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Proportion of selected congenital heart defects attributable to recognized risk factors

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Abstract

Purpose—To assess the contribution of multiple risk factors for two congenital heart defects—hypoplastic left heart syndrome (HLHS) and tetralogy of Fallot (TOF).

Methods—We used data from the National Birth Defects Prevention Study (1997–2011) to estimate average adjusted population attributable fractions for several recognized risk factors, including maternal prepregnancy overweight–obesity, pregestational diabetes, age, and infant sex.

Results—There were 594 cases of isolated simple HLHS, 971 cases of isolated simple TOF, and 11,829 controls in the analysis. Overall, 57.0% of HLHS cases and 37.0% of TOF cases were estimated to be attributable to risk factors included in our model. Among modifiable HLHS risk factors, maternal pre-pregnancy overweight–obesity accounted for the largest proportion of cases (6.5%). Among modifiable TOF risk factors, maternal prepregnancy overweight–obesity and maternal age of 35 years or older accounted for the largest proportions of cases (8.3% and 4.3%, respectively).

Conclusions—Approximately half of HLHS cases and one-third of TOF cases were estimated to be attributable to risk factors included in our models. Interventions targeting factors that can be modified may help reduce the risk of HLHS and TOF development. Additional research into the etiology of HLHS and TOF may reveal other modifiable risk factors that might contribute to primary prevention efforts.

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Keywords

Heart defects; congenital; Hypoplastic left heart syndrome; Population attributable fraction; Tetralogy of Fallot

Introduction

Congenital heart defects (CHDs) are the most common type of birth defects, occurring in almost 1 in 100 births [1–4]. CHDs are associated with significant mortality [5–7] and morbidity [8–10], as well as high healthcare costs and the need for lifelong care [11–16]. These aspects are particularly true for critical CHDs that typically require surgeries and extensive medical follow-up in the first year of life. Hypoplastic left heart syndrome (HLHS) and Tetralogy of Fallot (TOF) are two relatively common critical CHDs, estimated to occur in 2.3 per 10,000 live births and 3.4 per 10,000 live births in the United States, respectively, each year [17]. There are several recognized risk factors for HLHS and TOF, which include pregestational diabetes [18–20], maternal prepregnancy obesity [21–23], family history of a CHD [24–28], and use of certain medications during early pregnancy [29–31]. Although HLHS and TOF are considered etiologically distinct, we focused the current analysis on these two CHDs because they are relatively common, critical, and have several recognized risk factors.

The population attributable fraction (PAF) is a measure designed to estimate the burden of disease due to a specific causal risk factor, or risk factors, of interest. It can be interpreted as the proportion of disease that could potentially be prevented if a risk factor for the outcome is completely removed from the population, assuming the factor caused the disease [32,33]. Often, PAFs are estimated based on the assumption that risk factors act independently of others [33–35]. If this assumption is violated, PAF estimates can be biased, usually resulting in overestimation of the proportion of disease attributable to a particular risk factor and, if summed over multiple exposures, the overestimation of the proportion of disease due to multiple risk factors. Adjusting measures of PAF using multivariable methods allows for estimation of the proportion of disease attributable to a specific risk factor in the presence of other risk factors given the validity of assumptions of the relationships between the risk factors and the outcome. Additionally, using this multivariable approach enables estimation of the proportion of disease explained by a combination of risk factors, as well as providing an estimate for the proportion of disease because of exposures not considered in the analysis [34–36]. For conditions that are likely multifactorial and for which multiple risk factors have been identified, adjusted PAF (aPAF) estimates may assist with prioritizing the development of public health interventions or identifying areas for future research.

Our objectives were to estimate average aPAFs (aaPAFs) for recognized risk factors for HLHS and TOF using data from the National Birth Defects Prevention Study (NBDPS).

Materials and methods

NBDPS study population and methods

The NBDPS is a population-based case–control study that identified cases using 10 birth defects surveillance systems across the United States. Cases included infants and fetuses with one of more than 30 major birth defects identified through birth defects surveillance systems in the states of Arkansas (1998–2011), Iowa, New Jersey (1998–2002), and Utah (2003–2011), or select counties in California, Georgia, Massachusetts, North Carolina (2003–2011), New York, and Texas. Cases were live-born infants (all sites), stillbirths of 20 weeks gestation (nine sites), and elective terminations (eight sites).

Live-born controls without major birth defects were randomly selected from the same birth population as the cases using vital records or hospital birth logs [37,38]. All cases were reviewed by clinical geneticists to ensure case definitions were met. Cases with chromosomal anomalies and single-gene disorders were excluded. We analyzed data for infants born after October 1, 1997 with an estimated date of delivery through December 31, 2011. For this study, cases were limited to those with isolated (i.e., no additional noncardiac defects) and simple (i.e., no additional cardiac malformation present) HLHS or TOF [39]. Approximately 90% of HLHS cases and 80% of TOF cases in the NBDPS are simple and isolated.

