ORIGINAL RESEARCH

Mortality Following Pediatric Congenital Heart Surgery: An Analysis of the Causes of Death Derived From the National Death Index

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***Background*—**Prior research has focused on early outcomes after congenital heart surgery, but less is known about later risks. We aimed to determine the late causes of death among children (<21 years of age) surviving their initial congenital heart surgery.

***Methods and Results*—**This is a retrospective cohort study from the Pediatric Cardiac Care Consortium, a US-based registry of interventions for congenital heart defects (CHD). Excluding patients with chromosomal anomalies or inadequate identifiers, we matched those surviving their first congenital heart surgery (1982–2003) against the National Death Index through 2014. Causes of death were obtained from the National Death Index to calculate cause-specific standardized mortality ratios (SMRs). Among 31 132 patients, 2527 deaths (8.1%) occurred over a median follow-up period of 18 years. Causes of death varied by time after surgery and severity of CHD but, overall, 69.9% of deaths were attributed to the CHD or another cardiovascular disorder, with a SMR for CHD/cardiovascular disorder of 67.7 (95% confidence interval: 64.5–70.8). Adjusted odds ratios revealed increased risk of death from CHD/cardiovascular disorder in females [odds ratio=1.28; 95% confidence interval (1.04–1.58); P=0.018] with leading cardiovascular disorder contributing to death being cardiac arrest (16.8%), heart failure (14.8%), and arrhythmias (9.1%). Other major causes of death included coexisting congenital malformations (4.7%, SMR: 7.0), respiratory diseases (3.6%, SMR: 8.2), infections (3.4%, SMR: 8.2), and neoplasms (2.1%, SMR: 1.9).

***Conclusions*—**Survivors of congenital heart surgery face long-term risks of premature mortality mostly related to residual CHD pathology, heart failure, and arrhythmias, but also to other noncardiac conditions. Ongoing monitoring is warranted to identify target factors to address residual morbidities and improve long-term outcomes. **(*J Am Heart Assoc*. 2018;7:010624. DOI: 10.1161/JAHA.118.010624)**

Key Words: congenital heart disease • mortality • outcomes research • surgery

Children undergoing congenital heart surgery (CHS) are at risk for both early and late mortality, but most prior research has focused on survival to hospital discharge. Studies of long-term outcomes have shown elevated risk for premature mortality across all forms of congenital heart defects (CHD), and defined high-risk groups by CHD characteristics.[1–4] We recently examined this excess risk for survivors of CHS in the Pediatric Cardiac Care Consortium (PCCC), a large US-based registry for interventions for CHD[5] and found the standardized mortality ratio (SMR) to range from 4.3 times (95% confidence interval [CI] 3.7–5.0) for mild diseases, to 5.8 for moderate (95% CI: 4.2–7.9), 12.4 for severe two-ventricle (95% CI: 11.5–13.4) and 35 times (95% CI: 33–38) above the general population.[4] Less is known, though, about the eventual causes of death (COD) among patients surviving to hospital discharge after the initial CHS or after their final corrective or palliative surgery.[1,6–9]

Patients operated for CHD may be at risk for premature mortality related to abnormal cardiac function and arrhythmias, systemic and pulmonary vascular abnormalities, and impaired lung function.[7–12] In addition, they frequently have coexisting extracardiac abnormalities and predispositions for neurologic

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Accompanying Data S1, Tables S1 through S15 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010624

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Clinical Perspective

What Is New?

- Persistently elevated cardiovascular disorder–related risk across all severity forms of congenital heart defects (CHD) suggests that postoperative cardiovascular sequelae continue to impose a significant burden despite improvements in the surgical management of CHD.
- Excess mortality from non-CHD/noncardiovascular disorder causes remains unchanged over time, suggesting limited progress in the management or prevention of these additional non-CHD morbidities.

What Are the Clinical Implications?

- Myocardial protection during congenital heart surgery, emergence of new medications, provision of implantable defibrillators to those at risk for sudden arrhythmic death, and interdisciplinary clinical investigation may all attenuate the late risks from postoperative morbidities in the population with repaired CHD.

and cerebrovascular disorders, gastrointestinal/hepatic, renal, endocrine, and neoplastic disorders.[13–20] Patients with operated CHDs are also exposed to other risks such as additional interventions, diagnostic radiation,[21,22] chronic use of medications,[23] and psycho-emotional sequences[24,25] leading to suicidal behavior or alcoholism.[26] Furthermore, CHD patients are concurrently exposed to the same cardiovascular and other risk factors as the general population and may react differently to conditions such as aging and pregnancy.[10,18,27] These exposures may create an additive organ injury leading to increased morbidity above the general population.[28] Consequently, CHD patients are expected to experience different COD than the general population.

We recently reported the 25-year survival outcomes of 35 998 children undergoing CHS in the United States between 1982 and 2003 by linking the PCCC with the US National Death Index (NDI).[5] Long-term survival was decreased across all forms of CHD including even the mildest lesions.[4] We now examine the COD in this cohort to evaluate differential risks that may inform targeted surveillance for specific patient groups.

Methods

We conducted a retrospective cohort study using data from the PCCC registry enriched with prospectively collected data through linkage with the NDI. The study was approved by the Institutional Review Boards of the University of Minnesota and Emory University, by the NDI, and by the state birth registries of Minnesota, Arkansas, Ohio, South Carolina, and Missouri with waiver for informed consent for patients enrolled in the PCCC up to April 15, 2003, the date stricter Health Insurance Portability and Accountability Act rules took effect. The data, analytic methods, and study materials will be made available upon request from the corresponding author to qualified individuals completing necessary training requirements as set by the Institutional Review Board of Emory University. Shared data will be free of identifiers to protect the rights and privacy of the individuals who participate in this project as required by the Health Insurance Portability and Accountability Act Privacy Rule, and any local, state, and federal laws and regulations.

PCCC Registry

Details of the creation, activities, and function of the PCCC have been described before.[5,29] We queried the PCCC registry for patients who (1) were US residents; (2) underwent first CHS in a US PCCC center between January 1, 1982 and April 15, 2003; (3) were <21 years of age at the time of surgery; (4) survived to discharge after the CHS; and (5) had adequate identifiers for matching with the NDI.[30,31] We excluded low-birth-weight infants (<2.5 kg at the time of surgery) with isolated patent ductus arteriosus ligation and patients with known chromosomal abnormalities because of COD associated with the underlying condition.

We abstracted demographic and clinical variables including sex, age at first surgery, year of first surgery, type of surgery, and CHD diagnosis. Information about race was obtained from the PCCC, linkage to state birth records, or death records obtained from the NDI. The subset with race information available was classified as “black,” “white,” or “other race.”

Assignment of Cardiac Diagnosis and Classification of Defects

Each patient is assigned one primary diagnosis using a severity-based list of CHD and the operative strategy for the first reported CHS (Data S1).[31] We grouped conditions as mild, moderate, and severe lesions. The severe category was subdivided into single- (1V) and two-ventricle lesions (2V). Further subclassification of two-ventricular conditions into 1 of 8 categories was based on anatomo-pathophysiologic characteristics. If more than one CHD is present, patients are classified by the hierarchically most severe diagnosis. Lesions with coexistence of different pathophysiologies are classified as complex lesions to distinguish them from the plain forms of the primary CHD lesion.[31]

Death Ascertainment and Causes of Death Classification

Death was ascertained from the PCCC and by matching to NDI records through December 31, 2014.[30,31] COD were

provided by the NDI *Plus,* both as underlying and multiple or contributing COD (Data S1).[32] All COD are given as *International Classification of Disease* (*ICD*) codes.[33] Between 1982 to 1988, the NDI used the *ICD-9* revision, but beginning in 1999, the *ICD-10* revision is used. Because the PCCC includes data from both ICD revisions, all *ICD-10* codes were recoded to *ICD-9* for tabulation purposes.

Underlying COD were grouped in the following major ICD categories: (1) congenital heart disease (CHD); (2) diseases of the circulatory system (other than CHD) (termed herein cardiovascular disorders or CVD); (3) congenital malformations; (4) diseases of the respiratory system; (5) external causes of injury and poisoning; (6) infectious diseases; (7) neoplasms; and (8) other, where all other medical causes were lumped together. COD were compared across sexes and different age-strata (selected to match the Centers for Disease Control and Prevention reports of annual mortality), and to the general US population (Table S1).

Deaths by multiple COD were classified: (1) as CHD-associated death, when there is at least 1 ICD code related to CHD; (2) as CVD-associated death, when there is no ICD code related to CHD but at least 1 code related to CVD; or (3) as non-CHD/non-CVD death when there are no codes related to CHD or CVD.

US Mortality Data

Mortality data for the US population for the years 1982 to 2014 were downloaded from the CDC "Wonder" website and comprise age-, sex-, and year-specific death rates per 100 000 people.[34]

Statistical Analysis

Underlying COD classification was compared across sexes within age-group strata using χ^2 tests. Time of death from first surgery was categorized (<90 days, 90–365 days, 1–4 years, 5–9 years, 10–14 years, and >15 years) and treated as an ordinal variable to understand trends in cause-specific mortality. Associations between underlying COD and time from surgery were examined using a Cochran-Armitage test for trend.

SMRs were used to quantify the cause-specific rate of mortality in this CHD population compared with an age-, sex-, and calendar-year-matched US population (for additional information see Data S1).[31] Multivariable logistic regression was used to assess the association between race or sex and a specific COD. Models contained the overall effect of race or sex and other potential confounders: year of death, age at death, severity of CHD, sex, and race, as applicable.

All analyses were performed in SAS version 9.4 (SAS Institute Inc, Cary, NC) and an interactive figure was created using *plotly.*[35] Statistical significance was assessed at the 0.05 level unless otherwise noted.

Results

Characteristics of Study Population

Among the 35 998 patients who met inclusion criteria, we excluded 4866 (13.5%) patients with a known chromosomal abnormality. Patients excluded because of chromosomal anomalies tended to be younger at their first surgery, were more likely to be female, and have two-ventricle lesions with L-R physiology. The final cohort consisted of 31 132 patients, from 47 centers, discharged alive following their initial CHS.

A total of 2527 deaths (8.1%) occurred following discharge after the first CHS over a median follow-up period of 18.1 years (interquartile range: 14.5–22.2). Among the deaths, 1030 (40.8%) were female and 1497 were male (59.2%). Infants (<1 year of age) accounted for the largest share of deaths (n=994, 39.3%) followed by children aged 1 to 4 years (n=633, 25.0%). Median age at death was 1.8 years (interquartile range: 0.5–12.8). The median age of the cohort at the end of the study period was 20.9 years (interquartile range: 16.3–26.3) (Table 1).

Underlying COD

The underlying COD was CHD in 58.8% of deaths, with most of these (79.5%) occurring before 5 years of age. Other frequent COD included cardiovascular disorders (CVD) (11.1%), and external causes of injury (8.2%) (Figure 1) followed by coexisting noncardiac congenital anomalies (4.7%), respiratory diseases (3.6%), infections (3.4%), and neoplasms (2.1%). All other conditions were less frequent and accounted for the remaining 8.2% of deaths combined (Table S2).

CHD/CVD was the leading underlying COD in all patients up to 34 years of age; however, the relative percentage of deaths caused by CHD declined for both sexes as patients aged, while all other causes became more common after 20 years of age (Figure 2 and Table S3). Landmark analysis based on time after the first CHS revealed a similar trend with significant drop of the percentage of deaths caused by CHD at the 90-day, 1-year, and 5-year mark followed by a slower rate of decline thereafter (Table S4). An almost reverse trend with increased percentage of deaths caused by CVD, neoplasms, and external causes was noted with longer follow-up time post initial CHS. There is also a milder trend towards higher incidence of fatal respiratory conditions over time, while the percentage of deaths from associated malformations and infections remained relatively constant over the follow-up period.

