HHS Public Access

Author manuscript

Birth Defects Res. Author manuscript; available in PMC 2024 November 08.

Published in final edited form as:

Birth Defects Res. 2024 September ; 116(9): e2394. doi:10.1002/bdr2.2394.

Survival of Children With Critical Congenital Heart Defects in the National Birth Defects Prevention Study

Nina E. Forestieri[1], **Andrew F. Olshan**[2], **Matthew E. Oster**[3], **Elizabeth C. Ailes**[4], **Michael P. Fundora**[3,4], **Sarah C. Fisher**[5], **Charles Shumate**[6], **Paul A. Romitti**[7], **Rebecca F. Liberman**[8], **Wendy N. Nembhard**[9], **Suzan L. Carmichael**[10], **Tania A. Desrosiers**[2], **The National Birth Defects Prevention Study**

[1]Birth Defects Monitoring Program, State Center for Health Statistics, Division of Public Health, North Carolina Department of Health and Human Services, Raleigh, North Carolina, USA

[2]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[3]Division of Pediatric Cardiology, Children's Healthcare of Atlanta; and School of Medicine, Emory University, Atlanta, Georgia, USA

[4]Division of Birth Defects and Infant Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

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

[6]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas, USA

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

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

[9]Department of Epidemiology, College of Public Health; and Department of Pediatrics, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

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

Abstract

Background: Critical congenital heart defects (CCHDs) are associated with considerable morbidity and mortality. This study estimated survival of children with nonsyndromic CCHDs and evaluated relationships between exposures of interest and survival by CCHD severity (univentricular or biventricular function).

Correspondence: Nina E. Forestieri (nina.forestieri@dhhs.nc.gov).

Conflicts of Interest

The authors declare no conflicts of interest.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Methods: This analysis included 4380 infants with CCHDs (cases) born during 1999–2011 and enrolled in the National Birth Defects Prevention Study, a multisite, population-based case–control study of major birth defects. Cases were linked to state death files. Nonparametric Kaplan–Meier survival functions were used to estimate 1- and 5-year survival probabilities overall and by severity group (univentricular/biventricular) stratified by demographic and clinical exposure variables of interest. The log-rank test was used to determine whether stratified survival curves were equivalent. Survival and 95% confidence intervals (CIs) were also estimated using Cox proportional hazards modeling adjusted for maternal age, education, race/ethnicity, study site, and birth year.

Results: One- and five-year survival rates were 85.8% (CI 84.7–86.8) and 83.7% (CI 82.5–84.9), respectively. Univentricular 5-year survival was lower than biventricular case survival [65.3% (CI 61.7–68.5) vs. 89.0% (CI 87.8–90.1; $p < 0.001$)]. Clinical factors (e.g. preterm birth, low birthweight, and complex/multiple defects) were associated with lower survival in each severity group. Sociodemographic factors (non-Hispanic Black race/ethnicity, <high school education, smoking, and lower household income) were only associated with survival among biventricular cases.

Conclusions: Mortality among children with CCHDs occurred primarily in the first year of life. Survival was lower for those with univentricular defects, and social determinants of health were most important in predicting survival for those with biventricular defects.

Keywords

CCHD severity; critical congenital heart defects; early childhood mortality; National Birth Defects Prevention Study; survival analysis

1 | Introduction

Congenital heart defects (CHDs) are estimated to occur in 1% of all births in the United States (Hoffman and Kaplan 2002; Reller et al. 2008) and are the most common cause of infant mortality due to birth defects (Tsao et al. 2023). Approximately 25% of CHDs are considered *critical* CHDs (CCHDs), requiring surgical or catheter intervention in the first year of life (Mahle et al. 2009). Because of their association with considerable morbidity and mortality, CCHDs are meaningful targets for early screening and intervention, and all states now require universal pulse oximetry screening at birth in the hopes of improving survival of those with CCHDs not detected prenatally (Abouk et al. 2017; Eckersley et al. 2016; Glidewell et al. 2019; Kemper et al. 2011).

Several studies in recent years assessed the survival of infants with CCHDs, most of which focused on the period of infancy. Factors previously reported to be associated with reduced survival among infants include earlier birth era, earlier age at diagnosis, low birthweight, preterm birth, and the presence of extracardiac defects (Oster et al. 2013, 2014; Pace et al. 2018). Survival has also been reported to differ by sociodemographic factors such as maternal age, community-level economic disadvantages, maternal race/ethnicity, maternal education, and marital status (Kucik et al. 2014; Oster et al. 2013; Pace et al. 2018). However, associations between survival and sociodemographic characteristics may differ by

defect severity (Pace et al. 2018). Studies that assessed early childhood survival beyond infancy also reported similar clinical and sociodemographic risk factors, most notably earlier birth era, extracardiac defects, birthweight, gestational age, and race/ethnicity (Fixler et al. 2010; Nembhard et al. 2010, 2011; Wang, Hu, and Druschel 2010; Wang et al. 2013, 2015).

Many studies of survival in early childhood have been limited to either single geographic areas or inclusion of CCHDs lumped together with all birth defects or noncritical CHDs. We aimed to estimate survival of children with nonsyndromic CCHDs during the first 5 years of life using data from a large national study including a comprehensive set of CCHD phenotypes. We investigated factors that may increase the risk of mortality among infants with CCHDs and also evaluated survival by severity, which can help to inform clinical management and public health best practices.

2 | Methods

2.1 | Study Population

Live-born infants with CCHDs (cases) were identified through the National Birth Defects Prevention Study (NBDPS), a large, population-based multisite case–control study of major structural birth defects in the United States (Reefhuis et al. 2015). Briefly, participating sites ascertained potentially eligible cases through birth defects surveillance programs and identified eligible cases in their study area through medical record review and abstraction. Mothers of eligible cases who chose to participate completed a computer-based telephone interview in English or Spanish within 24 months of delivery. The interview included questions about the pregnancy; maternal health and pregnancy history; family demographics; nutritional, behavioral, and occupational exposures; use of over-the-counter and prescription medications, vitamins, and supplements; and a variety of environmental exposures. The NBDPS was approved by the Centers for Disease Control and Prevention Institutional Review Board (IRB) as well as the local IRBs for each participating site. This analysis included live-born infants with a CCHD delivered January 1, 1999, through December 31, 2011, from the following study sites: Arkansas (statewide), California (selected counties), Georgia (selected counties), Iowa (statewide), Massachusetts (selected counties), New York (selected counties), North Carolina (selected counties; 2003–2011 only), and Texas (selected counties). Available data on noninterviewed study-eligible CCHD cases were also included.

2.2 | Case Classification

The following 12 CCHDs were included in this analysis: coarctation of the aorta (COA), double outlet right ventricle (DORV), dextro-transposition of the great arteries (d-TGA), Ebstein anomaly (EA), hypoplastic left heart syndrome (HLHS), interrupted aortic arch (IAA), pulmonary atresia (PA), single ventricle (SV), total anomalous pulmonary venous return (TAPVR), tetralogy of Fallot (TOF), tricuspid atresia (TRIATR), and truncus arteriosus (TRUNC). Clinical information abstracted for each case was reviewed by a clinical geneticist; cases with single-gene conditions or chromosomal abnormalities were excluded. Interviewed cases were classified as either isolated, multiple, or complex (Rasmussen et al. 2003). Isolated cases had only one major defect diagnosed or two or more major defects diagnosed that were all part of the same organ system or developmentally

related to one other (i.e. isolated CCHDs could have more than one heart defect but did not have unrelated extracardiac defects). Multiple defect cases had at least one unrelated noncardiac birth defect in addition to the CCHD. Cases were considered "complex" if they had a previously described pattern of embryologically related major defects present, such as vertebrae, anus, cardiac, trachea, and limbs or VACTERL. For this analysis, CCHD cases were further categorized by severity as univentricular (HLHS, SV, TRIATR) or biventricular (d-TGA, COA, DORV, EA, IAA, TAPVR, TOF, TRUNC), with defects of univentricular function having the greatest severity and a higher risk of complications (Pace et al. 2018). PA (which included both PA with ventricular septal defect and PA with intact ventricular septum) in the absence of other CCHDs was excluded from these subgroupings due to variability in severity of this defect. Cases with more than one CCHD were categorized as univentricular or biventricular based on the defect with highest severity.

2.3 | Linkage to Death Records

All study sites provided data on infant mortality up to 1 year of age, and all but California provided mortality data for up to 5 years of age. Each study site linked their cases to state death files to identify deaths. Most sites used a probabilistic linkage method (with the exception of Texas, which used deterministic linkage). For cases that matched to a death record, the date of death, manner of death, state of death, and underlying cause of death were documented, as available. Early childhood survival during the first 5 years of life was assessed, as well as survival for the following intervals: <1 day, <7 days, <28 days, <1 year, <2 years, <3 years, and <4 years.