Mothers completed a computer-assisted telephone interview in either English or Spanish 6 weeks to 24 months after their estimated date of delivery. The interview was designed to assess demographic characteristics and maternal exposures to potential teratogens before and during pregnancy based on self-report. Potential risk factors assessed in NBDPS included prepregnancy height and weight, medication use, diet, illness before and during pregnancy, and environmental and occupational exposures, among others [38]. Overall, 70% of mothers of cases with HLHS, 71% of mothers of cases with TOF, and 65% of control mothers participated in the interview. The NBDPS was approved by the Institutional Review Boards at CDC and participating study sites.

Selection of risk factors for PAF assessment

For the aaPAF assessment, we considered recognized risk factors based on the published literature and previous analysis of the NBDPS data. We developed the initial list of risk factors using the following criteria: (1) at least two published studies with risk estimates specific to HLHS or TOF; (2) majority of risk factor association estimates in the published literature in consistent direction (e.g., majority indicated increased or majority indicated decreased risk); and (3) in absence of risk estimate for HLHS or TOF, study estimated risk for “CHDs.” Risk factors not meeting these criteria were not considered. After we developed the initial list of potential risk factors, we fit logistic regression models that included all risk factors of interest for each of the CHD outcomes. The PAF measures the proportion of disease that could be prevented if the risk factor of interest was removed from the population. As a result, we did not estimate PAF for factors whose elimination could potentially increase the risk of disease, that is, factors with estimated odds ratios (ORs) less than 1. However, all identified risk factors were retained in the models as potential

confounders to reduce the potential for bias. Therefore, while we included all identified risk factors in the logistic regression models on which the PAF estimates were based, aaPAFs were derived only for those factors with estimated ORs greater than 1.

Based on these criteria, we initially considered the following risk factors for HLHS: maternal pregestational diabetes (defined as a diagnosis of type I diabetes at any time or a diagnosis of type II diabetes before pregnancy) [18,19,40–42]; prepregnancy maternal overweight–obesity (body mass index [BMI] calculated as weight in kilograms divided by height in meters squared; overweight or obesity was considered having a BMI ≥ 25 kg/m²) [21,43–45]; maternal smoking any time during the month before conception (B1) through the third month of pregnancy (P3) [46,47]; maternal report of fever any time during B1-P3 [48,49]; maternal opioid use any time during B1-P3 [29,50,51]; maternal use of the antibiotics trimethoprim–sulfamethoxazole or nitrofurantoin any time during B1-P3 [30,52,53]; and maternal oral contraceptive use any time during the first month of pregnancy (P1) through P3 [51,54]. Although previous studies have shown a gradient increase in risk for HLHS and TOF with overweight and obese prepregnancy BMI [21,44,45,55,56], we chose to dichotomize the BMI measure into nonoverweight and overweight–obese categories in this analysis for two reasons. First, preliminary analyses using logistic regression models with all risk factors included indicated no improvement in estimation, based on the Akaike information criterion, of HLHS or TOF risk when using the continuous as opposed to categorized measures of BMI. Second, given the similarity of results using the categorized and continuous BMI measures, we chose to use the categorized measure to facilitate interpretation of the associated PAF estimate by focusing on the impact of modifying the number of women whose prepregnancy BMI would put them in the overweight–obese category. We included nonmodifiable risk factors (male sex [57–59], nonHispanic White race [60–62], and family history of a first-degree relative with CHD [27,28]) in the model to estimate the proportion of HLHS attributable to the full set of recognized risk factors. Although not included as a risk factor in the final model, maternal smoking in B1-P3 was also included as a potential confounder.

For TOF, we initially considered maternal age greater than or equal to 35 years, pregestational diabetes [18,19,42,63], prepregnancy maternal overweight–obesity [55,64], maternal smoking any time during B1-P3 [46,47], maternal report of fever any time during B1-P3 [48,49], maternal opioid exposure any time during B1-P3 [29,51], maternal selective serotonin reuptake inhibitor use any time during B1-P3 [31,65,66], and use of assisted reproductive technology or clomiphene citrate to become pregnant [67,68]. We included nonmodifiable risk factors (male sex [58,59], family history of a first-degree relative with CHD [24,25], and nulliparity [having no previous pregnancies] [59,69]) to estimate the proportion attributable to the full set of recognized risk factors. Although not included as a risk factor in the final model, maternal smoking in B1-P3 was included as a potential confounder.

