



ORIGINAL RESEARCH

Causes of Death and Cardiovascular Comorbidities in Adults With Congenital Heart Disease

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BACKGROUND: Little is known about the contemporary mortality experience among adults with congenital heart disease (CHD). The objectives of this study were to assess the age at death, presence of cardiovascular comorbidities, and most common causes of death among adults with CHD in a contemporary cohort within the United States.

METHODS AND RESULTS: Patients with CHD who had a healthcare encounter between 2008 and 2013 at 1 of 5 comprehensive CHD centers in North Carolina were identified by *International Classification of Diseases, Ninth Revision (ICD-9)*, code. Only patients who could be linked to a North Carolina death certificate between 2008 and 2016 and with age at death ≥ 20 years were included. Median age at death and underlying cause of death based on death certificate data were analyzed. The prevalence of acquired cardiovascular risk factors was determined from electronic medical record data. Among the 629 included patients, the median age at death was 64.2 years. Those with severe CHD ($n=157$, 25%), shunts ($n=202$, 32%), and valvular lesions ($n=174$, 28%) had a median age at death of 46.0, 65.0, and 73.3 years, respectively. Cardiovascular death was most common in adults with severe CHD (60%), with 40% of those deaths caused by CHD. Malignancy and ischemic heart disease were the most common causes of death in adults with nonsevere CHD. Hypertension and hyperlipidemia were common comorbidities among all CHD severity groups.

CONCLUSIONS: The most common underlying causes of death differed by lesion severity. Those with severe lesions most commonly died from underlying CHD, whereas those with nonsevere disease more commonly died from non-CHD causes.

Key Words: aging ■ congenital heart disease ■ death

Associated with improved pediatric surgical and perioperative outcomes, the population of patients living with congenital heart disease (CHD) is rapidly growing, with increasing numbers of patients surviving into late adulthood.¹ There are now an estimated 1.4 million adults and 1 million children living with CHD in the United States.² Although pediatric survival has improved, surgical strategies may not offer a cure for some forms of CHD; many patients are expected to experience sequelae of their original defect

and possible additional interventions throughout their lifetime. Furthermore, despite significant advances, the mortality rate in adults with CHD remains higher than that of the general population.^{3,4} A detailed understanding of long-term complications and causes of mortality can be helpful in effectively caring for adults with CHD as they age. Prior studies that focused on defining the most common causes of death in adults with CHD have either used a historical cohort or been based outside of the United States.³⁻⁹ The aims of the

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CLINICAL PERSPECTIVE

What Is New?

- This is one of the largest and most contemporary analyses of the most common causes of death in adults with congenital heart disease (CHD) in the United States.
- Patients with nonsevere CHD lived late into adulthood and most commonly died because of ischemic heart disease and malignancy.
- Hypertension and hyperlipidemia were prevalent at high rates among those with nonsevere CHD.
- Adults with severe CHD continue to die at a young age, most commonly because of their underlying congenital disease.

What Are the Clinical Implications?

- Long-term follow-up for all adults with CHD is important, regardless of disease severity.
- When following adult patients with nonsevere CHD longitudinally, special focus should be placed on acquired cardiovascular risk factor modification and age-appropriate cancer screening.

Nonstandard Abbreviations and Acronyms

CHD	congenital heart disease
ICD-9	<i>International Classification of Diseases, Ninth Revision</i>
IQR	interquartile range
NC	North Carolina

current study are to evaluate the age at death, presence of cardiovascular comorbidities, and the most common causes of death in a large, multicenter, contemporary cohort of adult patients with CHD within the United States.

METHODS

Because of the patient-level identifiers collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Centers for Disease Control and Prevention National Center on Birth Defects and Developmental Disabilities.

Data Source and Study Population

Data for this analysis were obtained from the North Carolina (NC) Congenital Heart Defect Surveillance

Network database. This database is composed of patients with CHD, as identified by *International Classification of Diseases, Ninth Revision (ICD-9)*, code in the electronic medical record, who had a healthcare encounter between 2008 and 2013 at 1 of 5 comprehensive CHD centers or affiliated satellite clinics included in the NC Congenital Heart Defect Surveillance Network. Of the 60 059 patients included in this database, those who could be linked to an NC death certificate between 2008 and 2016 and were ≥ 20 years old at the time of death were included. Therefore, only those patients with CHD who died during the study period were analyzed in this study. For comparison, all other NC death certificates between 2008 and 2016 with age at death ≥ 20 years were also analyzed. Institutional Review Board approval was obtained at all of the participating NC sites. The requirement for informed consent was waived.