2.4 | Exposure Variables

Clinical and demographic information was obtained from the maternal interview and from abstracted medical record information provided by each site's birth defects surveillance program. Clinical information on the infant included sex (male or female), defect classification (isolated or multiple/complex), gestational age at delivery (<32, 32–36, or ≥37 weeks), birthweight (<1500, 1500 to <2500, 2500 to <4000, or ≥4000 g), small for gestational age (SGA) (birthweight <10th percentile for gestational age based on published growth curves [Overpeck et al. 1999; Zhang and Bowes 1995]), plurality (singleton or multiple), season of birth (winter = December–February, spring = March–May, summer = June–August, or fall = September–November), first degree family history of CHD (yes or no), time period of birth (1999–2002, 2003–2005, 2006–2008, or 2009–2011), and timing of CHD diagnosis (prenatal or postnatal). Cases were considered prenatally diagnosed if there was a diagnostic fetal echocardiogram before birth noted in the infant's abstracted medical record information.

Parental demographic characteristics evaluated for potential associations with survival among CCHD cases included maternal and paternal age at delivery (<20, 20–25, 26–35, or >35 years), self-reported maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or other), maternal nativity (US-born and non-US-born), maternal primary language spoken at home (English or other), maternal education at delivery (<high school, high school, or >high school), and household annual income (<$10,000, $10,000–$50,000, or >$50,000). Maternal exposure data evaluated were number of previous live births and

stillbirths (0 or ≥1), prepregnancy body mass index (BMI; underweight <18.5, normal weight 18.5 to <25, overweight 25 to <30, or obese ≥30 kg/m^2), diagnosis of preexisting type 1 or type 2 diabetes, periconceptional (1 month prior to conception through the first trimester) use of tobacco or alcohol (any, none), and use of folic acid-containing supplements (none, <1 per day, or daily) or folate antagonist medications around the time of conception (1 month prior to the index pregnancy through the first month of pregnancy).

In addition, we examined information obtained from surveillance systems for CCHD cases that were eligible for NBDPS but did not participate in the maternal interview. For these noninterviewed cases, available data included infant sex, gestational age at delivery, plurality, season of birth, time period of birth, study site, maternal age at delivery, and maternal race/ethnicity. We categorized these cases into the same univentricular and biventricular groups as interviewed cases, based on the CCHD diagnoses that were documented. A clinical geneticist at each site reviewed clinical information on all cases to confirm eligibility and diagnoses (including CHD phenotypes); however, cases that were not interviewed were not classified further into isolated, multiple, or complex categories.

2.5 | Statistical Analysis

Demographic and clinical characteristics were examined for CCHD cases overall and stratified by biventricular or univentricular severity group. We considered differences of >5% between groups to be meaningful. Survival and cumulative incidence curves for each CCHD type were estimated using the Kaplan–Meier survival function. Estimated survival probabilities were calculated for 1 day, 7 days, 28 days, and annually for 1–5 years of life. Five-year survival (with length of follow-up terminated by death or censoring at age 5 years) was estimated for each severity group stratified by each demographic and clinical exposure variable of interest for cases with nonmissing data for the exposure variable. The log-rank test was used to determine whether the stratified survival curves were equivalent. Proportional hazards assumptions were assessed, and when appropriate, Cox proportional hazards models were used to examine associations between exposures of interest and survival among children with biventricular and univentricular defects. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were adjusted for the following variables selected a priori as potential confounders: maternal age at delivery, maternal race/ethnicity, maternal education at delivery, study site, and year of birth. Maternal race/ethnicity, maternal education and age at delivery, and time period of birth were also examined as exposures of interest, in which case all other potential confounders except the factor of interest were adjusted for. To investigate the potential for selection bias due to including only cases that participated in the maternal interview, we compared the distributions of available covariates between interviewed and noninterviewed case groups and compared survival curves between groups using a log-rank test for equivalence. Analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC).

3 | Results

There were 6862 live-born CCHD cases eligible for the NBDPS. Mothers of 4380 CCHD cases (3346 biventricular and 894 univentricular, excluding PA in the absence of other

CCHDs) participated in the NBDPS interview and were included in the primary analysis. Among these CCHD cases, 85.7% were classified as isolated and 14.3% as multiple/complex defects, with little variation between bi- and univentricular CCHD (Table 1). A prenatal CHD diagnosis was documented for 11.5% of biventricular cases and 25.1% of univentricular cases. Higher proportions of biventricular cases than univentricular cases had a maternal education at delivery greater than high school and household annual income >$50,000. Other clinical and demographic characteristics were similar between bi- and univentricular groups.

3.1 | Survival Probabilities in Infancy and Early Childhood

Estimated survival among included CCHD cases was 85.8% at <1 year (95% CI 84.7–86.8; 662 deaths) (Table 2). Among the 3723 cases that were linked to death records to age 5 years, there were 541 deaths during infancy and 64 additional deaths by age 5, for an overall 5-year survival estimate of 83.7% (95% CI 82.5–84.9) (Table 3). Of those cases that survived infancy, 98.0% survived to 5 years. HLHS cases had the lowest survival probability at 5 years (54.6%, 95% CI 49.7–59.3) and throughout most of early childhood, beginning in the early neonatal period (<7 days), whereas COA cases had the highest survival rate (93.7%, 95% CI 91.8–95.2 at age 5 years). Five-year survival was significantly lower for univentricular cases (65.3%, 95% CI 61.7–68.5) compared to biventricular cases (89.0%, 95% CI 87.8–90.1; $p < 0.001$, Figure 1).

3.2 | Biventricular Cases

For cases with biventricular CCHDs (the lower severity grouping), the clinical factors most strongly associated with 5-year survival were gestational age and birthweight, with the lowest survival among cases with the earliest gestational age at delivery (HR 6.12, 95% CI 4.31–8.68 for <32 weeks compared to term) and lowest birthweight (HR 5.56, 95% CI 3.89–7.95 for <1500 g compared to normal birthweight) (Table 4). Other factors associated with reduced survival included SGA (HR 2.02, 95% CI 1.54–2.64), plurality > 1 (HR 2.52, 95% CI 1.78–3.59), and having multiple co-occurring defects (HR 3.92, 95% CI 3.10–4.97 for multiple/complex vs. isolated classification). Infants diagnosed postnatally had better survival than those noted to have a prenatal diagnosis (HR 0.48, 95% CI 0.34–0.67).

Several demographic and maternal exposures were also associated with survival among cases with biventricular CCHDs. Survival at 5 years was lower among non-Hispanic Black compared to non-Hispanic White cases (HR 1.54, 95% CI 1.08–2.20). Maternal education less than high school (HR 1.45, 95% CI 1.03–2.03) and household income less than $10,000 per year (HR 1.71, 95% CI 1.13–2.59) were also associated with lower survival, whereas survival was higher for cases in the maternal age group of 26–35 years (HR 0.69, 95% CI 0.52–0.91). Infants whose mothers reported smoking during the periconceptional period had a lower survival rate than infants of nonsmokers (HR 1.34, 95% CI, 1.02–1.77). Survival probabilities were also higher for cases with paternal age 26–35 years, English maternal primary language, daily periconceptional use of folic acid-containing supplements, and no maternal history of preexisting diabetes; however, these associations were attenuated in the adjusted Cox models (Table 4). Survival estimates during infancy were similar to 5-year results, although we observed additional associations with infant sex (female HR 1.29, 95%

CI 1.03–1.63 compared to males) and maternal prepregnancy BMI (underweight HR 1.62, 95% CI 1.01–2.57 compared to normal weight), and attenuated associations with maternal age, maternal race/ethnicity, and maternal smoking (Table S1).

3.3 | Univentricular Cases

Among univentricular CCHD cases (the higher severity grouping), we observed no demographic factors associated with 5-year survival—only clinical factors (Table 4). Like the biventricular group, survival rates were lowest among infants born <32 weeks gestation (HR 3.55, 95% CI 1.99–6.36), very low birthweight at <1500 g (HR 4.48, 95% CI 2.59–7.73), SGA (HR 1.52, 95% CI 1.13–2.05), or with extracardiac birth defects (HR 2.09, 95% CI 1.54–2.85). Compared to infants with a prenatal CHD diagnosis, survival rates were higher for those diagnosed postnatally (HR 0.73, 95% CI 0.53–1.00). Survival curves also differed by maternal use of alcohol and folate antagonist medications, but these associations were attenuated after adjustment (Table 4). Results were similar for 1-year survival estimates (Table S1).