Table 1. Summary of Patient Characteristics in the PCCC Cohort

	Overall (N=31 132)	Died (N=2527)
Median age at surgery (y) (IQR)	0.96 (0.17–4.22)	0.16 (0.02–1.03)
Sex		
Females	14 695 (47.2%)	1030 (40.8%)
Males	16 437 (52.8%)	1497 (59.2%)
Race		
White	9421 (80.6%)	1885 (76.5%)
Black	1948 (16.7%)	500 (20.3%)
Other	327 (2.8%)	79 (3.2%)
Missing	19 439	63
Physiology		
Two-ventricle lesions		
L-R Shunt	12 361 (39.7%)	419 (16.6%)
ASD	5565 (17.9%)	134 (5.3%)
PDA	2784 (9.0%)	79 (3.1%)
VSD (simple)	3496 (11.2%)	126 (5.0%)
CCAVC (simple)	515 (1.7%)	80 (3.2%)
LHOL	5286 (17.0%)	331 (13.1%)
Cor-Tri	74 (0.2%)	3 (0.1%)
MS	69 (1.3%)	14 (0.6%)
AS/Sub-AS	1263 (4.1%)	88 (3.5%)
CoA	3668 (11.8%)	191 (7.6%)
IAA	212 (0.7%)	35 (1.4%)
APVR	1436 (4.6%)	65 (2.6%)
TAPVR	672 (2.2%)	50 (2.0%)
PAPVR	764 (2.5%)	15 (0.6%)
RVOTO	3596 (11.6%)	242 (9.6%)
PS/Sub-PS	697 (2.2%)	33 (1.3%)
PA/IVS	198 (0.6%)	22 (0.9%)
TOF	2701 (8.7%)	187 (7.4%)
TGA physiology (d-TGA simple)	1545 (5.0%)	113 (4.5%)
Complete mixing (TAC)	204 (0.7%)	48 (1.9%)
Complex lesions	2510 (8.1%)	345 (13.7%)
Complex CAVC	44 (0.1%)	23 (0.9%)
Complex d-TGA	228 (0.7%)	72 (2.9%)
Complex VSD	1620 (5.2%)	77 (3.1%)
Complex TOF	618 (2.0%)	173 (6.9%)
Miscellaneous	1846 (5.9%)	178 (7.0%)
I-TGA (2V)	200 (0.6%)	48 (1.9%)
MR/AI	388 (1.3%)	40 (1.6%)
TVA	158 (0.5%)	28 (1.1%)
Other	1100 (3.5%)	62 (2.5%)
SV	2348 (7.5%)	786 (31.1%)
Left heart	988 (3.2%)	250 (9.9%)
Right heart	806 (2.6%)	352 (13.9%)
Other	554 (1.8%)	184 (7.3%)
Severity (two-ventricle lesions)		
Mild	10 974 (35.3%)	307 (12.2%)
Moderate	10 833 (34.8%)	584 (23.1%)
Severe 2V	4252 (13.7%)	593 (23.5%)
N/A	2725 (8.8%)	257 (10.2%)
Era		
Early (1982–1992)	9057 (29.1%)	1063 (42.1%)
Mid (1993–1997)	10 356 (33.3%)	788 (31.2%)
Late (1998–2003)	11 719 (37.6%)	676 (26.8%)

Numbers in parentheses express % unless otherwise specified. 2V indicates 2 ventricles; APVR, abnormal pulmonary venous return; AS/Sub-AS, aortic stenosis/subaortic stenosis; ASD, atrial-septal defect; CCAVC, complete common atrioventricular canal; CoA, coarctation of the aorta; Cor-Tri, cor-triatriatum; IAA, interrupted aortic arch; IQR, interquartile range; LHOL, left heart obstructive lesions; L-R Shunt, left-to-right shunt lesions; MR/AI, mitral regurgitation/aortic insufficiency; MS, mitral stenosis; N/A, not classifiable; PA/IVS, pulmonary atresia with intact ventricular septum; PAPVR, partial APVR; PCCC, Pediatric Cardiac Care Consortium; PDA, patent ductus arteriosus; PS/Sub-PS, pulmonary stenosis/subpulmonary stenosis; RVOTO, right ventricular outflow tract obstruction; SV, single ventricle; TAC, truncus arteriosus communis; TAPVR, total APVR; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TVA, tricuspid valve anomaly; VSD, ventricular septal defect.

Contributing COD

Overall, when examining contributing COD, over two thirds of deaths (n=1722, 68.1%) had at least 1 ICD code defining CHD as the underlying or multiple COD (Figure 3A, 3B, and Table S5). CVD was listed as multiple COD in over half of all CHD-related deaths (54.1%) but only in 29.5% of the non-CHD/non-CVD deaths. The most frequent CVD listings were cardiac arrest (16.8%), heart failure (14.8%), and arrhythmias/conduction abnormalities (9.1%). Comparing frequency of multiple COD in patients over age 5 years (relative to those younger) revealed a relative decrease in cardiac arrest of 22.0% and heart failure by 19.5%, but an increase in arrhythmias by 38.8% and pulmonary heart disease by 13.8% (Table S6). Deaths coded as unrelated to CHD or CVD (Figure 3A and Table S7) were identified in 424 patients (6.8%). Most of these deaths were attributed to external causes but a significant number of them were attributed to coexisting malformations, respiratory diseases, and neoplasms (9%–10% each).

Comparison to the General US Population

Underlying COD was compared with the general US population, adjusted for age, sex, and year of death (Table 2). In

patients with operated CHD, the risk of death caused by CHD or CVD was 67.7 times higher (95% CI: 64.5–70.8) than the general population. The separate SMRs from CHD or CVD are displayed in Table S8. The overall SMR for CHD/CVD ranged from 17.6 for patients with mild CHD to 157.1 for severe two-ventricle and 501.9 for single ventricle (SV). The increased SMR for CHD/CVD death peaked among death events between 1 and 4 years of age, but declined steadily thereafter, reaching 7.58 (95% CI: 5.63–9.53) among deaths between 25 and 34 years of age. SMRs for underlying COD by major physiology groups are presented in Table S9.

Significantly increased SMRs were also noted for other COD such as associated congenital malformations (SMR 7.0; 95% CI: 5.74–8.27), respiratory diseases (SMR 8.24; 95% CI: 6.55–9.92), infections (SMR 8.16; 95% CI: 6.42–9.89), and neoplasms (SMR 1.91; 95% CI: 1.39–2.43) (Table 2). Additionally, there were age-specific differences in risk of death caused by neoplasms and external causes. The higher risk from neoplasms affected only ages 1 to 4 years and 15 to 19 years, most notably in the group with severe CHD. Finally, risk of death from external causes did not differ overall from the general population, but it was increased for ages <10 years and decreased for ages 25 to 34 years. In a sensitivity analysis excluding patients with an ICD code referring to events associated with surgical care (some of which may refer to operations for CHD), the differential risk persisted for those aged 5 to 9 years and 25 to 34 years (Table S10). Of interest, the proportion of deaths from motor vehicle accidents was higher, while the proportion for homicide/assaults was lower, for CHD patients >20 years of age compared with the general population (Table S11).

Comparison of Causes of Death by Patient Characteristics

The risk of death caused by CHD/CVD was higher in women (SMR in females 85.3; 95% CI: 79.2–91.3 versus men 58.7; 95% CI: 55.1–62.4) (Table 2). Adjusted odds ratios between females and males revealed increased odds of death from a CHD or CVD in females [odds ratio=1.28; 95% CI (1.04–1.58); P=0.018]. Women had higher percentage of deaths caused by contribution from pulmonary heart disease, while men were more prone to arrhythmias, but after adjustment for severity none of these reached significance (Table S5). Stratified analysis by age did not reveal any significant difference between females and males during the reproductive age between 20 and 34 years of age. In addition, there were only 3 events coded as deaths associated with pregnancy, childbirth, and the puerperium.

Adjusted odds ratios for COD by race demonstrated that blacks had mild decrease in the odds of deaths from neoplasms relative to whites, but increased odds of death from "other" causes. There was no difference in the percentage of the various contributing causes of death between whites and blacks (Table S12).

Most deaths in patients with moderate and severe CHD were associated with CHD/CVD (57.5% for moderate, 79.6% for severe two-ventricle, and 88.9% for SV) (Figure 3A and Table S13). For patients with mild CHD, 47.5% of death records included CHD or CVD among the multiple causes of death. Patent ductus arteriosus was the condition with the lowest frequency of CHD/CVD–associated deaths. Frequently reported CVDs as multiple COD included heart failure, cardiac arrest, and arrhythmias, but with considerable variation across the spectrum of CHD (Table S14). The in-depth analysis of the multiple COD is outside of the scope of this report.

An era effect was observed on the CHD/CVD–related risk of death with progressive decline over time across all categories of CHD. This decline was driven mostly by decreases in CHD-related mortality, while CVD-related risk of death remained relatively constant over time (Table S15).

Discussion

Risk of Death From CHD and Cardiovascular Causes of Death

Our data show the majority of premature mortality in patients surviving to hospital discharge after CHS is CHD related and occurs before 5 years of age (Figure S1) with a gradual decline as the follow-up time increases after the first operation. Much of this may reflect perioperative mortality following subsequent procedures, as patients undergoing staged surgical strategies are often reoperated within this age range.

Mortality from cardiovascular conditions not directly linked to the underlying CHD was the next most frequent cause of death, and was higher than the general population across all

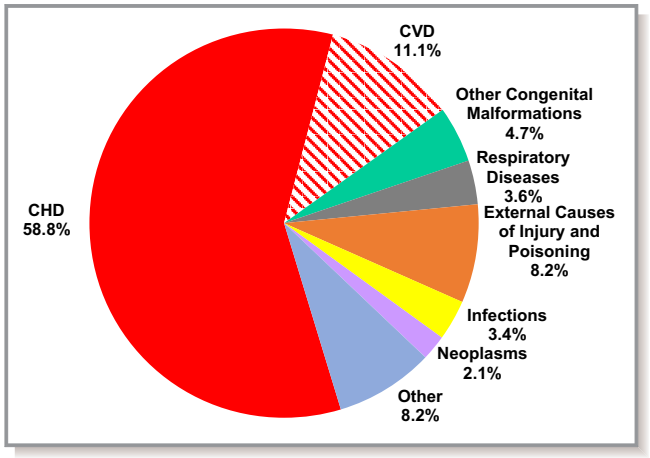

Figure 1. Underlying cause of death in patients undergoing congenital heart surgery. CHD indicates congenital heart defects; CVD, cardiovascular disorders.

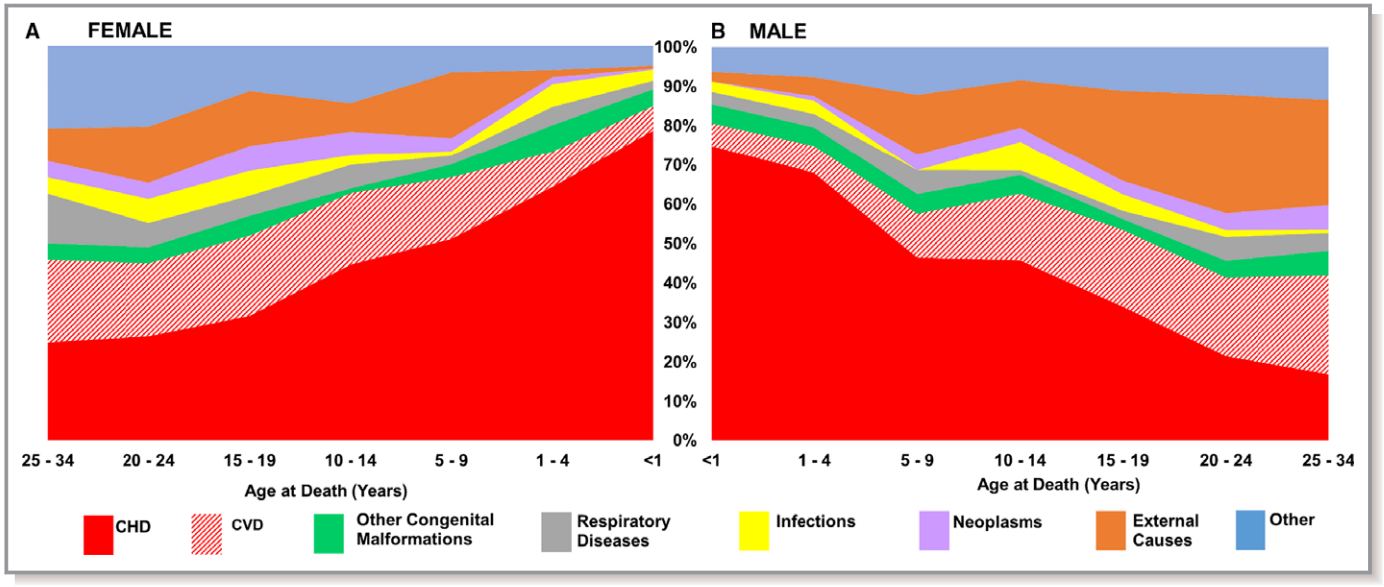

Figure 2. Underlying cause of death by age and sex (Female: **A**, Male: **B**). CHD indicates congenital heart defects; CVD, cardiovascular disorders.

severity groups, even for mild forms of CHD. The excess risk for CHD/CVD mortality persisted throughout the follow-up period, but gradually decreased over time.

Among the CVD conditions contributing to death, heart failure, arrhythmias, and conduction abnormalities were most frequent, highlighting the significant residual cardiovascular morbidity. Pulmonary heart disease, cerebrovascular conditions, and myocardial ischemia were less frequently reported. Over time after CHS, there was a shift from CHD and cardiac arrests towards more heart failure and arrhythmia-related deaths. As expected, there was considerable variation in the underlying and contributing COD between individual lesions, reflecting the differences in their underlying physiology, severity, and residual abnormalities. The detailed analysis of this variation is outside the scope of this report.

