team of clinicians with expertise in clinical genetics, pediatric cardiology, and cardiovascular epidemiology; only CHDs confirmed by echocardiography, cardiac catheterization, surgery, or autopsy were included. CHDs were classified as simple (anatomically discrete or well-recognized single cardiac defect), association (common uncomplicated combination of cardiac defects), or complex (those that could not be described as simple or association, such as those that occur as part of some single-ventricle or laterality defect), under eight diagnostic categories: conotruncal defects, septal defects, atrioventricular septal defects (AVSDs), anomalous pulmonary venous return, left ventricular outflow tract obstruction (LVOTO), right ventricular outflow tract obstruction (RVOTO), heterotaxy with CHD, and single ventricle/complex (Botto et al., 2007). Within each category, subtypes were defined. For example, TOF and d-TGA are subtypes of conotruncal defects. In addition, each CHD case was assigned either an isolated or a multiple (presence of extracardiac defects) phenotype.

ALCOHOL EXPOSURE

A telephone interview was administered to mothers from 6 weeks through 24 months after the EDD; participation rates were 66% for control and 68% for CHD case mothers. The interview collected information about frequency, amount, and type of alcohol consumed from 3 months before pregnancy through the end of the pregnancy. To assist with recall of exposures, a pregnancy calendar was used during the interview to provide the mother with estimated beginning and ending dates corresponding to each month of the pregnancy. Measures of maternal periconceptional alcohol consumption were defined using a previously developed approach (Romitti et al., 2007). Briefly, a mother who reported any alcohol consumption during the month before conception or any month of the first trimester of pregnancy was classified as consuming alcohol during the periconceptional period. Additional variables (maximum average drinks per month, binge drinking, and types of alcohol consumed) were used to detail her consumption pattern. The maximum average drinks per month was calculated based on reported quantity and frequency of alcohol consumption and categorized into four groups (1–4, 5–15, 16–30, and >30 drinks per month). The sex-specific norm of four or more drinks per occasion (Wechsler et al., 1995) was used to define binge drinking; consumption was then categorized as drinking without a binge episode, or drinking with one or more binge episodes. Types of alcohol consumed were classified as: beer only, wine only, distilled spirits only, and two or more types.

STATISTICAL ANALYSIS

Analyses were conducted using SAS, version 9.3 (SAS Institute, Cary, NC). Cases diagnosed with a CHD and unaffected controls with an EDD from October 1, 1997, through

December 31, 2007, were selected. Case and control mothers with an incomplete interview (n = 138 and n = 142, respectively), missing responses for periconceptional alcohol consumption (n = 187 and n = 194), reported consumption of >150 drinks per month (n = 12 and n = 22), reported prepregnancy diabetes (n = 259 and n = 52), or multiple or unknown number of babies carried in the index pregnancy (n = 611 and n = 269) were excluded from analysis. Using the proportion of control mother reports for any periconceptional alcohol consumption, a power analysis determined that 209 cases were required to detect an odds ratio (OR) of 1.5 at a significance level of 0.05 and power of 0.8. As such, any CHD category or subtype with 209 or more cases, after applying the exclusion criteria listed above, was analyzed. For all selected CHD categories and subtypes, additional analyses were conducted restricting to isolated cases within each category and subtype, except heterotaxy with CHD, because all cases in this category were classified as a multiple phenotype.

Chi-square tests were performed to compare case and control pregnancy characteristics (sex, gestational age, and family history of CHDs), maternal characteristics (race/ethnicity; age, education, and gravidity at delivery; prepregnancy body mass index and dietary folate equivalents [DFEs]; and periconceptional exposure to active or passive cigarette smoke and use of folic-acid-containing supplements), and study site. For each CHD category and subtype, crude ORs and adjusted ORs with 95% confidence intervals (CI) for each measure of maternal periconceptional alcohol consumption (any consumption, maximum average drinks per month, binge drinking, and types of alcohol) were estimated using unconditional logistic regression analysis. Covariates examined were case or control sex (male, female) and family history of CHDs (yes, no); maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other), age (<21, 21–25, 26–30, 31–35, >35 years) and education (≤12, 13–15, 16 or more years) at delivery, prepregnancy body mass index (underweight, normal weight, overweight, and obese) and DFEs (<600, ≥600 μg/day), periconceptional cigarette smoke exposure (none, active smoking only, passive smoking only, active and passive smoking) and use of folic-acid-containing supplements (yes, no); and study site (AR, CA, CDC/GA, IA, MA, NC, NJ, NY, TX, UT). Covariates that altered the crude OR by at least 10% were entered in the final model to obtain an adjusted OR. To examine the potential for differential recall of alcohol consumption between case and control mothers, interview reports of alcohol measures by 6-month intervals (1–6, 7–12, 13–18, and 19–24 months) between the EDD and interview and changes in drinking patterns before and after reported recognition of pregnancy were examined using Chi-square tests. Additionally, interactions between any periconceptional alcohol consumption and use of folic-acid-containing supplements were also tested. The significance of multiplicative interaction estimates was determined using p-values, and the significance of additive interaction estimates (i.e., the relative excess risk due to interaction) was determined using bootstrap 95% CI (Knol et al., 2007). The relative excess risk due to interaction and bootstrap 95% CI were calculated using a computer program created by Sandra Richardson, RN, MS (personal communication, New York State Department of Health, 2011).

