Circulation

ORIGINAL RESEARCH ARTICLE

Adults With Congenital Heart Disease: Trends in Event-Free Survival Past Middle Age

Mikael Dellborg, MD, PhD; Kok Wai Giang, PhD; Peter Eriksson, MD, PhD; Hans Liden, MD, PhD; Maria Fedchenko, MD, PhD; Anders Ahnfelt, MD; Annika Rosengren, MD, PhD; Zacharias Mandalenakis, MD, PhD

BACKGROUND: The survival of children with congenital heart disease has increased substantially over the past decades, with 97% currently reaching adulthood. The total effect of advanced treatment on future mortality and morbidity in adult survivors with congenital heart disease (CHD) is less well described.

METHODS: We used data from the Swedish National Inpatient, Outpatient, and Cause of Death Register to identify patients with CHD who were born between 1950 and 1999 and were alive at 18 years of age. Ten controls identified from the Total Population Register were matched for year of birth and sex and with each patient with CHD. Follow-up was from 1968 and 18 years of age until death or at the end of the study (2017). Survival percentage with 95% CI for all-cause mortality were performed with Kaplan-Meier survival function. Cox proportional hazard regression models with hazard ratios (HRs) and 95% CI were used to estimate the risk of all-cause mortality.

RESULTS: We included 37 278 patients with adult CHD (ACHD) and 412 799 controls. Mean follow-up was 19.2 years (±13.6). Altogether, 1937 patients with ACHD (5.2%) and 6690 controls (1.6%) died, a death rate of 2.73 per 1000 person-years and 0.84 per 1000 person years, respectively. Mortality was 3.2 times higher (95% CI, 3.0–3.4; $P<0.001$) among patients with ACHD compared with matched controls. Up to the maximum of 50 years of follow-up, >75% of patients with ACHD were still alive. Mortality was highest among patients with conotruncal defects (HR, 10.13 [95% CI, 8.78–11.69]), but also significantly higher for the more benign lesions, with the lowest risk in patients with atrial septal defects (HR, 1.36 [95% CI, 1.19–1.55]). At least 75% of patients with ACHD alive at 18 years of age lived past middle age and became sexagenerians.

CONCLUSIONS: In this large, nationwide, register-based cohort study of patients with ACHD surviving to 18 years of age, the risk of mortality up to 68 years of age was >3 times higher compared with matched controls without ACHD. Despite this, at least 75% of patients with CHD alive at 18 years of age lived past middle age and became sexagenerians. A notable risk decline in the mortality for patients with ACHD was seen for those born after 1975.

Key Words: adult congenital heart disease ■ cardiovascular morbidity ■ survival

Editorial, see p 939

Congenital heart disease (CHD) is the most common congenital malformation and occurs in 1% of all live births.[1] The development of congenital heart surgery, cardiac interventions, and medical treatment has significantly improved the prognosis in patients with CHD,[2,3] with survival of children with CHD increasing substantially over the past decades, and >97% reaching adulthood.[4] However, adults with CHD still face an increased risk of several acquired disorders, such as ischemic heart disease, diabetes, heart failure, atrial fibrillation, stroke, and cancer.[5–9]

Correspondence to: Mikael Dellborg, MD, PhD, Department of Molecular and Clinical Medicine/Cardiology, Sahlgrenska University Hospital/Östra, Diagnosvägen 11, SE-416 50 Gothenburg, Sweden. Email mikael.dellborg@gu.se

Supplemental Material, the podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.122.060834.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

For Sources of Funding and Disclosures, see page 937.

© 2022 The Authors. *Circulation* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial-NoDerivs License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited, the use is noncommercial, and no modifications or adaptations are made.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- In adult patients with congenital heart disease surviving to 18 years of age, the risk of mortality up to 68 years of age is >3 times higher compared with matched controls, although a notable decline in absolute and relative risk is noted for those born after 1975.
- Despite this, at least 75% of adult patients with congenital heart disease surviving to 18 years of age lived past middle age, becoming sexagenarians.

What Are the Clinical Implications?

- Adult patients with congenital heart disease surviving to 18 years of age will continue to need medical follow-up to detect and possibly prevent cardiovascular morbidity and mortality.
- Patients with congenital heart lesions of all complexities are at increased risk of mortality and morbidity compared with controls and in need of medical follow-up throughout adulthood.

Nonstandard Abbreviations and Acronyms

ACHD	adult congenital heart disease
CHD	congenital heart disease
HR	hazard ratio
ICD	*International Classification of Diseases*

Most palliative and corrective congenital heart surgery procedures and percutaneous interventions are carried out in early childhood. Additional heart surgery and cardiac interventions are often needed later in life and associate with prognosis among patients with adult CHD (ACHD).[10,11] The correction of cardiac malformations and subsequent increased survival of patients with complex CHD may also mean that a more vulnerable and palliated group of patients survive into adulthood. The number of adults has by now bypassed the number of children living with CHD, with a substantial proportion currently >60 years of age.[12] The total effect of advanced surgical, interventional, and medical treatment complemented by improved processes of, and access to, care on future prognosis in adults with respect to mortality and morbidity is so far not well described. Therefore, we aimed to investigate mortality and cardiovascular morbidity of patients with ACHD in Sweden during their adult lives, starting at 18 years of age.

METHODS

We obtained data from the National Hospital Inpatient Register (complete and mandatory and with national coverage since 1987, but with full coverage of all hospitals performing thoracic and congenital heart surgery after 1969), the National Hospital Outpatient Register (mandatory, started and complete since 2001), and the Cause of Death Register (complete and mandatory since 1968) for all patients with CHD born between 1950 and 1999 to identify patients with any CHD diagnosis surviving into adulthood during this period. All patients with CHD who died before 18 years of age were excluded. Follow-up data on mortality and comorbidities were collected for the study population until December 31, 2017, or death. National patient registers contain diagnoses at discharge and codes for diagnostic and interventional procedures. In Sweden, each individual is identified by a unique 12-digit personal number provided at birth. Diagnoses were coded according to the *International Classification of Diseases*, 8th revision (*ICD*-8), *ICD*-9, and *ICD*-10, as described in Table S1. Each patient with ACHD was matched by birth year and sex, with 10 control subjects without ACHD, obtained from the Total Population Register in Sweden.