The higher risk of death from CHD in females after discharge parallels our observations of in-hospital deaths after CHS.[36] A potential cause for that differential risk of death caused by CHD may be pregnancy-related events; however, the available number of events could not confirm this hypothesis. There were no sex differences for CVD-related deaths besides a trend towards more pulmonary heart disease–related deaths in females consistent with their reported higher incidence of pulmonary hypertension.[37]

Non-CHD/Non-CVD Causes of Death

In contrast to the CHD/CVD causes, risk of death from noncardiovascular causes generally increased with age. Among these causes, excess risk above the general population was noted for respiratory and infectious conditions. This is not surprising given the close relationship between cardiovascular and respiratory health, as well the increased vulnerability of these patients to infectious processes.[38–40] Similarly, the increased risk of death from neoplastic processes in patients with operated CHD has been observed before.[19,38] However, the large number of patients in our cohort allowed us to demonstrate an age-dependent risk of death from neoplasms and identify groups at highest risk. This excess risk may reflect increased incidence of certain forms of cancer, or increased vulnerability to complications of cancer treatment, or both.[41–43]

Risk of death from coexisting congenital anomalies was consistently increased across all age groups and likely reflects the high incidence of such extracardiac abnormalities in this group of patients.[44]

Interestingly, an age-dependent differential risk was noted for external causes of death. Not previously described, the higher risk from external causes in the group of 5 to 9 years of age suggests increased vulnerability to injuries and accidents during young childhood, when little control can be successfully applied over such exposures. On the other hand, the risk from external causes is moderated in the 25 to 34 years of age group, possibly because of activity restrictions, self-imposed limitations, decreased involvement in risky behaviors, or self-selection of a less-at-risk subgroup. Suicidal risk was elevated in an adult cohort with tetralogy of Fallot in Taiwan,[26] but was not a substantial source of death in our cohort.

Trends in Modality of Death

Comparing eras in this cohort demonstrates a promising trend towards decreasing CHD mortality. On the other

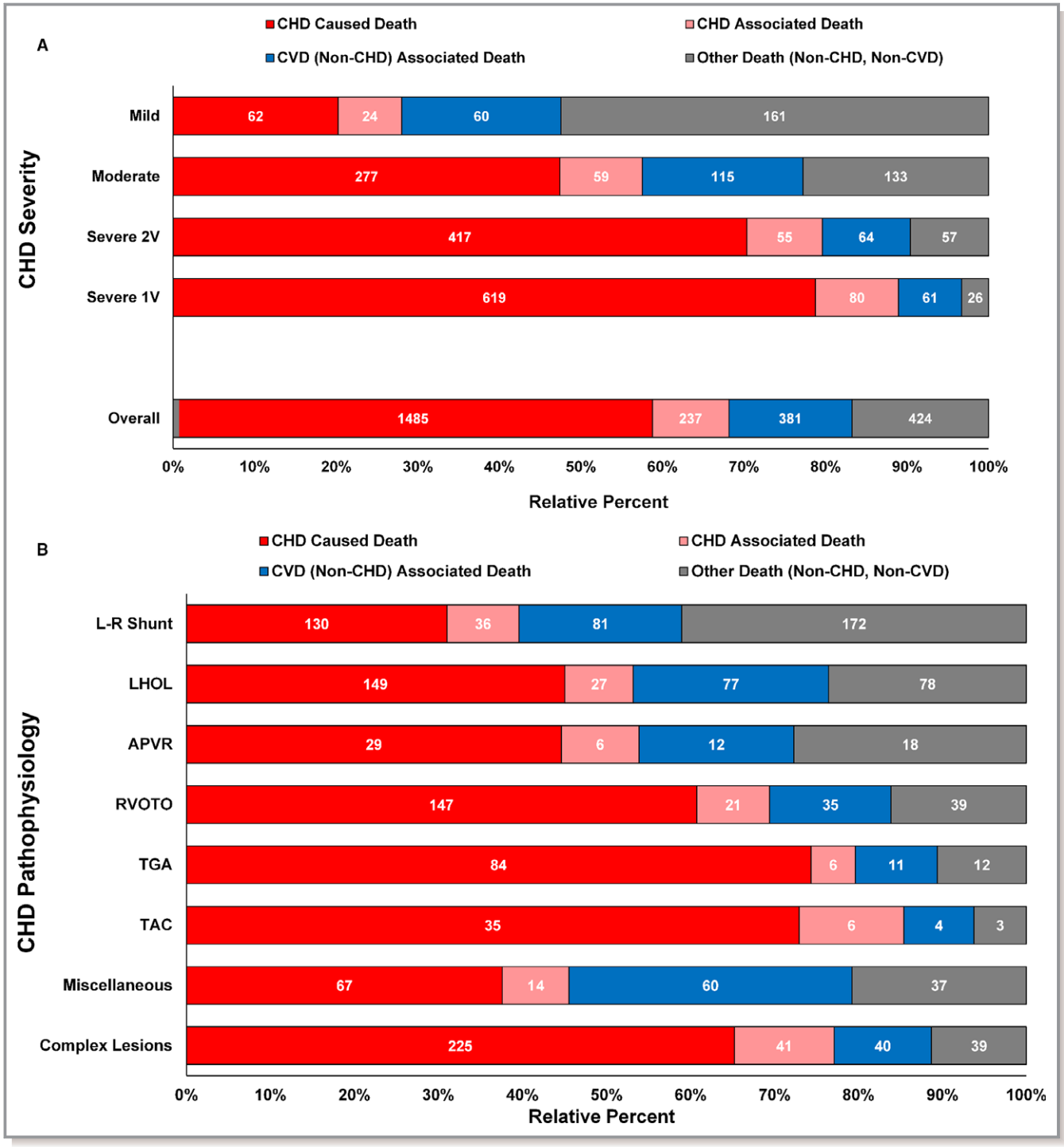

Figure 3. **A,** Underlying or multiple causes of death by CHD severity. 1V, 1 ventricle; 2V, 2 ventricles. **B,** Underlying or multiple causes of death by CHD pathophysiology. APVR indicates abnormal pulmonary venous return; CHD, congenital heart defects; CVD, cardiovascular disorders; L-R Shunt, left-to-right shunt lesions; LHOL, left heart obstructive lesions; RVOTO, right ventricular outflow tract obstruction; TAC, truncus arteriosus communis; TGA, transposition of the great arteries. Length of bars represents the relative percentage of death from a specific cause while the counts reflect the actual number of deaths in each category.

hand, the persistently elevated CVD-related risk in each era and across all severity forms of CHD suggests that postoperative cardiovascular sequelae continue to impose a significant burden despite improvements in treating CHD. Moreover, the excess mortality from other causes remained unchanged over time, suggesting limited progress in the management or prevention of these additional non-CHD morbidities.

Table 2. Cause-Specific SMR for Major Category Groups*

Underlying Cause of Death	Group	N	SMR (95%)	95% CI	*P* Value
CHD or CVD	Overall	1765	67.7	(64.5–70.8)	<0.001
	<1 y	819	107.9	(100.5–115.3)	<0.001
	1–4 y	469	201.4	(183.2–219.6)	<0.001
	5–9 y	117	118.5	(97.1–140.0)	<0.001
	10–14 y	104	84.7	(68.4–101.0)	<0.001
	15–19 y	118	50.9	(41.7–60.1)	<0.001
	20–24 y	70	32.4	(24.8–40.0)	<0.001
	25–34 y	58	7.58	(5.63–9.53)	<0.001
	Mild CHD	97	17.6	(14.1–21.1)	<0.001
	Moderate CHD	360	56.3	(50.5–62.1)	<0.001
	Severe 2V CHD	465	157.1	(142.8–171.4)	<0.001
	Severe 1V CHD	673	501.9	(463.9–539.8)	<0.001
	Females	748	85.3	(79.2–91.3)	<0.001
	Males	1017	58.7	(55.1–62.4)	<0.001
	Early Era†	632	167.6	(154.5–180.7)	<0.001
	Mid Era†	506	101.6	(92.8–110.5)	<0.001
	Late Era†	475	81.3	(74.0–88.6)	<0.001
Other congenital malformations	Overall	118	7.00	(5.74–8.27)	<0.001
	<1 y	46	3.83	(2.73–4.94)	<0.001
	1–4 y	36	20.5	(13.8–27.2)	<0.001
	5–9 y	8	9.42	(2.89–15.9)	0.012
	10–14 y	5	7.28	(0.90–13.7)	0.054
	15–19 y	8	14.1	(4.32–23.8)	0.009
	20–24 y	7	17.9	(4.63–31.1)	0.013
	25–34 y	8	15.2	(4.66–25.7)	0.008
	Mild CHD	27	7.38	(4.60–10.2)	<0.001
	Moderate CHD	38	6.76	(4.61–8.91)	<0.001
	Severe 2V CHD	20	4.68	(2.63–6.73)	<0.001
	Severe 1V CHD	21	9.96	(5.70–14.2)	<0.001
	Females	48	6.78	(4.86–8.69)	<0.001
	Males	70	7.17	(5.49–8.85)	<0.001
	Early Era†	31	6.60	(4.28–8.24)	<0.001
	Mid Era†	43	8.45	(5.94–11.00)	<0.001
	Late Era†	29	4.81	(3.06–6.56)	<0.001
Respiratory diseases	Overall	92	8.24	(6.55–9.92)	<0.001
	<1 y	27	10.9	(6.78–15.0)	<0.001
	1–4 y	25	14.8	(9.02–20.6)	<0.001
	5–9 y	8	8.50	(2.61–14.39)	0.013
	10–y	6	5.51	(1.10–9.92)	0.045
	15–19 y	7	6.71	(1.74–11.68)	0.024
	20–24 y	10	9.70	(3.69–15.72)	0.005

Continued

Table 2. Continued

Underlying Cause of Death	Group	N	SMR (95%)	95% CI	*P* Value
	25–34 y	8	3.50	(1.07–5.92)	0.043
	Mild CHD	22	5.96	(3.47–8.45)	<0.001
	Moderate CHD	23	5.96	(3.52–8.39)	<0.001
	Severe 2V CHD	24	14.3	(8.55–19.9)	<0.001
	Severe 1V CHD	14	18.7	(8.90–28.5)	<0.001
	Females	40	8.77	(6.05–11.49)	<0.001
	Males	52	7.87	(5.73–10.01)	<0.001
	Early Era†	26	10.5	(6.48–14.6)	<0.001
	Mid Era†	19	7.49	(4.12–10.86)	<0.001
	Late Era†	29	11.0	(7.00–15.0)	<0.001
Infections	Overall	85	8.16	(6.42–9.89)	<0.001
	<1 y	27	14.1	(8.76–19.4)	<0.001
	1–4 y	28	18.8	(11.9–25.8)	<0.001
	5–9 y	1	1.36	(0–4.01)	0.793
	10–14 y	8	13.7	(4.21–23.2)	0.009
	15–19 y	11	16.5	(6.75–26.3)	0.002
	20–24 y	5	5.40	(0.67–10.1)	0.068
	25–34 y	2	0.61	(0–1.46)	0.373
	Mild CHD	12	3.38	(1.47–5.29)	0.015
	Moderate CHD	20	5.51	(3.15–8.07)	<0.001
	Severe 2V CHD	22	16.5	(9.57–23.3)	<0.001
	Severe 1V CHD	24	41.2	(24.7–57.7)	<0.001
	Females	41	9.86	(6.84–12.87)	<0.001
	Males	44	7.03	(4.95–9.10)	<0.001
	Early Era†	18	7.43	(4.00–10.9)	<0.001
	Mid Era†	29	13.1	(8.30–17.8)	<0.001
	Late Era†	23	12.3	(7.24–17.3)	<0.001
Neoplasms	Overall	53	1.91	(1.39–2.43)	<0.001
	<1 y	1	2.51	(0–7.44)	0.547
	1–4 y	9	3.54	(1.23–5.87)	0.031
	5–9 y	7	1.99	(0.52–3.47)	0.188
	10–14 y	8	2.43	(0.75–4.11)	0.096
	15–19 y	10	2.85	(1.08–4.61)	0.040
	20–24 y	7	2.27	(0.59–3.94)	0.140
	25–34 y	8	0.98	(0.30–1.66)	0.949
	Mild CHD	18	1.66	(0.89–2.43)	0.092
	Moderate CHD	16	1.67	(0.85–2.49)	0.109
	Severe 2V CHD‡	10	3.78	(1.44–6.12)	0.020
	Severe 1V CHD‡	3	2.82	(0–6.01)	0.264
	Females	23	1.82	(1.08–2.57)	0.030
	Males	30	1.99	(1.23–2.70)	<0.001