Results

After the exclusions, the study sample included 7972 controls and 7076 cases. The median time between the EDD and interview was 7.8 months for control mothers and 10.5 months for case mothers. Compared with control pregnancies, case pregnancies were more often male, preterm, and had a family history of CHDs (Table 1). Compared with control mothers, case mothers were more likely to be older and less educated at delivery, have had three or more pregnancies, be overweight or obese before pregnancy, and have had periconceptional exposure to active or passive cigarette smoke. Case mothers were also less likely to report prepregnancy intake of at least 600 μg/day DFEs or periconceptional use of folic-acid-containing supplements. Additionally, the proportions of case and control mothers enrolled differed among study sites. No differences were found across racial/ethnic groups.

Examination of the proportions of case and control mother reports of alcohol consumption by time to interview did not produce statistically significant differences for any 6-month interval used. Also, no differences were observed between case and control mothers in reported changes in consumption patterns before and after recognition of pregnancy (data not shown). Additionally, within a CHD category, the ORs for isolated and multiple phenotypes combined were very similar to those for isolated cases only (data not shown). Given that only a small proportion of all cases (16%) were classified as multiple phenotype, results from the logistic regression analyses are presented only for isolated cases and those with heterotaxy with CHD.

Overall, 36.8% of control mothers reported periconceptional alcohol consumption; percentages were similar for case mothers, ranging from 31.5 to 40.0% (Table 2). After adjusting for covariates, an increased risk, albeit marginally statistically significant, was observed for the association between simple TOF and any periconceptional alcohol consumption. Significant or marginally significant reduced risks were associated with several CHD categories (including corresponding subtype[s]), specifically, any simple septal defect (secundum atrial septal defect [ASD2]), any simple LVOTO (aortic stenosis), and the simple RVOTO subtype, pulmonary valve stenosis (PVS). Associations were not statistically significant for all other CHDs examined. No statistically significant additive or multiplicative interactions for any alcohol consumption and use of folic-acid-containing supplements were found (data not shown).

Maternal reports of consumption of 1 to 4 drinks per month were associated with marginally statistically significant reduced risks for any simple LVOTO and simple PVS (Table 3). Consumption of 5 to 15 drinks per month was associated with a marginally significant increased risk of simple TOF, but with significant or marginally significant reduced risks for any simple septal defect (perimembranous VSD, ASD2), as well as any simple LVOTO (coarctation of the aorta). Consumption of 16 to 30 drinks per month was associated with significant or marginally significant reduced risks for any simple septal defect (ASD2), any simple LVOTO, and any simple RVOTO (PVS). The associations between each CHD and maternal reports of >30 drinks per month were similar to those for other consumption categories, but were less precise due to small numbers of exposed mothers. Despite evidence

of increased or reduced risks, no pattern of dose-response was observed for any CHD category or subtype.

Statistically significant or marginally significant reduced risks were associated with maternal reports of drinking without a binge episode and any simple septal defect (ASD2), any simple LVOTO (aortic stenosis), and simple PVS (Table 4). Drinking with one or more binge episodes was associated with a marginally significant increased risk for simple TOF, but reduced risks for any simple septal defect.

The adjusted OR for consumption of beer only showed marginal statistical significance for any simple LVOTO (Table 5). Mothers who consumed wine only had significant or marginally significant reduced risks for any simple septal defect, any simple LVOTO (aortic stenosis), and simple PVS. Mothers who consumed distilled spirits only had marginally significant increased risks for any simple RVOTO (PVS) and heterotaxy with CHD. Additionally, those who consumed two or more types of alcohol had marginally significant increased risks for any simple conotruncal defect (TOF); in contrast, significant or marginally significant reduced risks were associated with any simple septal defect (perimembranous VSD, ASD2), any simple LVOTO, and any simple RVOTO (PVS).

Discussion

This study presents a comprehensive evaluation of associations between maternal periconceptional alcohol consumption and CHDs, by type and timing of alcohol consumption and by type of CHD. For most CHDs examined, associations with maternal reports of periconceptional alcohol consumption were not statistically significant. For the remainder of the CHDs, associations were modestly reduced or increased but several of the corresponding confidence intervals contained one. Certain CHDs, such as septal defects, LVOTO, RVOTO, and/or their subtypes, showed significant inverse associations with alcohol consumption.

Because of the heterogeneity of CHDs, exclusion of CHDs with chromosomal or other single gene disorders in the NBDPS, and restriction of the current analyses to individual CHDs that met specific power estimates, associations between maternal alcohol consumption and all CHDs as a group were not examined. As such, these findings cannot be compared with some previous studies that examined all CHDs combined (Mills and Graubard, 1987; Tikkanen and Heinonen, 1990, 1991a; Shaw et al., 1992; Ferencz et al., 1997; Cedergren et al., 2002; Martinez-Frias et al., 2004; Mateja et al., 2012; Fung et al., 2013). With regard to specific CHD categories or subtypes, most previous studies did not report significant associations between any maternal alcohol consumption or quantity and frequency of consumption and conotruncal defects (Adams et al., 1989; Tikkanen and Heinonen, 1990, 1992a; Shaw et al., 1992; Carmichael et al., 2003; Grewal et al., 2008), TOF (Carmichael et al., 2003; Grewal et al., 2008), VSDs (Mills and Graubard, 1987; Tikkanen and Heinonen, 1990, 1991a,b; Strandberg-Larsen et al., 2011), ASDs (Mills and Graubard, 1987; Tikkanen and Heinonen, 1990; Strandberg-Larsen et al., 2011), coarctation of the aorta (Tikkanen and Heinonen, 1993), or hypoplastic left heart syndrome (Tikkanen and Heinonen, 1994). Similarly, significantly increased risks associated with maternal

reports of any alcohol consumption were not observed for these CHDs in the current study. A limited number of studies have reported significant associations between maternal alcohol consumption and specific CHD subtypes. In particular, Tikkanen and Heinonen (1992b) reported significant associations between any alcohol consumption during the first trimester and ASDs (adjusted relative risk = 1.9, 95% CI: 1.1–3.4), and Grewal et al. (2008) reported associations between less than one drinking day per week during the first month of pregnancy and d-TGA, compared with nondrinkers (crude OR = 1.9; 95% CI, 1.1–3.2); an increased risk was not found for those reporting one or more drinking days per week.