Statistical methods

We estimated crude PAFs (PAFs unadjusted for any other risk factor) using the formula $\text{Crude PAF} = P(\text{Risk factor}|\text{disease}) \times (1 - [1/\text{OR}])$; the OR is the crude OR for the risk

factor–outcome association. Our goal was to estimate the proportion of cases of HLHS or TOF that were attributable to each set of risk factors. The first step in developing this estimate was to estimate the aPAF for each risk factor. The aPAF for each risk factor was defined as the estimated proportion of cases that would be prevented if the effect of that risk factor was removed from the population, but the remaining effects of the other risk factors were still present. The aPAF for each risk factor was estimated using the algorithm given in Ruckinger et al. [34] and was based on fitting a logistic regression model with either HLHS or TOF as the outcome variable and all risk factors as independent variables. These aPAF estimates are dependent on the order in which other risk factors are removed, or kept, in the model. The aaPAF allows for an estimation of the PAF adjusted for other risk factors and independent of the order in which risk factors are removed from a population. To estimate the aaPAF, we first repeated the estimation of the aPAF for each risk factor for every possible sequence of removing the effect of that risk factor relative to the other risk factors being considered. These sequential aPAF estimates were then averaged across all possible sequences of removal to derive the aaPAF [65]. The aaPAF can therefore be thought of as the expected impact of removing each risk factor from the population across all possible sequences of doing so relative to the other risk factors. The aaPAF estimates can be summed across multiple exposures for a valid estimate of the total aaPAF due to a collection of risk factors [34–36,70]. This summation also allows for estimation of the proportion of disease due to etiologic factors not considered in the analysis by examining the proportion of disease unexplained by the model [34–36,70].

We used bootstrap sampling, as applied to data collected under a case–control design, to estimate 95% confidence intervals (CIs) for the crude PAFs and aaPAFs [71]. All CIs were truncated at zero under the assumption that elimination of a potential risk factor would not increase the number of cases of HLHS or TOF. We estimated crude PAFs and aaPAFs using a modified version of the SAS software (SAS Institute, version 9.3; Cary, NC) algorithm presented by Ruckinger et al. [34].

Information was missing from a subset of NBDPS participants for several risk factors considered in this analysis. For example, 9.8% of subjects were missing data on maternal report of fever, 4.6% on BMI, 2.4% on smoking, and 1.9% on use of opioids. Measures of all other risk factors were available for 99% or more of study participants. To address the potential impact of not having full information on risk factors missing on more than 1% of study subjects, we developed the PAF estimates using two approaches. First, we estimated the aaPAFs using the complete case data, limiting the analyses only to subjects with complete information on all risk factors. We then conducted a series of sensitivity analyses in which we used multiple imputation to estimate the missing risk factor values and then combined these estimated values with the observed information to derive aaPAF estimates for all study participants. The multiple imputations were conducted under three assumptions. First, that the missing risk factor data were missing at random (MAR), which we defined as no association between the unobserved value of the missing covariate and cases/control status given the values of all other covariates for that subject. Second, we proposed a not MAR (NMAR) scenario in which, given the values of all other covariates for a subject, cases with missing values for a risk factor were 50% less likely on average than controls to have a positive values for that risk factor, for example, to be overweight–obese. Finally, we

considered a second NMAR scenario in which we assumed that, given all other covariates, cases with a missing risk were 50% more likely to have a positive value for that risk factor than controls. The multiple imputations were carried out using a “plug-in” fully conditional specification approach [72]. Briefly, this entails assigning random starting values to all missing covariates and then using an iterative simulation approach in which the missing data are estimated given current values of all other observed and estimated risk factors. This process is continued until convergence of the estimated values for the missing covariates, as measured by stabilization of the marginal distribution of the risk factors within cases and controls. At convergence, this process results in a complete pseudo-data set in which no subjects have missing information for any of the risk factors of interest. Based on graphical assessment of the marginal distributions of the risk factors, we used 50 imputation iterations to create each complete pseudo-dataset. Twenty such complete pseudo-data sets were derived for each of the MAR, and two NMAR scenarios described previously. Imputed estimates of aaPAF, combined across the 20 imputed pseudo-data sets, were derived using standard multiple imputation methods [73].

Results

There were 594 cases of isolated simple HLHS, 971 cases of isolated simple TOF, and 11,829 controls. Mothers of HLHS cases were more likely to be of nonHispanic White race (64.7% vs. 57.8%), report a first-degree family history of a CHD (5.2% vs. 1.2%), have pregestational diabetes (2.0% vs. 0.6%), report any opioid use in B1-P3 (4.4% vs. 2.1%) or any trimethoprim–sulfamethoxazole or nitrofurantoin use in B1-P3 (2.7% vs. 1.6%), and report having had a fever in B1-P3 (12.8% vs. 11.0%) compared with control mothers (Table 1). HLHS cases were more likely than controls to be male (67.2% vs. 50.9%). Mothers of TOF cases were more likely to be greater than or equal to 35 years of age (18.7% vs. 14.1%), report a family history of a CHD (5.2% vs. 1.2%), have pregestational diabetes (2.8% vs. 0.6%), be overweight or obese (45.0% vs. 39.1%), report any opioid use in B1-P3 (3.2% vs. 2.1%) or any selective serotonin re-uptake inhibitor use in B1-P3 (5.2% vs. 3.2%), and report having had a fever in B1-P3 (11.5% vs. 11.0%) compared with control mothers (Table 1). TOF cases were also more likely than controls to be male (57.5% vs. 50.9%).

