Annals of Epidemiology 26 (2016) 838–845

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Original article

Proportion of selected congenital heart defects attributable to recognized risk factors

Regina M. Simeone MS, MPH [a,*], Sarah C. Tinker PhD [a], Suzanne M. Gilboa PhD [a], A.J. Agopian PhD [b], Matthew E. Oster MD [a,c], Owen J. Devine PhD [a,d], Margaret A. Honein PhD [a] and the National Birth Defects Prevention Study

[a] Division of Congenital and Developmental Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA
[b] Division of Epidemiology, Human Genetics and Environmental Sciences, University of Texas School of Public Health, Houston, TX
[c] Department of Pediatrics, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA
[d] Carter Consulting, Atlanta, GA

ARTICLE INFO

Article history:
Received 1 December 2015
Accepted 8 October 2016
Available online 26 October 2016

Keywords:
Heart defects, congenital
Hypoplastic left heart syndrome
Population attributable fraction
Tetralogy of Fallot

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 prepregnancy 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.

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

The authors have no conflicts of interest to disclose.
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

* Corresponding author. National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 4770 Buford Highway, MS E-86, Atlanta, GA 30341. Tel.: +1 404-498-3901; fax: +1 404-498-3040.
E-mail address: rsimeone@cdc.gov (R.M. Simeone).

http://dx.doi.org/10.1016/j.annepidem.2016.10.003
1047-2797/

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 $\geq$ 25 kg/m^2) [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.