Continued

Table 2. Continued

Underlying Cause of Death	Group	N	SMR (95%)	95% CI	*P* Value
	Early Era†	12	2.57	(1.11–4.00)	0.035
	Mid Era†	12	2.39	(1.04–3.75)	0.044
	Late Era†	13	2.56	(1.18–3.98)	0.027
External causes	Overall	207	1.08	(0.93–1.23)	0.293
	<1 y	17	4.75	(2.49–7.01)	0.001
	1– 4 y	22	1.72	(1.00–2.44)	0.049
	5– 9 y	30	3.28	(2.10–4.44)	<0.001
	10–14 y	16	1.38	(0.70–2.05)	0.272
	15–19 y	44	0.96	(0.68–1.25)	0.792
	20–24 y	42	0.95	(0.66–1.23)	0.708
	25–34 y	32	0.55	(0.36–0.74)	<0.001
	Mild CHD	70	1.00	(0.76–1.23)	0.978
	Moderate CHD	68	0.98	(0.75–1.21)	0.869
	Severe 2V CHD	25	1.34	(0.82–1.87)	0.201
	Severe 1V CHD	16	2.38	(1.22–3.55)	0.020
	Females	40	1.05	(0.76–1.36)	0.759
	Males	157	1.09	(0.91–1.26)	0.301
	Early Era†	55	1.78	(1.31–2.25)	0.001
	Mid Era†	39	1.22	(0.84–1.61)	0.253
	Late Era†	43	1.46	(1.03–1.90)	0.039
Other medical causes	Overall	207	2.06	(1.76–2.34)	<0.001
	<1 y	57	0.98	(0.73–1.24)	0.907
	1–4 y	44	7.62	(5.37–9.87)	<0.001
	5–9 y	18	5.21	(2.80–7.61)	<0.001
	10–14 y	19	4.79	(2.64–6.95)	<0.001
	15–19 y	25	4.48	(2.72–6.24)	<0.001
	20–24 y	24	3.85	(2.31–5.38)	<0.001
	25–34 y	20	1.41	(0.78–2.03)	0.192
	Mild CHD	61	2.38	(1.78–2.96)	<0.001
	Moderate CHD	59	1.75	(1.30–2.20)	0.001
	Severe 2V CHD	27	1.25	(0.78–1.72)	<0.001
	Severe 1V CHD	35	3.36	(2.25–4.47)	<0.001
	Females	80	2.05	(1.60–2.50)	<0.001
	Males	127	2.06	(1.70–2.42)	<0.001
	Early Era†	53	2.20	(1.60–2.79)	<0.001
	Mid Era†	60	2.41	(1.80–3.02)	<0.001
	Late Era†	52	1.71	(1.25–2.18)	0.003

1V indicates 1 ventricle; 2V, 2 ventricles; CHD, congenital heart defects; CI, confidence interval; CVD, cardiovascular disorder; SMR, standardized mortality ratio.

*Overall SMR and SMRs by era and CHD severity are adjusted for sex, year of death, and age at death. SMRs by sex are adjusted for age at death and year of death. SMRs by age strata are adjusted for year of death and sex.

†Deaths occurring after 15 years of follow-up were not included in the SMR calculations for era. This truncation was necessary for making follow-up time comparable among eras. As a result, death counts across eras do not sum to total death count for a specific cause.

‡Combined SMR for severe CHD: 3.50 (95% CI: 1.6–5.51) (*P*=0.001).

Comparison With Other Studies

Our findings are similar to those from the population-based study in Finland,[8] the only other large study of modes of death among patients with operated CHD. This study included about 11 000 patients and spanned over 60 years; however, most of these patients had lesions of mild or uncharacterized severity, and only a few of them have complex or single-ventricle forms of CHD. In contrast to the Finnish study, we found the effect of era on CHD-related mortality was seen across most CHD lesions and not just ventricular septal defect, perhaps related to the larger sample size or ability to distinguish CHD- versus CVD-related deaths in our cohort.

Other studies on this subject are not directly comparable to the PCCC and Finnish studies because they include a mixed population of adult-only patients with operated and unoperated CHD.[7,9,12,34,45–48] However, despite these methodological differences, the overall distribution of COD was very similar, at least for the lesions with sufficient numbers of patients.

Limitations

Limitations of this study are those inherent to its registry-based, retrospective nature. As a result, the number of eligible patients who survive to discharge by era may reflect the number and size of centers contributing data to the registry during the different era as well as the increased number of patients operated and surviving operations over time. In addition, information regarding subsequent procedures, residual defects, socioeconomic data, and lifestyle exposures is limited.

An additional limitation is the quality of COD codes available in the NDI-*Plus*; few deaths in our cohort fell in the unknown category, so this is unlikely to significantly affect the findings of our study, but there are other known limitations of this resource including risk for misclassification of chronic conditions, attribution errors, and use of mode instead of actual COD.[49] Nevertheless, the NDI has been used extensively to understand COD across a wide range of conditions and has been generally found to provide meaningful results.[50] Of importance for our study comparing COD between different pathophysiologies, there is no reason to believe that misattribution of COD would have been differential by lesion.

Despite these limitations, the concordance of our findings with similar studies supports the validity of the methodology used. As the PCCC contains a much larger number of patients than previously reported studies, the data suggest that our approach can be used with confidence to understand the specific risks associated with even the rarest CHD for which other cohorts contain very few events or no data at all.

Operative techniques and medical care continue to evolve; thus, long-term outcomes and cause-specific risks are expected to change over time. Experience has shown that apart from conditions with radical changes in their management, treatment for many conditions evolves gradually without major shifts in risk. Continuous monitoring of our cohort will allow us to identify major risks in survivors with operated CHD and focus on strategies that will reduce their hazards.

Conclusions

Survivors of CHS face long-term risks for premature mortality, with deaths attributed most often to residual CHD pathology, heart failure, and arrhythmias, but also to other noncardiac conditions. As a result, ongoing monitoring of this population is warranted and additional research is needed to identify modifiable factors that can be targeted to address residual morbidities and improve long-term outcomes.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Assignment of cardiac diagnosis and classification of defects

The list of conditions is modeled on previous published lists and includes 27 CHD diagnoses grouped into nine major underlying physiologies (eight for the two-ventricle lesions and one for single ventricle lesions) [1-3]. If more than one CHD is present, patients are classified by the hierarchically most severe diagnosis, except when lesions with different pathophysiology coexist, in which case, the lesion is listed separately within the complex group. Lesions not fitting into any of these major physiology groups are listed as miscellaneous.

Causes of death classification

Determination of the underlying and multiple (contributing) causes of death was provided by the NDI *Plus*, an optional service which uses an automated classification scheme reducing bias associated with manual coding [4]. Underlying COD is defined as "the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident of violence which produced fatal injury" and which is selected from an array of conditions reported on the death certificate [5]. In addition, the NDI *Plus* report includes up to 21 additional contributing causes of death, defined as conditions or injuries/exposures that contributed to the fatal outcome.

Between 1982 and 1988 deaths were coded using the ICD Ninth Revision *(ICD-9).* Beginning in 1999, the Tenth revision (ICD-10) codes were used. Because the PCCC includes data from both time periods, all ICD-10 codes were recoded to ICD-9 for tabulation purposes (Supplemental Table 1). Because external COD include codes related to "surgical misadventures", meaning complications of surgical and medical care not classified elsewhere, we conducted a sensitivity analysis and recalculated the SMRs after excluding these codes.

Calculation of cause-specific standardized mortality ratio (SMR) and comparison with the general US population

SMRs were obtained by dividing the observed number of deaths by the expected number of deaths based on the US mortality rates matched to the PCCC cohort. This method has been previously described [1] .

SMRs are provided with associated 95% confidence intervals (CIs). CIs for SMRs not containing 1 indicated that the CHD population's SMR for these particular causes differ significantly from that of the general population. When calculating SMRs by era, follow-up was truncated at 15 years to allow comparable follow-up times between eras. As a result, death occurring outside the 15 years of follow-up were excluded.

Because race was available for nearly all subjects that died, but missing for over 50% of the entire PCCC cohort, race-specific SMRs were not calculated. Instead, COD was tabulated for all deaths in the US population between 1982 and 2014 by age and race strata.

Table S1. ICD-9 and ICD-10 Codes Associated with Cause of Death Groupings.

Cause of Death Group	ICD-9	ICD-10
Infectious and Parasitic Diseases	001- 139	A00 – B99
Neoplasms	140 - 239	C00 – D49
Endocrine, nutritional and metabolic disease of immunity disorders *	240 – 279	E00 – E88
Diseases of blood and blood-forming organs*	280 – 289	D50 – D89
Mental Disorders*	290 – 319	F01 – F99
Diseases of the nervous system and sense organs*	320 – 389	G00 - G99, H00 – H59, H60 – H95
Diseases of the circulatory system†	390 – 459	I00 – I99
Diseases of the respiratory system	460 – 519	J00 – J99
Diseases of the digestive system *	520 – 579	K00 – K95
Diseases of the genitourinary system*	580 – 629	N00 – N99
Complications of pregnancy, childbirth and puerperium*	630 – 678	O00 – O99/9A
Diseases of the skin and subcutaneous tissue*	680 – 709	L00 – L99
Disease of the musculoskeletal system and connective tissue*	710 739	M00 – M99
Congenital malformations, deformations, and chromosomal abnormalities	740 – 759	Q00 – Q99
Congenital Heart Disease‡	745, 746, 747.0– 747.4	Q20-Q26

Non-CHD abnormalities	740 – 744, 747.5 – 747.9, 748 – 759	Q00-Q18, Q27-Q99
Certain conditions originating in the perinatal period*	760 – 779	P00 – P96
Symptoms, signs and ill-defined conditions*	780 – 799	R00 – R99
External causes of injury and poisoning	800 – 999 E800 – E999	S00-T88, V00 – Y89

ICD: International classification of diseases;

* Items in these categories were lumped together to define the group "other".
† Selected codes are indicative Cardiovascular Disorders (CVD) within the group of diseases of the circulatory system.
‡ Selected codes are indicative of Congenital Heart Defects (CHD) within the group of Congenital Heart Diseases

Table S2. Breakdown of "Other" Underlying Causes of Death.

Cause of Death	N= 207
Disease of the Nervous System and Sense Organs	54 (2.1%)
Symptoms, signs, and ill-defined conditions not otherwise specified	26 (1.0%)
Diseases of the Digestive System	42 (1.7%)
Endocrine, nutritional and metabolic diseases, and immunity disorders	28 (1.1%)
Certain conditions originating in the perinatal period	21 (0.8%)
Mental Disorders	5 (0.2%)
Diseases of the blood and blood forming organs	13 (0.5%)
Complications of pregnancy, childbirth and puerperium	3 (0.1%)
Diseases of the musculoskeletal system	5 (0.2%)
Disease of the genitourinary system	9 (0.4%)
Unknown	1 (0.04%)

Table S3. Underlying Cause of Death by Age-Sex Stratification.

