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ORIGINAL RESEARCH

Association of Alcohol Use Diagnostic Codes in Pregnancy and Offspring Conotruncal and Endocardial Cushion Heart Defects

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BACKGROUND: The pathogenesis of congenital heart disease (CHD) remains largely unknown, with only a small percentage explained solely by genetic causes. Modifiable environmental risk factors, such as alcohol, are suggested to play an important role in CHD pathogenesis. We sought to evaluate the association between prenatal alcohol exposure and CHD to gain insight into which components of cardiac development may be most vulnerable to the teratogenic effects of alcohol.

METHODS AND RESULTS: This was a retrospective analysis of hospital discharge records from the California Office of Statewide Health Planning and Development and linked birth certificate records restricted to singleton, live-born infants from 2005 to 2017. Of the 5 820 961 births included, 16 953 had an alcohol-related *International Classification of Diseases, Ninth and Tenth Revisions (ICD-9; ICD-10)* code during pregnancy. Log linear regression was used to calculate risk ratios (RR) for CHD among individuals with an alcohol-related *ICD-9 and ICD10* code during pregnancy versus those without. Three models were created: (1) unadjusted, (2) adjusted for maternal demographic factors, and (3) adjusted for maternal demographic factors and comorbidities. Maternal alcohol-related code was associated with an increased risk for CHD in all models (RR, 1.33 to 1.84); conotruncal (RR, 1.62 to 2.11) and endocardial cushion (RR, 2.71 to 3.59) defects were individually associated with elevated risk in all models.

CONCLUSIONS: Alcohol-related diagnostic codes in pregnancy were associated with an increased risk of an offspring with a CHD, with a particular risk for endocardial cushion and conotruncal defects. The mechanistic basis for this phenotypic enrichment requires further investigation.

Key Words: alcohol ■ cardiac development ■ cardiac outflow tract ■ cardiovascular disease risk factors ■ congenital cardiac defect ■ conotruncal defect ■ endocardial cushion defect ■ pregnancy

Congenital heart disease (CHD) is the most common birth defect in the world, affecting between 4 to12 per 1000 children born each year.[1–3] CHD is the leading cause of non-infectious infant mortality and the most resource-intensive birth defect. Multiple etiologic factors have been implicated in the development of CHD. Some of the non-modifiable risk factors include parental age, consanguinity, and genetic defects. It is well recognized that CHD is highly prevalent in syndromic disorders, including DiGeorge syndrome (22q11.2 deletion) and Down syndrome (trisomy 21).[4] It has been suggested that a genetic cause is likely responsible for 10%–15% of all CHD.[5,6] In contrast, it is estimated that as high as 30% of CHD may be explained by modifiable risk factors, such as use of non-fertility prescription medications, recreational drug use, and environmental toxins.[7,8] We chose to study an important modifiable risk factor: alcohol use during pregnancy.

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CLINICAL PERSPECTIVE

What Is New?

- This analysis of statewide births establishes that congenital heart defects are more commonly associated with the presence of an alcohol-related diagnosis during pregnancy.
- Conotruncal and endocardial cushion defects specifically are enriched with alcohol use during pregnancy.

What Are the Clinical Implications?

- Education and counseling are warranted during pregnancy about the risks of alcohol consumption and congenital heart defects in the fetus.
- Future studies evaluating the mechanistic relationship between the teratogenic effects of alcohol and specific heart defects will help develop approaches to prevent alcohol-related congenital heart defects.

Nonstandard Abbreviations and Acronyms

ASD	atrial septal defect
CCHD	critical congenital heart defect
CHD	congenital heart defect
DORV	double outlet right ventricle
FASD	fetal alcohol spectrum disorder
OSHPD	office of statewide health planning and development
TOF	Tetralogy of Fallot
VSD	ventricular septal defect

A few prior reports have suggested that alcohol use during pregnancy is associated with increased CHD.[9–13] Up to 30% of patients diagnosed with fetal alcohol spectrum disorder may harbor a CHD.[9] However, little information is available on which component of cardiac development may be most vulnerable to the teratogenic effects of alcohol. To address this question, we sought to evaluate the specific sub-type(s) of CHD that might be over-represented in pregnancies with alcohol-related diagnoses. Such an understanding could pave the way for studies to determine the adverse impact of alcohol on specific events during cardiogenesis.

Here, we investigate the association of offspring CHD and a maternal diagnostic code for alcohol use in a hospital discharge, emergency department, or ambulatory surgery record during pregnancy or delivery, using a large California-based administrative database through the San Diego Study of Outcomes in Mothers and Infants.

METHODS

Data Availability

The data, analytic methods, and study materials will not be made available to other researchers for the purposes of reproducibility or replicating the procedure as the data use agreement with the California Office of Statewide Health Planning and Development (OSHPD) prohibits distribution of patient-level data. Data can be requested from OSHPD (https://www.oshpd.ca.gov/HID/HIRC/index.html) by qualified researchers.

Study Population

In this retrospective cohort study conducted by the San Diego Study of Outcomes in Mothers and Infants, the sample was drawn from California live-born singletons from 2005 through 2017, as has been previously described.[14–16] Birth certificates, maintained by California Vital Statistics, were linked to hospital discharge, emergency department, and ambulatory surgery records maintained by OSHPD. These databases contain detailed information on maternal and infant characteristics, hospital discharge diagnoses, and procedures. Hospital discharge, emergency department, and ambulatory surgery files provided diagnoses and procedure codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9*) and *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10*) as reported to the California Office of Statewide Health Planning and Development by the health care facilities. The study sample was restricted to singletons born between 20- and 44-week gestation, with linked birth records for mother and infant, and infants without chromosomal abnormalities or other major structural birth defects (unless they also had a CHD). These noncardiac structural defects for the study were considered "major" if determined by clinical review as causing major morbidity and mortality that would likely be identified in the hospital at birth or lead to hospitalization during the first year of life (Figure 1).[17]

Exposures, Lesions, and Covariates

Because the time-period of this study included years when hospitals were reporting both *ICD-9* and *ICD-10* codes, both were used to identify variables for the study. The presence of an *ICD* code was coded as a "yes" for the purpose of our statistical analysis and lack of an *ICD-9* or *ICD-10* code was coded as a "no."