3.4 | Noninterviewed Cases

Of the live-born CCHD cases eligible for NBDPS, 64% participated in the maternal interview. To examine the potential for selection bias due to nonparticipation, distributions of available clinical and demographic characteristics were compared between the 4380 interviewed cases enrolled in NBDPS and the 2482 noninterviewed cases that were eligible for the study (Table S2). A greater proportion of interviewed CCHD cases were born at term (82.1% of interviewed cases vs. 76.6% of noninterviewed cases) and had non-Hispanic White maternal race/ethnicity (54.9% of interviewed cases vs. 46.2% of noninterviewed cases). There was also some variation in interview participation by study site and time period of birth. In the biventricular CCHD group, survival was significantly lower for noninterviewed cases at both 1 year ($p = 0.009$, Figure S1) and 5 years ($p = 0.002$; Figure S2). However, survival probabilities among univentricular CCHD cases did not differ by interview participation status.

4 | Discussion

This study estimated survival of children with CCHD up to age 5 years and identified factors associated with increased risk of mortality overall and by severity (biventricular vs. univentricular). Risk factors differed by severity subgroups. Although infant clinical factors such as gestational age and birthweight were predictors of survival for both groups, sociodemographic factors including maternal race/ethnicity, maternal age and education at delivery, and household income were only associated with survival among biventricular cases. Maternal smoking during pregnancy was also associated with reduced survival for biventricular cases. Demographic and maternal characteristics were not associated with survival for the higher-severity case group with univentricular CCHDs, potentially because the clinical severity of disease outweighs these other risk factors. Pace et al.'s (2018) analysis of factors associated with infant mortality among CHD cases in North Carolina similarly found that survival for univentricular heart defects was largely unassociated with sociodemographic factors, whereas survival for defects of lesser severity (biventricular

CCHDs and noncritical heart defects) was associated with a number of factors including race/ethnicity, maternal education, and marital status. Sociodemographic characteristics may reflect resource availability and institutional disparities affecting access to care, social supports, and the built environment. Although social determinants of health have been linked to mortality and other adverse outcomes for individuals with CHDs in many studies (Davey et al. 2021), these types of social and structural factors may have a greater impact on mortality risk for children with less severe defects.

Our finding that most deaths (89%) in early childhood occurred during infancy is consistent with a recent meta-analysis on long-term survival of individuals with CHDs, in which approximately 90% of early childhood deaths occurred by age 1 (Best and Rankin 2016). A study of 5-year survival of infants with functional single ventricle CCHDs also showed that most deaths occurred in the first year, a time period during which these infants must undergo high-risk surgical procedures (Fixler et al. 2010). Survival at all time points was significantly lower for univentricular CCHDs, largely driven by mortality among HLHS cases, which are typically responsible for 25%–40% of neonatal cardiac deaths (Siffel et al. 2015).

Infant clinical factors were significantly associated with survival among both biventricular and univentricular CCHD cases in this study. Survival rates were lowest for cases with multiple or complex defects and among those born at the earliest gestational ages and lowest birthweights. These risk factors have been well-documented in population-based studies of CHDs and other birth defects (Best, Tennant, and Rankin 2017; Nembhard et al. 2010; Steurer et al. 2018; Wang, Hu, and Druschel 2010). For the biventricular cases, plurality and prenatal diagnosis were also associated with reduced survival. Plurality (i.e. multi-fetal gestation) is a well-established risk factor for infant morbidity and mortality (Alexander et al. 2005). Paradoxically, prenatal diagnosis has previously been found to be associated with lower survival rates for infants with isolated CCHDs, possibly driven by more severe disease among cases that are diagnosed prenatally (Oster et al. 2014). In a prior study of CHDs in the NBDPS, CHD complexity and the presence of extracardiac defects were associated with prenatal diagnosis (Ailes et al. 2014). In our analysis, the rate of prenatal diagnosis for univentricular CCHDs was more than twice that of biventricular CCHDs. Although we analyzed univentricular and biventricular cases separately, there was still some variability in mortality across individual CHDs within these groups (e.g. lower survival for truncus arteriosus in the biventricular group and relatively higher survival for tricuspid atresia in the univentricular group), suggesting additional heterogeneity in risk within the severity classification.

Demographic factors including maternal age at delivery, maternal race/ethnicity, household income, and maternal education at delivery were associated with 5-year survival among biventricular CCHD cases but not univentricular ones. We observed higher survival rates among cases with maternal ages between 26 and 35 years. Other studies have reported younger maternal age to be associated with better survival (Oster et al. 2014). We also observed that children born to non-Hispanic Black mothers had the lowest survival of the racial/ethnic groups examined, consistent with several prior studies of CHDs and other birth defects (Fixler et al. 2010; Nembhard et al. 2010, 2011; Pace et al. 2018; Wang et al. 2013, 2015). Some studies additionally reported higher mortality among cases of Hispanic

ethnicity for certain defects (Fixler et al. 2010; Nembhard et al. 2010, 2011); however, we did not see this association in our study. Lower household income and maternal education less than high school were also associated with reduced survival. These factors have previously been associated with mortality at the census-tract level as well, persisting even after adjustment for individual characteristics including maternal race, nativity, education, age, birthweight, parity, and infant sex (Kucik et al. 2014).

Of the maternal health exposures examined, maternal smoking during the periconceptional period was the only factor associated with reduced survival after covariate adjustment, though we observed this among cases with biventricular but not univentricular CCHDs. Maternal smoking during pregnancy is a known risk factor for infant mortality, with SGA thought to be the primary mechanism for increased risk (Salihu et al. 2003). To our knowledge, prior research has not investigated this association among infants with heart defects. Maternal periconceptional smoking has been associated with the occurrence of multiple types of CHDs in the NBDPS and other studies (Bolin et al. 2022; Lee and Lupo 2012; Malik et al. 2008), but these studies did not examine mortality outcomes.

Strengths of this study include the large, multisite population-based sample of the NBDPS, with CCHDs classified by clinicians with expertise in pediatric cardiology. Classifications incorporated phenotype, complexity, and the presence of extracardiac anomalies. We were able to examine survival by specific types of CCHDs and to separately evaluate survival among higher-severity univentricular and lower-severity biventricular groups. In addition, the NBDPS maternal interview includes a breadth of individual-level exposure information. We included a number of maternal and infant clinical and sociodemographic factors in this analysis, some of which have been previously explored in relation to CCHD prevalence but not CCHD mortality, such as maternal BMI, preexisting diabetes, and periconceptional smoking, folic acid supplementation, and folate antagonist medication use.

There are also some limitations of this analysis. Although case classification in the NBDPS was designed to facilitate etiologic analyses, factors associated with the prevalence of congenital heart defects may be different than those associated with survival. We grouped CCHDs by severity based on univentricular and biventricular function, but the sample size of the univentricular group was small relative to the total number of cases, and there was some variation in survival among the defects in each of these groups. Mothers of the highest risk infants (including deceased infants) may have been less likely to participate in the interview. Among biventricular cases, we found slightly lower survival for noninterviewed cases compared to those who were interviewed, though we did not see this for univentricular cases. Deaths were ascertained from state death files within each study site. Although infant deaths are routinely sent to the jurisdiction of birth, some deaths after age 1 year may not have been identified due to migration of families out of state, name changes, or missing information on other variables used for linkage. Under this scenario, our results may be biased if out-of-state migration is related to severity or other important factors in our study, such as demographic characteristics. In addition, we were unable to investigate causes of death in this analysis. Although participating sites provided the underlying cause of death for cases linked to death certificates, we did not have information on immediate or additional contributing causes of death. Future studies evaluating causes of death in conjunction with

factors associated with CCHD mortality would be informative for prevention efforts. Since our intent was to leverage pooled data across the NBDPS, we also did not analyze results separately by site (though we did adjust for study site in our proportional hazards models) and recommend that future work investigate geographic differences in mortality as well.

We evaluated survival of children with nonsyndromic CCHDs during the first 5 years of life and identified several characteristics associated with higher mortality that differed by univentricular (more severe) versus biventricular subgroup (less severe). These findings can be used to inform clinical and public health best practices for targeted interventions to reduce mortality, such as improved access to care. In addition to evaluating pregnancy-related risk factors and promoting healthy behaviors before and during pregnancy (including avoidance of smoking), services that assess and address social determinants of health may influence survival, particularly for children with biventricular CCHDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the NBDPS participants. Coding of drug information in the NBDPS used the Slone Drug Dictionary under license from the Slone Epidemiology Center of Boston University. The findings and conclusions in this publication are those of the authors and do not necessarily represent the official position or views of the Centers for Disease Control and Prevention; North Carolina Department of Health and Human Services, Division of Public Health; and California Department of Public Health. The authors also thank Marc Peterson for replicating the analysis.