Although an increased risk was not observed with maternal reports of heavy drinking (more than 30 drinks per month) in the current study, a few studies have reported increased risk of CHDs among mothers who reported heavy drinking. For example, maternal reports of more than 10 drinks per week were associated with VSDs (Williams et al., 2004), and reports of consumption of more than 92 grams of absolute alcohol (estimated as more than 500 ml wine or 1000 ml beer) per day were associated with any CHD (Martinez-Frias et al., 2004).

Consistent with results from some previous studies (Adams et al., 1989; Williams et al., 2004; Grewal et al., 2008; Strandberg-Larsen et al., 2011), a statistically significant increased risk of pregnancies affected by CHDs among mothers who reported periconceptional binge drinking was not observed. Mateja et al. (2012) examined binge drinking in the 3 months before pregnancy and reported significant increased risks for any CHD with interactions between binge drinking and cigarette smoking. In analyses of CHD subtypes, Carmichael et al. (2003) found that mothers who reported binge drinking less than once per week had an increased risk of offspring with d-TGA compared with pregnancies of nondrinking mothers, although no associations were found between maternal binge drinking and any conotruncal defect or TOF alone. The authors indicated that their small number of cases may have produced imprecise risk estimates and chance findings (Carmichael et al., 2003).

The current study did not show significantly increased associations between type of alcohol consumed and most CHD subtypes, although some significantly reduced associations were found with LVOTO, RVOTO, and septal defects. No studies of types of alcohol consumed and risk of CHDs are available for comparison.

The lack of significantly increased risk for CHDs associated with maternal reports of alcohol consumption in the current study may be due, in part, to light or moderate levels of reported drinking. Only 6 to 9% of case and control mothers reported consuming a maximum average drinks per month level that exceeded 15 drinks. Although a systematic review failed to find convincing evidence of adverse effects of light or moderate prenatal alcohol exposure on malformations (Henderson et al., 2007), the teratogenic threshold of alcohol consumption has not been established; pregnant women are encouraged to follow public health policy recommendations about abstinence from alcohol.

The retrospective data collection approach in the NBDPS may have contributed to under-reporting of alcohol consumption by mothers of affected pregnancies due to the negative social stigma associated with such consumption. A previous study, which compared

prospective and retrospective maternal reports of alcohol consumption and examined changes in mean reports of consumption and exposure category by pregnancy outcome, reported no significant differences among these comparisons suggesting little, if any recall bias (Verkerk et al., 1994). Similarly, no differences were observed for reported consumption between cases and controls by 6-month intervals between EDD and interview or before and after pregnancy recognition suggesting reports of alcohol consumption did not change as a function of pregnancy outcome (i.e., case mothers reported less alcohol consumption due to presence of CHD) or timing of pregnancy recognition. Another limitation is that alcohol consumption was self-reported in the NBDPS interview. Participants were asked to report the number of standard drinks consumed (i.e., one beer, one glass of wine, one mixed drink, or one shot of liquor) within broadly defined time periods (e.g., month, day, occasion). As a result, the grams of ethanol consumed and dose of ethanol absorbed during a critical exposure period could not be reliably estimated. Moreover, there is a potential bias from nonparticipation in the NBDPS; however, NBDPS control participants were compared with all births in the NBDPS base population from 1997 through 2003 and were found to be representative on several characteristics (Cogswell et al., 2009). Also, the percentages of mothers of case and control pregnancies who reported any periconceptional alcohol consumption or binge drinking were similar to those reported in a national survey of reproductive-aged women (Marchetta et al., 2012). In addition, some rare CHD categories, such as atrioventricular septal defects, anomalous pulmonary venous return, and single ventricle/complex CHDs were not examined in this study due to insufficient statistical power. Lastly, our study was limited by the lack of a reliable biomarker for alcohol consumption, as well as possibly unmeasured confounders.

The strengths of the current study include use of a population-based design with a large sample size and a systematic classification of CHDs. This allowed examinations of associations between maternal periconceptional alcohol consumption and several CHDs that have not been studied previously, such as LVOTO, RVOTO, and PVS, as well as common types of association CHDs. In addition, interview data collected consisted of detailed maternal reports of alcohol consumption, which permitted the examination of a wider spectrum of consumption patterns.

In summary, most associations between maternal reports of periconceptional alcohol consumption and CHDs did not support the suggested teratogenic effects seen in animal models. Statistically significant increased or reduced associations observed may have been due to multiple testing. They may also reflect, in part, limitations with retrospective exposure assessment or unmeasured confounders. Future studies should continue to improve measurement of alcohol consumption.

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TABLE 1.