Maternal alcohol-related diagnoses during pregnancy and maternal comorbidities (preexisting diabetes, non-alcohol substance-related diagnoses during pregnancy, and mental health diagnoses complicating pregnancy) were identified from *ICD-9* and *ICD-10* codes in a hospital discharge, emergency department,

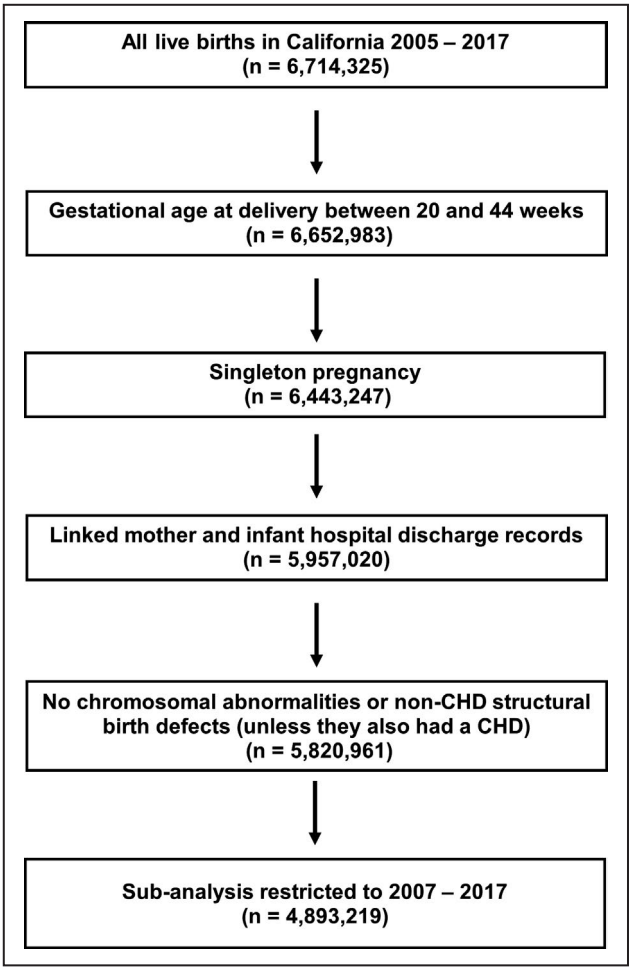

Figure 1. Selection of samples for study from the California Office of Statewide Health Planning and Development.
All infant and maternal information was obtained from hospital discharge, emergency department, or ambulatory surgery records through the California Office of Statewide Health Planning and Development. Only singleton, live-births were analyzed for which linked mother-infant records were available. Accounting for the widespread impacts of chromosomal abnormalities that may mask the specific actions of alcohol use during pregnancy, only infants without chromosomal abnormalities with a congenital heart defect were analyzed. A subset of infants was further examined between 2007 and 2017, during which time pre-pregnancy body mass index and maternal nicotine-related diagnostic codes were collected allowing for statistical analysis controlling for these potential confounding variables known to be associated with congenital heart defects.

or ambulatory surgery records during pregnancy or delivery as has been utilized in previous studies (Table S1).[18–20]

Maternal race and ethnicity was also drawn from birth certificate records, as were maternal age, education, parity, and payer for delivery. Public insurance as the payer source was used as a proxy for low economic status. Maternal pre-pregnancy body mass index (BMI; calculated from pre-pregnancy weight and height) was used to classify maternal obesity (BMI ≥30 kg/m^2). Instances where one of these covariates was not present in the mother or infant's records were recorded as "missing." *ICD-9* and *ICD-10* codes for nicotine-related diagnoses (Table S1) were only available in a subset of the years analyzed, 2007 to 2017, and therefore were examined only in those years (Table S2). Nicotine exposure status was also assessed from self-reported tobacco use included in the infant's birth certificate and coded as present if noted in any of the sources. The covariates in this study were selected a priori based on assumptions about the underlying biologic mechanisms of birth defect pathogenesis and epidemiology and are in accordance with consensus in the relevant literature.[21–23]

Infant CHDs were defined from *ICD-9* and *ICD-10* codes in a hospital discharge, emergency department, or ambulatory surgery record any time during the first year of the infant's life, as has been utilized in previous studies (Table S1).[8,16,24,25] The inclusion of these defects in the infant's record(s) and documentation with an *ICD-9* or *ICD-10* code require a definitive diagnosis and as such must have been diagnosed by echocardiogram or another advanced modality such as cardiac MRI or CT. CHD was grouped as critical and non-critical, wherein a critical CHD (CCHD) was defined as requiring urgent and significant intervention to prevent major morbidity and mortality.[26] Atrial septal defect (ASD), ventricular septal defect (VSD), the simultaneous presence of an ASD and VSD, and additional defects that did not meet the definition of a CCHD (categorized as "other") were considered non-critical congenital heart defects. Common arterial trunk, transposition of the great vessels, Tetralogy of Fallot (TOF), double outlet right ventricle (DORV), single common ventricle, endocardial cushion defect, anomalies of the pulmonary valve, tricuspid atresia and stenosis, Ebstein's anomaly, congenital stenosis of the aortic valve, hypoplastic left heart syndrome, coarctation of the aorta, and anomalies of the great veins were considered CCHDs. Common arterial trunk, transposition of great vessels, DORV, TOF, anomalies of pulmonary valve, and congenital stenosis of the aortic valve were considered to be abnormalities of the outflow tract.[23]

Statistical Analysis

Maternal characteristics (race and ethnicity, age at delivery, education, parity, and payer for delivery) and comorbidities (preexisting diabetes, non-alcohol substance-related code during pregnancy, and mental health diagnosis complicating pregnancy) were compared between mothers with and without an alcohol-related diagnosis during pregnancy using Chi-square statistics.

Log-linear regression with complete case analysis was used to calculate the risk ratios (RR) and 95% confidence intervals (CI) of an infant with a CHD (any and

by subgroup) among mothers with an alcohol-related diagnosis during pregnancy versus mothers who did not have an alcohol-related diagnosis code. Three models were estimated: (1) unadjusted, (2) adjusted for maternal demographic factors, and (3) adjusted for maternal demographic factors and comorbidities.

To measure the robustness of findings, we performed a number of sensitivity analyses. First, we limited the data to the years where pre-pregnancy BMI and nicotine were captured on birth records (2007–2017) and repeated multivariable models with additional adjustment for pre-pregnancy obesity and the presence of a nicotine-related diagnostic code during pregnancy. Second, administrative databases may have sub-adequate capture of important confounders such as nutritional status, nicotine, other substance use and obesity,[27,28] leading to residual confounding even upon multivariable adjustment. Thus, we calculated the e-value, or the strength of an unmeasured confounder necessary to negate the observed multivariable exposure-outcome association, as has been previously reported.[18] E-values were computed for "any cardiac defect," "endocardial cushion defect," and "abnormalities of the cardiac outflow tract" in fully adjusted models both with and without nicotine adjustment (R package *episensr*). The e-value is the minimum strength of the association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome, conditional on the measured covariates, to fully explain away the observed exposure-outcome association.[29,30] By reporting the association on the risk ratio scale, the e-value is appropriate for both rare outcomes (such as ours), but also for common outcomes with a simple transformation of the equation.[30]

A P value of <0.05 was considered significant for all analyses. Per institutional review board restrictions, no n's <5 were displayed. All analyses were performed using Statistical Analysis Software version 9.4 (Cary, NC) or R 4.0.5. Methods and protocols for the study were approved by the Committee for the Protection of Human Subjects within the Health and Human Services Agency of the State of California and the University of California San Diego Institutional Review Board; the requirement for informed consent was waived.