The study was approved by the regional research ethics board in Gothenburg (Gbg 912-16, T619-18) and complied with the Declaration of Helsinki. In collaboration with Statistics Sweden, we received data from the Swedish National Board of Health and Welfare, in which all national registration numbers were replaced with a unique code for each individual, and because of this provision, informed consent was waived by the regional research ethics board. Data are available from the sources stated in the article on request to the data providers, fulfilling legal and regulatory requirements, and with permission from the Swedish Ethical Review Authority.

The study design has been described previously.[4,5]

Definitions

CHD was defined as present in patients with at least one registered diagnosis of CHD (Table S1) in the National Hospital Inpatient Register, National Hospital Outpatient Register, or Cause of Death Register.

We used hierarchical categorization of CHD to classify patients with CHD into 6 different groups, as suggested by Botto et al[13] and subsequently modified by Liu et al,[14] and used in other CHD population studies[3–9] (Table S2). Lesion group 1 included patients with conotruncal defects, such as common arterial trunk, transposition of the great arteries, double-outlet ventricle, aorto-pulmonary septum defects, and tetralogy of Fallot. Lesion group 2 comprised patients with severe nonconotruncal defects, such as common ventricle, hypoplastic left heart syndrome, and endocardial cushion defects. Lesion group 3 included patients with coarctation of the aorta. Lesion group 4 comprised all patients with ventricular septal defect. Lesion group 5 encompassed all patients with atrial septal defect. And lesion group 6 included all patients with any other heart and circulatory system anomalies and all other CHD diagnoses not included in the other 5 lesion groups.

Congenital cardiac intervention was defined as patients with CHD having undergone at least one cardiovascular surgery or cardiac interventional catheterization procedure related to CHD according to the classification of operations in Sweden, sixth version,[15] or classification of surgical

Table 1. Baseline Characteristics of the Study Population

	ACHD N=37 278	Controls† N=412 799
Men, n (%)	19 290 (51.7)	214 286 (51.9)
Year of birth, mean±SD	1979.9±14.2	1980.2±13.8
FU, mean±SD, years after 18 y	19.0±13.8	19.2±13.6
Age at end of FU, mean±SD	37.0±13.8	37.2±13.6
Lesion group n (%)		
1: Conotruncal	2914 (7.8%)	38 430 (9.3%)
2: Severe nonconotruncal	1929 (5.2%)	30 797 (7.5%)
3: Coarctation of the aorta	2509 (6.7%)	27 500 (6.7%)
4: VSD	7652 (20.5%)	80 284 (19.4%)
5: ASD	7530 (20.2%)	76 476 (18.5%)
6: All other*	14 744 (39.6%)	159 312 (38.6%)
Birth period		
1950–1969	9921 (26.6%)	101 046 (24.5%)
1970–1989	14 608 (39.2%)	172 430 (41.8%)
1990–1999	12 749 (34.2%)	139 323 (33.8%)
Diabetes <18 years of age	251 (0.7%)	165 (0.4%)
Congenital cardiac‡ intervention >18 y	8975 (24.1%)	12 (0%)§
Congenital cardiac intervention >18 y	3787 (10.2%)	875 (0.2%)

Diabetes includes types 1 and 2. ACHD indicates adult congenital heart disease; ASD, atrial septal defect; FU, follow-up; and VSD, ventricular septal defect.

*Lesion group 6 includes all other congenital heart disease diagnoses that are not included in lesion groups 1 through 5.

†Controls are matched at birth, with 10 controls for each case, and a disproportionate number of controls reflects mortality before 18 years of age in cases.

‡Congenital cardiac interventions include congenital heart surgery and congenital catheter interventions.

§Congenital cardiac interventions in controls represent misclassification of cardiac interventions for noncongenital heart disease.

Table 2. Mortality and Composite Events After 18 Years of Age per 1000 Person-Years by Case/Control, Type of Lesion, Period of Birth, and Cardiac Intervention (Yes/No)

	Person-years	Deaths/%	Population	IR*
Mortality				
ACHD, n	708 851	1937/5.2	37 278	2.73
Controls, n	7 918 012	6690/1.6	412 799	0.84
Lesion group				
1: Conotruncal	46 601	320/11.0	2914	6.87
2. Severe non-conotruncal	36 317	204/10.6	1929	5.62
3. Coarctation of the aorta	52 654	170/6.8	2509	3.23
4. VSD	119 995	304/4.0	7652	2.53
5. ASD	180 273	254/3.4	7530	1.41
6. All other, including valves	273 008	685/4.6	14 744	2.51
Birth period				
1950–1969	370 428	1313	9921	3.54
1970–1989	272 394	554	14 608	2.03
1990–1999	66 028	70	12 749	1.06
Cong cardiac int				
No	408 159	1169	22 971	2.86
Yes	300 692	768	14 307	2.55

Events and composite event. Composite events: atrial fibrillation, heart failure, ischemic stroke, myocardial infarction, or death, whichever came first. ACHD indicates adult congenital heart disease; ASD, atrial septal defect; Cong cardiac int, congenital cardiac interventions, including congenital heart surgery and congenital catheter interventions; IR, incidence rate; and VSD, ventricular septal defect.

*Per 1000 person-years.

procedures in Swedish, version 1.9,[16] and including >500 different surgical or interventional codes.

Cardiovascular morbidity during follow-up was defined as a discharge or outpatient diagnosis with any of the following: myocardial infarction, heart failure, atrial fibrillation, ischemic stroke, diabetes type 1 or type 2, hyperlipidemia, or hypertension according to *ICD*-8, *ICD*-9, and *ICD*-10 codes.