Underlying Cause of Death	Overall N (%)	Females (N = 1,030)	Males (N = 1,497)	P-value
Overall				
CHD	1,485 (58.8%)	638 (61.9%)	847 (56.6%)	0.007*
CVD	280 (11.1%)	110 (10.7%)	170 (11.4%)	0.595
Other congenital malformations	118 (4.7%)	48 (4.7%)	70 (4.7%)	0.985
Respiratory diseases	92 (3.6%)	40 (3.9%)	52 (3.5%)	0.589
Infections	85 (3.4%)	41 (4.0%)	44 (2.9%)	0.154
Neoplasms	53 (2.1%)	23 (2.2%)	30 (2.0%)	0.693
External Causes of Injury and Poisoning	207 (8.2%)	50 (4.9%)	157 (10.5%)	<0.001*
Other Medical Causes of Death	207 (8.2%)	80 (7.8%)	127 (8.5%)	0.519
Age < 1 (n = 994)		n = 421	n = 573	
CHD	760 (76.5%)	331 (78.6%)	429 (74.9%)	0.168
CVD	59 (5.9%)	26 (6.2%)	33 (5.8%)	0.784
Other congenital malformations	46 (4.6%)	18 (4.3%)	28 (4.9%)	0.651
Respiratory diseases	27 (2.7%)	9 (2.1%)	18 (3.2%)	0.336
Infections	27 (2.7%)	12 (2.9%)	15 (2.6%)	0.824
Neoplasms	1 (0.1%)	1 (0.2%)	0 (0%)	0.243
External Causes of Injury and Poisoning	17 (1.7%)	3 (0.7%)	14 (2.4%)	0.038*
Other Medical Causes of Death	57 (5.7%)	21 (5.0%)	36 (6.3%)	0.386

Underlying Cause of Death	Overall N (%)	Females (N = 1,030)	Males (N = 1,497)	P-value
Age 1 – 4 years (n = 633)		n = 280	n = 353	
CHD	420 (66.4%)	180 (64.3%)	240 (68.0%)	0.327
CVD	49 (7.7%)	25 (8.9%)	24 (6.8%)	0.319
Other congenital malformations	36 (5.7%)	19 (6.8%)	17 (4.8%)	0.288
Respiratory diseases	25 (4.0%)	13 (4.6%)	12 (3.4%)	0.425
Infections	28 (4.4%)	16 (5.7%)	12 (3.4%)	0.160
Neoplasms	9 (1.4%)	5 (1.8%)	4 (1.1%)	0.491
External Causes of Injury and Poisoning	22 (3.5%)	5 (1.8%)	17 (4.8%)	0.039*
Other Medical Causes of Death	44 (7.0%)	17 (6.1%)	27 (7.7%)	0.438
Age 5 – 9 years (n = 189)		n = 90	n = 99	
CHD	92 (48.7%)	46 (51.1%)	46 (46.5%)	0.523
CVD	25 (13.2%)	14 (15.6%)	11 (11.1%)	0.368
Other congenital malformations	8 (4.2%)	3 (3.3%)	4 (5.1%)	0.558
Respiratory diseases	8 (4.2%)	2 (2.2%)	6 (6.1%)	0.191
Infections	1 (0.5%)	1 (1.1%)	0 (0%)	0.293
Neoplasms	7 (3.7%)	3 (3.3%)	4 (4.0%)	0.797
External Causes of Injury and Poisoning	30 (15.9%)	15 (16.7%)	15 (15.2%)	0.776
Other Medical Causes of Death	18 (9.5%)	6 (6.7%)	12 (12.1%)	0.202

Underlying Cause of Death	Overall N (%)	Females (N = 1,030)	Males (N = 1,497)	P-value
Age 10 – 14 Years (n = 166)		n = 83	n = 83	
CHD	75 (45.2%)	37 (44.6%)	38 (45.8%)	0.876
CVD	29 (17.5%)	15 (18.1%)	14 (16.9%)	0.838
Other congenital malformations	5 (3.0%)	1 (1.2%)	4 (4.8%)	0.173
Respiratory diseases	6 (3.6%)	5 (3.0%)	1 (1.2%)	0.096
Infections	8 (4.8%)	2 (2.4%)	6 (7.2%)	0.147
Neoplasms	8 (4.8%)	5 (6.0%)	3 (3.6%)	0.469
External Causes of Injury and Poisoning	16 (9.6%)	6 (7.2%)	10 (12.1%)	0.293
Other Medical Causes of Death	19 (11.5%)	12 (14.5%)	7 (8.4%)	0.223
Age 15 – 19 Years (n = 223)		n = 79	n = 144	
CHD	74 (33.2%)	25 (31.7%)	49 (34.0%)	0.718
CVD	44 (19.7%)	16 (20.3%)	28 (19.4%)	0.885
Other congenital malformations	8 (3.6%)	4 (5.1%)	4 (2.9%)	0.380
Respiratory diseases	7 (3.1%)	4 (5.1%)	3 (2.1%)	0.222
Infections	11 (4.9%)	5 (6.3%)	6 (4.2%)	0.476
Neoplasms	10 (4.5%)	5 (6.3%)	5 (3.5%)	0.324
External Causes of Injury and Poisoning	44 (19.7%)	11 (13.9%)	33 (22.9%)	0.107
Other Medical Causes of Death	25 (11.2%)	9 (11.4%)	16 (11.1%)	0.949

Underlying Cause of Death	Overall N (%)	Females (N = 1,030)	Males (N = 1,497)	P-value
Age 20 – 24 Years (n = 165)		n = 49	n = 116	
CHD	38 (23.0%)	13 (26.5%)	25 (21.6%)	0.488
CVD	32 (19.4%)	9 (18.4%)	23 (19.8%)	0.828
Other congenital malformations	7 (4.2%)	2 (4.1%)	5 (4.3%)	0.947
Respiratory diseases	10 (6.1%)	3 (6.1%)	8 (6.0%)	0.983
Infections	5 (3.0%)	3 (6.1%)	2 (1.7%)	0.132
Neoplasms	7 (4.2%)	2 (4.1%)	5 (4.3%)	0.947
External Causes of Injury and Poisoning	42 (25.5%)	7 (14.3%)	35 (30.2%)	0.032*
Other Medical Causes of Death	24 (14.6%)	10 (20.4%)	14 (12.1%)	0.165
Age 25 – 34 Years (n = 136)		n = 24	n = 112	
CHD	25 (18.4%)	6 (25.0%)	19 (17.0%)	0.356
CVD	33 (24.3%)	5 (20.8%)	28 (25.0%)	0.666
Other congenital malformations	8 (5.9%)	1 (4.2%)	7 (6.3%)	0.694
Respiratory diseases	8 (5.9%)	3 (12.5%)	5 (4.5%)	0.129
Infections	2 (1.5%)	1 (4.2%)	1 (0.9%)	0.227
Neoplasms	8 (5.9%)	1 (4.2%)	7 (6.3%)	0.694
External Causes of Injury and Poisoning	32 (23.5%)	2 (8.3%)	30 (26.8%)	0.053
Other Medical Causes of Death	20 (14.7%)	5 (20.8%)	15 (13.4%)	0.350

CHD: Congenital Heart Defects; CVD: Cardiovascular Disorders

*Indicates comparisons with statistically significant difference ($p<0.05$).

Table S4. Underlying Cause of Death by Time since Initial Congenital Heart Surgery.

	Overall	< 90d (N = 594)	90d – 365d (N = 587)	1 – 4yrs (N = 566)	5 - 9yrs (N = 226)	10 - 14yrs (N = 226)	>15yrs (N = 328)	P-value*
CHD	1485 (58.8%)	480 (80.8%)	397 (67.6%)	361 (63.8%)	86 (38.1%)	73 (32.3%)	88 (26.8%)	<0.001†
CVD	280 (11.1%)	40 (6.7%)	41 (7.0%)	47 (8.3%)	40 (17.7%)	48 (21.2%)	64 (19.5%)	<0.001†
Other Congenital Anomalies	118 (4.7%)	20 (3.4%)	32 (5.5%)	36 (6.4%)	7 (3.1%)	8 (3.5%)	15 (4.6%)	0.943
Respiratory Diseases	92 (3.6%)	9 (1.5%)	28 (4.8%)	19 (3.4%)	9 (4.0%)	9 (4.0%)	18 (5.5%)	0.013†
Infections	85 (3.4%)	11 (1.9%)	26 (4.4%)	21 (3.7%)	3 (1.3%)	9 (4.0%)	15 (4.6%)	0.150
Neoplasms	53 (2.1%)	0	1 (0.2%)	11 (1.9%)	14 (6.2%)	11 (4.9%)	16 (4.9%)	<0.001†

External Causes	207 (8.2%)	9 (1.5%)	21 (3.6%)	29 (5.1%)	43 (19.0%)	35 (15.5%)	70 (21.3%)	<0.001[†]
Other Causes	207 (8.2%)	25 (4.2%)	41 (7.0%)	42 (7.4%)	24 (10.6%)	33 (14.6%)	42 (12.8%)	<0.001[†]

CHD: Congenital Heart Defects; CVD: Cardiovascular Disorders

[*] P-value was calculated from the Cochran Armitage test for trend, which accounts for the ordinal degree of time since surgery.

[†]Indicates comparisons with statistically significant difference ($p<0.05$).

Table S5. Frequency of CHD and CVD Codes as Contributing Causes of Death.

Underlying or Associated Cause of Death	Overall N=2,527	Females N = 1030	Males N = 1497	AOR*	95% CI	Adjusted P-value †
Congenital heart diseases (CHD)	1,722 (68.1%)	740 (71.8%)	982 (65.6%)	1.33	(1.06 – 1.66)	0.013 ‡
Cardiovascular diseases (CVD)	1,308 (51.8%)	539 (52.3%)	769 (51.4%)	1.09	(0.92 – 1.30)	0.308
Cardiac Arrest	424 (16.8%)	171 (16.6%)	253 (16.9%)	0.99	(0.79 – 1.25)	0.953
Heart Failure	373 (14.8%)	151 (14.7%)	222 (14.8%)	0.96	(0.75 – 1.22)	0.723
Other Heart Disease	226 (8.9%)	93 (9.0%)	133 (8.9%)	1.23	(0.90 – 1.68)	0.190
Arrhythmias	230 (9.1%)	81 (7.9%)	149 (10.0%)	0.81	(0.60 – 1.10)	0.179
Dysrhythmias	195 (7.7%)	66 (6.4%)	129 (8.6%)	0.75	(0.54 – 1.05)	0.091
Conduction Disorder	44 (1.7%)	21 (2.0%)	23 (1.5%)	1.58	(0.83 – 3.03)	0.168
Pulmonary Heart Disease	153 (6.1%)	75 (7.3%)	78 (5.2%)	1.39	(0.98 – 1.98)	0.063
Cerebrovascular Conditions	96 (3.8%)	38 (3.7%)	58 (3.9%)	0.87	(0.55 – 1.39)	0.562
Ischemic Heart Disease	82 (3.2%)	31 (3.0%)	51 (3.4%)	1.15	(0.70 – 1.87)	0.586
Cardiomyopathy	76 (3.0%)	24 (2.3%)	52 (3.5%)	0.81	(0.45 – 1.44)	0.465
Valve Disease	64 (2.5%)	19 (1.8%)	45 (3.0%)	0.91	(0.47 – 1.79)	0.791

Diseases of the Vein and Lymph Nodes	42 (1.7%)	24 (2.3%)	18 (1.2%)	1.76	(0.95 – 3.29)	0.075
Disease of the Capillaries	38 (1.5%)	7 (0.7%)	31 (2.1%)	0.43	(0.16 – 1.19)	0.105
Endocarditis	34 (1.4%)	9 (0.9%)	25 (1.7%)	0.91	(0.36 – 2.28)	0.836
Rheumatic Heart Disease	29 (1.2%)	12 (1.2%)	17 (1.1%)	0.98	(0.40 – 2.36)	0.959
Hypertensive Disease	13 (0.5%)	3 (0.3%)	10 (0.7%)	0.97	(0.22 – 4.20)	0.968

CHD: Congenital Heart Defects; CVD: Cardiovascular Disorders; CI: confidence interval

* AOR: Adjusted Odds. AOR was calculated for females/males using females as the reference group.
† P-value corresponds to the adjusted difference between females and males obtained from a multivariable logistic regression model adjusting for age, severity of lesion, and year of death.
‡Indicates comparisons with statistically significant difference ($p<0.05$).

Table S6. Summary Statistics for Multiple Causes of Death*.

	<5 years of age			≥ 5 years of age			P-value †
	Overall	**Median**	**IQR**	**Overall**	**Median**	**IQR**	
CHD	82.7%	83.4%	(69.0% - 89.3%)	41.9%	46.6%	(22.3% - 71.4%)	<0.001 ‡
CVD	50.8%	55.0%	(48.5% - 60.0%)	53.6%	57.6%	(44.4% - 65.3%)	0.179
Heart Failure	15.9%	14.0%	(11.3% - 21.8%)	12.8%	13.0%	(4.9% - 18.4%)	0.037*
Arrhythmia	8.0%	7.7%	(0 – 12.0%)	11.1%	10.8%	(5.9% - 18.2%)	0.009*
Cardiac Arrest	18.2%	20.0%	(15.0% - 24.1%)	14.2%	13.6%	(9.1% - 22.2%)	0.011*
Pulmonary Heart Disease	5.8%	6.7%	(2.6% – 11.1%)	6.6%	5.7%	(0% - 10.0%)	0.432
Cerebrovascular Conditions	3.3%	3.6%	(0 – 5.7%)	4.8%	4.3%	(1.8% - 9.1%)	0.056

CHD: Congenital Heart Defects; CVD: Cardiovascular Disorders; IQR: interquartile range

* Summary statistics were tabulated by underlying physiology subgroups

† P-value compares percentage of deaths with a specific multiple cause of death code across patients that died before and after 5 years of age using a Chi-square test.

‡Indicates comparisons with statistically significant difference ($p<0.05$).

Table S7. Underlying Cause of Death in Patients with non-CHD/non-CVD Associated Death.

Cause of Death	N= 424
External Causes of Injury and Poisoning	166 (39.2%)
Congenital Malformation, Deformities or Other Congenital Anomaly	42 (9.9%)
Disease of the Respiratory System	39 (9.2%)
Neoplasms	40 (9.4%)
Disease of the Nervous System and Sense Organs	29 (6.8%)
Symptoms, signs, and ill-defined conditions not otherwise specified	25 (5.9%)
Infectious and Parasitic Diseases	24 (5.7%)
Diseases of the Digestive System	15 (3.5%)
Endocrine, nutritional and metabolic diseases, and immunity disorders	15 (3.5%)
Certain conditions originating in the perinatal period	12 (2.8%)
Mental Disorders	4 (0.9%)
Diseases of the blood and blood forming organs	4 (0.9%)
Complications of pregnancy, childbirth and puerperium	3 (0.7%)
Diseases of the musculoskeletal system	3 (0.7%)
Disease of the genitourinary system	3 (0.7%)

CHD: Congenital Heart Defects; CVD: Cardiovascular Disorders

Table S8. SMRs for Congenital Heart Defects (CHD) or Cardiovascular Disorders (CVD).