Selected Characteristics of Control and Case Pregnancies and Mothers, National Birth Defects Prevention Study, 1997 through 2007

	Control		Case[a]		
Characteristic	***N*[b]**	**%[c]**	***N*[b]**	**%[c]**	***p*-value**
Pregnancy					
Phenotype					-
Isolated (without extracardiac defects)	-	-	5926	83.7	
Multiple (with extracardiac defects)	-	-	1150	16.3	
Sex					0.003
Female	3920	49.2	3310	46.8	
Male	4044	50.8	3761	53.2	
Gestational age					<0.001
Term (37–45 weeks)	7336	92.0	5466	78.0	
Preterm (<37 weeks)	635	8.0	1545	22.0	
Family history of a CHD					<0.001
No	7877	98.8	6817	96.3	
Yes	95	1.2	259	3.7	
Mother					
Age at delivery					0.023
<21 years	1163	14.6	976	13.8	
21–25 years	1951	24.5	1715	24.2	
26–30 years	2244	28.2	1920	27.1	

Characteristic	Control		Case[a]		*p*-value
	N[b]	%[c]	*N*[b]	%[c]	
31–35 years	1819	22.8	1655	23.4	
>35 years	795	10.0	810	11.5	
Race/ethnicity					0.909
Non-Hispanic white	4689	59.0	4148	58.8	
Non-Hispanic black	876	11.0	800	11.3	
Hispanic	1851	23.3	1656	23.5	
Other	526	6.6	456	6.5	
Education					<0.001
≤12 years	3318	41.7	3104	43.9	
13–15 years	2151	27.0	1973	27.9	
≥16 years	2495	31.3	1995	28.2	
Gravidity					0.022
1	2339	29.3	2102	29.7	
2	2336	29.3	1933	27.3	
≥3	3296	41.4	3038	43.0	
Pre-pregnancy body mass index					<0.001
Underweight (<18.5 kg/m^2)	415	5.4	375	5.5	
Normal weight (18.5–24.9 kg/m^2)	4228	55.3	3428	50.6	
Overweight (25.0–29.9 kg/m^2)	1739	22.7	1620	23.9	
Obese (≥30.0 kg/m^2)	1264	16.5	1346	19.9	

Characteristic	Control		Case[a]		p-value
	N[b]	%[c]	N[b]	%[c]	
Texas	925	11.6	999	14.1	
Utah	584	7.3	601	8.5	

[a]Cases were those who had any of the selected subtypes of congenital heart defects. Subtypes included in the present study were each congenital heart defect that provided a statistical power of 0.8.

[b]Total number may vary due to incomplete or missing data.

[c]May not total 100 due to rounding.

CDC, Centers for Disease Control and Prevention; CHD, congenital heart defect.

TABLE 2.

Odds Ratios[a] for Associations between Congenital Heart Defects and Any Maternal Periconceptional Alcohol Consumption, National Birth Defects Prevention Study, 1997 through 2007

	Periconceptional alcohol consumption					
	No (Reference)		Yes			
	N[b]	%[c]	*N*[b]	%[c]	OR	95% CI
Control	5041	63.2	2931	36.8		
Isolated simple conotruncal[d]	753	62.1	459	37.9	1.0	[0.9, 1.2]
TOF[e]	369	60.0	246	40.0	1.2	[1.0, 1.4]
d-TGA[f]	262	62.5	157	37.5	1.0	[0.8, 1.3]
Isolated simple septal[e]	1327	65.8	691	34.2	0.8	[0.8, 0.9]
VSD-PM[e]	522	64.6	286	35.4	0.9	[0.8, 1.1]
ASD2[g]	531	68.0	250	32.0	0.8	[0.7, 1.0]
ASD-NOS[h]	178	68.5	82	31.5	0.8	[0.6, 1.1]
Isolated septal association[d,i]	276	64.3	153	35.7	1.0	[0.8, 1.2]
Isolated simple LVOTO[j]	646	66.7	322	33.3	0.8	[0.7, 0.9]
HLHS[k]	258	66.8	128	33.2	0.9	[0.7, 1.2]
COA[l]	237	65.8	123	34.2	0.8	[0.7, 1.1]
AS[m]	145	68.4	67	31.6	0.7	[0.5, 1.0]
Isolated LVOTO association[e,i]	179	65.1	96	34.9	1.0	[0.7, 1.2]

	Periconceptional alcohol consumption					
	No (Reference)		Yes			
	N[b]	%[c]	N[b]	%[c]	OR	95% CI
Isolated simple RVOTO[d]	530	65.6	278	34.4	0.9	[0.8, 1.1]
PVS[d,n]	435	66.8	216	33.2	0.8	[0.7, 1.0]
Isolated RVOTO association[i,o]	141	65.3	75	34.7	0.9	[0.7, 1.2]
Heterotaxy with CHD[p]	152	65.2	81	34.8	1.1	[0.8, 1.5]

[a] Odds ratios were adjusted, where appropriate, for confounding factors that altered the odds ratio for a given subtype of CHDs by at least 10%.

[b] Total number for each CHD may vary across tables due to incomplete or missing data.

[c] Percentage of complete data, may not total 100 due to rounding.

[d] Crude odds ratio was presented because no covariate altered the odds ratio by at least 10%.

[e] Adjusted for periconceptional active or passive smoking exposure.

[f] Adjusted for pre-pregnancy body mass index.

[g] Adjusted for education, periconceptional active or passive smoking exposure, and study site.

[h] Adjusted for maternal race/ethnicity, education, periconceptional active or passive smoking exposure, and study site.