Funding:

This work was supported by cooperative agreements from the Centers for Disease Control and Prevention to the North Carolina Center for Birth Defects Research and Prevention at the University of North Carolina, Chapel Hill (U50CCU422096 and 5U01DD001036) as well as to the other Centers for Birth Defects Research and Prevention that participated in the NBDPS (PA 96043, PA 02081, and FOADD09-001).

Data Availability Statement

Data from the National Birth Defects Prevention Study (NBDPS) are not publicly available. The study questionnaires and process for accessing the data used in this study are described at https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html. The code book and analytic code may be made available upon request.

References

Abouk R, Grosse SD, Ailes EC, and Oster ME. 2017. “Association of US State Implementation of Newborn Screening Policies for Critical Congenital Heart Disease With Early Infant Cardiac Deaths.” Journal of the American Medical Association 318: 2111–2118. 10.1001/jama.2017.17627. [PubMed: 29209720]

Ailes AC, Gilboa SM, Riehle-Colarusso T, et al. 2014. “Prenatal Diagnosis of Non-Syndromic Congenital Heart Defects.” Prenatal Diagnosis 34: 214–222. 10.1002/pd.428. [PubMed: 24222433]

Alexander GR, Wingate MS, Salihu H, and Kirby RS. 2005. “Fetal and Neonatal Mortality Risks of Multiple Births.” Obstetrics & Gynecology Clinics 32: 1–16. 10.1016/j.ogc.2004.10.005. [PubMed: 15644285]

Best KE, and Rankin J. 2016. "Long-Term Survival of Individuals Born With Congenital Heart Disease: A Systematic Review and Meta-Analysis." Journal of the American Heart Association 5: e002846. 10.1161/JAHA.115.002846. [PubMed: 27312802]

Best KE, Tennant PWG, and Rankin J. 2017. "Survival, by Birth Weight and Gestational Age, in Individuals With Congenital Heart Disease: A Population-Based Study." Journal of the American Heart Association 6: e005213. 10.1161/JAHA.116.005213. [PubMed: 28733436]

Bolin EH, Gokun Y, Romitti PA, et al. 2022. "Maternal Smoking and Congenital Heart Defects, National Birth Defects Prevention Study, 1997–2011." Journal of Pediatrics 240: 79–86. 10.1016/j.jpeds.2021.09.005. [PubMed: 34508749]

Davey B, Sinha R, Lee JH, Gauthier M, and Flores G. 2021. "Social Determinants of Health and Outcomes for Children and Adults With Congenital Heart Disease: A Systematic Review." Pediatric Research 89: 275–294. 10.1038/s41390-020-01196-6. [PubMed: 33069160]

Eckersley L, Sadler L, Parry E, Finucane K, and Gentles TL. 2016. "Timing of Diagnosis Affects Mortality in Critical Congenital Heart Disease." Archives of Disease in Childhood 101: 516–520. 10.1136/archdischild-2014-307691. [PubMed: 26130379]

Fixler DE, Nembhard WN, Salemi JL, Ethen MK, and Canfield MA. 2010. "Mortality in First 5 Years in Infants With Functional Single Ventricle Born in Texas, 1996 to 2003." Circulation 121: 644–650. 10.1161/CIRCULATIONAHA.109.881904. [PubMed: 20100974]

Glidewell J, Grosse SD, Riehle-Colarusso T, et al. 2019. "Actions in Support of Newborn Screening for Critical Congenital Heart Disease—United States, 2011–2018." Morbidity and Mortality Weekly Report 68: 107–111. 10.15585/mmwr.mm6805a3. [PubMed: 30730872]

Hoffman JL, and Kaplan S. 2002. "The Incidence of Congenital Heart Disease." Journal of the American College of Cardiology 39: 1890–1900. 10.1016/s0735-1097(02)01886-7. [PubMed: 12084585]

Kemper AR, Mahle WT, Martin GR, et al. 2011. "Strategies for Implementing Screening for Critical Congenital Heart Disease." Pediatrics 128: e1259–e1267. 10.1542/peds.2011-1317. [PubMed: 21987707]

Kucik JE, Nembhard WN, Donohue P, et al. 2014. "Community Socioeconomic Disadvantage and the Survival of Infants With Congenital Heart Defects." American Journal of Public Health 104, no. 11: e150–e157. 10.2105/AJPH.2014.302099. [PubMed: 25211743]

Lee LJ, and Lupo PJ. 2012. "Maternal Smoking During Pregnancy and the Risk of Congenital Heart Defects in Offspring: A Systematic Review and Metaanalysis." Pediatric Cardiology 34: 398–407. 10.1007/s00246-012-0470-x. [PubMed: 22886364]

Mahle WT, Newburger JW, Matherne GP, et al. 2009. "Role of Pulse Oximetry in Examining Newborns for Congenital Heart Disease: A Scientific Statement From the American Heart Association and American Academy of Pediatrics." Circulation 120: 447–458. 10.1161/CIRCULATIONAHA.109.192576. [PubMed: 19581492]

Malik S, Cleves MA, Honein MA, et al. 2008. "Maternal Smoking and Congenital Heart Defects." Pediatrics 121: e810–e816. 10.1542/peds.2007-1519. [PubMed: 18381510]

Nembhard WN, Salemi JL, Ethen MK, Fixler DE, and Canfield MA. 2010. "Mortality Among Infants With Birth Defects: Joint Effects of Size at Birth, Gestational Age, and Maternal Race/Ethnicity." Birth Defects Research Part A: Clinical and Molecular Teratology 88: 728–736. 10.1002/bdra.20696. [PubMed: 20672351]

Nembhard WN, Salemi JL, Ethen MK, Fixler DE, DiMaggio A, and Canfield MA. 2011. "Racial/Ethnic Disparities in Risk of Early Childhood Mortality Among Children With Congenital Heart Defects." Pediatrics 127: e1128–e1138. 10.1542/peds.2010-2702. [PubMed: 21502234]

Oster ME, Kim CH, Kusano AS, et al. 2014. "A Population-Based Study of the Association of Prenatal Diagnosis With Survival Rate for Infants With Congenital Heart Defects." American Journal of Cardiology 113: 1036–1040. 10.1016/j.amjcard.2013.11.066. [PubMed: 24472597]

Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, and Correa A. 2013. "Temporal Trends in Survival Among Infants With Critical Congenital Heart Defects." Pediatrics 131: e1502–e1508. 10.1542/peds.2012-3435. [PubMed: 23610203]

Overpeck MD, Hediger ML, Zhang J, Trumble AC, and Klebanoff MA. 1999. "Birth Weight for Gestational Age of Mexican American Infants Born in the United States." Obstetrics & Gynecology 93: 943–947. 10.1016/S0029-7844(98)00553-5. [PubMed: 10362159]

Pace ND, Oster ME, Forestieri NE, Enright D, Knight J, and Meyer RE. 2018. "Sociodemographic Factors and Survival of Infants With Congenital Heart Defects." Pediatrics 142: e20180302. 10.1542/peds.2018-0302. [PubMed: 30111552]

Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, and Moore CA. 2003. "Guidelines for Case Classification for the National Birth Defects Prevention Study." Birth Defects Research Part A: Clinical and Molecular Teratology 67: 193–201. 10.1002/bdra.10012. [PubMed: 12797461]

Reefhuis J, Gilboa SM, Anderka M, et al. 2015. "The National Birth Defects Prevention Study: A Review of the Methods." Birth Defects Research Part A: Clinical and Molecular Teratology 103: 656–669. 10.1002/bdra.23384. [PubMed: 26033852]

Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, and Correa A. 2008. "Prevalence of Congenital Heart Defects in Metropolitan Atlanta, 1998–2005." Journal of Pediatrics 153: 807–813. 10.1016/j.jpeds.2008.05.059. [PubMed: 18657826]

Salihu HM, Aliyu MH, Pierre-Louis BJ, and Alexander GR. 2003. "Levels of Excess Infant Deaths Attributable to Maternal Smoking During Pregnancy in the United States." Maternal and Child Health Journal 7: 219–227. 10.1023/a:1027319517405. [PubMed: 14682499]