A composite outcome was constructed of the occurrence of atrial fibrillation, ischemic stroke, heart failure, myocardial infarction, diabetes (type 1 or type 2), or death, whichever occurred first.

Statistical Analysis

All analyses were performed with statistical software (R v3.5.2; R Foundation for Statistical Computing, Vienna, Austria). Categorical data are presented descriptively as numbers and percentages and continuous as means with SD. In the present study, patients with ACHD and controls were followed up from 18 years of age until death (of all causes) or the end of the study (December 31, 2017), whichever occurred first, or as a composite event (atrial fibrillation, ischemic stroke, heart failure, diabetes type 1 or type 2, myocardial infarction, or death, whichever occurred first). Incidence rates were reported as the number of events per 1000 person-years, and were estimated as the number of deaths divided by the total follow-up time of the population. Survival percentage with 95% CIs for all-cause mortality and composite events were performed with Kaplan-Meier survival function. A P value of <0.05 was considered statistically significant. Cox proportional-hazard regression models with hazard ratios (HRs) and 95% CIs were used to estimate the risk of all-cause mortality in patients with ACHD and controls. The reference group for all Cox analyses was the control population. The results from the risk models are presented as unadjusted and adjusted models (adjusted for hypertension and diabetes). A cubic spline model with 4 knots and 95% CI was performed to estimate the mortality risk per increase in birth year, and 1950 was used as the reference year.

RESULTS

We identified 37 278 patients with ACHD and 412 799 matched controls. There were slightly more men than women, and the duration of follow-up from birth was about 37 years for cases and controls (Table 1), with follow-up after 18 years of age, accordingly about 19 years. During 7 918 012 person-years of follow-up, there were

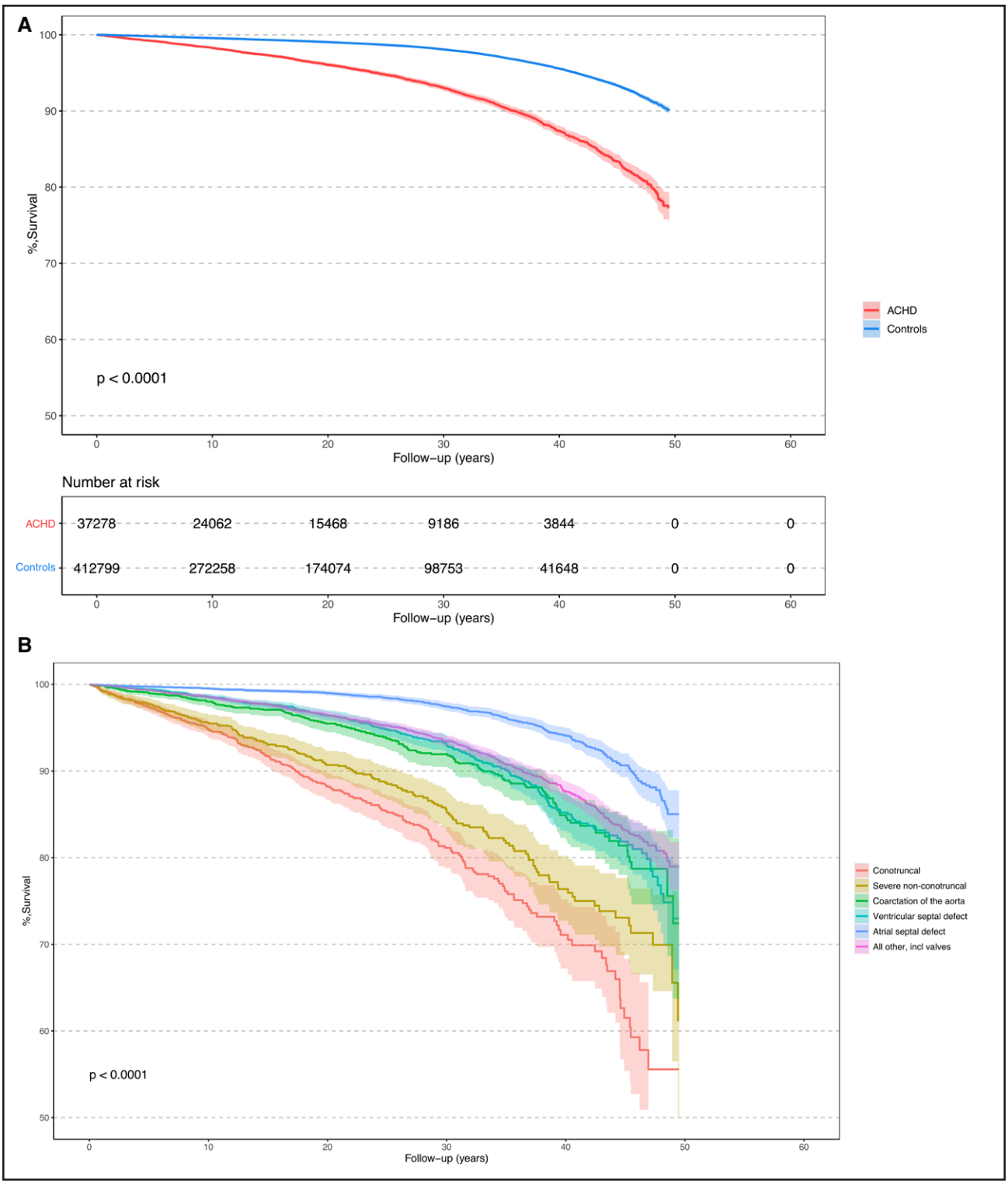

Figure 1. Survival in ACHD and controls from 18 years of age.
A, Kaplan-Meier survival curves of patients with ACHD and matched controls. Whereas 90% of controls survive for 50 years, until 68 years of age, just <80% of patients with ACHD do. **B**, Kaplan-Meier survival curves of patients with ACHD according to lesion group. The most severe lesion groups (1 and 2), 12.9% of patients, represent 27% of deaths. Lesion group 1: conotruncal defects; group 2: severe nonconotruncal defects; group 3: coarctation of the aorta; group 4: ventricular septal defect; group 5: atrial septal defect; group 6: all other lesions including valves. **C**, Kaplan-Meier survival curves of patients with ACHD and matched controls according to birth period and lesion group. The most marked change is observed in the mortality of the most complex lesions (ie, groups 1 and 2). ACHD indicates adult congenital heart disease; and incl, including. (*Continued*)