[i] LVOTO associations include COA+AS, COA+VSD, COA+VSD+ASD; RVOTO associations include PVS+VSD, PVS+ASD; septal associations include VSD+ASD.

[j] Adjusted for maternal race/ethnicity.

[k] Adjusted for pre-pregnancy body mass index and study site.

[l] Adjusted for maternal age, education, and periconceptional active or passive smoking exposure.

[m] Adjusted for maternal race/ethnicity, pre-pregnancy body mass index, periconceptional active or passive smoking exposure, and study site.

[n] The control group for PVS had 7515 controls after excluding those who were born before Jan 1, 2002 in California, because cases of PVS in California were not ascertained before that date; 4715 (62.7%) controls reported no periconceptional alcohol consumption and 2800 (37.3%) controls reported periconceptional alcohol consumption.

[o] Adjusted for education and periconceptional active or passive smoking exposure.

[p] Adjusted for maternal race/ethnicity and education.

AS, aortic stenosis; ASD, atrial septal defect; ASD2, secundum atrial septal defect; CHD, congenital heart defects; CI, confidence interval; COA, coarctation of the aorta; d-TGA, dextro-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; LVOTO, left ventricular outflow tract obstruction; NOS, not otherwise specified; OR, odds ratio; VSD-PM, perimembranous ventricular septal defect; PVS, pulmonary valve stenosis; RVOTO, right ventricular outflow tract obstruction; TOF, tetralogy of Fallot.

TABLE 3.

Odds Ratios[a] for Associations between Congenital Heart Defects and Maternal Reports of Maximum Average Alcoholic Drinks Consumed per Month, National Birth Defects Prevention Study, 1997 through 2007

	No alcohol (reference)		Maximum average drinks per month															
			1-4				5-15				16-30				>30			
	N[b]	%[c]	N[b]	%[c]	OR	95% CI	N[b]	%[c]	OR	95% CI	N[b]	%[c]	OR	95% CI	N[b]	%[c]	OR	95% CI
Control	5041	63.5	1339	16.9			924	11.6			412	5.2			222	2.8		
Isolated simple conotruncal[d]	753	62.3	217	18.0	1.1	[0.9, 1.3]	145	12.0	1.1	[0.9, 1.3]	63	5.2	1.0	[0.8, 1.3]	30	2.5	0.9	[0.6, 1.3]
TOF[e]	369	60.3	108	17.7	1.1	[0.9, 1.4]	81	13.2	1.2	[1.0, 1.6]	36	5.9	1.3	[0.9, 1.8]	18	2.9	1.2	[0.7, 2.0]
d-TGA[f]	262	62.7	78	18.7	1.1	[0.9, 1.5]	52	12.4	1.1	[0.8, 1.5]	18	4.3	0.7	[0.4, 1.2]	8	1.9	0.7	[0.3, 1.4]
Isolated simple septal[e]	1327	65.9	343	17.0	1.0	[0.8, 1.1]	195	9.7	0.7	[0.6, 0.9]	83	4.1	0.7	[0.5, 0.9]	65	3.2	0.9	[0.7, 1.2]
VSD-PM[e]	522	64.8	148	18.4	1.1	[0.9, 1.3]	79	9.8	0.8	[0.6, 1.0]	33	4.1	0.7	[0.5, 1.1]	24	3.0	0.9	[0.6, 1.4]
ASD2[g]	531	68.2	122	15.7	1.0	[0.8, 1.2]	67	8.6	0.7	[0.6, 1.0]	31	4.0	0.7	[0.5, 1.0]	28	3.6	1.0	[0.6, 1.5]
ASD-NOS[h]	178	68.7	38	14.7	0.9	[0.6, 1.3]	25	9.7	0.8	[0.5, 1.3]	11	4.3	0.8	[0.4, 1.5]	7	2.7	0.6	[0.3, 1.5]
Isolated septal association[d,i]	276	64.6	65	15.2	0.9	[0.7, 1.2]	50	11.7	1.0	[0.7, 1.3]	22	5.2	1.0	[0.6, 1.5]	14	3.3	1.2	[0.7, 2.0]
Isolated simple LVOTO[j]	646	66.8	157	16.2	0.8	[0.7, 1.0]	91	9.4	0.7	[0.5, 0.9]	43	4.5	0.7	[0.5, 1.0]	30	3.1	0.9	[0.6, 1.4]
HLHS[k]	258	66.8	62	16.1	1.0	[0.7, 1.3]	34	8.8	0.8	[0.6, 1.2]	22	5.7	1.1	[0.7, 1.7]	10	2.6	0.9	[0.4, 1.7]
COA[l]	237	65.8	66	18.3	1.0	[0.7, 1.3]	32	8.9	0.7	[0.5, 1.0]	13	3.6	0.6	[0.4, 1.1]	12	3.3	1.2	[0.6, 2.2]
AS[m]	145	68.7	29	13.7	0.7	[0.5, 1.1]	23	10.9	0.8	[0.5, 1.3]	8	3.8	0.6	[0.3, 1.2]	6	2.8	0.7	[0.3, 1.8]
Isolated LVOTO Association[e,i]	179	65.1	43	15.6	0.9	[0.6, 1.3]	33	12.0	1.0	[0.7, 1.5]	14	5.1	1.0	[0.6, 1.8]	6	2.2	0.9	[0.4, 2.0]