Siffel C, Riehle-Colarusso T, Oster ME, and Correa A. 2015. "Survival of Children With Hypoplastic Left Heart Syndrome." Pediatrics 136: e864–e870. 10.1542/peds.2014-1427. [PubMed: 26391936]

Steurer MA, Baer RJ, Burke E, et al. 2018. "Effect of Fetal Growth on 1-Year Mortality in Neonates With Critical Congenital Heart Disease." Journal of the American Heart Association 7: e009693. 10.1161/JAHA.118.009693. [PubMed: 30371167]

Tsao CW, Aday AW, Almarzooq ZI, et al. 2023. "Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association." Circulation 147: e93–e621. 10.1161/CIR.0000000000001123. [PubMed: 36695182]

Wang Y, Hu J, and Druschel CM. 2010. "A Retrospective Cohort Study of Mortality Among Children With Birth Defects in New York State, 1983–2006." Birth Defects Research Part A: Clinical and Molecular Teratology 88: 1023–1031. 10.1002/bdra.20711. [PubMed: 20683907]

Wang Y, Liu G, Canfield MA, et al. 2015. "Racial/Ethnic Differences in Survival of United States Children With Birth Defects: A Population-Based Study." Journal of Pediatrics 166: 819–826. 10.1016/j.jpeds.2014.12.025. [PubMed: 25641238]

Wang Y, Liu G, Druschel CM, and Kirby RS. 2013. "Maternal Race/Ethnicity and Survival Experience of Children With Congenital Heart Disease." Journal of Pediatrics 163: 1437–1442.e2. 10.1016/j.jpeds.2013.06.084. [PubMed: 23932315]

Zhang J, and Bowes JWA. 1995. "Birth-Weight-For-Gestational-Age Patterns by Race, Sex, and Parity in the United States Population." Obstetrics & Gynecology 86: 200–208. 10.1016/0029-7844(95)00142-E. [PubMed: 7617350]

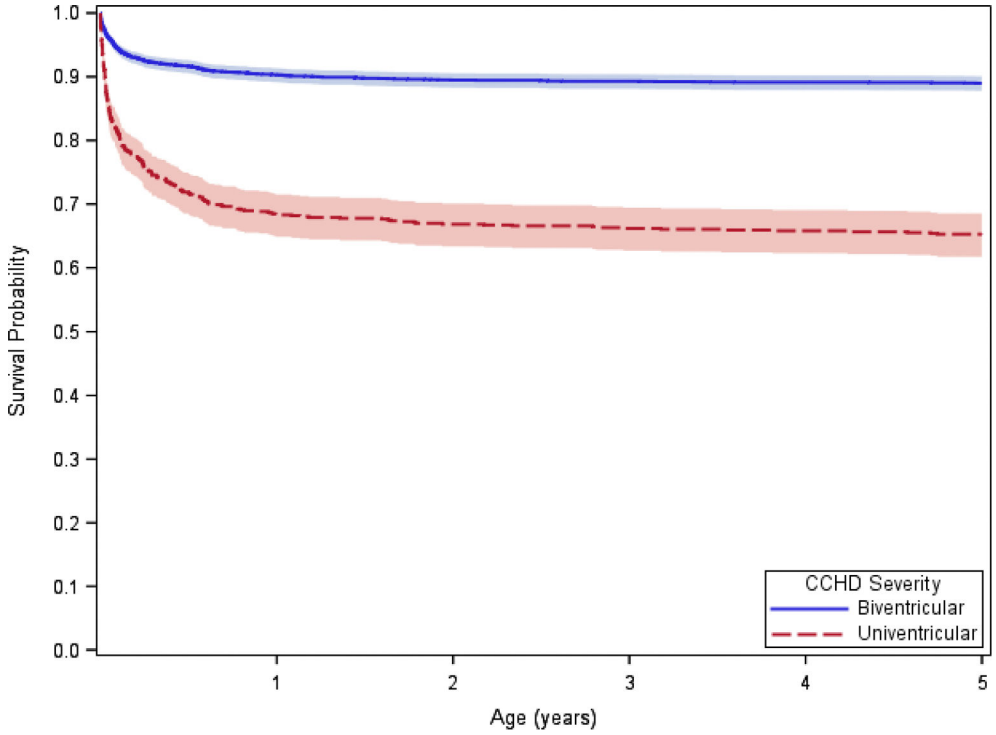

FIGURE 1 |.

Survival in early childhood (<5 years) among children with critical congenital heart defects (CCHDs) enrolled in the National Birth Defects Prevention Study, by severity, 1999–2011. Cases with more than one CCHD were categorized as biventricular or univentricular based on the defect with highest severity. Pulmonary atresia was not included in biventricular/univentricular groups. Excludes California. $p < 0.001$ (log-rank test).

TABLE 1 |

Clinical and demographic characteristics of children with critical congenital heart defects (CCHDs) enrolled in the National Birth Defects Prevention Study, 1999–2011.

	Any CCHD *N* (%)	Biventricular CCHD[a] *N* (%)	Univentricular CCHD[b] *N* (%)
Total	4380	3346	894
Infant sex			
Male	2712 (61.9)	2065 (61.7)	554 (62.0)
Female	1665 (38.0)	1279 (38.2)	339 (37.9)
Missing	*3 (0.1)*	*2 (0.1)*	*1 (0.1)*
Defect classification			
Isolated	3754 (85.7)	2847 (85.1)	778 (87.0)
Multiple/Complex	626 (14.3)	499 (14.9)	116 (13.0)
Prenatal CHD diagnosis			
Yes	630 (14.4)	386 (11.5)	224 (25.1)
No	3469 (79.2)	2729 (81.6)	629 (70.4)
Missing	*281 (6.4)*	*231 (6.9)*	*41 (4.6)*
Gestational age at delivery			
<32 weeks	162 (3.7)	125 (3.7)	26 (2.9)
32–36 weeks	620 (14.2)	483 (14.4)	112 (12.5)
≥37 weeks	3597 (82.1)	2737 (81.8)	756 (84.6)
Missing	*1 (0.0)*	*1 (0.0)*	*0 (0.0)*
Birthweight			
<1500 g	161 (3.7)	128 (3.8)	24 (2.7)
1500–<2500 g	584 (13.3)	446 (13.3)	118 (13.2)
2500–<4000 g	3304 (75.4)	2499 (74.7)	703 (78.6)
≥4000 g	291 (6.6)	243 (7.3)	40 (4.5)
Missing	*40 (0.9)*	*30 (0.9)*	*9 (1.0)*
Small for gestational age			
Yes	751 (17.2)	559 (16.7)	172 (19.2)
No	3316 (75.7)	2552 (76.3)	664 (74.3)
Missing/out of range	*313 (7.2)*	*235 (7.0)*	*58 (6.5)*

	Any CCHD *N* (%)	Biventricular CCHD[a] *N* (%)	Univentricular CCHD[b] *N* (%)
Plurality			
Singleton	4108 (93.8)	3141 (93.9)	845 (94.5)
Multiple	264 (6.0)	198 (5.9)	48 (5.4)
Missing	*8 (0.2)*	*7 (0.2)*	*1 (0.1)*
Season of birth			
Winter	1018 (23.2)	775 (23.2)	206 (23.0)
Spring	1073 (24.5)	837 (25.0)	199 (22.3)
Summer	1170 (26.7)	908 (27.1)	228 (25.5)
Fall	1119 (25.6)	826 (24.7)	261 (29.2)
First-degree family history of CHD			
Yes	165 (3.8)	124 (3.7)	37 (4.1)
No	4215 (96.2)	3222 (96.3)	857 (95.9)
Time period of birth			
1999–2002	1400 (32.0)	1049 (31.4)	312 (34.9)
2003–2005	1039 (23.7)	807 (24.1)	197 (22.0)
2006–2008	1025 (23.4)	789 (23.6)	202 (22.6)
2009–2011	916 (20.9)	701 (21.0)	183 (20.5)
Study site			
Arkansas	577 (13.2)	440 (13.2)	119 (13.3)
California[c]	657 (15.0)	497 (14.9)	140 (15.7)
Georgia	630 (14.4)	476 (14.2)	132 (14.8)
Iowa	452 (10.3)	345 (10.3)	94 (10.5)
Massachusetts	638 (14.6)	515 (15.4)	96 (10.7)
New York	418 (9.5)	323 (9.7)	82 (9.2)
North Carolina	431 (9.8)	315 (9.4)	104 (11.6)
Texas	577 (13.2)	435 (13.0)	127 (14.2)
Maternal age			
<20 years	520 (11.9)	392 (11.7)	107 (12.0)
20–25 years	1204 (27.5)	917 (27.4)	254 (28.4)
26–35 years	2193 (50.1)	1664 (49.7)	460 (51.5)
>35 years	463 (10.6)	373 (11.2)	73 (8.2)