HLHS population attributable fraction

After excluding women missing any risk factors included in the full model, there were 494 cases of HLHS (83.2%) and 10,061 controls (85.1%). The aaPAF for the full combination of included risk factors for HLHS was 57.0% (95% CI, 47.1%–65.9%; Table 2). Non-modifiable risk factors (nonHispanic White race, male sex, and family history of a CHD) cumulatively accounted for the greatest proportion of HLHS cases (approximately 45.6%), whereas modifiable risk factors cumulatively accounted for approximately 11.4%. Among modifiable risk factors, maternal prepregnancy overweight–obesity accounted for the largest proportion of cases (6.5%), followed by any opioid use in B1-P3 (1.5%), and maternal report of having had a fever in B1-P3 (1.4%). Assuming approximately 960 US cases of HLHS each year and 100% elimination of the risk due to modifiable risk factors, if our findings are generalizable, approximately 110 cases of HLHS could be prevented annually by eliminating the risk due to this set of modifiable exposures.

TOF population attributable fraction

The number of potential TOF risk factors meeting our selection criteria for aaPAF estimation, 10, exceeded the limit of computation feasibility given our use of bootstrapping, CI estimation, and multiple imputations for sensitivity analyses. As a result, we did not estimate the aaPAF for fever related to TOF. We made the choice to exclude fever due to the fact that preliminary analysis indicated both a small adjusted OR for fever (1.1 with 95% CI of 0.9–1.3) and a small estimated aaPAF of less than 1%. However, fever was retained in the TOF logistic regression model as a covariate to adjust for potential confounding and included in the missing data sensitivity analysis for TOF to reduce the chance for inducing bias.

After excluding women missing any risk factors included in the full model, there were 827 cases of TOF (85.2%) and 10,077 controls (85.2%). Using, these complete data, the estimated aaPAF for the full combination of included risk factors for TOF was 37.0% (95%, CI 29.8%–45.7%; Table 3). Cumulatively, the nonmodifiable risk factors of male sex, family history of a CHD, and nulliparity accounted for slightly over half (18.6%) of the total aaPAF. Among modifiable risk factors, which summed to 18.4%, maternal prepregnancy overweight–obesity had the greatest aaPAF (8.3%), followed by being 35 years of age or older (4.3%), and pregestational diabetes (1.9%). Assuming approximately 1654 US cases of TOF each year and 100% elimination of the risk due to modifiable exposures, if our findings are generalizable, approximately 304 cases of TOF could be prevented annually by eliminating the risk due to this set of modifiable exposures.

Sensitivity analyses

Sensitivity analyses assessing the potential impact of missing data for risk factors yielded aaPAFs estimates for HLHS that were very similar to those from the complete cases analysis (Table 4). However, when we assumed that mothers of cases who were missing information on reported fever during B1-P3 were 50% less likely than controls, given all other covariates, to have had a fever during pregnancy, the estimated aaPAF associated with fever decreased from 1.4% in the complete case analysis to 0.6%. When we assumed that cases missing fever information were 50% more likely than controls to have had a fever, the aaPAF increased to 1.9%. This impact of the form of the NMAR assumption on missing fever information reflects the significant amount of missing data on reported history of fever and indicates that there is substantial uncertainty concerning the true magnitude of the aaPAF for fever's impact on the risk of HLHS. Multiple imputation-based sensitivity analyses assessing the potential impact of missing risk factor information on the estimates of aaPAF for TOF indicated no meaningful differences in the complete case aaPAF estimates and those derived under the MAR and NMAR scenarios (Table 4).

Discussion

In this analysis, we assessed the contribution of established and strongly suspected risk factors for HLHS and TOF to the occurrence of these CHDs using methods that account for the presence of other risk factors. Our results suggest that, adjusted for other risk factors, maternal prepregnancy overweight–obesity, maternal opioid use in B1-P3, maternal report of

fever in B1-P3, and maternal pregestational diabetes account for the highest proportion of modifiable risk factors for HLHS cases in the NBDPS, whereas maternal prepregnancy overweight–obesity, maternal age of 35 years or more, and maternal pregestational diabetes account for the highest proportion of modifiable risk factors for TOF cases in the NBDPS. For both HLHS and TOF cases, non-modifiable risk factors account for a substantial proportion of cases in the NBDPS.