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	No alcohol (reference)		Maximum average drinks per month															
			1-4				5-15				16-30				>30			
	N[b]	%[c]	*N*[b]	%[c]	OR	95% CI	*N*[b]	%[c]	OR	95% CI	*N*[b]	%[c]	OR	95% CI	*N*[b]	%[c]	OR	95% CI
Isolated simple RVOTO[d]	530	65.8	130	16.2	0.9	[0.8, 1.1]	92	11.4	0.9	[0.8, 1.2]	28	3.5	0.6	[0.4, 1.0]	25	3.1	1.1	[0.7, 1.6]
PVS[d,n]	435	67.0	97	15.0	0.8	[0.7, 1.0]	77	11.9	0.9	[0.7, 1.2]	19	2.9	0.5	[0.3, 0.8]	21	3.2	1.1	[0.7, 1.7]
Isolated RVOTO association[i,o]	141	65.6	37	17.2	1.0	[0.7, 1.5]	18	8.4	0.7	[0.4, 1.2]	13	6.1	1.1	[0.6, 2.0]	6	2.8	0.8	[0.3, 1.9]
Heterotaxy with CHD[p]	152	65.8	42	18.2	1.2	[0.9, 1.8]	18	7.8	0.8	[0.5, 1.3]	13	5.6	1.3	[0.7, 2.4]	6	2.6	1.0	[0.4, 2.4]

[a] Odds ratios were adjusted, where appropriate, for confounding factors that altered the odds ratio for a given subtype of CHDs by at least 10%.

[b] Total number for each CHD may vary across tables due to incomplete or missing data.

[c] Percentage of complete data, may not total 100 due to rounding.

[d] Crude odds ratio was presented because no covariate altered the odds ratio by at least 10%.

[e] Adjusted for periconceptional active or passive smoking exposure.

[f] Adjusted for pre-pregnancy body mass index.

[g] Adjusted for education, periconceptional active or passive smoking exposure, and study site.

[h] Adjusted for maternal race/ethnicity, education, periconceptional active or passive smoking exposure, and study site.

[i] LVOTO associations include COA+AS, COA+VSD, COA+VSD+ASD; RVOTO associations include PVS+VSD, PVS+ASD; septal associations include VSD+ASD.

[j] Adjusted for maternal race/ethnicity.

[k] Adjusted for pre-pregnancy body mass index and study site.

[l] Adjusted for maternal age, education, and periconceptional active or passive smoking exposure.

[m] Adjusted for maternal race/ethnicity, pre-pregnancy body mass index, periconceptional active or passive smoking exposure, and study site.

[n] The control group for PVS had 7515 controls after excluding those who were born before Jan 1, 2002 in California, because cases of PVS in California were not ascertained before that date; 4715 (62.7%) controls reported no periconceptional alcohol consumption, the number of controls reporting 1-4, 5-15, 16-30, and >30 maximum average drinks per month was 1271 (16.9%), 881 (11.7%), 400 (5.3%), and 214 (2.8%), respectively.

[o] Adjusted for education and periconceptional active or passive smoking exposure.

[p] Adjusted for maternal race/ethnicity and education.

AS, aortic stenosis; ASD, atrial septal defect; ASD2, secundum atrial septal defect; CHD, congenital heart defects; CI, confidence interval; COA, coarctation of the aorta; d-TGA, dextro-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; LVOTO, left ventricular outflow tract obstruction; NOS, not otherwise specified; OR, odds ratio; VSD-PM, perimembranous ventricular septal defect; PVS, pulmonary valve stenosis; RVOTO, right ventricular outflow tract obstruction; TOF, tetralogy of Fallot.

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TABLE 4.

Odds Ratios[a] for Associations between Congenital Heart Defects and Maternal Reports of Alcohol Binge Episodes, National Birth Defects Prevention Study, 1997 through 2007

	No alcohol (reference)		Binge drinking status							
			Drinking without a binge episode				Drinking with one or more binge episodes			
	N[b]	%[c]	N[b]	%[c]	OR	95% CI	N[b]	%[c]	OR	95% CI
Control	5041	63.5	1941	24.4			963	12.1		
Isolated simple conotruncal[d]	753	62.3	297	24.6	1.0	[0.9, 1.2]	158	13.1	1.1	[0.9, 1.3]
TOF[e]	369	60.1	159	25.9	1.1	[0.9, 1.4]	86	14.0	1.3	[1.0, 1.7]
d-TGA[f]	262	62.8	97	23.3	1.0	[0.8, 1.2]	58	13.9	1.1	[0.8, 1.5]
Isolated simple septal[e]	1327	65.9	441	21.9	0.8	[0.8, 1.0]	246	12.2	0.8	[0.7, 1.0]
VSD-PM[e]	522	64.8	190	23.6	0.9	[0.8, 1.1]	93	11.6	0.9	[0.7, 1.1]
ASD2[g]	531	68.1	151	19.4	0.9	[0.7, 1.0]	98	12.6	0.8	[0.7, 1.1]
ASD-NOS[h]	178	68.5	52	20.0	0.9	[0.6, 1.3]	30	11.5	0.7	[0.5, 1.2]
Isolated septal association[d,i]	276	64.5	94	22.0	0.9	[0.7, 1.1]	58	13.6	1.1	[0.8, 1.5]
Isolated simple LVOTO[j]	646	66.9	199	20.6	0.7	[0.6, 0.9]	121	12.5	0.9	[0.7, 1.1]
HLHS[k]	258	66.8	76	19.7	0.8	[0.6, 1.1]	52	13.5	1.1	[0.8, 1.5]
COA[l]	237	65.8	84	23.3	0.8	[0.6, 1.1]	39	10.8	0.9	[0.6, 1.3]
AS[m]	145	69.1	38	18.1	0.6	[0.4, 1.0]	27	12.9	0.8	[0.5, 1.3]
Isolated LVOTO association[e,i]	179	65.1	69	25.1	1.0	[0.8, 1.4]	27	9.8	0.8	[0.5, 1.3]