	Any CCHD *N* (%)	Biventricular CCHD[a] *N* (%)	Univentricular CCHD[b] *N* (%)
Paternal age			
<20 years	158 (3.6)	116 (3.5)	36 (4.0)
20–25 years	901 (20.6)	674 (20.1)	196 (21.9)
26–35 years	2166 (49.5)	1669 (49.9)	441 (49.3)
>35 years	1003 (22.9)	771 (23.0)	190 (21.3)
Missing	*152 (3.5)*	*116 (3.5)*	*31 (3.5)*
Maternal race/ethnicity			
Non-Hispanic White	2406 (54.9)	1871 (55.9)	459 (51.3)
Non-Hispanic Black	476 (10.9)	337 (10.1)	123 (13.8)
Hispanic	1186 (27.1)	891 (26.6)	259 (29.0)
Other	312 (7.1)	247 (7.4)	53 (5.9)
Maternal nativity			
US-born	3318 (75.8)	2522 (75.4)	687 (76.9)
Non-US	931 (21.3)	718 (21.5)	183 (20.5)
Missing	*131 (3.0)*	*106 (3.2)*	*24 (2.7)*
Maternal primary language			
English	3342 (76.3)	2544 (76.0)	687 (76.9)
Non-English	905 (20.7)	694 (20.7)	183 (20.5)
Missing	*133 (3.0)*	*108 (3.2)*	*24 (2.7)*
Maternal education			
<High school	771 (17.6)	567 (17.0)	182 (20.4)
High school	1044 (23.8)	780 (23.3)	229 (25.6)
>High school	2432 (55.5)	1891 (56.5)	459 (51.3)
Missing	*133 (3.0)*	*108 (3.2)*	*24 (2.7)*
Household annual income			
<$10,000	799 (18.2)	592 (17.7)	177 (19.8)
$10,000–$50,000	1782 (40.7)	1329 (39.7)	397 (44.4)
>$50,000	1452 (33.2)	1153 (34.5)	254 (28.4)
Mssing	*347 (7.9)*	*272 (8.1)*	*66 (7.4)*
Number of previous live births and stillbirths			
0	1678 (38.3)	1301 (38.9)	323 (36.1)

	Any CCHD *N* (%)	Biventricular CCHD[a] *N* (%)	Univentricular CCHD[b] *N* (%)
≥1	2681 (61.2)	2028 (60.6)	567 (63.4)
Missing	*21 (0.5)*	*17 (0.5)*	*4 (0.5)*
Prepregnancy BMI			
Underweight <18.5	198 (4.5)	155 (4.6)	37 (4.1)
Normal weight 18.5–<25	2026 (46.3)	1572 (47.0)	399 (44.6)
Overweight 25–<30	993 (22.7)	749 (22.4)	206 (23.0)
Obese ≥30	931 (21.3)	701 (21.0)	196 (21.9)
Missing	*232 (5.3)*	*169 (5.1)*	*56 (6.3)*
Folic acid supplementation[d]			
None	1955 (44.6)	1476 (44.1)	441 (46.0)
<1/day	1103 (25.2)	833 (24.9)	237 (26.5)
Daily use	1234 (28.2)	972 (29.1)	224 (25.1)
Missing	*88 (2.0)*	*65 (1.9)*	*22 (2.5)*
Preexisting type I or II diabetes			
Yes	147 (3.4)	104 (3.1)	37 (4.1)
No	4202 (95.9)	3216 (96.1)	852 (95.3)
Missing	*31 (0.7)*	*26 (0.8)*	*5 (0.6)*
Maternal alcohol use[e]			
Yes	1627 (37.2)	1265 (37.8)	308 (34.5)
No	2618 (59.8)	1971 (58.9)	562 (62.9)
Missing	*135 (3.1)*	*110 (3.3)*	*24 (2.7)*
Maternal smoking[e]			
Yes	786 (17.9)	598 (17.9)	165 (18.5)
No	3477 (79.4)	2653 (79.3)	708 (79.2)
Missing	*117 (2.7)*	*95 (2.8)*	*21 (2.4)*
Folate antagonist medication[d,f]			
Yes	48 (1.1)	35 (1.1)	13 (1.5)
No	4330 (98.9)	3309 (98.9)	881 (98.6)
Missing	*2 (0.1)*	*2 (0.1)*	*0 (0.0)*

Note: Cases with more than one CCHD were categorized as biventricular or univentricular based on the defect with highest severity. Pulmonary atresia in the absence of other CCHDs (*N* = 140) was not included in biventricular/univentricular groups.

Abbreviations: BMI, body mass index; CCHD, critical congenital heart defect; CHD, congenital heart defect.

[a]Includes coarctation of the aorta, dextro-transposition of the great arteries, truncus arteriosus, double outlet right ventricle, Ebstein anomaly, interrupted aortic arch, tetralogy of Fallot, and total anomalous pulmonary venous return.

[b]Includes hypoplastic left heart syndrome, single ventricle, and tricuspid atresia.

[c]Mortality data for California were only available up to 1 year of age.

[d]Beginning 1 month prior to pregnancy through the first month of pregnancy.

[e]Beginning 1 month prior to pregnancy through the first trimester.

[f]Folate antagonist medications included any of the following drug components: tetroxoprim, brodimoprim, pyrimethamine, pyrimethamine bitartrate, pentamidine, pentamidine isethionate, trimethoprim, trimethoprim sulfate, trimethoprim HCL, methotrexate, pemetrexed, pralatrexate, triamterene, sulfasalazine, valproic acid, valproate sodium, divalproex sodium, cholestyramine resin, colestipol HCL, colesevelam, phenobarbital, primidone, phenytoin sodium, phenytoin, carbamazepine, phenobarbital sodium, seromycin, and proguanil HCL.

TABLE 2 |

Survival probabilities (%) during the first year of life among children with critical congenital heart defects (CCHDs) enrolled in the National Birth Defects Prevention Study, 1999–2011.

	N (births)	*N* (deaths)	<1 day % (95% CI)	<7 days % (95% CI)	<28 days % (95% CI)	<1 year % (95% CI)
Any CCHD	4380	622	98.9 (98.5–99.2)	96.3 (95.7–96.8)	92.5 (91.6–93.2)	85.8 (84.7–86.8)
Pulmonary atresia	208	49	98.6 (95.6–99.5)	94.2 (90.1–96.7)	85.1 (79.5–89.3)	76.4 (70.1–81.6)
Univentricular CCHD	894	278	97.4 (96.2–98.3)	91.6 (89.6–93.3)	82.8 (80.1–85.1)	68.9 (65.8–71.8)
Hypoplastic left heart syndrome	496	203	96.8 (94.8–98.0)	88.7 (85.6–91.2)	76.8 (72.8–80.3)	59.1 (54.6–63.3)
Single ventricle	255	60	97.6 (94.8–98.9)	94.5 (90.9–96.7)	87.5 (82.7–91.0)	76.5 (70.8–81.2)
Tricuspid atresia	143	15	99.3 (95.1–99.9)	96.5 (91.8–98.5)	95.1 (90.0–97.6)	89.5 (83.2–93.5)
Biventricular CCHD	3346	313	99.3 (99.0–99.5)	97.6 (97.1–98.1)	95.3 (94.6–96.0)	90.6 (89.6–91.6)
Coarctation of the aorta	901	49	99.8 (99.1–99.9)	99.1 (98.2–99.6)	98.2 (97.1–98.9)	94.6 (92.9–95.9)
Dextro-transposition of the great arteries	625	53	99.0 (97.9–99.6)	97.6 (96.1–98.5)	95.0 (93.0–96.5)	91.5 (89.0–93.5)
Double outlet right ventricle	264	55	97.7 (95.0–99.0)	94.7 (91.2–96.8)	89.8 (85.4–92.9)	79.2 (73.8–83.6)
Ebstein anomaly	129	20	96.9 (91.9–98.8)	94.6 (89.0–97.4)	89.1 (82.4–93.4)	84.5 (77.0–89.7)
Interrupted aortic arch	62	16	100	91.9 (81.7–96.6)	82.3 (70.3–89.8)	74.2 (61.4–83.3)
Tetralogy of Fallot	1030	69	99.9 (99.3–100)	98.3 (97.4–99.0)	97.3 (96.1–98.1)	93.3 (91.6–94.7)
Total anomalous pulmonary venous return	247	25	100	97.6 (94.7–98.9)	93.5 (89.6–96.0)	89.9 (85.4–93.0)
Truncus arteriosus	103	34	96.1 (90.0–98.5)	91.3 (83.9–95.4)	81.6 (72.6–87.8)	67.0 (57.0–75.2)

Abbreviations: CCHD, critical congenital heart defect; CI, confidence interval.

