ORIGINAL RESEARCH

Survival in Children With Congenital Heart Disease: Have We Reached a Peak at 97%?

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BACKGROUND: Despite advances in pediatric health care over recent decades, it is not clear whether survival in children with congenital heart disease (CHD) is still increasing.

METHODS AND RESULTS: We identified all patients with CHD using nationwide Swedish health registries for 1980 to 2017. We examined the survival trends in children with CHD; we investigated the mortality risk in patients with CHD compared with matched controls without CHD from the general population using Cox proportional regression models and Kaplan–Meier survival analysis. Among 64,396 patients with CHD and 639,012 matched controls without CHD, 3845 (6.0%) and 2235 (0.3%) died, respectively. The mean study follow-up (SD) was 11.4 (6.3) years in patients with CHD. The mortality risk was 17.7 (95% CI, 16.8–18.6) times higher in children with CHD compared with controls. The highest mortality risk was found during the first 4 years of life in patients with CHD (hazard ratio [HR], 19.6; 95% CI, 18.5–20.7). When stratified by lesion group, patients with non-conotruncal defects had the highest risk (HR, 97.2; 95% CI, 80.4–117.4). Survival increased substantially according to birth decades, but with no improvement after the turn of the century where survivorship reached 97% in children with CHD born in 2010 to 2017.

CONCLUSIONS: Survival in children with CHD has increased substantially since the 1980s; however, no significant improvement has been observed this century. Currently, >97% of children with CHD can be expected to reach adulthood highlighting the need of life-time management.

Key Words: congenital heart disease ■ nationwide ■ pediatric ■ registry study ■ survivorship

Congenital heart disease (CHD) is the most common major congenital malformation, having a prevalence of ≈9 per 1000 live births.1,2 Thanks to the development of pediatric health care over the past 70 years, survival among patients with CHD has effectively increased: >90% of such children born in the early 1990s reached adulthood.3–5 The improvement has been based on developments in diagnostic techniques, catheter interventions,6 and several surgical innovations, such as the following: surgical treatment of aortic coarctation7; repair of atrioventricular septal defects8; Mustard and Senning atrial corrections9,10; Rastelli procedure11; the arterial switch12; and the creation of single-ventricle Fontan circulation.13 Despite this improvement, the mortality during the first 4 years of life among patients with CHD remains comparatively high3,14–17; the need for further improvement in pediatric care persists.

Advances in pediatric cardiovascular surgery and cardiac interventional catheterization since the new
CLINICAL PERSPECTIVE

What Is New?
- We report for the first time in a large, national cohort study the survival in children with congenital heart disease born until the late 2010s.
- The overall mortality risk was 18 times higher in children with congenital heart disease compared with matched controls without congenital heart disease during a period of almost 40 years follow-up.
- Survival increased substantially according to birth decades, but no further overall improvement was noticed after the turn of the century.

What Are the Clinical Implications?
- Children with the most complex congenital malformations, such as non-conotruncal defects, had the highest risk of mortality and could be considered a risk group.
- The mortality was still high during the first 4 years of life in children with congenital heart disease which indicates that continuous monitoring and early intervention may be beneficial.
- Over 97% of children with congenital heart disease expected to reach adulthood and the need of lifetime management is mandatory.

CENTURY HAS SHOWN IMPROVED OUTCOMES IN SELECTED GROUPS OF PATIENTS WITH CHD.\textsuperscript{18–23} IN ADDITION, THE ANTE NATAL DIAGNOSIS OF CONGENITAL HEART MALFORMATIONS HAS BEEN INTRODUCED; CURRENTLY 37% OF ALL CHD IS DIAGNOSED PERNATALLY.\textsuperscript{24} HOWEVER, IT IS UNCLEAR WHETHER RECENT DEVELOPMENTS HAVE HAD AN EFFECT ON THE SURVIVAL OF PEDIATRIC PATIENTS WITH CHD OVER THE PAST DECADE. ACCORDINGLY, WE EXAMINED THE SURVIVAL TRENDS AND RISK OF MORTALITY IN CHILDREN WITH CONGENITAL HEART DISEASE COMPARED WITH CONTROLS WITHOUT CHD FROM THE GENERAL POPULATION WITHIN A NATIONWIDE, REGISTRY-BASED COHORT IN SWEDEN FROM 1980 TO 2017.