	No alcohol (reference)		Binge drinking status							
			Drinking without a binge episode				Drinking with one or more binge episodes			
	N[b]	%[c]	N[b]	%[c]	OR	95% CI	N[b]	%[c]	OR	95% CI
Isolated simple RVOTO[d]	530	66.0	182	22.7	0.9	[0.7, 1.1]	91	11.3	0.9	[0.7, 1.1]
PVS[d,n]	435	67.2	137	21.2	0.8	[0.7, 1.0]	75	11.6	0.9	[0.7, 1.1]
Isolated RVOTO association[i,o]	141	65.6	49	22.8	1.0	[0.7, 1.4]	25	11.6	0.8	[0.5, 1.3]
Heterotaxy with CHD[p]	152	65.5	48	20.7	1.0	[0.7, 1.4]	32	13.8	1.3	[0.9, 1.9]

[a] Odds ratios were adjusted, where appropriate, for confounding factors that altered the odds ratio for a given subtype of CHDs by at least 10%.

[b] Total number for each CHD may vary across tables due to incomplete or missing data.

[c] Percentage of complete data, may not total 100 due to rounding.

[d] Crude odds ratio was presented because no covariate altered the odds ratio by at least 10%.

[e] Adjusted for periconceptional active or passive smoking exposure.

[f] Adjusted for pre-pregnancy body mass index.

[g] Adjusted for education, periconceptional active or passive smoking exposure, and study site.

[h] Adjusted for maternal race/ethnicity, education, periconceptional active or passive smoking exposure, and study site.

[i] LVOTO associations include COA+AS, COA+VSD, COA+VSD+ASD; RVOTO associations include PVS+VSD, PVS+ASD; septal associations include VSD+ASD.

[j] Adjusted for maternal race/ethnicity.

[k] Adjusted for pre-pregnancy body mass index and study site.

[l] Adjusted for maternal age, education, and periconceptional active or passive smoking exposure.

[m] Adjusted for maternal race/ethnicity, pre-pregnancy body mass index, periconceptional active or passive smoking exposure, and study site.

[n] The control group for PVS had 7515 controls after excluding those who were born before Jan 1, 2002 in California, because cases of PVS in California were not ascertained before that date; 4715 (62.7%) controls reported no periconceptional alcohol consumption, the number of controls reporting dinking without a binge episode and drinking with one or more binge episodes was 1854 (24.7%) and 919 (12.2%), respectively.

[o] Adjusted for education and periconceptional active or passive smoking exposure.

[p] Adjusted for maternal race/ethnicity and education.

AS, aortic stenosis; ASD, atrial septal defect; ASD2, secundum atrial septal defect; CHD, congenital heart defects; CI, confidence interval; COA, coarctation of the aorta; d-TGA, dextro-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; LVOTO, left ventricular outflow tract obstruction; NOS, not otherwise specified; OR, odds ratio; VSD-PM, perimembranous ventricular septal defect; PVS, pulmonary valve stenosis; RVOTO, right ventricular outflow tract obstruction; TOF, tetralogy of Fallot.

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TABLE 5.

Odds Ratios[a] for Associations between Congenital Heart Defects and Maternal Reports of Type of Alcohol Consumed, National Birth Defects Prevention Study, 1997 through 2007

	No alcohol (reference)		Type of alcohol consumed															
			Beer only				Wine only				Distilled spirits only				Two or more types			
	N[b]	%[c]	*N*[b]	%[c]	OR	95% CI	*N*[b]	%[c]	OR	95% CI	*N*[b]	%[c]	OR	95% CI	*N*[b]	%[c]	OR	95% CI
Control	5041	63.3	598	7.5			808	10.2			508	6.4			1009	12.7		
Isolated simple conotruncal[d]	753	62.1	80	6.6	0.9	[0.7, 1.1]	129	10.6	1.1	[0.9, 1.3]	78	6.4	1.0	[0.8, 1.3]	172	14.2	1.1	[1.0, 1.4]
TOF[e]	369	60.0	45	7.3	1.1	[0.8, 1.5]	68	11.1	1.2	[0.9, 1.5]	41	6.7	1.1	[0.8, 1.6]	92	15.0	1.3	[1.0, 1.7]
d-TGA[f]	262	62.5	27	6.4	0.9	[0.6, 1.3]	49	11.7	1.2	[0.8, 1.6]	28	6.7	1.0	[0.7, 1.5]	53	12.7	1.0	[0.7, 1.4]
Isolated simple septal[e]	1327	65.8	151	7.5	0.9	[0.7, 1.1]	177	8.8	0.8	[0.7, 1.0]	151	7.5	1.0	[0.8, 1.2]	212	10.5	0.7	[0.6, 0.9]
VSD-PM[e]	522	64.6	58	7.2	0.9	[0.7, 1.2]	81	10.0	1.0	[0.8, 1.2]	58	7.2	1.0	[0.8, 1.4]	89	11.0	0.8	[0.6, 1.0]
ASD2[g]	531	68.0	59	7.6	0.9	[0.6, 1.2]	58	7.4	0.9	[0.6, 1.2]	61	7.8	1.0	[0.7, 1.3]	72	9.2	0.7	[0.5, 0.9]
ASD-NOS[h]	178	68.5	15	5.8	0.7	[0.4, 1.1]	17	6.5	0.8	[0.4, 1.3]	23	8.9	1.3	[0.8, 2.1]	27	10.4	0.8	[0.5, 1.2]
Isolated septal association[d,i]	276	64.3	39	9.1	1.2	[0.8, 1.7]	35	8.2	0.8	[0.6, 1.1]	27	6.3	1.0	[0.6, 1.5]	52	12.1	0.9	[0.7, 1.3]
Isolated simple LVOTO[j]	646	66.7	63	6.5	0.8	[0.6, 1.0]	87	9.0	0.7	[0.6, 0.9]	66	6.8	0.9	[0.7, 1.2]	106	11.0	0.7	[0.6, 0.9]
HLHS[k]	258	66.8	23	6.0	0.8	[0.5, 1.3]	37	9.6	1.0	[0.7, 1.5]	25	6.5	0.9	[0.6, 1.4]	43	11.1	0.9	[0.6, 1.3]
COA[l]	237	65.8	24	6.7	0.9	[0.6, 1.3]	35	9.7	0.8	[0.5, 1.1]	25	6.9	1.1	[0.7, 1.7]	39	10.8	0.8	[0.5, 1.1]
AS[m]	145	68.4	16	7.6	0.9	[0.5, 1.5]	13	6.1	0.5	[0.2, 0.9]	15	7.1	1.0	[0.6, 1.7]	23	10.9	0.7	[0.4, 1.1]
Isolated LVOTO association[e,i]	179	65.3	17	6.2	0.9	[0.5, 1.5]	23	8.4	0.8	[0.5, 1.3]	17	6.2	1.0	[0.6, 1.7]	38	13.9	1.1	[0.8, 1.6]