TABLE 3 |

Survival probabilities (%) in early childhood (<5 years) among children with critical congenital heart defects (CCHDs) enrolled in the National Birth Defects Prevention Study, 1999–2011.

	N (births)	*N* (deaths)	<2 years % (95% CI)	<3 years % (95% CI)	<4 years % (95% CI)	<5 years % (95% CI)
Any CCHD	3723	605	84.5 (83.3–85.6)	84.2 (83.0–85.3)	84.0 (82.7–85.1)	83.7 (82.5–84.9)
Pulmonary atresia	176	47	73.9 (66.7–79.7)	73.3 (66.1–79.2)	73.3 (66.1–79.2)	73.3 (66.1–79.2)
Univentricular CCHD	754	262	66.8 (63.4–70.1)	66.2 (62.7–69.4)	65.8 (62.3–69.0)	65.3 (61.7–68.5)
Hypoplastic left heart syndrome	410	186	56.3 (51.4–61.0)	55.4 (50.4–60.0)	54.9 (49.9–59.5)	54.6 (49.7–59.3)
Single ventricle	228	63	74.1 (67.9–79.3)	73.7 (67.5–78.9)	73.2 (67.0–78.5)	72.4 (66.1–77.7)
Tricuspid atresia	116	13	89.7 (82.5–94.0)	89.7 (82.5–94.0)	89.7 (82.5–94.0)	88.8 (81.5–93.3)
Biventricular CCHD	2849	314	89.5 (88.3–90.5)	89.3 (88.1–90.4)	89.1 (87.9–90.2)	89.0 (87.8–90.1)
Coarctation of the aorta	794	50	94.1 (92.2–95.5)	94.1 (92.2–95.5)	93.8 (91.9–95.3)	93.7 (91.8–95.2)
Dextro-transposition of the great arteries	540	52	91.1 (88.4–93.2)	90.9 (88.2–93.1)	90.7 (88.0–92.9)	90.4 (87.6–92.6)
Double outlet right ventricle	204	56	72.5 (65.9–78.1)	72.5 (65.9–78.1)	72.5 (65.9–78.1)	72.5 (65.9–78.1)
Ebstein anomaly	114	20	82.5 (74.1–88.3)	82.5 (74.1–88.3)	82.5 (74.1–88.3)	82.5 (74.1–88.3)
Interrupted aortic arch	50	14	72.0 (57.4–82.4)	72.0 (57.4–82.4)	72.0 (57.4–82.4)	72.0 (57.4–82.4)
Tetralogy of Fallot	872	72	92.5 (90.6–94.1)	92.1 (90.1–93.7)	91.9 (89.8–93.5)	91.7 (89.7–93.4)
Total anomalous pulmonary venous return	196	25	87.2 (81.7–91.2)	87.2 (81.7–91.2)	87.2 (81.7–91.2)	87.2 (81.7–91.2)
Truncus arteriosus	90	31	65.6 (54.8–74.4)	65.6 (54.8–74.4)	65.6 (54.8–74.4)	65.6 (54.8–74.4)

Abbreviations: CCHD, critical congenital heart defect; CI, confidence interval.

TABLE 4 |

Survival probabilities (%) and adjusted hazard ratios at 5 years for children with biventricular or univentricular critical congenital heart defects (CCHDs) enrolled in the National Birth Defects Prevention Study, by clinical and demographic characteristics, 1999–2011.

	Biventricular CCHD[a] *N* = 2849			Univentricular CCHD[b] *N* = 754		
	% (95% CI)	*p* [c]	HR[d] (95% CI)	% (95% CI)	*p* [c]	HR[d] (95% CI)
Infant sex						
Male	89.7 (88.2–91.1)	0.11	1.00 (Ref)	65.2 (60.7–69.4)	0.91	1.00 (Ref)
Female	87.8 (85.7–89.6)		1.24 (0.99–1.56)	65.5 (59.7–70.7)		0.98 (0.76–1.27)
Defect classification						
Isolated	92.0 (90.9–93.0)	<0.001	1.00 (Ref)	68.3 (64.6–71.7)	<0.001	1.00 (Ref)
Multiple/Complex	70.8 (66.2–75.0)		**3.92 (3.10–4.97)**	44.2 (34.1–53.9)		**2.09 (1.54–2.85)**
prenatal CHD diagnosis						
Yes	87.1 (83.3–90.1)	0.10	1.00 (Ref)	65.6 (58.9–71.5)	0.91	1.00 (Ref)
No	89.7 (88.5–90.9)		**0.48 (0.34–0.67)**	65.3 (61.0–69.2)		**0.73 (0.53–1.00)**
Gestational age at delivery						
<32 weeks	57.9 (47.3–67.1)	<0.001	**6.12 (4.31–8.68)**	33.3 (14.9–53.1)	<0.001	**3.55 (1.99–6.36)**
32–36 weeks	81.6 (77.5–85.0)		**2.06 (1.56–2.72)**	52.5 (42.3–61.8)		**1.92 (1.37–2.69)**
≥37 weeks	91.6 (90.4–92.6)		1.00 (Ref)	68.3 (64.5–71.8)		1.00 (Ref)
Birthweight						
<1500 g	59.4 (49.2–68.2)	<0.001	**5.56 (3.89–7.95)**	27.3 (11.1–46.4)	<0.001	**4.48 (2.59–7.73)**
1500–<2500 g	80.8 (76.5–84.4)		**2.18 (1.65–2.88)**	52.9 (42.9–61.9)		**1.83 (1.31–2.54)**
2500–<4000 g	91.3 (90.0–92.4)		1.00 (Ref)	69.0 (65.1–72.5)		1.00 (Ref)
≥4000 g	94.1 (89.9–96.6)		0.71 (0.39–1.27)	64.7 (46.3–78.2)		1.13 (0.63–2.05)
Small for gestational age						
Yes	82.5 (78.8–85.7)	<0.001	**2.02 (1.54–2.64)**	54.9 (46.4–62.6)	0.001	**1.52 (1.13–2.05)**
No	91.2 (90.0–92.3)		1.00 (Ref)	68.4 (64.4–72.1)		1.00 (Ref)
Plurality						
Singleton	89.7 (88.4–90.7)	<0.001	1.00 (Ref)	65.4 (61.7–68.7)	0.76	1.00 (Ref)
Multiple	79.0 (72.2–84.3)		**2.52 (1.78–3.59)**	63.6 (47.7–75.9)		1.17 (0.70–1.95)
Season of birth						