Public health interventions that focus on risk factors with the highest PAF are likely to have the greatest impact because the PAF is a function of the prevalence of the risk factor and the magnitude of its association with disease. Given this, the results of our study support public health interventions targeting maternal prepregnancy overweight–obesity, maternal periconceptional opioid use, and maternal pregestational diabetes. While we combined maternal prepregnancy overweight–obesity into one category for an assessment of total impact of BMI, when modeled alone, maternal prepregnancy obesity yielded an aaPAF of 3.0% and 3.6% for HLHS and TOF, respectively; this suggests that interventions targeting only prepregnancy obesity could also have an impact on the prevention of HLHS and TOF. Because nonmodifiable risk factors account for such a large proportion of HLHS and TOF, efforts should also be directed at understanding the underlying mechanisms of these factors, which may point to genetic risks (e.g., male sex) or to related, unmeasured risk factors not captured in our analysis that may be modifiable (e.g., access to healthcare). In particular, the association with male sex, which accounted for a higher proportion of risk than any other variable, might reflect sex differences in risk for HLHS and TOF development or *in utero* survival. More research is needed to determine if such differences might be related to genetic risk factors on sex chromosomes or other factors (e.g., interaction between infant sex and autosomal genetic factors, factors related to hormone regulation). Our results indicate that 43.0% of HLHS cases and 63.0% of TOF cases in the NBDPS are not explained by any of the risk factors we examined, offering research opportunities focused on other as yet unidentified risks.

Our study was subject to several limitations. First, our sample sizes of 494 and 827 cases of HLHS and TOF, respectively, are relatively small, leading to some imprecise estimates of ORs and aaPAFs. Second, we assumed that all risk factors included in the respective models were causal and that, if eliminated, would remove 100% of the risk due to that risk factor. Although the risk factors included were supported by the literature, the causality of all risk factors is not well established and in many cases is unlikely to be established conclusively with the available observational data. Third, even though we attempted to assess the implications of missing risk factor information among NBDPS subjects on the aaPAF estimates, these assessments were, by definition, based on unverifiable assumptions. As a result, despite the fact that that we saw little difference between the complete case and imputed estimates, there could be meaningful impacts of the missing data under scenarios we did not consider. In addition, because of information that was not collected in the NBDPS, we were not able to model all potential risk factors, such as maternal hypertension, or occupational exposures. This means that our estimates of the total aaPAF are potentially underestimates because they do not account for all suspected risk factors, but only those for which we had sufficient data available in the NBDPS for analysis. Finally, approximately

35% of invited participants did not participate in the NBDPS and, while we treat participation as random in our analysis, we have no means to verify this assumptions.

It should be remembered that the validity of the PAF estimates in general rely on several unverifiable assumptions. For example, we have assumed that we have correctly specified the true associations between HLHS and TOF and the risk factors using logistic regression models. There likely exist unmeasured confounders and/or effect measure modifications that could potentially alter the PAF estimates or bias results. In addition, these estimates are based on observed associations while estimation of PAF relies on an assumption of causation. Also, our PAF estimates may not be generalizable to other populations (e.g., those without mandatory folic acid fortification) because the PAF is dependent on exposure frequency and measures of association that may be specific to the NBDPS. Finally, similar to other studies of birth defects, we are unable to assess the possibility that some of the observed associations are due to differences in embryo/fetal survival rather than CHD development (e.g., infant sex could influence early survival among cases with CHDs rather than cause CHDs). If these assumptions are violated, our findings may not be valid and should be interpreted with caution.

Despite these limitations, our study had several strengths. We used data from a population-based case–control study in which cases were carefully reviewed to ensure that they met inclusion criteria. We were able to examine PAFs adjusted for other risk factors, giving a better idea of how recognized risk factors might impact development of HLHS or TOF in the presence of other risk factors.

In summary, this study provided an analysis of the proportion of HLHS and TOF cases attributable to recognized risk factors. aaPAF methods are rarely done in the context of birth defects, which are complex conditions, often with multiple recognized risk factors. These methods could serve as a model for estimating aaPAFs for other CHDs with complex etiologies. Results from this study may help to guide future public health interventions, as well as suggest directions for future research into nonmodifiable risk factors for these two serious CHDs.