	Group	N	SMR	95% CI	p-value
CHD	**Overall**	**1485**	**153.4**	**(145.6 – 161.2)**	**< 0.001**
	< 1 year	760	124.5	(115.7 – 133.4)	<0.001
	1 – 4 years	420	287.2	(259.7 – 314.7)	<0.001
	5 – 9 years	92	200.0	(159.1 – 240.8)	<0.001
	10 – 14 years	75	161.2	(124.7 – 197.6)	<0.001
	15 – 19 years	74	151.7	(117.1 – 186.2)	<0.001
	20 – 24 years	38	135.5	(92.4 – 178.6)	<0.001
	25 – 34 years	25	66.3	(40.3 – 92.3)	<0.001
	Mild CHD	62	27.9	(20.9 – 36.4)	<0.001
	Moderate CHD	277	84.9	(74.9 – 94.9)	<0.001
	Severe 2V CHD	417	178.4	(161.3 – 195.5)	<0.001
	Severe 1V CHD	619	550.8	(507.4 – 594.2)	<0.001
	Females	638	170.7	(157.5 – 184.0)	<0.001

	Males	847	142.5	(132.9 – 152.1)	<0.001
	Early (1982-1992)	564	185.4	(170.1 – 200.7)	<0.001
	Mid (1993-1997)	435	148.8	(134.8 – 162.8)	<0.001
	Late (1998-2003)	398	133.5	(120.4 – 146.6)	<0.001
CVD	**Overall**	**280**	**11.8**	**(10.4 – 13.2)**	**<0.001**
	< 1 year	59	24.7	(18.4 – 30.9)	<0.001
	1 – 4 years	49	33.7	(24.3 – 43.1)	<0.001
	5 – 9 years	25	26.1	(15.9 – 36.3)	<0.001
	10 – 14 years	29	22.5	(14.3 – 30.7)	<0.001
	15 – 19 years	44	19.6	(13.8 – 25.4)	<0.001
	20 – 24 years	32	11.9	(7.79 – 16.1)	<0.001
	25 – 34 years	33	3.61	(2.38 – 4.84)	<0.001
	Mild CHD	35	4.08	(2.73 – 5.43)	<0.001
	Moderate CHD	83	10.1	(7.94 – 12.3)	<0.001
	Severe 2V CHD	48	20.6	(14.8 – 26.5)	<0.001

Severe 1V CHD	54	57.0	(41.8 – 72.2)	<0.001
Females	110	13.0	(10.6 – 15.4)	<0.001
Males	170	11.1	(9.44 – 12.8)	<0.001
Early (1982-1992)*	68	20.7	(15.8 – 25.6)	<0.001
Mid (1993-1997)*	71	19.1	(14.6 – 23.5)	<0.001
Late (1998-2003)*	77	21.7	(16.9 – 26.6)	<0.001

1V: one ventricle; 2V: two ventricle; CHD: Congenital Heart Defects; CVD: Cardiovascular Disorders; SMR: Standardized mortality ratio

* Deaths occurring after 15 years of follow-up were not included in the SMR calculations for era. This truncation was necessary for making follow-up time comparable among era. As a result, death counts across eras do not sum to total death count for a specific cause.

Table S9. SMR for Underlying Causes of Death by Major Physiology Group.

Group	Underlying Cause of Death	Overall		
		N	SMR	95% CI
Left-to-right Shunt	CHD	130	51.2	(42.4 – 59.9)
	CVD	45	4.70	(3.33 – 6.07)
	Other congenital malformations	31	7.40	(4.80 – 10.0)
	Respiratory diseases	26	6.28	(3.87 – 8.70)
	Infections	20	5.04	(2.83 – 7.25)
	Neoplasms	22	1.82	(1.06 – 2.58)
	External Causes of Injury and Poisoning	76	0.97	(0.75 – 1.19)
	Other Medical Causes of Death	69	2.38	(1.82 – 2.94)
LHOL	CHD	149	75.0	(63.0 – 87.0)
	CVD	62	11.6	(8.69 – 14.4)
	Other congenital malformations	15	4.35	(2.15 – 6.56)
	Respiratory diseases	14	6.29	(2.99 – 9.58)
	Infections	10	4.49	(1.71 – 7.28)
	Neoplasms	13	2.38	(1.09 – 3.68)
	External Causes of Injury and Poisoning	41	0.96	(0.76 – 1.26)
	Other Medical Causes of Death	27	1.27	(0.79 – 1.75)
APVR	CHD	29	60.0	(38.2 – 81.8)
	CVD	7	6.08	(1.58 – 10.59)

Group	Underlying Cause of Death	Overall		
		N	SMR	95% CI
	Other congenital malformations	3	3.57	(0 – 7.61)
	Respiratory diseases	5	9.31	(1.15 – 17.46)
	Infections	3	6.00	(0 – 12.80)
	Neoplasms	2	1.52	(0 – 3.64)
	External Causes of Injury and Poisoning	12	1.31	(0.57 – 2.05)
	Other Medical Causes of Death	4	0.80	(0.02 – 1.58)
RVOTO	CHD	147	116.4	(97.6 – 135.3)
	CVD	30	14.4	(9.2 – 19.5)
	Other congenital malformations	15	6.77	(3.35 – 10.2)
	Respiratory diseases	4	3.23	(0.06 – 6.39)
	Infections	5	4.80	(0.59 – 9.01)
	Neoplasms	3	1.13	(0 – 2.40)
	External Causes of Injury and Poisoning	20	1.07	(0.60 – 1.54)
	Other Medical Causes of Death	18	1.51	(0.81 – 2.21)
TGA physiology	CHD	84	90.2	(70.9 – 109.5)
(d-TGA simple)	CVD	9	10.5	(3.66 – 17.4)
	Other congenital malformations	2	1.18	(0 – 2.81)
	Respiratory diseases	4	6.11	(0.12 – 12.10)
	Infections	2	3.95	(0 – 9.42)

Group	Underlying Cause of Death	Overall		
		N	SMR	95% CI
	Neoplasms	2	2.06	(0 – 4.91)
	External Causes of Injury and Poisoning	7	0.99	(0.26 – 1.72)
	Other Medical Causes of Death	3	0.35	(0 – 0.75)
Complete mixing (TAC)	CHD	35	354.2	(236.8 – 471.5)
	CVD	4	49.2	(0.99 – 97.5)
	Other congenital malformations	2	10.8	(0 – 25.8)
	Respiratory diseases	2	29.6	(0 – 70.6)
	Infections	2	39.2	(0 – 93.6)
	Neoplasms	0	--	--
	External Causes of Injury and Poisoning	1	1.59	(0 – 4.69)
	Other Medical Causes of Death	2	2.21	(0 – 5.26)
Complex Lesions	CHD	225	295.4	(256.8 – 334.0)
	CVD	29	16.4	(10.4 – 22.4)
	Other congenital malformations	11	8.28	(3.38 – 13.17)
	Respiratory diseases	13	15.4	(7.0 – 23.7)
	Infections	15	19.2	(9.5 – 28.9)
	Neoplasms	4	1.97	(0.04 – 3.90)
	External Causes of Injury and Poisoning	15	1.08	(0.50 – 1.53)
	Other Medical Causes of Death	33	4.27	(2.81 – 5.72)

Group	Underlying Cause of Death	Overall		
		N	SMR	95% CI
Miscellaneous	CHD	67	135.9	(103.3 – 168.4)
	CVD	40	20.6	(14.2 – 27.0)
	Other congenital malformations	18	21.5	(11.6 – 31.4)
	Respiratory diseases	10	14.1	(5.4 – 22.8)
	Infections	4	5.21	(0.10 – 10.33)
	Neoplasms	4	1.98	(0.04 – 3.92)
	External Causes of Injury and Poisoning	19	1.34	(0.74 – 1.94)
	Other Medical Causes of Death	16	2.76	(1.41 – 4.11)
SV	CHD	619	550.8	(507.4 – 594.2)
	CVD	54	57.0	(41.8 - 72.2)
	Other congenital malformations	21	9.96	(5.70 – 14.2)
	Respiratory diseases	14	18.7	(8.9 – 28.5)
	Infections	24	41.2	(24.7 – 57.7)
	Neoplasms	3	2.82	(0 – 6.01)
	External Causes of Injury and Poisoning	16	2.38	(1.22 – 3.55)
	Other Medical Causes of Death	35	3.36	(2.25 – 4.47)

APVR: abnormal pulmonary venous return; ASD: atrial septal defect; CHD: Congenital Heart Defects; CVD: Cardiovascular Disorders; LHOL: left heart obstructive lesions; RVOTO: right ventricular outflow tract obstruction; SV: single ventricle; TAC: truncus arteriosus communis; TGA: transposition of the great arteries.

Table S10. SMR for External Causes of Death Excluding Surgical Misadventures.

Overall	**SMR**	**95% CI**	**P- value**
	0.97	(0.83 – 1.11)	0.664
< 1 year	2.51	(0.87 – 4.16)	0.071
1 – 4 years	1.17	(0.58 – 1.77)	0.567
5 – 9 years	3.05	(1.92 – 4.18)	<0.001*
10 – 14 years	1.29	(0.64 – 1.95)	0.381
15 – 19	0.92	(0.64 – 1.20)	0.563
20 – 24 years	0.92	(0.64 – 1.21)	0.592
25 – 34 years	0.55	(0.36 – 0.74)	<0.001*
Females	0.88	(0.61 – 1.14)	0.368
Males	1.00	(0.84 – 1.16)	0.997
Early (1982-1992) †	1.52	(1.09 – 1.96)	0.019
Mid (1993-1997) †	1.07	(0.71 – 1.43)	0.713
Late (1998-2003) †	1.26	(0.85 – 1.66)	0.215

CI: confident interval; SMR: Standardized mortality ratio

* Indicates comparisons with statistically significant difference ($p<0.05$).

† Deaths occurring after 15 years of follow-up were not included in the SMR calculations for era. This truncation was necessary for making follow-up time comparable among era. As a result, death counts across eras do not sum to total death count for a specific cause.

Table S11. List of External Causes of Death by Age Group and Estimates from Age-matched US Population of Deaths by External Causes from 1981-2014.

External Cause of Death	N (%)	Estimates from US population from 1981 – 2014
Accident or Poisoning		
< 1 year	8 (47.1%)	59.00%
1 – 4 years	12 (54.6%)	51.70%
5 – 9 years	12 (40.0%)	37.40%
10 – 14 years	10 (22.7%)	27.20%
15 – 19 years	10 (22.7%)	13.30%
20 – 24 years	11 (26.2%)	16.00%
25 – 34 years	1 (33.3%)	22.40%
≥ 35 years	1 (25.0%)	29.30%
Moving Vehicle or Transport Accident		
< 1 year	0 (0%)	11.60%
1 – 4 years	1 (4.6%)	30.10%
5 – 9 years	14 (46.7%)	51.00%
10 – 14 years	7 (43.8%)	46.50%
15 – 19 years	23 (52.3%)	48.60%
20 – 24 years	17 (40.5%)	22.60%
25 – 34 years	1 (33.3%)	20.30%
≥ 35 years	1 (25.0%)	14.00%
Suicide		
< 1 year	0 (0%)	0%

External Cause of Death	N (%)	Estimates from US population from 1981 – 2014
1 – 4 years	0 (0%)	0%
5 – 9 years	0 (0%)	0.30%
10 – 14 years	1 (6.3%)	12.10%
15 – 19 years	6 (13.6%)	16.10%
20 – 24 years	8 (19.1%)	18.40%
25 – 34 years	1 (33.3%)	21.90%
≥ 35 years	1 (25.0%)	24.80%
Homicide/Assault		
< 1 year	1 (5.9%)	22.20%
1 – 4 years	1 (4.6%)	14.80%
5 – 9 years	2 (6.7%)	8.90%
10 – 14 years	1 (6.3%)	11.60%
15 – 19 years	3 (6.8%)	20.10%
20 – 24 years	5 (11.9%)	22.60%
25 – 34 years	0 (0%)	20.30%
≥ 35 years	0 (0%)	14.00%
Surgical misadventures		
< 1 year	8 (47.1%)	2.00%
1 – 4 years	7 (31.8%)	0.10%
5 – 9 years	2 (6.7%)	0.10%
10 – 14 years	1 (6.3%)	0.50%

External Cause of Death	N (%)	Estimates from US population from 1981 – 2014
15 – 19 years	2 (4.6%)	0.10%
20 – 24 years	1 (2.4%)	0.10%
25 – 34 years	0 (0%)	0.30%
≥ 35 years	0 (0%)	0.50%
Other External Cause		
< 1 year	0 (0%)	5.30%
1 – 4 years	1 (4.6%)	2.40%
5 – 9 years	0 (0%)	1.60%
10 – 14 years	1 (6.3%)	2.10%
15 – 19 years	0 (0%)	1.80%
20 – 24 years	0 (0%)	2.50%
25 – 34 years	0 (0%)	3.70%
≥ 35 years	1 (25.0%)	4.80%

Table S12. Distribution of Underlying and Multiple Causes of Death by Race.