Study Definitions

CHD diagnoses were grouped by lesion severity for all analyses. The groupings of *severe*, *shunt*, and *valve* were predetermined by the Centers for Disease Control and Prevention Congenital Heart Defect Surveillance Network using a previously described method that categorizes CHD diagnostic codes into mutually exclusive hierarchical groups, similar to Marelli et al, integrating both hemodynamic severity and basic anatomical characteristics.^{10,11} Diagnoses included in each group with corresponding *ICD-9* codes are shown in Table S1. The category of *other* included CHD *ICD-9* codes that could not be classified as severe, shunt, or valve. Patients with more than one lesion were classified by the lesion of highest severity (severe > shunt > valve > other). To ensure that only patients with CHD were included, the *ICD-9* code 745.5 (atrial septal defect [secundum] or patent foramen ovale) was not included in the analysis. Furthermore, as the *other* CHD category represents a highly heterogeneous group of diagnoses, it was excluded from the cause of death portion of the analysis.

Statistical Analysis

Baseline characteristics were summarized as medians (25th–75th percentiles) for continuous variables and percentages (frequencies) for categorical variables. Median age at death, with interquartile ranges (IQRs), was analyzed for the overall CHD cohort, as well as for each lesion severity group. *P* values for median age at death among patients with CHD versus all NC deaths was generated using a 2-sided Wilcoxon rank-sum test. *P* values for median age at death among CHD lesion severity groups versus other lesion severity groups were generated using the Kruskal-Wallis test (overall), followed by pairwise comparisons with

Wilcoxon rank-sum test with Tukey adjustment for multiple comparisons.

The underlying cause of death, as reported on each NC death certificate, was categorized into descriptive groups by the study team. Descriptive groups were further categorized as cardiovascular death, noncardiovascular death, and CHD death (a subgroup of cardiovascular death). Crude mortality rates for all-cause mortality, cardiovascular mortality, and CHD-related mortality were calculated using the number of deaths during the study period (2008–2013) at age ≥ 20 years as the numerator and the NC Congenital Heart Defect Surveillance Network population age >20 years at study midpoint as the denominator. Crude mortality rates were presented per 1000 patients per year.

A proportionate mortality analysis comparing cardiovascular death versus noncardiovascular death and CHD death versus non-CHD cardiovascular death was completed. For comparison, median age at death and underlying cause of death analyses were repeated using all other NC death certificates between 2008 and 2016 with age at death ≥ 20 years. To further understand the observed differences in age at death and causes of death, the prevalence of risk factors for acquired cardiovascular disease was analyzed for the overall cohort, as well as by lesion severity group, using electronic health record data. *P* values were obtained from the Fisher exact test. All analyses were performed using SAS v9.4 TS1M4 (SAS, Inc, Cary, NC).

RESULTS

Baseline Characteristics and Age at Death

Baseline characteristics are summarized in Table 1. Age at death is presented in Table 2. A total of 629 adult patients with CHD who died in NC during the study period were included (Figure 1). Of those included, 157 (25%) were characterized as having severe CHD, 202 (32%) were characterized as having a shunt lesion, and 174 (28%) were characterized as having a

Table 1. Baseline Characteristics

Characteristic	Adults (N=629)
Sex	
Men	344 (54.7)
Women	285 (45.3)
Lesion severity group	
Severe	157 (25.0)
Shunt	202 (32.1)
Valve	174 (27.7)
Other*	96 (15.3)

Data are given as number (percentage).

*Congenital heart disease diagnosis code not classified as severe, shunt, or valve.

valvular lesion. A total of 96 patients (15%) could not be classified in the severe, shunt, or valve group. The median age at death for all patients with CHD was 64.2 years (IQR, 47.5–76.5 years). Those with severe CHD, shunts, and valvular lesions had a median age of death at 46.0 (IQR, 34.3–76.5), 65.0 (IQR, 51.8–75.1), and 73.3 (IQR, 56.4–81.5) years, respectively. Among all other adult NC death certificates during the study period, the median age at death was 76.5 (IQR, 63.6–86.0) years.