RESULTS

Characteristics of Study Sample

A total of 5 820 961 births were included in the analysis. Half of the mothers in the cohort (50.2%) were of Hispanic ethnicity, most (78.8%) were between 18 and 34 years of age, 49.4% had more than 12 years of education, and 47.1% had public insurance for delivery. Of individuals in the sample, 16 953 (0.29%) had a diagnostic code for alcohol use during pregnancy. Individuals with an alcohol-related code during pregnancy differed significantly from those without on every demographic factor and comorbidity measured (Table 1).

Relationship Between CHD and Presence of an Alcohol-Related Diagnostic Code During Pregnancy

The prevalence of CHD was greater in infants born to individuals with an alcohol-related diagnostic code during pregnancy versus those without (2.86% versus 1.55%; Model 3 RR, 1.33; 95% CI, 1.21–1.46; Table 2). Individuals with an alcohol-related code during pregnancy were at increased risk for having an infant with a non-critical CHD and CCHD even after adjusting for maternal demographics and comorbidities (Model 3 non-critical CHD RR, 1.28; 95% CI, 1.15–1.42; CCHD RR, 1.52; 95% CI, 1.26–1.84; Table 2). Sensitivity analysis of the subset of data from years containing pre-pregnancy BMI and nicotine-related diagnostic codes during pregnancy continued to demonstrate infants born to individuals with an alcohol-related diagnostic code during pregnancy were at increased risk for any CHD, non-critical CHD, and CCHD (Model 3 CHD RR, 1.27; 95% CI, 1.15–1.40; non-critical CHD RR, 1.21; 95% CI, 1.08–1.36; CCHD RR, 1.48; 95% CI, 1.20–1.81; Table S3).

CHD Sub-Types Associated with Alcohol-Related Diagnostic Code Presence During Pregnancy

Infants born to individuals with an alcohol-related diagnostic code were found to have a significant risk for nearly all forms of non-critical CHD, across all 3 statistical models, compared with those without. The lone exception was isolated VSD which was only significant in Models 1 and 2 (Model 2 RR, 1.42; 95% CI, 1.09–1.85; Table S4). The most common non-critical lesion was an isolated ASD affecting 1% of those with an associated alcohol-related diagnostic code compared with 0.57% of those without (Model 3 RR, 1.19; 95% CI, 1.02–1.39; Table S4). This was followed by "other" (0.63% versus 0.29%; Model 3 RR, 1.36; 95% CI 1.12–1.66; Table S4) and then the combined presence of an ASD and VSD (0.19% versus 0.11%; Model 3 RR, 1.52; 95% CI, 1.06–2.17; Table S4). These lesions suffer from screening bias in diagnosis, as well as challenges in newborn diagnosis such as distinguishing between an ASD and patent foramen ovale.[31] These lesions were thus included in the overall non-critical CHD category of the main analysis and sub-analysis (Table 2 and Table S3), but individual lesions were analyzed separate from the rest of the specific lesions, which do not carry the same diagnostic bias (Table S4).

Table 1. Maternal Characteristics of Individuals by *ICD-9* and *ICD-10* Code for Alcohol Use Affecting the Fetus, San Diego Study of Outcomes in Mothers and Infants, 2005 to 2017

	Total sample	No alcohol-related diagnostic code	Alcohol-related diagnostic code	
	n (%)	n (%)	n (%)	*P* value
Sample	5 820 961	5 804 008	16 953	
Maternal demographic factors				
Race and ethnicity				<0.0001
Hispanic	2 922 678 (50.2)	2 916 059 (50.2)	6619 (39.0)	
Non-Hispanic				
White	1 578 784 (27.1)	1 572 539 (27.1)	6245 (36.8)	
Black	291 495 (5.0)	289 235 (5.0)	2260 (13.3)	
Asian	771 232 (13.3)	770 770 (13.3)	462 (2.7)	
American Indian/Alaska Native	9576 (0.2)	9463 (0.2)	113 (0.7)	
Native Hawaiian/Pacific Islander	23 491 (0.4)	23 398 (0.4)	93 (0.6)	
Missing	97 967 (1.7)	97 646 (1.7)	321 (1.9)	
Other*	158 805 (2.7)	157 759 (2.7)	1046 (6.2)	
Maternal age at delivery (y)				<0.0001
<18	138 579 (2.4)	137 936 (2.4)	643 (3.8)	
18–34	4 585 577 (78.8)	4 571 806 (78.8)	13 771 (81.2)	
>34	1 096 600 (18.8)	1 094 061 (18.9)	2539 (15.0)	
Missing	205 (0.0)	205 (0.0)	0 (0.0)	
Education (y)				<0.0001
<12	1 298 970 (22.3)	1 294 211 (22.3)	4759 (28.1)	
12	1 427 603 (24.5)	1 421 911 (24.5)	5692 (33.6)	
>12	2 877 135 (49.4)	2 871 369 (49.5)	5766 (34.0)	
Missing	217 253 (3.7)	216 517 (3.7)	736 (4.3)	
Parity				<0.0001
Nulliparous	2 260 599 (38.8)	2 253 994 (38.8)	6605 (39.0)	
Multiparous	3 556 264 (61.1)	3 545 950 (61.1)	10 314 (60.8)	
Missing	4098 (0.1)	4064 (0.1)	34 (0.2)	
Payer for delivery				<0.0001
Public	2 739 911 (47.1)	2 728 857 (47.0)	11 054 (65.2)	
Not public	3 081 050 (52.9)	3 075 151 (53.0)	5899 (34.8)	
Maternal comorbidities				
Preexisting diabetes	50 140 (0.9)	4 9793 (0.9)	347 (2.1)	<0.0001
Drug use code during pregnancy	101 808 (1.8)	86 483 (1.5)	6299 (37.2)	<0.0001
Mental health diagnosis complicating pregnancy	252 326 (4.3)	242 375 (4.2)	9951 (58.7)	<0.0001

*Includes those who were documented as “other race and ethnicity” or documented as having 2 or more races/ethnicities.