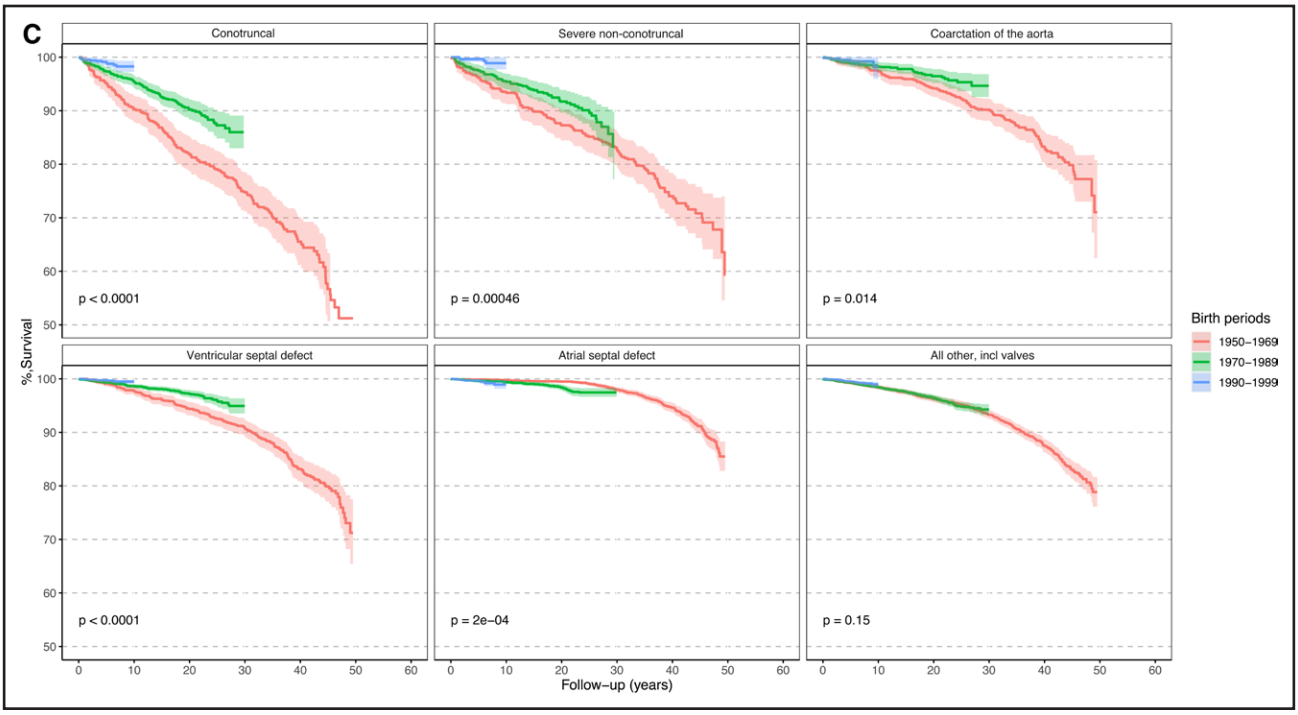

Figure 1 Continued.

6690 deaths (1.6%) among controls corresponding to a death rate of 0.84 per 1000 person-years and 1937 deaths (5.2%) during 708 851 person-years of follow-up, with a death rate of 2.73 per 1000 person-years for patients with ACHD.

Mortality rates declined over time (Table 2), varied by complexity, and the highest rate was found in the most complex groups (ie, conotruncal and severe nonconotruncal defects; lesion groups 1 and 2). The most complex lesions made up 12.9% of all patients with ACHD and accounted for 524 of 1937 deaths (ie, 27% of deaths). Mortality was slightly lower among the 34% of the ACHD population who had undergone a cardiac intervention.

Overall, mortality after 18 years of age was higher among patients with ACHD compared with controls (HR, 3.20 [95% CI, 3.04–3.37]; $P<0.001$; Figure 1A). Even so, after 50 years of follow-up, >75% of patients with ACHD were still alive. The risk of mortality also remained significantly higher in all lesion groups when adjusted for diabetes type 1 or type 2 or hypertension (Table 3).

Mortality was also significantly higher in patients with ACHD compared with controls for the less complex lesion groups 3 to 6 (ie, coarctation of the aorta, ventricular septal defects, atrial septal defects, and all other lesions including valvular lesions; Figure 1B). Mortality declined over the 3 successive birth cohorts 1950 to 1969, 1970 to 1989, and 1990 to 1999 ($P<0.001$; Figure 1C). In particular, as shown in Figure 2, the HR of mortality per birth year started to decline in the middle of the 1970s, with a steady, near-linear decline with each birth year afterward.

Mortality after 18 years of age declined over the 3 successive birth cohorts for patients with complex disease (ie, patients with conotruncal and severe nonconotruncal

Table 3. Mortality Risk in Adult Patients With Congenital Heart Disease Compared With Matched Controls According to Lesion Group

Lesion group	HR (95% CI)	*P* value
Conotruncal		
Unadjusted	10.13 (8.78–11.69)	<0.001
*Adjusted	10.03 (8.70–11.58)	<0.001
Severe nonconotruncal		
Unadjusted	7.45 (6.30–8.82)	<0.001
*Adjusted	7.36 (6.21–8.72)	<0.001
Coarctation of the aorta		
Unadjusted	3.78 (3.18–4.50)	<0.001
*Adjusted	3.66 (3.07–4.37)	<0.001
VSD		
Unadjusted	3.66 (3.22–4.17)	<0.001
*Adjusted	3.65 (3.20–4.15)	<0.001
ASD		
Unadjusted	1.37 (1.20–1.56)	<0.001
*Adjusted	1.36 (1.19–1.55)	<0.001
All other, incl valves		
Unadjusted	2.93 (2.69–3.19)	<0.001
*Adjusted	2.90 (2.66–3.15)	<0.001

ASD indicates atrial septal defect; HR, hazard ratio; and VSD, ventricular septal defect.