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Table 1
Distribution of recognized risk factors for HLHS and TOF among cases and controls in the NBDPS, 1997–2011

Risk factors	Controls (n = 11,829)*			HLHS (n = 594)			TOF (n = 971)		
	N	%	Crude OR (95% CI)	N	%	Crude OR (95% CI)	N	%	Crude OR (95% CI)
Maternal race									
Non-Hispanic White	6836	57.8	64.7	384	64.7	1.3 (1.1–1.6)	549	56.5	0.9 (0.8–1.1)
Other	4986	42.2	210	35.4	Ref	422	43.5	Ref	
Missing	7	0.1							
Male sex									
Yes	6024	50.9	399	67.2	2.0 (1.7–2.4)	558	57.5	1.3 (1.1–1.5)	
No	5793	49.0	193	32.5	Ref	412	42.4	Ref	
Missing	12	0.1	2	0.3		1	0.1		
Nulliparous [†]									
Yes	3471	29.3	150	25.3	0.8 (0.7–1.0)	303	31.2	1.1 (0.9–1.3)	
No	8307	70.2	441	74.2	Ref	665	68.5	Ref	
Missing	51	0.4	3	0.5		3	0.3		
Maternal age (y)									
35	1664	14.1	83	14.0	1.0 (0.8–1.3)	182	18.7	1.4 (1.2–1.7)	
<35	10,165	85.9	511	86.0	Ref	789	81.3	Ref	
First-degree family history of CHD									
Yes	139	1.2	31	5.2	4.6 (3.1–6.9)	50	5.2	4.6 (3.3–6.4)	
No	11,690	98.8	563	94.8	Ref	921	94.9	Ref	
Pregestational diabetes [‡]									
Yes	74	0.6	12	2.0	3.3 (1.8–6.1)	27	2.8	4.6 (2.9–7.1)	
No	11,676	98.7	579	97.5	Ref	936	96.4	Ref	
Missing	79	0.7	3	0.5		8	0.8		
Pregnancy overweight-obesity ^{††}									
Yes	4631	39.1	255	42.9	1.2 (1.0–1.4)	437	45.0	1.3 (1.1–1.4)	
No	6644	56.2	311	52.4	Ref	497	51.2	Ref	
Missing	554	4.7	28	4.7		37	3.8		

Risk factors	Controls (n = 11,829)*			HLHS (n = 594)			TOF (n = 971)		
	N	%	Crude OR (95% CI)	N	%	Crude OR (95% CI)	N	%	Crude OR (95% CI)
Periconceptional opioid use [§]									
Yes	246	2.1	2.6	4.4	2.2 (1.4-3.2)	31	3.2	1.6 (1.1-2.3)	
No	11,364	96.1	559	94.1	Ref	923	95.1	Ref	
Missing	219	1.9	9	1.5		17	1.8		
First-trimester oral contraceptive use ^{//}									
Yes	377	3.2	25	4.2	1.3 (0.9-2.0)	30	3.1	1.0 (0.7-1.4)	
No	11,393	96.3	565	95.1	Ref	937	96.5	Ref	
Missing	59	0.5	4	0.7		4	0.4		
Periconceptional trimethoprim-sulfamethoxazole or nitrofurantoin [§]									
Yes	190	1.6	16	2.7	1.7 (1.0-2.8)	18	1.9	1.2 (0.7-1.9)	
No	11,622	98.3	577	97.1	Ref	950	97.8	Ref	
Missing	17	0.1	1	0.2		3	0.3		
Periconceptional selective serotonin reuptake inhibitor use [§]									
Yes	378	3.2	28	4.7	1.5 (1.0-2.2)	50	5.2	1.6 (1.2-2.2)	
No	11,269	95.0	559	94.1	Ref	905	93.2	Ref	
Missing	215	1.8	7	1.2		16	1.7		
Assisted reproductive technology or clomiphene citrate for help becoming pregnant ^{//}									
Yes	336	2.8	22	3.7	1.3 (0.8-2.0)	42	4.3	1.5 (1.1-2.1)	
No	11,427	96.6	569	95.8	Ref	926	95.4	Ref	
Missing	66	0.6	3	0.5		3	0.3		
Periconceptional fever [#]									
Yes	1296	11.0	76	12.8	1.2 (1.0-1.6)	112	11.5	1.1 (0.9-1.3)	
No	9466	80.0	453	76.3	Ref	760	78.3	Ref	
Missing	1067	9.0	65	10.9		99	10.2		
Periconceptional smoking ^{**}									
Yes	2075	17.5	98	16.5	0.9 (0.7-1.2)	155	16.0	0.9 (0.7-1.1)	
No	9454	79.9	485	81.7	Ref	793	81.7	Ref	
Missing	300	2.5	11	1.9		23	2.4		
Periconceptional alcohol ^{***}									

Risk factors	Controls (n = 11,829)*			HLHS (n = 594)			TOF (n = 971)		
	N	%	Crude OR (95% CI)	N	%	Crude OR (95% CI)	N	%	Crude OR (95% CI)
Yes	4280	36.2	0.9 (0.7–1.1)	201	33.8	0.9 (0.7–1.1)	365	37.6	1.1 (0.9–1.2)
No	7210	61.0	Ref	383	64.5	Ref	574	59.1	Ref
Missing	339	2.9		10	1.7		32	3.3	

Bolded text indicates significant at $P < .05$.

* The total number of controls was 11,829; 10,061 controls were included in the HLHS analysis, and 10,077 controls were included in the TOF analysis because of missing values for included variables.