Initial examination of the composition of CCHD lesions between infants born to individuals with a code for alcohol and those without demonstrated a greater degree of heterogeneity amongst offspring born to individuals without an associated alcohol code (Figure 2). The most common lesion was anomalies of the pulmonary valve in both groups comprising 29% of all CCHD in infants born to those without and 38% in those with alcohol-related diagnoses. To further shed light on the specific defects over-represented in children born to individuals with an alcohol-related diagnosis in pregnancy, we utilized the segmental approach to classify CCHD lesions, beginning with inflow defects and ending with the great arteries.[32] No statistical difference in risk was found for anomalies of the great veins (Table 2). Children born to individuals with

Table 2. Adjusted Relative Risk for Associations Between Congenital Heart Defects and *ICD-9* and *ICD-10* Code for Alcohol Use Affecting the Fetus, San Diego Study of Outcomes in Mothers and Infants, 2005 to 2017

	Alcohol-related diagnostic code	No alcohol-related diagnostic code	Model 1: Unadjusted	Model 2: Adjusted for Maternal Demographics	Model 3: Adjusted for Maternal Demographics and Comorbidities
	n (%)	n (%)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Sample	16 953	5 804 008			
No congenital heart defect	16 468 (97.1)	5 713 803 (98.45)	Reference	Reference	Reference
Any congenital heart defect	485 (2.86)	90 205 (1.55)	1.84 (1.68–2.01)*	1.73 (1.58–1.89)*	1.33 (1.21–1.46)*,†
Any non-critical congenital heart defect	365 (2.15)	70 158 (1.21)	1.79 (1.61–1.98)*	1.68 (1.51–1.86)*	1.28 (1.15–1.42)*
Any critical congenital heart defect	120 (0.71)	20 047 (0.35)	2.04 (1.71–2.45)*	1.93 (1.60–2.32)*	1.52 (1.26–1.84)*
Anomalies of great veins	12 (0.07)	2603 (0.04)	1.59 (0.90–2.80)	1.56 (0.86–2.82)	1.17 (0.64–2.15)
Endocardial cushion defect	13 (0.08)	1247 (0.02)	3.59 (2.08–6.20)*	3.27 (1.85–5.78)*	2.71 (1.49–4.90)*,‡
Tricuspid atresia and stenosis	9 (0.05)	1730 (0.03)	1.79 (0.93–3.45)	1.57 (0.78–3.15)	0.86 (0.42–1.75)
Ebstein's anomaly	§	591 (0.01)	n/a‖	n/a‖	n/a‖
Hypoplastic left heart syndrome	10 (0.06)	2070 (0.04)	1.67 (0.89–3.10)	1.39 (0.72–2.68)	1.32 (0.68–2.59)
Single common ventricle	§	1240 (0.02)	n/a‖	n/a‖	n/a‖
Abnormalities of the cardiac outflow tract	77 (0.45)	12 533 (0.22)	2.11 (1.69–2.64)*	2.02 (1.60–2.54)*	1.62 (1.27–2.05)*,¶
Coarctation of the aorta	18 (0.11)	4078 (0.07)	1.52 (0.96–2.42)	1.30 (0.80–2.13)	1.15 (0.70–1.90)

*$P<0.05$.
†e-value RR 1.99, lower CI 1.71.
‡e-value RR 4.86, lower CI 2.34.
§Not displayed when n<5.
‖Relative Risk (RR) not calculated when n<5.
¶e-value RR 2.62, lower CI 1.86.

an alcohol-related code were at increased risk for an endocardial cushion defect (Model 3 RR 2.71, 95% CI 1.49, 4.90). No significant risk was found amongst defects related to individual atrioventricular valves (tricuspid atresia and stenosis, Ebstein's anomaly), or ventricles (hypoplastic left heart syndrome, single common ventricle). Abnormalities of the outflow tract (including common arterial trunk, transposition of the great arteries, DORV, TOF, anomalies of the pulmonary valve, and congenital stenosis of the aortic valve) were increased in children born to individuals with an alcohol-related code during pregnancy (Model 3 RR, 1.62; 95% CI, 1.27–2.05). Coarctation of the aorta was not found to have an associated significant risk. Both endocardial cushion defect (Model 3 RR, 3.30; 95% CI, 1.81–6.02; Table S3) and abnormalities of the outflow tract (Model 3 RR, 1.52; 95% CI, 1.17–1.97; Table S3) maintained significance when examining the subset of data containing pre-pregnancy BMI and nicotine-related diagnostic codes during pregnancy.

Outflow tract development consists of several crucial events resulting in full maturation, including alignment, septation, rotation, and subsequent remodeling. Abnormalities in these events lead to distinct CHD phenotypes. We, therefore, analyzed the sub-types of lesions within the abnormalities of the outflow tract category. Only anomalies of the pulmonary valve were found to reach significance across all 3 statistical models (Model 3 RR 1.96, 95% CI 1.43, 2.67; Table 3). Transposition of the great vessels trended toward significance, however the number of children with transposition was fewer than 20 and significance was not reached when controlling for maternal demographics. While TOF did reach significance when controlling for maternal demographics (Model 2 RR 1.84, 95% CI 1.16, 2.92; Table 3), it lost significance when further controlling for comorbidities, also likely related to the small numbers. This suggests that outflow tract alignment (anomalies of the pulmonary valve and TOF) more so than septation (common arterial truncus) or rotation