Underlying Cause of Death

The all-cause mortality rate among all patients with CHD was 11.6 per 1000 patients per year. The cardiovascular and CHD-specific mortality rates were 4.9 and 1.5 per 1000 patients per year, respectively. The most common causes of death by group are presented in Figure 2. The most common causes of death among all adults with CHD in the death cohort were malignancy (14%), CHD (14%), ischemic heart disease (11%), infection (8%), and lung disease (7%). The most common causes of death among those with severe CHD, shunts, and valvular CHD were CHD (41%), ischemic heart disease (15%), and cancer (17%), respectively. Malignancy was either the most common or the second most common cause of death in all CHD groups. Ischemic heart disease was either the most common or the second most common cause of death in all groups, except among those with severe CHD. Among all other adult deaths in NC in this same time period, the most common causes were malignancy (22%), ischemic heart disease (13%), and chronic neurologic disease (dementia) (10%).

The proportion of deaths attributable to cardiovascular disease versus all other causes is summarized in Figure 3. The proportion of deaths attributable to CHD versus non-CHD cardiovascular disease is presented in Figure 4. Among all adults with CHD, 43% died from any cardiovascular cause, with 33% of those deaths attributable to CHD. In those with severe CHD, most deaths were attributable to a cardiovascular cause (60%), with 68% of the cardiovascular deaths attributable to CHD. Among those with shunts and valvular CHD, 42% and 34% of deaths were attributable to any cardiovascular cause, respectively, with a minority of those cardiovascular deaths attributable to CHD (21% and 8%, respectively). When analyzing all NC death certificates during the study period, 27% of the deaths were attributable to any cardiovascular cause, with 0.1% of those cardiovascular deaths attributable to CHD.

Prevalence of Risk Factors for Acquired Cardiovascular Disease

The prevalence of acquired cardiovascular risk factors in our study population is presented in Table 3.

Table 2. Age at Death

Variable	Age at Death, Median (IQR), y	P Value (vs All NC)*	P Value (vs Other Lesion Severity Groups)†
All NC death certificates	76.5 (63.6–86.0)
All CHD cohort	64.2 (47.5–76.5)	<0.0001	<0.001 (Overall)
Severe CHD	46.0 (34.3–63.0)	<0.0001	<0.001 (Severe vs shunt)
Shunt CHD	65.0 (51.8–75.1)	<0.0001	0.003 (Shunt vs valve)
Valve CHD	73.3 (56.4–81.5)	<0.0001	<0.001 (Valve vs severe)
Other CHD	69.9 (59.7–79.6)	<0.0001	...‡

CHD indicates congenital heart disease; IQR, interquartile range; and NC, North Carolina.

*Two-sided Wilcoxon rank-sum test.

†Kruskal-Wallis test (overall) and Wilcoxon rank-sum test (pairwise, with Tukey adjustment for multiple comparisons).

‡Other CHD group not included in pairwise tests with CHD severity groups because of high heterogeneity among included diagnosis codes.

Most patients with CHD had hypertension (63.1%). Hypertension was more common among those with shunt and valve lesions (63.9% and 74.7%, respectively) than in those with severe CHD (47.1%). Nearly half of all patients with CHD had hyperlipidemia (48.5%). Hyperlipidemia was also more common among those with shunt and valve lesions (49% and 64.4%, respectively) than in those with severe CHD (35.0%). Diabetes mellitus and chronic kidney disease were both seen in around one third of patients with CHD, both among all included patients and when analyzed by CHD severity group.

DISCUSSION

In this analysis, we identified several notable findings. First, among patients with nonsevere CHD, the age at death was approaching, but still younger than, that of the general population. Second, the most common causes of death differed by lesion severity, with CHD being the most common cause of death only among those with severe disease. Third, patients with severe CHD more commonly died from CHD and any cardiovascular disease than those with nonsevere disease. Finally, among those with nonsevere CHD, ischemic

heart disease and malignancy were the most common causes of death.