*Adjusted for hypertension, diabetes.

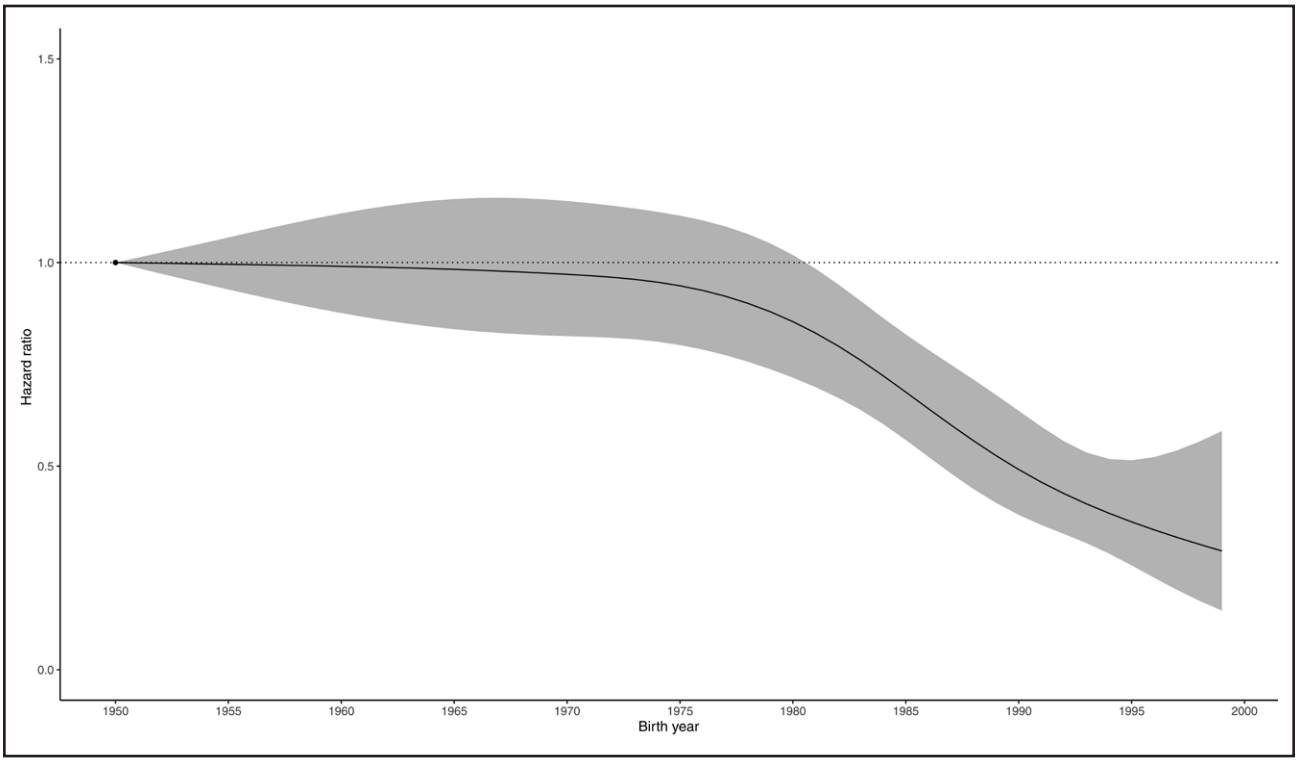

Figure 2. Risk of mortality among adult patients with congenital heart disease by birth year (patients with congenital heart disease only).

Restricted cubic spline model. Hazard ratio per unit of increase of birth year. Starting in the mid-1970s, the mortality declined over time, and for those born after 1975, the hazard ratio decreased steadily per birth year.

defects; lesion groups 1 and 2), but for patients with ACHD with less complex disease, the decline was smaller and not statistically significant (Figure S1).

In general, the excess mortality seen among patients with ACHD became less prominent with increasing age and length of follow-up. For patients with conotruncal and severe nonconotruncal defects (ie, with complex disease; lesion groups 1 and 2), the HR of death was highest in the first years after age 18, with an adjusted HR of 114.83 (95% CI, 45.31–290.96) during the first year, subsequently declining to an HR of 8.01 (95% CI, 6.70–9.58) after 30 years of follow-up compared with controls. For patients with ACHD with coarctation of the aorta, ventricular septal defect, atrial septal defect, and other lesions including valvular lesions (ie, less complex disease; lesions groups 3–6), the similarly adjusted HR was 21.41 (95% CI, 13.00–35.26) for the first year after age 18, declining to 7.32 (95% CI, 6.93–7.72) after 30 years of follow-up compared with controls.

Patients with ACHD had a higher risk of developing atrial fibrillation, heart failure, nonfatal myocardial infarction, nonfatal stroke, diabetes or of dying compared with controls (18.2% versus 3.1%; $P<0.001$; incidence ratio, 11.02 versus 2.22 per 1000 patient-years; Figure 3; Table 4). The adjusted HR for a composite event was 5.41 (95% CI, 5.27–5.56) overall and 10.01 (95% CI, 9.33–10.74) and 4.95 (95% CI, 4.80–5.10) for patients with complex or less complex disease, respectively. The excess of events was driven by more patients with ACHD diagnosed with atrial fibrillation (7.1% versus 0.7%; $P<0.001$), heart failure (5.3% versus 0.4%; $P<0.001$), ischemic stroke (5.9% versus 0.4%; $P<0.001$), and diabetes (4.2% versus 1.5%; $P<0.001$) compared with controls.