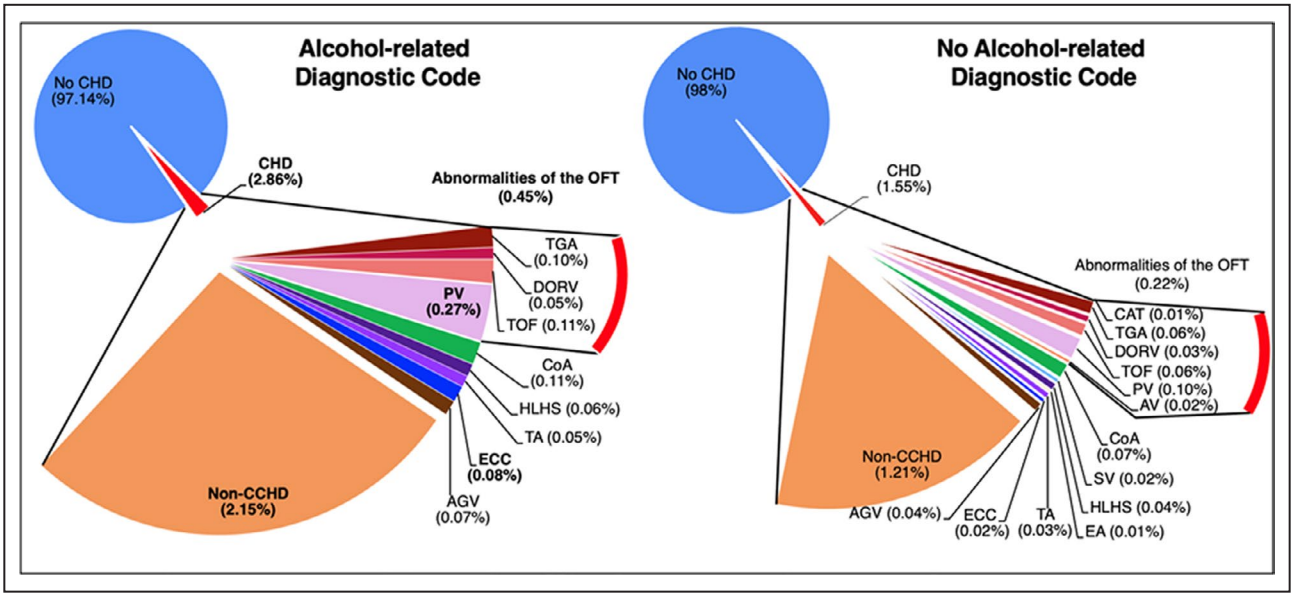

Figure 2. Proportion of Individual Lesions in Congenital Heart Defect Populations with Prenatal Alcohol Exposure Compared to Unexposed.

Comparison of the lesions within exposed (Alcohol-related Diagnostic Code – mother or infant had an associated *ICD-9/10* code for alcohol use affecting the fetus, n=16 953) and unexposed (No Alcohol-related Diagnostic Code; n=5 804 008) individuals demonstrated exposed individuals had a higher incidence of congenital heart defects (n=485, 2.86%) compared with unexposed (n=90 205, 1.55%). Exposed individuals additionally had a higher incidence of critical CHDs (CCHD) requiring intervention than unexposed (n=120 vs n=20 047, 0.71% vs 0.35%). Amongst exposed vs unexposed, endocardial cushion defects (ECC, n=13 vs n=1247, 0.08% vs 0.02%) and abnormalities of the cardiac outflow tract (OFT) were the most common critical CHD lesions (n=77 vs n=12 533, 0.45% vs 0.22%). Percentages shown are of total participants in each exposure group. Due to the non-exclusive nature of CHDs in the data set, the sum of percentages shown of each individual CHD is not equal to the total percentage of participants in each exposure group that have any CHD. Bold = lesions that have significantly increased relative risk across statistical models. AGV indicates Anomalies of the Great Veins; AV, Congenital stenosis of the aortic valve; CAT, Common Arterial Truncus; CoA, Coarctation of the Aorta; DORV, Double Outlet Right Ventricle; EA, Ebstein's Anomaly; ECC, Endocardial Cushion Defect; HLHS, Hypoplastic Left Heart Syndrome; PV, Anomalies of the pulmonary valve; SV, Single Common Ventricle; TA, Tricuspid Atresia and Stenosis; TGA, Transposition of the Great Arteries; and TOF, Tetralogy of Fallot.

(transposition of the great arteries) defects may be more associated with alcohol use during pregnancy.

Bias Analysis Accounting for Additional Confounders

In the bias analysis, once again there was a significant difference for all maternal demographic factors and co-morbidities between those with an alcohol-related diagnostic code and those without, with the single exception being pre-pregnancy obesity (P=0.605). We found that unmeasured confounders would need to increase both the likelihood of having an alcohol-related diagnosis and the likelihood of a cardiac defect by 56% (RR 1.86, lower CI 1.56) to negate the observed adjusted risk ratio of 1.27 (Table S3). A confounder would need to increase likelihood of outcome and exposure by 202% to negate the observed adjusted risk ratio of 3.30 for endocardial cushion defect (RR 6.05, lower CI 3.02; Table S3) and by 62% to negate the adjusted risk ratio of 1.52 of cardiac outflow tract abnormalities (RR 2.41, lower CI 1.62; Table S3).

DISCUSSION

A substantial portion of heart development in humans is complete by the sixth week of pregnancy, which also is on average when pregnancy is discovered. A majority of U.S. women of childbearing age report consuming alcohol, with almost a third consuming alcohol during pregnancy, mainly in the first trimester.[9,33] Combined with the fact that nearly half of pregnancies are unplanned,[34] these data demonstrate widespread risk for unintentional alcohol use during the first trimester of pregnancy when organogenesis, including heart development, occurs. Hence, studying the association between maternal alcohol use diagnostic codes and CHD is of intrinsic scientific merit. We studied population data from hospital records of over 5 million children in the state of California. After accounting for maternal age, race and ethnicity, diabetes, substance use, mental health disorders, and excluding major chromosomal abnormalities, these analyses demonstrated that alcohol-related diagnoses during pregnancy are associated with an increased

Table 3. Adjusted Relative Risk for Associations Between Cardiac Outflow Tract Defects and *ICD-9* Code for Alcohol Use Affecting the Fetus, San Diego Study of Outcomes in Mothers and Infants, 2005 to 2017

	Alcohol-related diagnostic code	No alcohol-related diagnostic code	Model 1: Unadjusted	Model 2: Adjusted for Maternal Demographics	Model 3: Adjusted for Maternal Demographics and Comorbidities
	n (%)	n (%)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Abnormalities of the cardiac outflow tract	77 (0.45)	12 533 (0.22)	2.11 (1.69–2.64)*	2.02 (1.60–2.54)*	1.62 (1.27–2.05)*
Common arterial truncus	†	472 (0.01)	n/a‡	n/a‡	n/a‡
Transposition of great vessels	17 (0.10)	3615 (0.06)	1.62 (1.01–2.61)*	1.58 (0.97–2.58)	1.46 (0.88–2.41)
DORV	9 (0.05)	1933 (0.03)	1.60 (0.83–3.09)	1.66 (0.86–3.19)	1.39 (0.71–2.72)
Tetralogy of Fallot	19 (0.11)	3444 (0.06)	1.90 (1.21–2.98)*	1.84 (1.16–2.92)*	1.42 (0.88–2.28)
Anomalies of pulmonary valve	46 (0.27)	5823 (0.10)	2.72 (2.03–3.63)*	2.48 (1.84–3.36)*	1.96 (1.43–2.67)*
Congenital stenosis of aortic valve	†	964 (0.02)	n/a‡	n/a‡	n/a‡

DORV indicates double outlet right ventricle.
* $P<0.05$.
† Not displayed when n<5.
‡ Relative Risk (RR) not calculated when n<5.

prevalence of all forms of CHD, both non-critical and CCHD, in the offspring.