The current study showed that, with the exception of those with severe CHD, the median age at death was approaching, but still younger than, that seen in the general population. Patients with severe CHD continue to die at a comparatively young age, whereas those with nonsevere CHD frequently live into late adulthood. Given that our analysis excluded patients who died during childhood (before the age of 20 years), these results suggest that patients with nonsevere CHD who survive childhood have excellent long-term survival. This finding highlights the improving management of long-term sequelae of mild and moderate CHD during adulthood. Conversely, those with severe disease continue to experience early mortality compared with the general population, even when the sickest children who do not survive to adulthood are excluded from analysis.

The most common causes of death seen in adults with CHD differed by the severity of the underlying congenital lesion. Historical studies demonstrated that complications of CHD, specifically heart failure and arrhythmias, were the most common causes of death among all patients with CHD.^{3–5,7–9} In our analysis, however, CHD was the most commonly reported underlying cause of death only among those with severe CHD, whereas those with nonsevere disease most commonly died due to non-CHD causes.

Malignancy was 1 of the 2 most common causes of death among patients with nonsevere CHD, and was the most common cause of death in the general population. It has previously been suggested that adults with CHD are at risk for malignancy because of cumulative exposure to ionizing radiation from cardiac procedures over the course of their lifetime.¹² Our analysis further underscores the importance of close monitoring for the development of malignancy with vigilant age-appropriate cancer screening in adults with CHD.

Among patients with nonsevere CHD, ischemic heart disease was also 1 of the 2 most common

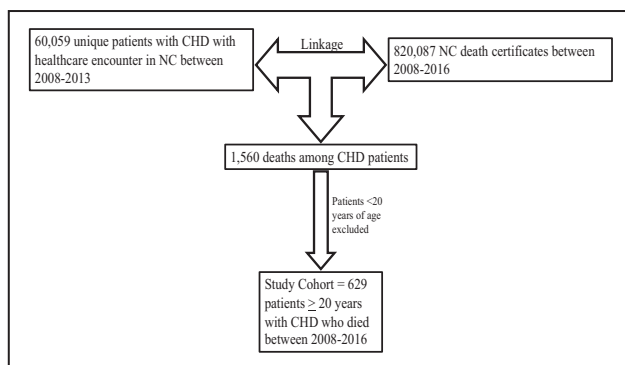


Figure 1. Derivation of patient cohort.

CHD indicates congenital heart disease; and NC, North Carolina.