DISCUSSION

In this large, nationwide, registry-based study of patients with ACHD who survived until 18 years of age, we found that mortality during adulthood until a maximal attained age of 68 years was 3.2 times higher than that of matched controls born without CHD. After a mean follow-up of 19.2 years, 5.2% of patients with ACHD died, corresponding to a mortality rate of 2.73/1000 person-years. Our findings are slightly lower than previous reports of adult cohorts coming from large tertiary ACHD referral centers. Yu et al reported ~4 deaths/1000 patient-years,[17] and a recent study from the Brompton Center with 9.1 years of follow-up reported 7.3 deaths/1000 patient-years.[18] The higher death rates probably reflect a population with an enrichment of complex cases, as can be expected from highly specialized centers compared with our unselected national population. Among our patients with ACHD alive at 18 years of age, >75% were

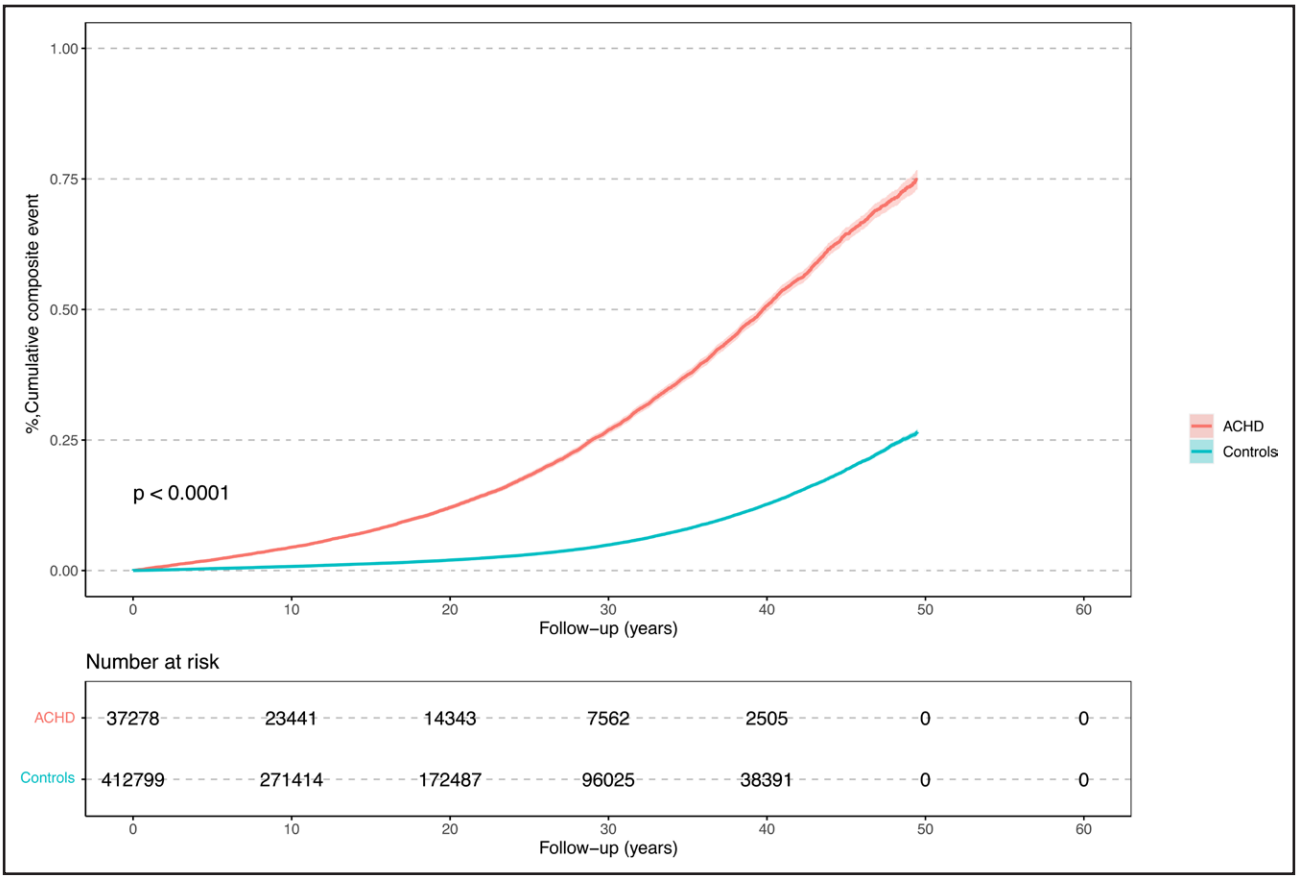

Figure 3. Cumulative composite events among patients with ACHD and matched controls.
Kaplan-Meier survival curves. Composite event: atrial fibrillation, heart failure, nonfatal myocardial infarction, nonfatal ischemic stroke, diabetes, or death. ACHD indicates adult congenital heart disease.

still alive after 50 years of follow-up, with about 50% of patients with complex ACHD, conotruncal, or severe nonconotruncal defects still alive at 68 years of age. This is comparable to data from the Dutch National Congenital Corvitia Registry (CONCOR),[19] which reported a median survival to 53, 75, or 84 years, depending on CHD complexity (mild, moderate, or severe).

We also found that less complex lesions such as coarctation, atrial septal defect, ventricular septal defect, or valvular lesions as the principal CHD diagnosis were associated with a significantly higher mortality compared with controls. This is in accordance with previously reported Danish data, which found that during long-term follow-up in adult life, even fewer complex lesions were associated with significantly increased relative risk of death of 1.9 and an increased risk of morbidity of 3.9[20] compared with the general population.

We previously reported that mortality in CHD in Sweden has decreased over the years, with similar findings reported from other countries as well.[2,4] For patients with CHD who have entered adulthood, we similarly found a declining absolute and relative mortality compared with controls over time. It is worth noting that despite more patients with more complex lesions surviving into adulthood, the overall absolute and relative risks for older patients despite this have declined over time. This is in accordance with data from the CONCOR Registry.