Prior work on individuals with fetal alcohol spectrum disorder (FASD), often characterized by exposure to chronic drinking throughout pregnancy, has shown that more than 28% of children recognized as having an FASD harbor a CHD.[10,35] A major strength of the current study is the use of California OSHPD administrative data, which allowed for inclusion of all statewide births, rather than from a single institution or small networks. This eliminated sampling biases inherent in existing studies, as well as bias introduced by sample restriction to those who were already seeking care, as information was collected during obstetric care and not solely during treatment of the infant's CHD.[10,36] Our findings contribute to the growing literature that alcohol exposure during pregnancy is a modifiable risk factor not just in neurologic development, but also for cardiac development. Efforts to increase awareness and education about the risks can modify behavior to avoid maternal alcohol consumption. In addition, the potential impact of dietary modifications, such as folate ingestion, to counteract the effect of alcohol have been studied in the context of neurologic development and may have relevance in CHD as well.[13,37–42] We were unable to evaluate the impact of maternal dietary folate consumption or supplementation in this study due to lack of these data in the data set.

Understanding the specific type(s) of CHD that are more frequent in children prenatally exposed to alcohol would allow us to decipher which aspect of cardiac development is particularly vulnerable to the teratogenicity of alcohol. The heart develops from cardiogenic mesodermal cells from 2 distinct sub-populations, namely the first (FHF) and second heart field (SHF).[21] Whereas FHF contributes to the majority of the atria and all of the left ventricle, the SHF contributes to the right ventricle and both outflow tracts. Cells from the cardiac neural crest migrate down to septate the outflow tract. Pro-epicardial cells form the epicardium of the heart. It is possible, in fact likely, that alcohol has a variable impact on these different developmental pathways. There has been conflicting evidence on which specific CCHD lesions in children are most associated with prenatal alcohol exposure.[9,10,35] Our findings are concordant with prior studies showing that outflow tract defects occur more frequently in children with prenatal alcohol exposure.[43] Interestingly, common arterial trunk was not observed in children born to individuals with an associated alcohol use code, implying that outflow tract septation may not be affected by alcohol exposure. Rotation defects, primarily transposition, did not remain significant after accounting for maternal characteristics. DORV codes as used in our study cohort did not allow for further granularity in terms of normally related or malposed great vessels. As such, rotational defects also appear to be susceptible to a lesser extent to the teratogenic effects of alcohol. Pulmonary valve abnormalities followed by TOF were the outflow tract lesions most likely to be associated with prenatal alcohol exposure. We thus interpret the results of this study to indicate that outflow tract

alignment and subsequent maturation events are most impacted by maternal alcohol use.

Another unique aspect of our study is that in our cohort, endocardial cushion defects, also known as an atrioventricular canal defects, were also associated with prenatal alcohol exposure. The atrioventricular valves are formed by both FHF and posterior SHF cells. Endocardial cushion defects have been observed in an animal model of prenatal alcohol exposure in which alcohol exposure was targeted to the timepoint when SHF progenitors begin specification (between embryonic days 6 and 7) and are most vulnerable.[38] Mutations in *Tbx1*, a crucial transcription factor for posterior SHF proliferation and differentiation that is associated with DiGeorge syndrome, leads to endocardial cushion defects.[44] Thus, the higher prevalence of outflow tract alignment and endocardial cushion defects may result from abnormalities in the SHF, which would indicate that SHF cells are somehow uniquely susceptible to alcohol-induced teratogenicity. Endocardial to mesenchymal transformation (EMT) plays a critical role in the development of both atrioventricular and semilunar valves. Thus, an alternative interpretation could be that alcohol exposure specifically affects EMT leading to endocardial cushion defects (atrioventricular valve impact) and pulmonary valve abnormalities (semilunar valve impact). It is also possible that specific molecular pathways that play a role in outflow tract alignment and endocardial cushion maturation are particularly susceptible to alcohol, thereby leading to a preponderance of these 2 CHD subtypes. Notch signaling and TGF-β signaling pathways are examples of molecular pathways relevant to both of these developmental processes.[45–49] Further research is required to decipher a potential molecular basis for the CHD subtypes observed following alcohol exposure.

It is likely that alcohol interacts with other risk factors, including teratogens, to impact heart development, and the concomitant presence of these factors impacts the phenotypic expression. In this regard, gene-environment interactions are of particular significance. This has been examined in an animal study of prenatal alcohol exposure and limb development,[50] wherein prenatal alcohol exposure in mice carrying heterozygous mutations for *Sonic Hedgehog* and *Gli* genes resulted in a higher incidence of forelimb defects than prenatal alcohol exposure in genetically wild-type mice. A minority of CHD cases can be ascribed to a monogenic cause.[10,13] In other cases, it is conceivable that a genetic mutation, which by itself may not result in a phenotypic lesion, establishes a permissive genetic environment. The addition of a teratogen, such as alcohol, to this susceptible environment could result in an increased incidence of CHD. This effect may be further exacerbated if specific mutations in crucial developmental pathways establish a genetic background that is uniquely susceptible to the teratogenic effects of acute prenatal alcohol exposure. In this regard, population studies identifying defects in specific genetic pathways in children with alcohol-related CHD are a necessary future step to fully understand the incomplete penetrance and phenotypic variability documented in this field of research.

There are important limitations to our work. The first consideration is that as with any observational study, confounding is always of concern. We selected potential confounders a priori to reflect the documented relationship between maternal sociodemographic and prenatal factors and adverse birth outcomes. Although the level of confounding necessary to fully explain our findings in bias analyses gives confidence in our results, the true magnitude of the association may differ. Further, administrative data are limited not only in the confounders captured, but also by the potential for misclassification of exposures and outcomes based on frequency of interaction with providers, system-level differences in documenting and capture of information, and the reliance of data that were not captured for research purposes. These limitations, which are well documented with respect to administrative data, should be considered when interpreting the results.

A limitation specific to this study is the reliance on *ICD-9 and ICD-10* codes for exposure classification. The incidence of and phenotypic variability in CHD associated with prenatal alcohol exposure may be related to the timing, duration, and dosage of alcohol exposure.[10] It is known that alcohol consumption behavior, both in relation to temporality and dosage, varies greatly.[51] Our study is unable to directly address these differences due to the use of diagnostic codes to define exposure. *ICD-9 and ICD-10* codes only capture cases of maternal drinking during pregnancy that both rose to the attention of the provider and were judged severe enough to warrant assignment of this diagnostic code. The low sensitivity of this metric means that the study's underlying bias is likely toward the null, as the ability to capture mild or moderate alcohol use during pregnancy is low and these women would be classified as unexposed. It is likely that much of the alcohol consumption captured in our study is mainly chronic or binge drinking of larger quantities of alcohol and that our work may have greatest relevance in comparison to studies of these forms of exposure rather than mild exposure. Further, modification of effects by chronicity and dosage of alcohol likely exist for presence of any defect as well as with specific lesions such as TOF, the severity of the associated malformation, as well as the extent and composition of epigenetic modifications resulting from alcohol exposure.[10,35,52,53] These inquiries are not possible in administrative data that relies on *ICD-9 and ICD-10* codes, and should be assessed in future work. However, the fact CHD

reached significance across our statistical models demonstrates the robust nature of our results.