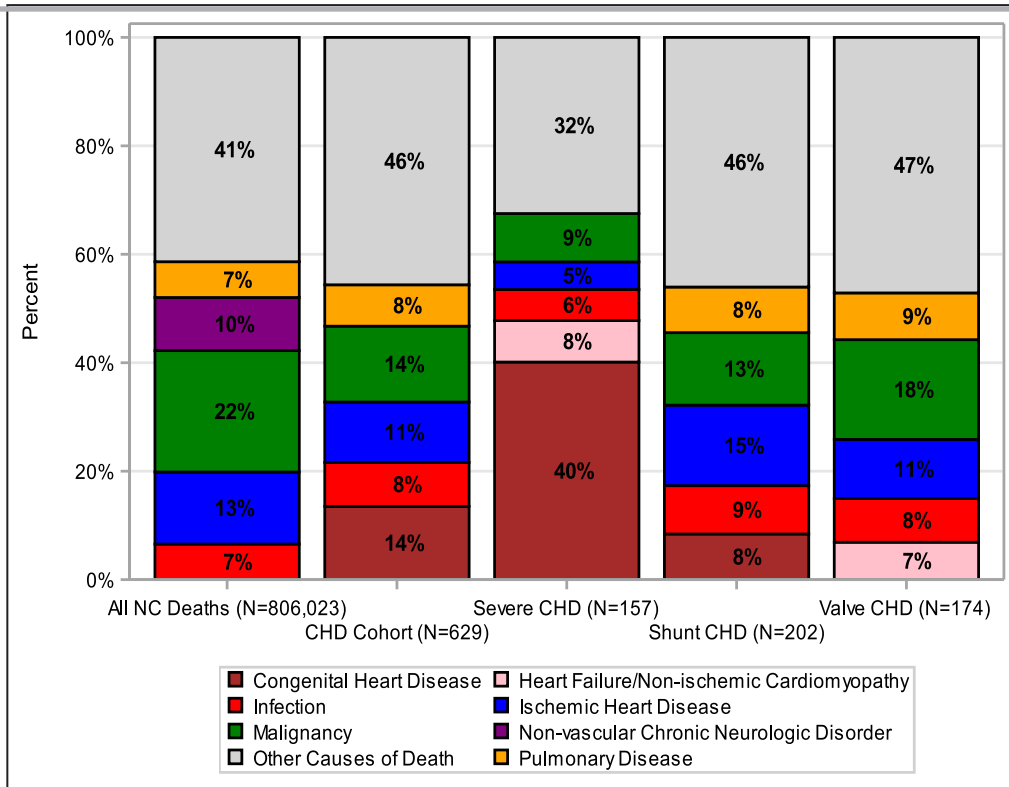


Figure 2. Top 5 most common causes of death. “Other” represents a compilation of all other causes of death not included in the top 5. CHD indicates congenital heart disease; and NC, North Carolina.

causes of death in all groups. Similarly, ischemic heart disease was the second most common cause of death in the general population. Although there has

been disagreement in the literature about the importance of coronary artery disease in patients with CHD, a more recent analysis demonstrated that as the life

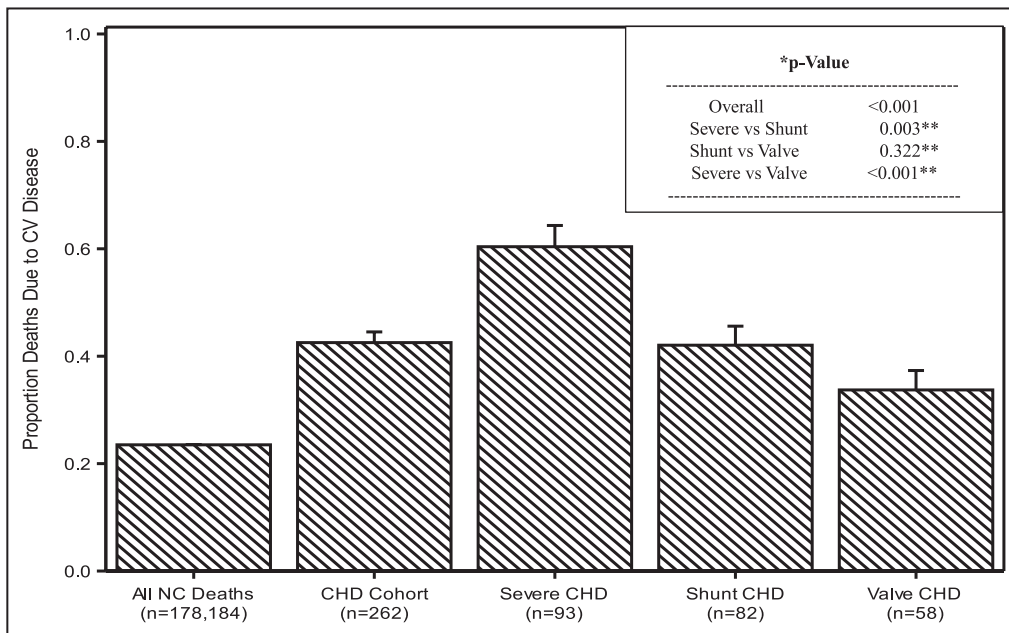


Figure 3. Deaths attributable to cardiovascular disease vs all other causes among all patients in North Carolina (NC) and those with congenital heart disease (CHD).

The CHD group is further divided by lesion severity into severe CHD, shunt CHD, and valve CHD. *P values obtained from the Fisher exact test. **The Tukey adjustment for multiple comparisons was applied. CV indicates cardiovascular.