Our study represents a nationwide spectrum, including many patients with less complex disease. This is illustrated by the intervention rate of 24.8% before 18 years of age. During follow-up, 13.5% of the patients needed surgery or catheter intervention in some form.

Over the years, and in the most recent decades, despite the survival of more individuals with more complex disease, mortality declined compared with controls for all patients with ACHD, reflecting the improvement in congenital heart care. This is demonstrated in Figure 2, in which a major improvement in prognosis may be seen for children born in the mid-1970s and onward. The advances in invasive heart catheterizations and interventions may be one of the keys to the further improvement of cardiovascular morbidity and mortality in fragile elderly patients with ACHD. Our data demonstrate the effect, on a national level, of the advances in surgical treatment of complex congenital heart conditions that successively came into use during the 1970s and 1980s, on the basis of reports of novel, innovative operative techniques and medications.[21–26] The importance of structured care during adulthood has also been pointed out,[27] and ACHD units came into use in Sweden in the early- to mid-1990s,

Table 4. Incidence Rate of Individual Parts of Composite End Point and of Composite End Point

Events	Person-years	Events	Population	IR*
Nonfatal MI				
Controls, n	7 903 079	2330	412 799	2.95
ACHD, n	705 607	543	37 278	7.70
Heart failure				
Controls, n	7 909 762	1701	412 799	2.15
ACHD, n	696 838	1962	37 278	28.16
Ischemic stroke				
Controls, n	7 908 227	1495	412 799	1.89
ACHD, n	692 611	2206	37 278	31.85
Atrial fibrillation				
Controls, n	7 899 768	2774	412 799	3.51
ACHD, n	687 616	2649	37 278	38.52
Diabetes				
Controls, n	7 866 222	6399	412 799	8.13
ACHD, n	700 951	990	37 278	14.12
Composite				
Controls, n	7 826 350	17 409	412 799	2.22
ACHD, n	659 174	7261	37 278	11.02

Diabetes: includes types 1 and 2. Composite: nonfatal MI, hospitalization for heart failure, ischemic stroke, atrial fibrillation, diabetes, or death, whichever came first. ACHD indicates adult congenital heart disease; IR, incidence ratio; and MI, myocardial infarction.

*Per 1000 person-years.

coinciding with the patients with CHD born in the mid-1970s turning 18 years of age.

Strengths and Limitations

The present study reports the outcome of ~9 million person-years, representing a nationwide cohort with very few patients or controls lost to follow-up. The study increases the number of reported deaths among adults with CHD substantially, adding close to another 2000 deaths to the literature. However, there are also some limitations. First and foremost, there was a lack of access to clinical and patient-specific data, such as the results of specific investigations and data on clinical course and terminal events. Second, the accuracy of comorbidity codes in patients with CHD has been only partially determined. Third, improved diagnostic tools such as echocardiography may also have changed the denominator for, in particular, less complex lesions such as ventricular septal defect or atrial septal defect. Fourth, atrial septal defect and patent foramen ovale (PFO) have the same *ICD* code, and our cohort will include a limited number of patients with PFO who died during follow-up. Fifth, patients with simple malformations, such as spontaneously closed ventricular septal defects, seen as outpatients only before 2000, and subsequently discharged from pediatric cardiology as "healthy," will not have been included. However, all patients, as well as those with simple lesions such as atrial septal defect and ventricular septal defect who died at any time after 18 years of age and until the end of 2017, will have been included, as will all patients regardless of lesion severity who were seen as inpatients or outpatients after 2000. Last, although we describe the overall improvement in the prognosis of ACHD, treating the broad spectrum of ACHD as a single cohort represents a significant oversimplification of the differences in pathophysiology, clinical presentation, and management.

CONCLUSIONS

In this large, nationwide, register-based cohort study of patients with ACHD surviving to 18 years of age, the risk of mortality up to 68 years of age was >3 times higher compared with matched controls without CHD. Despite the high mortality risk, >75% of adult patients with ACHD lived past middle age and became sexagenerians. A notable decline in the absolute and relative risk of death for patients with ACHD was seen for those born after 1975.

ARTICLE INFORMATION

Received May 12, 2022; accepted November 21, 2022.

All relevant aggregated data underlying this article are available in the article and in its online Supplemental Material.

Affiliations

Institute of Medicine, Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden (M.D., K.W.G., P.E., M.F., A.A., A.R., Z.M.). Adult Congenital Heart Disease Unit (M.D., P.E., A.A., Z.M.), Department of Pediatrics, Queen Silvias Pediatric Hospital (H.L.), Sahlgrenska University Hospital, Gothenburg, Sweden.

Sources of Funding

This work was funded by the Swedish state under the ALF agreement (grant No. 236611), the Swedish Heart-Lung Foundation (grant Nos. 20090724 and 20180644), and the Swedish Research Council (2018-02527, VRREG 2019-00193).

Disclosures

None.

Supplemental Material

Figure S1

Tables S1 and S2

REFERENCES

1. Van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, Roos-Hesselin JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011;58:2241–2247. doi: 10.1016/j.jacc.2011.08.025
2. Moons P, Bovijn L, Budts W, Belmans A, Gewillig M. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. *Circulation.* 2010;122:2264–2272. doi: 10.1161/CIRCULATIONAHA.110.946343
3. Mandalenakis Z, Rosengren A, Skoglund K, Lappas G, Eriksson P, Dellborg M. Survivorship in children and young adults with congenital heart disease in Sweden. *JAMA Intern Med.* 2017;177:224–230. doi: 10.1001/jamainternmed.2016.7765