	White (N = 1885)	Black (N = 500)	Other (N = 79)	AOR* (95% CI)	Adjusted P-value†
Underlying Cause of Death					
CHD	1127 (59.8%)	272 (54.4%)	48 (60.8%)	1.02 (0.80 – 1.31)	0.875
CVD	209 (11.1%)	63 (12.6%)	6 (7.6%)	0.96 (0.67 – 1.36)	0.807
Other congenital anomalies	92 (4.9%)	21 (4.2%)	2 (2.5%)	0.67 (0.39 – 1.17)	0.161
Respiratory diseases	68 (3.6%)	20 (4.0%)	3 (3.8%)	1.14 (0.67 – 1.95)	0.629
Infections	65 (3.5%)	19 (3.8%)	1 (1.3%)	1.03 (0.59 – 1.79)	0.930
Neoplasms	42 (2.2%)	5 (1.0%)	0 (0%)	0.38 (0.15 – 1.00)	0.050‡
External Causes of Injury and Poisoning	147 (7.8%)	40 (8.0%)	11 (13.9%)	0.84 (0.55 – 1.29)	0.425
Other Causes of Death	135 (7.2%)	60 (12.0%)	8 (10.1%)	1.58 (1.11 – 2.26)	0.012‡
Multiple Cause of Death					
Congenital Heart Disease	1298 (68.9%)	330 (66.0%)	52 (65.8%)	1.21 (0.92 – 1.60)	0.177

Cardiovascular Disease	986 (52.3%)	266 (53.2%)	39 (49.4%)	1.10 (0.89 – 1.37)	0.372
Heart Failure	287 (15.2%)	68 (13.6%)	12 (151.2%)	0.98 (0.72 – 1.32)	0.875
Dysrhythmias/Conduct Disorder	167 (8.9%)	51 (10.2%)	8 (10.1%)	1.22 (0.86 – 1.74)	0.268
Cardiac Arrest	319 (16.9%)	91 (18.2%)	11 (13.9%)	1.20 (0.91 – 1.58)	0.201
Pulmonary Heart Disease	119 (6.3%)	25 (5.0%)	8 (10.1%)	0.86 (0.54 – 1.35)	0.499
Cerebrovascular Disease	75 (4.0%)	14 (2.8%)	5 (6.3%)	0.54 (0.31 – 1.14)	0.120
Cardiomyopathy	50 (2.7%)	22 (4.4%)	3 (3.8%)	1.42 (0.76 – 2.65)	0.266

CHD: Congenital Heart Defects; CVD: Cardiovascular Disorders

[*] AOR: Adjusted Odds Ratio. AOR was calculated for African American/Blacks only using Whites as the reference group. Due to the small sample size of "Other" race, AOR were not computed for this group.

[†] P-value corresponds to the adjusted difference between Whites and Blacks and was obtained from a multivariable logistic regression model adjusting for age, sex, severity of lesion, and year of death.

[‡] Indicates comparisons with statistically significant difference ($p<0.05$).

Table S13. Modes of Death by CHD group.

Characteristic		CHD Associated		CVD Associated		Non-CHD/Non-CVD	
		N	%	N	%	N	%
Sex							
Male		982	65.6%	236	15.8%	279	18.6%
Female		740	71.8%	145	14.1%	145	14.1%
Age at death (years)							
< 1		849	85.4%	78	7.9%	67	6.7%
1 – 4		496	78.4%	67	10.6%	70	11.1%
5 – 9		104	55.0%	31	16.4%	54	28.6%
10 – 14		91	54.8%	37	22.3%	38	22.9%
15 – 19		92	41.3%	62	27.8%	69	30.9%
20 – 24		50	30.3%	46	27.9%	69	41.8%
25 – 34		37	27.2%	49	36.0%	50	36.8%
Severity							
Mild CHD		86	28.0%	60	19.5%	161	52.4%
Moderate CHD		336	57.5%	115	19.7%	133	22.8%
Severe 2V CHD		472	79.6%	64	10.8%	57	9.6%
Severe 1V CHD		699	88.9%	61	7.8%	26	3.3%
Physiology							
Left-to-Right Shunt		166	39.6%	81	19.3%	172	41.1%
	PDA	7	8.9%	21	26.6%	51	64.6%
	ASD	29	21.6%	31	23.1%	74	55.2%

Characteristic	CHD Associated		CVD Associated		Non-CHD/Non-CVD	
	N	%	N	%	N	%
VSD (simple)	62	49.2%	21	16.7%	43	34.1%
CCAVC (simple)	68	85.0%	8	10.0%	4	5.0%
LHOL	176	53.2%	77	23.3%	78	23.6%
Cor-Tri	3	100%	0	0%	0	0%
MS	7	50%	5	35.7%	2	14.3%
AS/Sub-AS	37	42.1%	29	33.0%	22	25.0%
COA	104	54.5%	39	20.4%	48	25.1%
IAA	25	71.4%	4	11.4%	6	17.1%
APVR	35	53.9%	12	18.5%	18	27.7%
TAPVR	29	58.0%	9	18.0%	12	24.0%
PAPVR	6	40.0%	3	20.0%	6	40.0%
RVOTO	168	69.4%	35	14.5%	39	16.1%
PS/Sub-PS	14	42.4%	9	27.3%	10	30.3%
PA/IVS	18	81.8%	2	9.1%	2	9.1%
TOF	136	72.7%	24	12.8%	27	14.4%
TGA physiology (d-TGA simple)	90	79.7%	11	9.7%	12	10.6%
Complete Mixing (TAC)	41	85.4%	4	8.3%	3	6.3%
Complex Lesions	266	77.1%	40	11.6%	39	11.3%
Complex CAVC	16	69.6%	3	13.0%	4	17.4%
Complex d-TGA	61	84.7%	8	11.1%	3	4.2%

Characteristic		CHD Associated		CVD Associated		Non-CHD/Non-CVD	
		N	%	N	%	N	%
	Complex VSD	36	46.8%	18	23.4%	23	29.9%
	Complex TOF	153	88.4%	11	6.4%	9	5.2%
Miscellaneous		81	45.5%	60	33.7%	37	20.8%
	l-TGA (2V)	35	72.9%	10	20.8%	3	6.3%
	MR/AI	16	40.0%	20	50.0%	4	10.0%
	TVA	19	67.9%	5	17.9%	4	14.3%
	Other	11	17.7%	25	40.3%	26	41.9%
SV		699	88.9%	61	7.8%	26	3.3%
	Left Heart	221	88.4%	20	8.0%	9	3.6%
	Right Heart	314	89.2%	29	8.2%	9	2.6%
	Other	164	89.1%	12	6.5%	8	4.4%
Era							
Early (1982-1992)		723	68.0%	160	15.1%	180	16.9%
Mid (1993-1997)		523	66.4%	122	15.5%	143	18.2%
Late (1998-2003)		476	70.4%	99	14.6%	101	14.9%

1V: one ventricle; 2V: two ventricle; APVR: abnormal pulmonary venous return; ASD: atrial septal defect; AS/Sub-AS: aortic stenosis/sub-aortic stenosis; CCAVC: complete common atrioventricular canal; CoA: coarctation of the aorta; Cor-Tri: cor-triatriatum; IAA: interrupted aortic arch; L-R Shunt: left-to-right shunt lesions; LHOL: left heart obstructive lesions; MR/AI: mitral regurgitation/aortic insufficiency; MS: mitral stenosis; N/A: not classifiable; PA/IVS: pulmonary atresia with intact ventricular septum; PAPVR: partial APVR; PDA: patent ductus arteriosus; PS/Sub-PS: pulmonary stenosis/sub-pulmonary stenosis; RVOTO: right ventricular outflow tract obstruction; SV: single ventricle; TAC: truncus arteriosus communis; TAPVR: total APVR; TGA: transposition of the great arteries; TOF: tetralogy of Fallot; TVA: tricuspid valve anomaly; VSD: ventricular septal defect.

Table S14. Underlying and Contributing Causes of Death by CHD Group.

	Underlying Cause of Death			CHD or CVD Contributing Causes of Death		
	Cause	**N**	**(%)**	**Cause**	**N**	**(%)**
Left-to-right Shunt	CHD	130	31.0%	CHD	166	39.6%
	CVD	45	10.7%	CVD	176	42.0%
	Other congenital malformations	31	7.4%	Heart Failure	48	11.5%
	Respiratory diseases	26	6.2%	Dysrhythmias/Conduct Disorder	33	7.9%
	Infections	20	4.8%	Cardiac Arrest	52	12.4%
	Neoplasms	22	5.3%	Pulmonary Heart Disease	37	8.8%
	External Causes of Injury and Poisoning	76	18.1%	Cerebrovascular Disease	14	3.3%
	Other Medical Causes of Death	69	16.5%	Cardiomyopathy	16	3.8%
LHOL	CHD	149	45.0%	CHD	176	53.2%
	CVD	62	18.7%	CVD	186	55.2%
	Other congenital malformations	15	4.5%	Heart Failure	54	16.3%
	Respiratory diseases	14	4.2%	Dysrhythmias/Conduct Disorder	27	8.2%

	Underlying Cause of Death			CHD or CVD Contributing Causes of Death		
	Cause	**N**	**(%)**	**Cause**	**N**	**(%)**
	Infections	10	3.0%	Cardiac Arrest	50	15.1%
	Neoplasms	13	3.9%	Pulmonary Heart Disease	23	7.0%
	External Causes of Injury and Poisoning	41	12.4%	Cerebrovascular Disease	14	4.2%
	Other Medical Causes of Death	27	8.2%	Cardiomyopathy	15	4.5%
	Respiratory diseases	6	3.1%	Dysrhythmias/Conduct Disorder	15	7.9%
	Infections	5	2.6%	Cardiac Arrest	26	13.6%
	Neoplasms	9	4.7%	Pulmonary Heart Disease	15	7.9%
	External Causes of Injury and Poisoning	26	13.6%	Cerebrovascular Disease	5	2.6%
	Other Medical Causes of Death	13	6.8%	Cardiomyopathy	5	2.6%
APVR	CHD	29	44.6%	CHD	35	53.9%
	CVD	7	10.8%	CVD	32	49.2%

	Underlying Cause of Death			CHD or CVD Contributing Causes of Death		
	Cause	**N**	**(%)**	**Cause**	**N**	**(%)**
	Other congenital malformations	3	4.6%	Heart Failure	5	7.7%
	Respiratory diseases	5	7.7%	Dysrhythmias/Conduct Disorder	4	6.2%
	Infections	3	4.6%	Cardiac Arrest	9	13.9%
	Neoplasms	2	3.1%	Pulmonary Heart Disease	15	23.1%
	External Causes of Injury and Poisoning	12	18.5%	Cerebrovascular Disease	0	0%
	Other Medical Causes of Death	4	6.2%	Cardiomyopathy	1	1.5%
RVOTO	CHD	147	60.7%	CHD	168	69.4%
	CVD	30	12.4%	CVD	126	52.1%
	Other congenital malformations	15	6.2%	Heart Failure	35	14.5%
	Respiratory diseases	4	1.7%	Dysrhythmias/Conduct Disorder	29	12.6%
	Infections	5	2.1%	Cardiac Arrest	44	18.2%
	Neoplasms	3	1.2%	Pulmonary Heart Disease	8	3.3%

	Underlying Cause of Death			CHD or CVD Contributing Causes of Death		
	Cause	**N**	**(%)**	**Cause**	**N**	**(%)**
	External Causes of Injury and Poisoning	20	8.3%	Cerebrovascular Disease	13	5.4%
	Other Medical Causes of Death	18	7.4%	Cardiomyopathy	7	2.9%
TGA physiology (d-TGA simple)	CHD	84	74.3%	CHD	90	79.7%
	CVD	9	8.0%	CVD	69	61.1%
	Other congenital malformations	2	1.8%	Heart Failure	19	16.8%
	Respiratory diseases	4	3.5%	Dysrhythmias/Conduct Disorder	18	15.9%
	Infections	2	1.8%	Cardiac Arrest	26	23.0%
	Neoplasms	2	1.8%	Pulmonary Heart Disease	9	8.0%
	External Causes of Injury and Poisoning	7	6.2%	Cerebrovascular Disease	4	3.5%
	Other Medical Causes of Death	3	2.7%	Cardiomyopathy	3	2.7%
	CHD	35	/72.9%	CHD	41	85.4%