	Biventricular CCHD[a] N = 2849			Univentricular CCHD[b] N = 754		
	% (95% CI)	p [c]	HR[d] (95% CI)	% (95% CI)	p [c]	HR[d] (95% CI)
Winter	88.6 (86.0–90.8)	0.98	1.05 (0.76–1.45)	65.5 (57.9–72.1)	0.67	1.13 (0.77–1.66)
Spring	89.1 (86.5–91.1)		1.00 (Ref)	69.6 (62.1–75.9)		1.00 (Ref)
Summer	89.3 (86.9–91.2)		0.91 (0.66–1.25)	62.9 (55.8–69.3)		1.17 (0.81–1.68)
Fall	88.9 (86.3–91.0)		0.94 (0.68–1.29)	63.7 (56.9–69.7)		1.17 (0.82–1.69)
First-degree family history of CHD						
Yes	90.0 (82.7–94.3)	0.70	1.04 (0.56–1.90)	58.8 (40.6–73.2)	0.38	1.33 (0.77–2.30)
No	88.9 (87.7–90.1)		1.00 (Ref)	65.6 (62.0–68.9)		1.00 (Ref)
Time period of birth						
1999–2002	87.1 (84.7–89.2)	0.06	1.37 (0.98–1.90)	63.2 (57.1–68.7)	0.09	1.42 (0.98–2.05)
2003–2005	91.3 (88.9–93.2)		0.96 (0.66–1.38)	60.0 (51.8–67.2)		1.47 (1.00–2.17)
2006–2008	88.3 (85.7–90.5)		1.21 (0.86–1.71)	69.8 (62.3–76.0)		1.01 (0.68–1.51)
2009–2011	89.7 (87.0–91.8)		1.00 (Ref)	68.7 (61.0–75.1)		1.00 (Ref)
Maternal age						
<20 years	85.1 (80.7–88.5)	<0.001	0.82 (0.57–1.19)	66.7 (55.5–75.6)	0.53	0.75 (0.48–1.19)
20–25 years	85.7 (83.0–88.0)		1.00 (Ref)	60.7 (53.6–67.1)		1.00 (Ref)
26–35 years	91.4 (89.8–92.7)		**0.69 (0.52–0.91)**	66.6 (61.8–70.9)		0.88 (0.65–1.18)
>35 years	89.6 (85.8–92.4)		0.96 (0.64–1.42)	69.4 (56.3–79.2)		0.84 (0.50–1.41)
Paternal age						
<20 years	81.8 (72.7–88.1)	0.02	1.05 (0.61–1.81)	65.4 (44.0–80.3)	0.92	0.85 (0.41–1.78)
20–25 years	87.1 (84.0–89.6)		1.00 (Ref)	63.9 (55.8–70.9)		1.00 (Ref)
26–35 years	90.1 (88.5–91.6)		1.01 (0.72–1.41)	65.1 (60.0–69.6)		0.93 (0.63–1.36)
>35 years	89.8 (87.2–91.8)		1.30 (0.83–2.04)	67.8 (60.3–74.3)		0.85 (0.50–1.43)
Maternal race/ethnicity						
Non-Hispanic White	91.2 (89.8–92.5)	<0.001	1.00 (Ref)	67.2 (62.5–71.5)	0.42	1.00 (Ref)
Non-Hispanic Black	83.5 (79.0–87.1)		**1.54 (1.08–2.20)**	66.4 (57.0–74.2)		1.04 (0.71–1.55)
Hispanic	85.4 (82.3–88.0)		0.96 (0.67–1.39)	61.0 (53.4–67.8)		1.03 (0.70–1.52)
Other	89.2 (84.0–92.7)		1.21 (0.76–1.90)	60.0 (43.2–73.3)		1.23 (0.71–2.13)
Maternal nativity						
US-born	89.1 (87.8–90.4)	0.999	1.00 (Ref)	65.9 (61.9–69.5)	0.79	1.00 (Ref)

	Biventricular CCHD[a] *N* = 2849			Univentricular CCHD[b] *N* = 754		
	% (95% CI)	*p* [c]	HR[d] (95% CI)	% (95% CI)	*p* [c]	HR[d] (95% CI)
Non-US	89.1 (86.1–91.5)		0.82 (0.58–1.17)	65.2 (56.6–72.5)		0.95 (0.63–1.43)
Maternal primary language						
English	90.0 (88.7–91.2)	0.003	1.00 (Ref)	65.9 (61.9–69.5)	0.92	1.00 (Ref)
Non-English	85.4 (82.0–88.2)		1.26 (0.87–1.84)	65.2 (56.5–72.6)		0.82 (0.51–1.30)
Maternal education						
<High school	83.0 (79.0–86.4)	<0.001	**1.45 (1.03–2.03)**	60.7 (52.0–68.4)	0.34	1.16 (0.80–1.69)
High school	88.1 (85.4–90.4)		1.04 (0.77–1.40)	67.8 (60.5–74.0)		0.92 (0.67–1.27)
>High school	91.0 (89.5–92.2)		1.00 (Ref)	66.5 (61.7–70.8)		1.00 (Ref)
Household annual income						
<$10,000	83.3 (79.6–86.4)	<0.001	**1.71 (1.13–2.59)**	61.3 (52.6–68.9)	0.32	1.02 (0.64–1.63)
$10,000–$50,000	88.3 (86.3–90.1)		1.34 (0.97–1.85)	64.2 (58.8–69.1)		1.05 (0.75–1.46)
>$50,000	93.0 (91.3–94.4)		1.00 (Ref)	69.1 (62.7–74.6)		1.00 (Ref)
Number of previous live births and stillbirths						
0	88.6 (86.6–90.3)	0.56	1.07 (0.83–1.37)	67.3 (61.4–72.4)	0.43	0.95 (0.72–1.26)
≥1	89.3 (87.7–90.6)		1.00 (Ref)	64.2 (59.7–68.3)		1.00 (Ref)
Prepregnancy BMI						
Underweight <18.5	84.7 (77.0–89.9)	0.09	1.58 (0.97–2.57)	69.0 (48.8–82.5)	0.64	0.93 (0.47–1.85)
Normal weight 18.5–<25	90.4 (88.7–91.8)		1.00 (Ref)	65.6 (60.3–70.3)		1.00 (Ref)
Overweight 25–<30	88.7 (86.0–90.9)		1.12 (0.84–1.50)	67.3 (59.6–73.8)		0.92 (0.66–1.28)
Obese ≥30	87.7 (84.7–90.1)		1.14 (0.84–1.54)	62.1 (54.4–69.0)		1.11 (0.81–1.52)
Folic acid supplementation[e]						
None	87.6 (85.6–89.4)	<0.001	1.16 (0.83–1.62)	65.7 (60.3–70.6)	0.46	0.95 (0.69–1.32)
<1/day	86.8 (84.1–89.1)		1.36 (0.97–1.91)	62.4 (55.3–68.8)		1.09 (0.78–1.54)
Daily use	93.0 (91.1–94.5)		1.00 (Ref)	68.1 (61.3–73.9)		1.00 (Ref)
Preexisting diabetes						
Yes	81.1 (71.4–87.8)	0.02	1.62 (0.97–2.70)	71.4 (53.4–83.5)	0.42	0.71 (0.36–1.39)
No	89.4 (88.1–90.5)		1.00 (Ref)	65.0 (61.4–68.4)		1.00 (Ref)
Maternal alcohol use[f]						
Yes	90.3 (88.4–91.9)	0.13	1.03 (0.81–1.32)	71.7 (65.9–76.7)	0.01	0.78 (0.59–1.04)

Birth Defects Res. Author manuscript; available in PMC 2024 November 08.

	Biventricular CCHD[a] N = 2849			Univentricular CCHD[b] N = 754		
	% (95% CI)	p[c]	HR[d] (95% CI)	% (95% CI)	p[c]	HR[d] (95% CI)
No	88.4 (86.7–89.8)		1.00 (Ref)	62.2 (57.6–66.4)		1.00 (Ref)
Maternal smoking[f]						
Yes	86.3 (83.2–89.0)	0.02	**1.34 (1.02–1.77)**	65.5 (57.2–72.6)	0.89	1.08 (0.78–1.49)
No	89.8 (88.5–91.0)		1.00 (Ref)	65.9 (62.0–69.6)		1.00 (Ref)
Folate antagonist medication[e,g]						
Yes	90.0 (72.1–96.7)	0.85	0.89 (0.29–2.79)	41.7 (15.2–66.5)	0.04	1.98 (0.92–4.26)
No	89.0 (87.8–90.1)		1.00 (Ref)	65.6 (62.1–68.9)		1.00 (Ref)

Note: Cases with more than one CCHD were categorized as biventricular or univentricular based on the defect with highest severity. Pulmonary atresia was not included in biventricular/univentricular groups. Excludes California.

Abbreviations: BMI, body mass index; CCHD, critical congenital heart defect; CI, confidence interval; CHD, congenital heart defect; HR, hazard ratio; Ref, reference group.

[a] Includes coarctation of the aorta, dextro-transposition of the great arteries, truncus arteriosus, double outlet right ventricle, Ebstein anomaly, interrupted aortic arch, tetralogy of Fallot, and total anomalous pulmonary venous return.

[b] Includes hypoplastic left heart syndrome, single ventricle, and tricuspid atresia.

[c] *p*-value for the log-rank test of trend comparing stratified Kaplan–Meier survival curves.

[d] Hazard ratio, adjusted for maternal age, maternal race/ethnicity, maternal education, study site, and year of birth; bold = 95% CI excludes 1.00.

[e] Beginning 1 month prior to pregnancy through the first month of pregnancy.

[f] Beginning 1 month prior to pregnancy through the first trimester.

[g] Folate antagonist medications included any of the following drug components: tetroxoprim, brodimoprim, pyrimethamine, pyrimethamine bitartrate, pentamidine, pentamidine isethionate, trimethoprim, trimethoprim sulfate, trimethoprim HCL, methotrexate, pemetrexed, pralatrexate, triamterene, sulfasalazine, valproic acid, valproate sodium, divalproex sodium, cholestyramine resin, colestipol HCL, colesevelam, phenobarbital, primidone, phenytoin sodium, phenytoin, carbamazepine, phenobarbital sodium, seromycin, and proguanil HCL.