METHODS

Data Source and Study Population
Sweden is a northern European country of almost 10 million inhabitants with a through taxation publicly financed healthcare system. There are 70 acute care hospitals, all publicly financed and all but a handful also run by the regional authorities. Two complete university affiliated congenital heart care units exist where all congenital heart surgery, pediatric and adult, is performed. We linked data from Swedish health registers to identify patients who were born from January 1, 1980 to December 31, 2017 and who were recorded at any time with a diagnosis of CHD with at least 1 of the following registers: National Hospital Inpatient (complete since 1987, but with coverage of all hospitals performing thoracic surgery since 1970); National Hospital Outpatient (complete since 2001); and National Cause of Death Registers in Sweden (complete since 1968). All diagnoses were coded according to the International Statistical Classification of Diseases, Eighth, Ninth, and Tenth Revisions (ICD-8, ICD-9, ICD-10). Follow-up and co morbidity data were collected until December 31, 2017 or death. Each patient with CHD was matched by birth year and sex with 10 control individuals without diagnosis of CHD from the Total Population Register in Sweden.\textsuperscript{26} We used hierarchical CHD categorization to classify patients with CHD into different groups according to CHD lesions. The study design has been described previously.\textsuperscript{3,26,27} The study was conducted according to the ethical guidelines of the Declaration of Helsinki and it was approved by the Gothenburg Regional Research Ethics Board (Gpg 912-16, T 616-18). All national registration numbers were replaced with a unique code for every individual in the final data set by the Swedish National Board of Health and Welfare and under collaboration with the Statistics Sweden. The requirement for informed consent was waived. The data, methods used in the analysis, and study materials used to conduct the present study will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Definitions
We defined patients with CHD as having at least 1 hospital discharge, an outpatient visit, or a death certificate with a registered ICD-8, ICD-9, and ICD-10 diagnosis of CHD (Table S1). To categorize CHD into different lesion groups according to severity, we used the hierarchical classification initially suggested by Botto et al and subsequently used in observational studies.\textsuperscript{27–30} (Table S2). Lesion group 1 was defined as patients with conotruncal defects (such as common arterial trunk, transposition of the great vessels, double-outlet right ventricle, double-outlet left ventricle, discordant atrioventricular connection, tetralogy of Fallot, and aortopulmonary septal defect). Lesion group 2 was defined as patients with non-conotruncal defects (such as endocardial cushion defects, common ventricle, and hypoplastic left heart syndrome). We defined lesion group 3 as patients with coarctation of the aorta. Lesion group 4 was defined as patients with ventricular septal defect. Lesion group 5 was defined as patients with atrial septal defect. Lesion group 6 included all other heart and circulatory system anomalies and all other CHD diagnoses not included in lesion groups 1 to 5.
Cardiac intervention was defined as patients with CHD having undergone at least 1 cardiovascular surgery or cardiac interventional catheterization related to CHD, according to the classification of operations (Sixth edition, Swedish version) or following the classification of surgical procedures (1.9 edition, Swedish version).

Statistical Analysis
Baseline characteristics were reported as proportions and percentages of sex, birth period, and number of deaths for patients with CHD and controls separately. For continuous variables, mean and median with SD and interquartile range were reported. We used survival analysis techniques to compare patients with CHD and matched controls in terms of mortality outcomes. Incidence rate was estimated as the number of deaths divided by total follow-up time and reported as per 10,000 person-years. We estimated survival by means of the Kaplan–Meier estimator; we compared patients with CHD with controls (both overall and within groups) from birth until the age of 18 years. We compared the survival curves using non-parametric log-rank tests. We did not adjust for any confounders such as comorbidities because the follow-up of the study started at birth and there were no recorded comorbidities at that time. Patients with CHD and matched controls that died shortly after birth were accounted in the present study; however, those who died the same date as their date of birth, were given 1 day of follow-up.

Hazard ratios (HRs) and the associated 95% CIs were calculated by means of the Cox proportional hazards model. We used 2-sided P values and considered a P value of <0.05 as statistically significant. Statistical analyses were conducted with SAS software (version 9.4; SAS Institute, Cary, NC, USA) or R software (version 3.6.1; Free Software Foundation for Statistical Computing, Vienna, Austria).

RESULTS
We identified 64,396 patients with CHD and 639,012 matched controls; the characteristics of the study population appear in Table 1. The majority of the patients with CHD and matched controls were born in Sweden; 94.8% and 83.2% respectively. From birth and with a mean (SD) follow-up of 11.4 (6.3) years in patients with CHD and 12.2 (6.0) years in matched controls, 3845 (6.0%) and 2235 (0.3%) respectively, died. The characteristics were similar for male and females in the study population (Table S3).