We must consider as well that alcohol use is often associated with polysubstance use.[54–60] We controlled for the presence of *ICD-9 and ICD-10* codes indicating substance-related diagnoses during pregnancy—these codes included broad-based categories of use of cannabis, hallucinogens, cocaine, amphetamine, sedatives, and non-prescription use of opioids and anti-depressants. As with documentation of alcohol exposure, there were severe limitations on identifying individual substances used, frequency of use, and quantity used. Importantly, these administrative data do not contain information on use of specific psychotropic drugs such as serotonin reuptake inhibitors and lithium, which may impact heart development.[61–65] While we controlled for the presence of *ICD-9 and ICD-10* codes for mental health diagnoses in addition to adjusting for general substance-related diagnoses, these do not completely mitigate unexplained confounding.

One substance with particularly strong relevance to CHD pathogenesis and concurrent use with alcohol that we were able to capture, is nicotine.[60,66,67] Only a subset of the total time-period covered by this data set included collection of nicotine-related diagnostic codes. To allow for examination of nicotine's impact on our data, we performed a sensitivity analysis where we limited the analysis to years with nicotine captured on birth records (in addition to maternal pre-pregnancy BMI), observing some attenuation but, overall, little change in our results.

Socioeconomic status is also known to be associated with CHD prevalence.[8] While we adjusted for socioeconomic status by controlling for those on public insurance, we would have liked to have adjusted for mothers being a recipient of the Special Supplemental Nutrition Program for Women, Infants and Children (WIC) as an additional way to capture socioeconomic status. It is additionally important to consider the geographic restrictions of our analysis, given that all cases and controls were from California and as such cannot control for regional and environmental exposure differences outside of the state.

Finally, many lesions failed to reach significance despite demonstrating a percentage difference compared with those without maternal alcohol use diagnostic codes. This may be due to the small number of individuals with those lesions as well as the fact that presence of a defect was determined by presence of a relevant *ICD-9* or *ICD-10* code which may lead to misclassification in instances where the code was omitted in the hospital discharge summary. Given that there is likely no differential rate of such an omission based on any individual's exposure or outcome status, this would also add bias toward the null hypothesis given the potential for missed diagnoses. Certain lesions may reach significance in a larger cohort and the presence of such a bias adds to the power of our findings where statistical significance was found.

Recognizing these various limitations, we reported the e-value on adjusted models of cardiac defects, endocardial cushion defects and cardiac outflow tract anomalies to determine the extent to which confounding resulting from uncaptured or poorly captured variables would need to be present to fully explain our findings. The e-values reported for all 3 demonstrated any such confounding variable would have to increase the likelihood of the lesion and presence of an alcohol-related diagnosis by more than 50%. Therefore, we believe the significant associations established by our statistical models are robust despite the limitations of the data set.

In summary, our study demonstrates that alcohol exposure during pregnancy, as established by the presence of an alcohol-related *ICD-9 and ICD-10* code for alcohol use affecting the fetus, is associated with complex CHD, and conotruncal and endocardial cushion defects are particularly enriched in this group. Future research should focus on the mechanistic basis for the phenotypic variability and particular enrichment of specific heart defects with alcohol use during pregnancy.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. ICD codes used in the study

	ICD-9	ICD-10
Alcohol-related diagnostic codes		
Alcohol dependence (maternal record)	303	F10
Alcohol abuse (maternal record)	305.0	F10
Newborn affected by maternal use of alcohol (infant record)	760.71	P04.3, Q86.0
Maternal comorbidities (all from maternal record unless otherwise indicated)		
Preexisting diabetes	648.0, 249, 250	O24.0, O24.1, O24.2, O24.3, E10, E11, E12, E13, E14, P70.1 (infant)
Other substance-related diagnosis pregnancy	304, 305.2, 305.3, 305.4, 305.5, 305.6,	P04.4, F11, F12, F13, F14, F15, F16, F18, F19

	305.7, 305.8, 305.9, 648.3	
Mental health diagnosis complicating pregnancy	648.4	O99.3
Nicotine-related diagnoses	649.0	305.1, Z72.0, F17.2, P04.2
Congenital heart defects (all from infant record)		
Atrial Septal Defect	754.4,	Q21.0, Q21.2
Ventricular Septal Defect	745.5	Q21.1, Q21.2
Common arterial truncus	745.0	Q20.0
Transposition of great vessels	745.1	Q20.1, Q20.2, Q20.3, Q20.5, Q20.8
Double outlet right ventricle	745.11	Q20.1
Tetralogy of Fallot	745.2	Q21.3
Single common ventricle	745.3	Q20.4

Endocardial cushion defect	745.6	Q21.2
Other bulbus cordis anomalies and anomalies of cardiac septal closure	745.8	Q20.8
Unspecified defect of septal closure	745.9	Q21.9
Congenital pulmonary valve anomaly	746.0	Q22.0, Q22.1, Q22.2, Q22.3
Congenital tricuspid atresia and stenosis	746.1	Q22.4, Q22.6, Q22.8, Q22.9
Ebstein's anomaly	746.2	Q22.5
Congenital stenosis of aortic valve	746.3	Q23.0
Congenital insufficiency of aortic valve	746.4	Q23.1
Congenital mitral stenosis	746.5	Q23.2
Congenital mitral insufficiency	746.6	Q23.3

Hypoplastic left heart syndrome	746.7	Q23.4
Other specified anomalies of heart	746.8	Q23.8, Q23.9, Q24.0, Q24.1, Q24.2, Q24.3, Q24.4, Q24.5, Q24.6, Q24.8
Unspecified congenital anomaly of heart	746.9	Q20.9, Q24.9
Coarctation of the aorta	747.1	Q25.1
Other anomalies of aorta	747.2	Q25.2, Q25.3, Q25.4, Q25.8, Q25.9
Anomalies of pulmonary artery	747.3	Q25.5, Q25.6, Q25.71, Q25.72, Q25.79
Anomalies of great veins	747.4	Q26.0, Q26.1, Q26.2, Q26.3, Q26.4, Q26.8, Q26.9

Table S2. Maternal Characteristics of Individuals by ICD-9 and ICD-10 Code for Alcohol Use Affecting the Fetus, San Diego Study of Outcomes in Mothers and Infants, 2007-2017