[†]No previous pregnancies.

[‡]Type I diabetes diagnosed any time or type II diabetes diagnosed before the pregnancy.

[§]Any reported use between the month before through the third month of pregnancy.

//Any reported use between the first through the third month of pregnancy.

[¶]Use of intracytoplasmic sperm injection, *in vitro* fertilization, gamete intrafallopian transfer, zygote intrafallopian transfer, or clomiphene citrate.

[#]Maternal report of fever in the month before through the third month of pregnancy.

^{**}Maternal report in the month before through the third month of pregnancy.

^{††}Body mass index 25 kg/m².

Table 2

aaPAF estimates for recognized suspected risk factors for HLHS among isolated, simple cases of HLHS*, NBDPS, 1997–2011

Risk factors [†]	Proportion exposed among cases (%) [‡]	Proportion exposed among controls (%) [‡]	Adjusted ORs (95% CI) [§]	Crude PAF (%) (95% CI)	aaPAF (%) (95% CI) ^{,§}
Maternal nonHispanic White race	64.6	57.8	1.4 (1.1–1.7)	16.2 (6.5–25.4)	13.4 (4.8–21.2)
Male sex	67.4	51.0	2.1 (1.7–2.5)	33.5 (25.4–42.0)	29.4 (22.4–36.8)
First-degree family history of CHD	5.2	1.2	4.4 (2.9–6.9)	4.1 (2.4–6.1)	2.8 (1.4–4.4)
Pregestational diabetes [¶]	2.0	0.6	1.8 (0.8–4.2)	1.4 (0.3–2.6)	0.4 (0.0–1.2)
Prepregnancy overweight–obesity ^{‡‡}	45.1	41.1	1.2 (1.0–1.5)	6.8 (0.0–13.6)	6.5 (0.0–11.8)
Periconceptional opioid use [#]	4.4	2.1	1.9 (1.2–3.1)	2.4 (0.7–4.2)	1.5 (0.3–3.0)
Periconceptional trimethoprim–sulfamethoxazole or nitrofurantoin use [#]	2.7	1.6	1.5 (0.9–2.6)	1.1 (0.0–2.6)	0.8 (0.0–1.8)
Periconceptional fever ^{**}	14.4	12.0	1.2 (0.9–1.5)	2.6 (0.0–6.2)	1.4 (0.0–4.3)
First-trimester oral contraceptive use ^{††}	4.2	3.2	1.4 (0.9–2.2)	1.1 (0.0–2.8)	0.8 (0.0–2.5)
Total average PAF					57.0 (47.1–65.9)

Bolded text indicates significant at $P < .05$; all CIs were truncated at 0 under the assumption that elimination of potential exposure would not increase cases of HLHS.

* Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A. National Birth Defects Prevention Study. Seeking causes: classifying and evaluating congenital heart defects in etiologic studies. Birth Defects Res A Clin Mol Teratol. 2007 Oct; 79(10):714–27.

[†] Model adjusted for all variables included in table, as well as periconceptional smoking.

[‡] Proportion among cases and controls not missing data for specific risk factor.

[§] Adjusted ORs and PAFs are based on 494 cases and 10,061 controls.

^{||} CIs for aaPAF estimated through bootstrap sampling with 1000 replications.

[¶] Type I diabetes diagnosed any time or Type II diabetes diagnosed before the pregnancy.

[#] Any reported use between the month before through the third month of pregnancy.

^{**} Maternal report of fever between the month before through the third month of pregnancy.

^{††} Any use in between the first through the third month of pregnancy.

^{‡‡} Body mass index ≥ 25 kg/m².

Table 3

aaPAF estimates for recognized risk factors for TOF among isolated simple cases of TOF*, NBDPS Prevention Study, 1997–2011

Risk factors [†]	Proportion exposed among cases (%) [‡]	Proportion exposed among controls (%) [‡]	Adjusted OR (95% CI) [§]	Crude PAF (%) (95% CI)	aaPAF (%) (95% CI)
Male sex	57.5	51.0	1.3 (1.1–1.5)	13.4 (7.0–19.5)	10.8 (4.8–16.5)
First-degree family history of CHD	5.2	1.2	4.4 (3.0–6.3)	4.0 (2.7–5.5)	3.1 (1.9–4.4)
Nulliparous [¶]	31.3	29.5	1.2 (1.0–1.4)	2.6 (0.0–7.0)	4.6 (1.2–8.6)
Maternal age 35 y or older	18.7	14.1	1.4 (1.1–1.6)	5.4 (2.4–8.4)	4.3 (1.5–6.9)
Pregestational diabetes [#]	2.8	0.6	4.5 (2.8–7.2)	2.2 (1.3–3.3)	1.9 (0.9–2.8)
Prepregnancy overweight–obesity ^{§§}	46.8	41.1	1.3 (1.1–1.5)	9.7 (4.4–15.7)	8.3 (3.3–13.4)
Use of assisted reproductive technology or clomiphene citrate for help becoming pregnant ^{**}	4.3	2.9	1.4 (1.0–2.0)	1.5 (0.1–2.9)	1.2 (0.0–2.4)
Periconceptional opioid use ^{**}	3.3	2.1	1.7 (1.1–2.5)	1.2 (0.0–2.3)	1.3 (0.1–2.5)
Periconceptional selective serotonin reuptake inhibitors ^{††}	5.2	3.3	1.5 (1.1–2.1)	2.0 (0.4–3.6)	1.5 (0.4–2.7)
Total average PAF					37.0 (29.8–45.7)