4. Mandalenakis Z, Giang KW, Eriksson P, Liden H, Synnergren M, Wåhlander H, Fedchenko M, Rosengren A, Dellborg M. Survival in children with congenital heart disease: have we reached a peak at 97%? *J Am Heart Assoc*. 2020;9:e017704. doi: 10.1161/JAHA.120.017704
5. Fedchenko M, Mandalenakis Z, Giang KW, Rosengren A, Eriksson P, Dellborg M. Long-term outcomes after myocardial infarction in middle-aged and older patients with congenital heart disease – a nationwide study. *Eur Heart J*. 2021;42:2577–2586. doi: 10.1093/eurheartj/ehaa874
6. Björk A, Mandalenakis Z, Giang KW, Rosengren A, Eriksson P, Dellborg M. Incidence of type 1 diabetes mellitus and effect on mortality in young patients with congenital heart defect - a nationwide cohort study. *Int J Cardiol*. 2020;310:58–63.
7. Mandalenakis Z, Karazisi C, Skoglund K, Rosengren A, Lappas G, Eriksson P, Dellborg M. Risk of cancer among children and young adults with congenital heart disease compared with healthy controls. *JAMA Netw Open*. 2019;2:e196762. doi: 10.1001/jamanetworkopen.2019.6762
8. Bergh N, Skoglund K, Fedchenko M, Bollano E, Eriksson P, Dellborg M, Giang KW, Mandalenakis Z. Risk of heart failure in congenital heart disease: a nationwide register-based cohort study [published online December 19, 2022]. *Circulation*. doi: 10.1161/CIRCULATIONAHA.122.061546
9. Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Gilljam T, Hansson PO, Skoglund K, Fedchenko M, Dellborg M. Atrial fibrillation burden in young patients with congenital heart disease. *Circulation*. 2018;137:928–937. doi: 10.1161/CIRCULATIONAHA.117.029590
10. Jain PN, Salciccioli KB, Guffey D, Byun J, Cotts TB, Ermis P, Gaies M, Ghanayem N, Kim F, Lasa J, et al. Risk factors for perioperative morbidity in adults undergoing cardiac surgery at children's hospitals. *Ann Thorac Surg*. 2022;113:2062–2070. doi: 10.1016/j.athoracsur.2021.04.002
11. Perinpanayagam M, Larsen SH, Emmertsen K, Moller MB, Hjortdal VE. Nineteen years of adult congenital heart surgery in a single center. *World J Pediatr Congenit Heart Surg*. 2017;8:182–188. doi: 10.1177/2150135116682454
12. Tutarel O, Kempny A, Alonso-Gonzalez R, Jabbour R, Li W, Uebing A, Dimopoulos K, Swan L, Gatzoulis MA, Diller GP. Congenital heart disease beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality. *Eur Heart J*. 2014;35:725–732. doi: 10.1093/eurheartj/eht257
13. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A; National Birth Defects Prevention Study. Seeking causes: classifying and evaluating congenital heart defects in etiologic studies. *Birth Defects Res A Clin Mol Teratol*. 2007;79:714–727. doi: 10.1002/bdra.20403
14. Liu S, Joseph KS, Luo W, Leon JA, Lisonkova S, Van den Hof M, Evans J, Lim K, Little J, Sauve R, et al; Canadian Perinatal Surveillance System (Public Health Agency of Canada). Effect of folic acid food fortification in Canada on congenital heart disease subtypes. *Circulation*. 2016;134:647–655. doi: 10.1161/CIRCULATIONAHA.116.022126
15. Klassifikation av Operationer. Sjätte upplagan. 1993. Accessed December 27, 2022. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/klassifikationer-och-koder/klassifikation-av-operationer-sjatte-upplagan.pdf
16. Klassifikation av Kirurgiska Åtgärder 1997. Updated November 2004. Accessed December 27, 2022. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/dokument-webb/klassifikationer-och-koder/klassifikation-av-kirurgiska-atgarder-kumulativ-andringslista-1997-2004-forsta-upplagan.pdf
17. Yu C, Moore BM, Kotchetkova I, Cordina RL, Celermajer DS. Causes of death in a contemporary adult congenital heart disease cohort. *Heart*. 2018;104:1678–1682. doi: 10.1136/heartjnl-2017-312777
18. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, Babu-Narayan S, Wort SJ, Dimopoulos K, Gatzoulis MA. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. *Circulation*. 2015;132:2118–2125. doi: 10.1161/CIRCULATIONAHA.115.017202
19. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, Vliegen HW, Grobbee DE, Mulder BJ. Mortality in adult congenital heart disease. *Eur Heart J*. 2010;31:1220–1229. doi: 10.1093/eurheartj/ehq032
20. Videbæk J, Laursen HB, Olsen M, Høfsten DE, Johnsen SP. Long-term nationwide follow-up study of simple congenital heart disease diagnosed in otherwise healthy children. *Circulation*. 2016;133:474–483. doi: 10.1161/CIRCULATIONAHA.115.017226
21. Elliott RB, Starling MB, Neutze JM. Medical manipulation of the ductus arteriosus. *Lancet*. 1975;1:140–142. doi: 10.1016/s0140-6736(75)91432-4
22. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax*. 1971;26:240–248. doi: 10.1136/thx.26.3.240
23. Mustard WT, Keith JD, Trusler GA, Fowler R, Kidd L. The surgical management of transposition of the great vessels. *J Thorac Cardiovasc Surg*. 1964;48:953–958.
24. Senning A. Surgical treatment of transposition of the great vessels. *Mal Cardiovasc*. 1965;6:421–433.
25. Jatene AD, Fontes VF, Paulista PP, de Souza LC, Neger F, Galantier M, Souza JE. Successful anatomic correction of transposition of the great vessels. A preliminary report. *Arq Bras Cardiol*. 1975;28:461–464.
26. Norwood WI, Lang P, Casteneda AR, Campbell DN. Experience with operations for hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg*. 1981;82:511–519.
27. Mylotte D, Pilote L, Ionescu-Ittu R, Abrahamowicz M, Khairy P, Therrien J, Mackie AS, Marelli A. Specialized adult congenital heart disease care: the impact of policy on mortality. *Circulation*. 2014;129:1804–1812. doi: 10.1161/CIRCULATIONAHA.113.005817