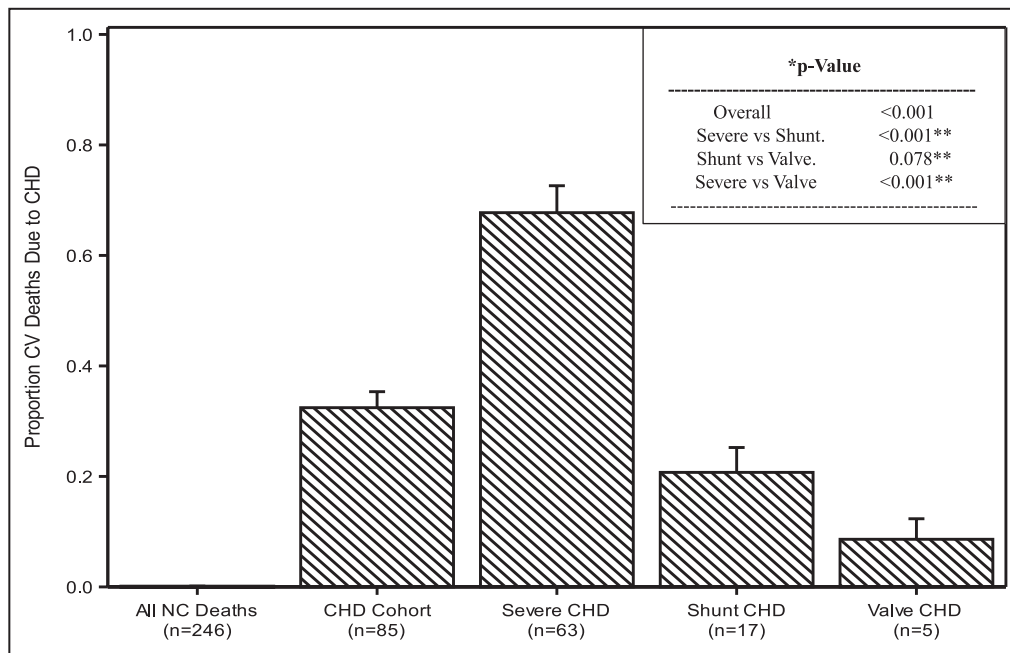


Figure 4. Deaths attributable to congenital heart disease (CHD) vs noncongenital cardiovascular disease among all patients in North Carolina (NC) and those with CHD.

The CHD group is further divided by lesion severity into severe CHD, shunt CHD, and valve CHD. *P values obtained from the Fisher exact test. **The Tukey adjustment for multiple comparisons was applied. CV indicates cardiovascular.

expectancy of patients with CHD increased over time, the most common cause of death in patients with noncyanotic CHD shifted from CHD-related complications to ischemic heart disease.^{7,13} In a more contemporary cohort, our analysis again demonstrates that acquired heart disease is an important cause of death in patients with nonsevere CHD.

To better understand why ischemic heart disease has emerged as an important cause of death in patients with nonsevere CHD, the prevalence of risk factors for acquired cardiovascular disease among patients with CHD was assessed. This analysis demonstrated that hypertension and hyperlipidemia were prevalent at high rates among those with nonsevere CHD. Patients with severe CHD had lower rates of these risk factors, likely because an earlier age at death precluded the development of these age-related conditions. Prior studies have demonstrated

that patients with CHD frequently do not receive medical therapy for management of acquired modifiable cardiovascular risk factors.¹⁴ These results suggest the importance of acquired cardiovascular disease risk factor management in adult patients with CHD, particularly those with nonsevere disease, a practice that has the potential to be overlooked because of the complexity of patients' cardiac history.

Limitations

Because CHD and cause of death diagnoses were based on electronic health record and death certificate data, the accuracy of these diagnoses was dependent on physician documentation. The end points of this study were not adjudicated, and clinical information surrounding the death event was not available. Therefore, in some cases in which general diagnoses, such as heart failure and respiratory failure, were used, it was difficult to determine whether the cause of death could have been related to CHD. In addition, in this descriptive analysis, the cardiovascular comorbidities of CHD, such as pulmonary hypertension, arrhythmias, and thrombosis, which may have directly contributed to death caused by CHD, were not evaluated as covariates. Because only NC death certificates were linked, patients who died outside of NC were not included. However, on the basis of 2017 US Census Bureau data showing the rate of migration out of NC to be ~3% per year, it is unlikely that this significantly affected our

Table 3. Risk Factors for Acquired Cardiovascular Disease

Characteristic	Severe (N=157)	Shunt (N=202)	Valve (N=174)	P Value*
Hypertension	74 (47.1)	129 (63.9)	130 (74.7)	<0.001
Diabetes mellitus	36 (22.9)	68 (33.7)	70 (40.2)	0.003
Chronic kidney disease	56 (35.7)	74 (36.6)	58 (33.3)	0.804
Hyperlipidemia	55 (35.0)	99 (49.0)	112 (64.4)	<0.001

Values presented are counts (percentages) for categorical variables. *P values obtained from the Fisher exact test.