Bolded text indicates significant at $P < .05$; all CIs were truncated at 0 under the assumption that elimination of potential exposure would not increase cases of TOF.

* Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A, NBDPS. Seeking causes: classifying and evaluating CHDs in etiologic studies. Birth Defects Res A Clin Mol Teratol. 2007 Oct; 79(10):714–27.

[†] Model adjusted for all variables included in table, as well as periconceptional fever and periconceptional smoking.

[‡] Proportion among those not missing data for specific risk factor.

[§] Adjusted ORs and PAFs are based on 827 cases and 10,077 controls.

^{||} CIs for aaPAF estimated through bootstrap sampling with 1000 replications.

[¶] No previous pregnancies.

[#] Type I diabetes diagnosed any time or Type II diabetes diagnosed before the pregnancy.

^{**} Use of intracytoplasmic sperm injection, *in vitro* fertilization, gamete intrafallopian transfer, zygote intrafallopian transfer, or clomiphene citrate.

^{††} Any reported use between the month before through the third month of pregnancy.

^{§§} Body mass index > 25 kg/m².

Table 4

Sensitivity analyses assessing potential impact of missing data for recognized risk factors on aaPAF estimates for isolated, simple cases of HLHS and TOF*, NBDPS1997–2011

Risk factors	aaPAF (%), complete case data [†]	aaPAF (%), MAR [‡]	aaPAF (%), NMAR scenario 1 [§]	aaPAF (%), NMAR scenario 2
HLHS				
Maternal nonHispanic White race	13.4	12.1	12.3	12.0
Male sex	29.4	28.5	28.8	28.2
First-degree family history of CHD	2.8	2.9	2.9	2.9
Pregestational diabetes [¶]	0.4	0.6	0.6	0.5
Prepregnancy overweight–obesity [#]	6.5	5.6	4.3	6.8
Periconceptional opioid use ^{**}	1.5	1.5	1.5	1.4
Periconceptional trimethoprim–sulfamethoxazole or nitrofurantoin use ^{**}	0.8	0.6	0.6	0.6
Periconceptional fever ^{††}	1.4	1.5	0.6	1.9
First-trimester oral contraceptive use ^{‡‡}	0.8	0.8	0.8	0.8
TOF				
Male sex	10.8	11.5	11.6	11.4
First-degree family history of CHD	3.1	3.1	3.2	3.1
Nulliparous ^{§§}	4.6	4.6	4.5	4.7
Maternal age 35 y or older	4.3	4.2	4.2	4.2
Pregestational diabetes [¶]	1.9	1.9	1.9	1.8
Prepregnancy overweight–obesity [#]	8.3	7.7	6.4	8.8
Use of assisted reproductive technology or clomiphene citrate for help becoming pregnant ^{////}	1.2	1.0	1.1	1.0
Periconceptional opioid use ^{**}	1.3	1.0	1.1	1.0
Periconceptional selective serotonin reuptake inhibitors ^{**}	1.5	1.5	1.5	1.5

* Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A, National Birth Defects Prevention Study. Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies. *Birth Defects Res A Clin Mol Teratol.* 2007 Oct; 79(10):714–27.

[†] Cases and controls with complete information on all risk factors.

[‡] Missing data imputed assuming no association between unobserved missing covariates and case and control status.

[§] Missing data imputed assuming that cases are 50% less likely than controls to have a positive value for the missing covariate.

^{||} Missing data imputed assuming that cases are 50% more likely than controls to have a positive value for the missing covariate.

[¶] Type I diabetes diagnosed any time or Type II diabetes diagnosed before the pregnancy.

[#] BMI ≥ 25 kg/m².

^{**} Any report of use between the month before through the third month of pregnancy.

^{††} Maternal report of fever between the month before through the third month of pregnancy.

^{††}Any reported use in between the first through the third month of pregnancy.

^{§§}No previous pregnancies.

^{///}Use of intracytoplasmic sperm injection, *in vitro* fertilization, gamete intrafallopian transfer, zygote intrafallopian transfer, or clomiphene citrate.

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