	Total sample	No alcohol-related diagnostic code	Alcohol-related diagnostic code	
	n (%)	n (%)	n (%)	p-value
Sample	4,893,219	4,878,537	14,682	
Maternal Demographic Factors				
Race/ethnicity				< 0.0001
Hispanic	2,469,657 (50.5)	2,463,696 (50.5)	5,961 (40.6)	
Non-Hispanic				
White	1,285,413 (26.3)	1,280,270 (26.2)	5,143 (35.0)	
Black	246,502 (5.0)	244,540 (5.0)	1,962 (13.4)	
Asian	666,740 (13.6)	666,347 (13.7)	393 (2.7)	
American Indian/Alaska Native	9,576 (0.2)	9,463 (0.2)	113 (0.8)	
Native Hawaiian/Pacific Islander	19,821 (0.4)	19,735 (0.4)	86 (0.6)	
Other*	203,819 (4.2)	202,746 (4.2)	1,073 (7.3)	

Maternal age at delivery (years)				< 0.0001
< 18	109,320 (2.2)	108,787 (2.2)	533 (3.6)	
18 – 34	3,847,140 (78.6)	3,835,174 (78.6)	11,966 (81.5)	
> 34	936,590 (19.1)	934,407 (19.2)	2,183 (14.9)	
Missing	169 (0.0)	169 (0.0)	0 (0.0)	
Education (years)				< 0.0001
< 12	998,493 (20.4)	994,587 (20.4)	3,906 (26.6)	
12	1,222,320 (25.0)	2,474,951 (50.7)	5,009 (34.8)	
> 12	2,480,059 (50.7)	2,474,951 (50.7)	5,108 (34.8)	
Missing	192,347 (3.9)	191,688 (3.9)	659 (4.5)	
Parity				< 0.0001
Nulliparous	1,900,401 (38.8)	1,894,631 (38.8)	5,770 (39.3)	
Multiparous	2,988,953 (61.1)	2,980,071 (61.1)	8,882 (60.5)	
Missing	3,865 (0.1)	3,835 (0.1)	30 (0.2)	
Payer for delivery				< 0.0001
Public	2,300,607 (47.0)	2,290,988 (47.0)	9,619 (65.5)	
Not public	2,592,612 (53.0)	2,587,549 (53.0)	5,063 (34.5)	
Maternal Comorbidities				
Preexisting diabetes	41,007 (0.8)	40,701 (0.8)	306 (2.1)	< 0.0001
Drug use code during pregnancy	81,467 (1.7)	75,918 (1.6)	5,549 (37.8)	< 0.0001

Mental health diagnosis complicating pregnancy	226,459 (4.6)	217,718 (4.5)	8,741 (59.5)	< 0.0001
Obesity (BMI ≥30 kg/m^2)	995,904 (20.4)	992,941 (20.4)	2,963 (20.2)	0.6051
Smoking	120,044 (2.5)	115,646 (2.4)	4,398 (30.0)	< 0.0001

*Includes those who were documented as “other race/ethnicity,” documented as having two or more races/ethnicities, or race/ethnicity was not documented.

Table S3. Adjusted Relative Risk for Associations between Congenital Heart Defects and ICD-9 and ICD-10 Codes for Alcohol Use Affecting the Fetus Controlling for Nicotine-Related Diagnoses and Body Mass Index, San Diego Study of Outcomes in Mothers and Infants, 2007-2017

	Alcohol-related diagnostic code	**No Alcohol-related diagnostic code**	**Adjusted for Maternal Demographics, Comorbidities**
	n (%)	**n (%)**	**RR (95% CI)**
Sample	14,682	4,878,537	
No congenital heart defect	14,247 (97.11)	4,800,426 (98.40)	Reference
Any congenital heart defect	425 (2.89)	78,111 (1.60)	**1.27 (1.15, 1.40)** ‡
Any non-critical congenital heart defect	332 (2.19)	61,015 (1.60)	**1.21 (1.08, 1.36)**
Any critical congenital heart defect	103 (0.70)	17,096 (0.35)	**1.48 (1.20, 1.81)**
Anomalies of great veins	10 (0.07)	2,270 (0.05)	1.01 (0.52, 1.98)

Endocardial cushion defect	13 (0.09)	1,037 (0.02)	**3.30 (1.81, 6.02** [§]
Tricuspid atresia and stenosis	7 (0.05)	1,576 (0.03)	0.77 (0.36, 1.65)
Ebstein's anomaly	*	509 (0.01)	n/a[†]
Hypoplastic left heart syndrome	9 (0.06)	1,750 (0.04)	1.49 (0.76, 2.93)
Single common ventricle	*	1,054 (0.02)	n/a[†]
Abnormalities of the cardiac outflow tract	64 (0.44)	10,552 (0.22)	**1.52 (1.17, 1.97)** [‖]
Coarctation of the aorta	17 (0.12)	3,502 (0.07)	1.22 (0.73, 2.05)

Bold when p < 0.05

* not displayed when n < 5

[†]Relative Risk (RR) not calculated when n < 5

[‡]e-value 1.86, lower CI 1.56

[§]e-value 6.05, lower CI 3.02

[‖]e-value 2.41, lower CI 1.62

Table S4. Adjusted Relative Risk for Associations between Non-Critical Congenital Heart Defects and ICD-9 and ICD-10 Code for Alcohol Use Affecting the Fetus, San Diego Study of Outcomes in Mothers and Infants, 2005-2017

	Alcohol-related diagnostic code	**No alcohol-related diagnostic code**	**Model 1: Unadjusted**	**Model 2: Adjusted for Maternal Demographics**	**Model 3: Adjusted for Maternal Demographics and Comorbidities**
	n (%)	n (%)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Any non-critical congenital heart defect	365 (2.15)	70,158 (1.21)	**1.79 (1.61, 1.98)**	**1.68 (1.51, 1.86)**	**1.28 (1.15, 1.42)**
Isolated VSD	57 (0.34)	13,976 (0.24)	**1.41 (1.09, 1.83)**	**1.42 (1.09, 1.85)**	1.28 (0.98, 1.68)
Isolated ASD	169 (1.00)	32,965 (0.57)	**1.77 (1.52, 2.06)**	**1.62 (1.39, 1.89)**	**1.19 (1.02, 1.39)**
Isolated VSD + ASD	33 (0.19)	6,114 (0.11)	**1.87 (1.33, 2.63)**	**1.82 (1.28, 2.57)**	**1.52 (1.06, 2.17)**

Other	106 (0.63)	17,103 (0.29)	**2.14** **(1.77, 2.59)**	**1.97** **(1.62, 2.39)**	**1.36** **(1.12, 1.66)**

Bold when p < 0.05