	Underlying Cause of Death			CHD or CVD Contributing Causes of Death		
	Cause	**N**	**(%)**	**Cause**	**N**	**(%)**
Complete mixing (TAC)	CVD	4	8.3%	CVD	24	50.0%
	Other congenital malformations	2	4.2%	Heart Failure	9	18.8%
	Respiratory diseases	2	4.2%	Dysrhythmias/Conduct Disorder	2	4.2%
	Infections	2	4.2%	Cardiac Arrest	8	16.7%
	Neoplasms	0	0%	Pulmonary Heart Disease	2	4.2%
	External Causes of Injury and Poisoning	1	2.1%	Cerebrovascular Disease	2	4.2%
	Other Medical Causes of Death	2	4.2%	Cardiomyopathy	0	0%
Complex Lesions	CHD	225	65.2%	CHD	266	77.1%
	CVD	29	8.4%	CVD	182	52.8%
	Other congenital malformations	11	3.2%	Heart Failure	49	14.2%
	Respiratory diseases	13	3.8%	Dysrhythmias/Conduct Disorder	29	8.4%
	Infections	15	4.4%	Cardiac Arrest	78	22.6%

	Underlying Cause of Death			CHD or CVD Contributing Causes of Death		
	Cause	**N**	**(%)**	**Cause**	**N**	**(%)**
	Neoplasms	4	1.2%	Pulmonary Heart Disease	23	6.7%
	External Causes of Injury and Poisoning	15	4.4%	Cerebrovascular Disease	15	4.4%
	Other Medical Causes of Death	33	9.6%	Cardiomyopathy	4	2.0%
SV	CHD	619	78.8%	CHD	699	88.9%
	CVD	54	6.9%	CVD	398	50.6%
	Other congenital malformations	21	2.7%	Heart Failure	132	16.8%
	Respiratory diseases	14	1.8%	Dysrhythmias/Conduct Disorder	66	8.4%
	Infections	24	3.1%	Cardiac Arrest	121	15.4%
	Neoplasms	3	0.4%	Pulmonary Heart Disease	28	3.6%
	External Causes of Injury and Poisoning	16	2.0%	Cerebrovascular Disease	24	3.1%
	Other Medical Causes of Death	35	4.5%	Cardiomyopathy	16	2.0%

Underlying Cause of Death			CHD or CVD Contributing Causes of Death		
Cause	**N**	**(%)**	**Cause**	**N**	**(%)**
External Causes of Injury and Poisoning	7	2.0%	Cerebrovascular Disease	7	2.0%
Other Medical Causes of Death	14	4.0%	Cardiomyopathy	8	2.3%

APVR: abnormal pulmonary venous return; CHD: Congenital Heart Defects; CVD: Cardiovascular Disorders; LHOL: left heart obstructive lesions; RVOTO: right ventricular outflow tract obstruction; SV: Single ventricle; TAC: truncus arteriosus communis; TGA: transposition of the great arteries.

Table S15. Era Effect on the SMR for CVD/CHD-associated Death by Physiology Group.

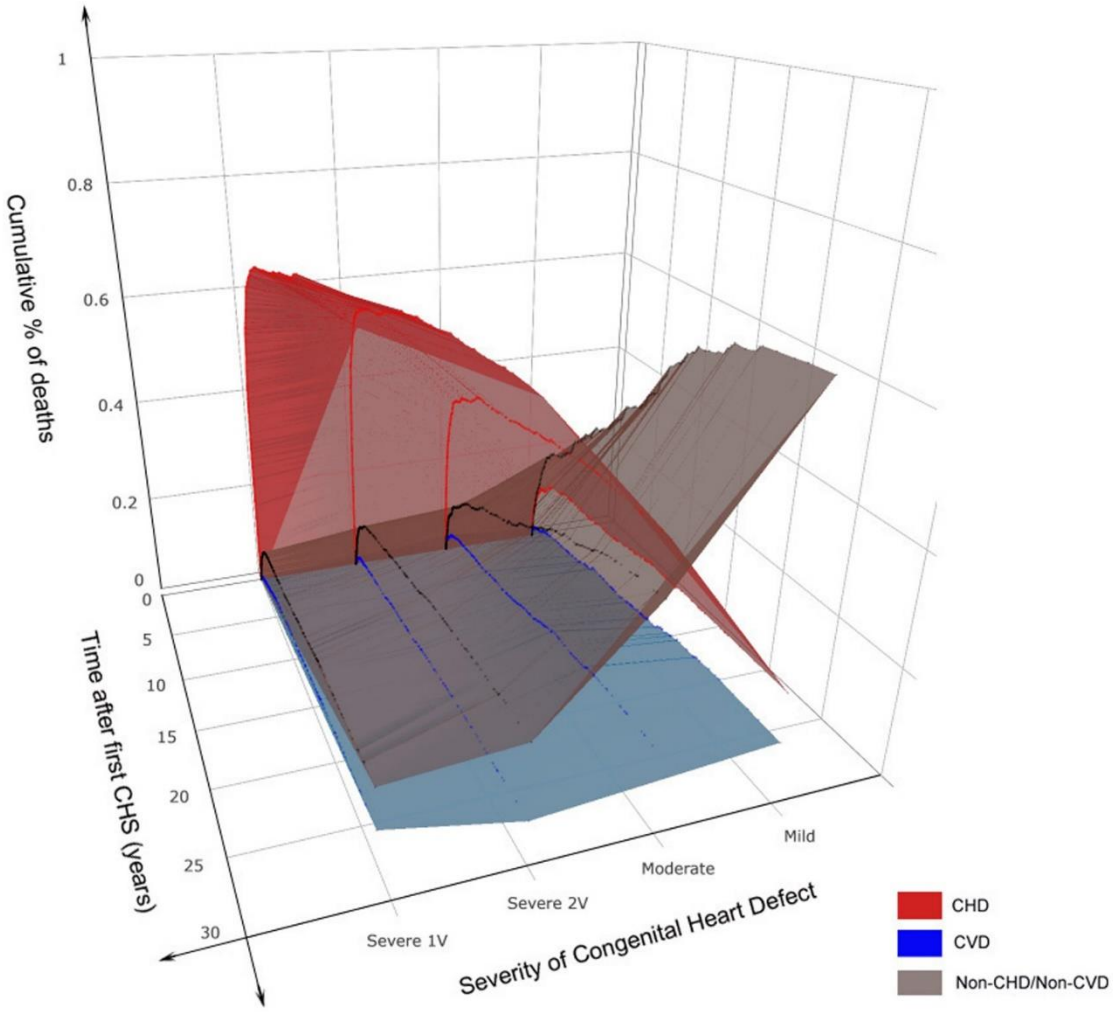
	CHD/CVD			CHD			CVD		
CHD Diagnosis	**Early**	**Mid**	**Late**	**Early**	**Mid**	**Late**	**Early**	**Mid**	**Late**
Two-ventricle	167.6	101.6	81.3	185.4	148.8	133.5	20.7	19.1	21.7
	(154.5 – 180.7)	(92.8 – 110.5)	(74.0 – 88.6)	(170.1 – 200.7)	(134.8 – 162.8)	(120.4 – 146.6)	(15.8 – 25.6)	(14.6 – 23.5)	(16.9 – 26.6)
Left-to-right	85.1	42.6	28.4	69.8	53.1	41.1	9.67	7.87	7.42
shunt	(65.3 – 104.9)	(30.8 – 54.4)	(19.1 – 37.7)	(52.0 – 87.7)	(36.5 – 69.8)	(25.6 – 56.6)	(4.2 – 15.2)	(3.22 – 12.53)	(2.57 – 12.3)
LHOL	123.7	71.4	64.6	87.8	71.1	68.2	21.6	19.3	24.9
	(95.5 – 151.9)	(52.7 – 90.1)	(48.2 – 80.9)	(65.2 – 110.4)	(49.3 – 98.8)	(47.3 – 89.1)	(11.0 – 32.2)	(9.6 – 29.1)	(13.7 – 36.1)
APVR	74.4	81.2	47.0	50.0	95.6	48.7	13.0	5.50	14.9
	(28.3 – 120.6)	(40.1 – 122.3)	(17.9 – 76.2)	(15.3 – 84.6)	(45.5 – 145.7)	(12.6 – 84.7)	(0 – 31.0)	(0 – 16.3)	(0 – 31.7)
RVOTO	196.9	135.8	100.3	155.8	115.6	75.0	14.6	32.7	28.5
	(149.7 – 244.0)	(99.9 – 171.7)	(68.8 – 131.8)	(117.1 – 194.6)	(81.5 – 149.8)	(48.2 – 101.9)	(1.8 – 27.4)	(13.4 – 52.0)	(9.88 – 47.1)
TGA physiology	197.3	71.0	71.0	149.1	57.8	54.8	18.7	10.3	5.46
(d-TGA simple)	(139.0 – 255.6)	(39.9 – 102.1)	(38.2 – 103.7)	(103.5 – 194.8)	(31.1 – 84.5)	(28.7 – 80.8)	(0 – 39.9)	(0 – 24.6)	(0 – 16.2)
Complete mixing	653.6	358.3	389.2	511.9	295.4	239.6	59.1	0 *	130.3
(TAC)	(342.9 – 964.3)	(110.0 – 606.6)	(169.0 – 609.4)	(261.1 – 762.7)	(90.7 – 500.1)	(80.1 – 396.1)	(0 – 174.9)	--	(0 – 277.8)
Complex Lesions	424.3	297.6	215.6	344.2	326.7	231.3	16.9	25.1	33.1
	(331.9 – 516.7)	(233.9 – 361.2)	(163.6 – 267.7)	(267.3 – 421.1)	(253.8 – 399.7)	(171.3 – 291.4)	(0.34 – 33.4)	(6.50 – 46.7)	(11.5 – 54.7)
Mild	47.7	24.4	22.6	32.0	24.8	32.0	8.07	7.16	6.56
	(31.4 – 64.0)	(14.8 – 34.0)	(13.7 – 31.5)	(19.2 – 44.8)	(12.7 – 37.0)	(17.2 – 46.8)	(2.80 – 13.3)	(2.48 – 11.8)	(1.70 – 11.4)

CHD Diagnosis	CHD/CVD			CHD			CVD		
	Early	Mid	Late	Early	Mid	Late	Early	Mid	Late
Moderate	142.8	77.8	53.3	116.4	91.7	56.7	17.2	17.2	15.5
	(118.6 – 167.1)	(63.2 – 92.4)	(41.5 – 65.1)	(95.0 – 137.7)	(72.6 – 110.9)	(42.4 – 71.1)	(9.46 – 24.9)	(9.85 – 24.6)	(8.52 – 22.4)
Severe	266.9	174.8	140.9	217.3	172.2	134.6	22.2	23.1	35.4
	(227.4 – 306.5)	(145.5 – 204.1)	(115.5 – 166.2)	(184.1 – 250.4)	(142.1 – 202.2)	(108.5 – 160.7)	(8.46 – 36.0)	(9.46 – 36.8)	(18.6 – 52.2)
Single ventricle	881.4	496.5	433.7	712.9	490.3	444.3	91.9	69.4	55.8
	(768.4 – 994.3)	(426.7 – 566.4)	(374.0 – 493.3)	(618.3 – 807.5)	(418.3 – 562.4)	(381.0 – 507.7)	(46.8 – 136.9)	(35.4 – 103.4)	(26.6 – 85.1)

APVR: abnormal pulmonary venous return; CHD: Congenital heart defects; CVD: Cardiovascular Condition; LHOL: left heart obstructive lesions; RVOTO: right ventricular outflow tract obstruction; TAC: truncus arteriosus communis; TGA: transposition of the great arteries.

* Not enough events to calculate a meaningful SMR

Figure S1. Distribution of cumulative causes of death after the first congenital heart surgery (CHS).



A 3D interactive plot can be accessed at https://www.pcccweb.com/files/CODCIv6.html. The interactive plot allows assessment of the relative percentage of deaths by major modality for each group of severity of congenital heart defect at desired time after the first congenital heart surgery (CHS) up to the maximum follow up time available. Deaths attributed to congenital heart defects (CHD) are the leading cause of mortality in the early postoperative period for all lesions, but deaths due to other causes steadily increase over time in particular for the milder forms. Cardiovascular conditions (CVD) contribute similarly to deaths at all ages. 1V: one ventricle; 2V: two ventricle; CHD: Congenital Heart Defects; CHS: Congenital Heart Surgery; CVD: Cardiovascular Disorders

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