SUPPLEMENTAL MATERIAL

Table S1. CHD ICD-9 Codes and Severity Groupings.

Category	ICD-9-CM Code	Code Description
SEVERE	745.0	Common Truncus
	745.1	Transposition of the Great Arteries (TGA)
	745.10	Complete TGA (dextro-TGA)
	745.11	DORV, or incomplete TGA
	745.12	Corrected TGA (levo-TGA)
	745.19	Other TGA
	745.2	Tetralogy of Fallot
	745.3	Single Ventricle, or cor triloculare
	745.6	Endocardial Cushion Defect (AVSD)
	745.60	Endocardial Cushion Defect (AVSD) unspecified
	745.69	Endocardial Cushion Defect, Other
	746.01	Pulmonary valve atresia or absence
	746.1	Tricuspid atresia, stenosis or absence
	746.7	Hypoplastic left heart syndrome
	747.11	Interrupted aortic arch
	747.41	Total anomalous pulmonary venous return (TAPVR)
SHUNT	745.4	Ventricular septal defect
	745.5	Atrial septal defect (ASD) (secundum) or PFO
	745.61	ASD (primum)
	745.8	Other specified defect of septal closure
	745.9	Unspecified defect of septal closure
	747.0	PDA
	747.42	Partial anomalous venous return (PAPVR)
VALVE	746.0	Anomalies of pulmonary valve

	746.00	Pulmonary valve anomaly, unspecified
	746.02	Pulmonary valve stenosis
	746.09	Pulmonary valve anomaly, other
	746.2	Ebstein's Anomaly
	746.3	Aortic valve stenosis
	746.4	Aortic insufficiency or bicuspid/unicuspid aortic valve
	746.5	Mitral stenosis or mitral valve abnormalities
	746.6	Mitral insufficiency
	746.81	Subaortic stenosis
	746.83	Infundibular or subvalvar pulmonary stenosis
	747.10 or 747.1	Coarctation of aorta
	747.22	Atresia or stenosis of aorta
	747.3	Anomalies of Pulmonary artery
	747.31	Pulmonary artery atresia, coarctation, or hypoplasia
	747.39	Anomalies of Pulmonary artery, other
OTHER ONLY <i>(case only has one or more codes in this category)</i>	745.7	Cor biloculare
	746.8	Other Specified anomalies of heart
	746.82	Cor triatriatum
	746.84	Obstructive anomalies of heart
	746.85	Coronary artery anomaly
	746.87	Malposition of heart or apex
	746.89	Other specified anomaly of heart (various types)
	746.9	Unspecified defect of heart
	747.2	Other anomaly of the aorta
	747.20	Anomalies of aorta, unspecified
	747.21	Anomaly of aortic arch
	747.29	Other anomaly of aorta
	747.4	Anomalies of great veins

	747.40	Anomalies of great veins, unspecified
	747.49	Other anomalies of great veins
	747.9	Unspecified anomalies of circulatory system
	648.5X	Congenital Cardiovascular disorder complicating pregnancy, childbirth or puerperium
	V13.65	Personal history of corrected congenital malformations of the heart and circulatory system

results. Because only patients with CHD with a health-care encounter at a tertiary care center within NC during the study period were included, the results may not be generalizable to all patients with CHD. Finally, because patients were not followed up longitudinally, a survival analysis, which would be a more rigorous way to assess age at death, was not possible.

CONCLUSIONS

With the exception of those with severe disease, patients with CHD frequently live into late adulthood, placing them at risk for mortality related to both acquired cardiovascular and noncardiovascular disease. Patients with severe CHD remain at risk for early mortality, primarily related to their underlying congenital heart condition. Those with severe CHD are significantly more likely to die from CHD and any cardiovascular cause than those with nonsevere disease. These results highlight the importance of close long-term follow-up for all adults with CHD, with a focus on age-appropriate cancer screening and acquired risk factor modification in those with nonsevere CHD. Further advances in the long-term prevention of CHD-related mortality in patients with severe CHD are still needed.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Table S1

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