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	No alcohol (reference)		Type of alcohol consumed															
			Beer only				Wine only				Distilled spirits only				Two or more types			
	N[b]	%[c]	*N*[b]	%[c]	OR	95% CI	*N*[b]	%[c]	OR	95% CI	*N*[b]	%[c]	OR	95% CI	*N*[b]	%[c]	OR	95% CI
Isolated simple RVOTO[d]	530	65.6	53	6.6	0.8	[0.6, 1.1]	78	9.7	0.9	[0.7, 1.2]	69	8.5	1.3	[1.0, 1.7]	78	9.7	0.7	[0.6, 0.9]
PVS[d,n]	435	66.8	43	6.6	0.8	[0.6, 1.1]	55	8.5	0.8	[0.6, 1.0]	58	8.9	1.3	[1.0, 1.8]	60	9.2	0.7	[0.5, 0.9]
Isolated RVOTO association[i,o]	141	65.6	23	10.7	1.3	[0.8, 2.0]	18	8.4	0.9	[0.5, 1.5]	12	5.6	0.8	[0.4, 1.5]	21	9.8	0.7	[0.5, 1.2]
Heterotaxy with CHD[p]	152	65.2	18	7.7	1.1	[0.7, 1.8]	18	7.7	1.0	[0.6, 1.6]	21	9.0	1.5	[1.0, 2.5]	24	10.3	1.0	[0.6, 1.5]

[a] Odds ratios were adjusted, where appropriate, for confounding factors that altered the odds ratio for a given subtype of CHDs by at least 10%.

[b] Total number for each CHD may vary across tables due to incomplete or missing data.

[c] Percentage of complete data, may not total 100 due to rounding.

[d] Crude odds ratio was presented because no covariate altered the odds ratio by at least 10%.

[e] Adjusted for periconceptional active or passive smoking exposure.

[f] Adjusted for pre-pregnancy body mass index.

[g] Adjusted for education, periconceptional active or passive smoking exposure, and study site.

[h] Adjusted for maternal race/ethnicity, education, periconceptional active or passive smoking exposure, and study site.

[i] LVOTO associations include COA+AS, COA+VSD, COA+VSD+ASD; RVOTO associations include PVS+VSD, PVS+ASD; septal associations include VSD+ASD.

[j] Adjusted for maternal race/ethnicity.

[k] Adjusted for pre-pregnancy body mass index and study site.

[l] Adjusted for maternal age, education, and periconceptional active or passive smoking exposure.

[m] Adjusted for maternal race/ethnicity, pre-pregnancy body mass index, periconceptional active or passive smoking exposure, and study site.

[n] The control group for PVS had 7515 controls after excluding those who were born before Jan 1, 2002 in California, because cases of PVS in California were not ascertained before that date; 4715 (62.7%) controls reported no periconceptional alcohol consumption, the number of controls reporting beer only, wine only, distill spirits only, and two or more types of alcohol consumed was 562 (7.5%), 781 (10.4%), 479 (6.4%), and 970 (12.9%), respectively.

[o] Adjusted for education and periconceptional active or passive smoking exposure.

[p]Adjusted for maternal race/ethnicity and education.

AS, aortic stenosis; ASD, atrial septal defect; ASD2, secundum atrial septal defect; CHD, congenital heart defects; CI, confidence interval; COA, coarctation of the aorta; d-TGA, dextro-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; LVOTO, left ventricular outflow tract obstruction; NOS, not otherwise specified; OR, odds ratio; VSD-PM, perimembranous ventricular septal defect; PVS, pulmonary valve stenosis; RVOTO, right ventricular outflow tract obstruction; TOF, tetralogy of Fallot.