Overall, the risk of mortality was 17.7 times higher for patients with CHD (95% CI, 16.8–18.6; P<0.001) than in matched controls (Table 2). All the lesion groups in patients with CHD had increased mortality risk compared with matched controls. The highest relative risk of mortality was found in patients with non-conotruncal defects (such as endocardial cushion defects, common ventricle, and hypoplastic left heart syndrome) with an HR of 97.2 (95% CI, 80.4–117.4; P<0.001).

Overall survival probability in patients with CHD and matched controls appear in Figure S1. The survival curve in patients with CHD diverged within from the survival curve for controls, mostly within the first 4 years of life when mortality was higher for patients with CHD. However, the survival curves continued to separate more modestly until the age of 18 years (P<0.001).

The survival trends for patients with CHD and matched controls according to birth period are shown in Figure 1. Survival increased markedly in patients with CHD that were born in the 1980s, 1990s, and 2000s. However, we did not observe any change in survival in patients with CHD born in the 2010s compared with such patients born in the 2000s: there was practically identical survival (almost 97%) over the first years in the 2 birth cohorts. We did not find any significant difference in the survival trends between male and female patients with CHD (Figure S2).

Table 1. Study Population Characteristics

| Characteristics          | Patients With Congenital Heart Disease (n=64 396) | Controls (n=639 012) |
|--------------------------|--------------------------------------------------|----------------------|
| Male, n (%)              | 32 334 (50.2)                                   | 323 340 (50.6)       |
| Mean follow-up, y (SD)   | 11.4 (6.3)                                      | 12.2 (6.0)           |
| Median follow-up, y (IQR)| 12.5 (5.6–18.0)                                 | 13.7 (6.8–18.0)      |
| Born in Sweden, n (%)    | 61 054 (94.8)                                   | 531 866 (83.2)       |
| Deaths, n (%)            | 3845 (6.0)                                      | 2235 (0.3)           |
| Birth period             |                                                  |                      |
| Born 1980–1989, n (%)    | 9814 (15.2)                                     | 98 140 (15.4)        |
| Born 1990–1999, n (%)    | 13 997 (21.7)                                   | 139 970 (21.9)       |
| Born 2000–2009, n (%)    | 21 459 (33.3)                                   | 212 177 (33.2)       |
| Born 2010–2017, n (%)    | 19 126 (29.7)                                   | 188 725 (29.5)       |

IQR indicates interquartile range.
The risk of mortality according to birth period in patients with CHD relative to that of controls appears in Table 3. In all birth periods, patients with CHD had higher risk of mortality than matched controls; that difference decreased over the birth period. Patients with CHD born in the 1980s had the highest relative mortality: HR, 29.0; 95% CI, 26.2 to 31.9; \( P < 0.001 \). However, the risk was similar in patients with CHD born during the 2000s and 2010s: HR, 10.7 (95% CI, 9.6–11.9; \( P < 0.001 \)) and HR, 11.4 (95% CI, 10.0–13.0; \( P < 0.001 \)) respectively.

Altogether, 23.2% (n=14,971) of patients with CHD underwent a cardiac intervention related to their CHD between birth and the age of 18 years. Survival increased in patients with CHD with and without cardiac intervention until the 2000s (Figure 2). However, in the past decade, no further improvement in survival appeared in patients with CHD who had undergone at least 1 cardiac intervention: the mortality was up to 4.5% at the age of 7 years.

Survival showed a significant improvement in patients with CHD who were born between the 1980s and 2010s,
particularly in those with complex congenital malformations (Figure S3). Among complex lesion groups, survival improved from about 70% and 50%, respectively, at the age of 18 years to >90% in lesion group 1 and >80% in lesion group 2; the latter included highly complex conditions such as hypoplastic left heart syndrome. However, survival was stable and similar in all lesion groups after the millennium: no further improvement was evident.

The risk of mortality in patients with CHD, compared with controls, declined dramatically with increasing age and by birth period (Table S4). The highest mortality was found during the first 4 years of life in patients with CHD born in the 1980s (HR, 34.3, 95% CI, 30.7–38.3, \(P<0.001\)); however, the HRs decreased by two thirds in the most recent birth period cohort (2010–2017).

A sensitivity analysis was performed after excluding individuals that were not born in Sweden and the overall risk of mortality in patients with CHD born in Sweden was 15.7 times higher (95% CI, 14.9–16.5) compared with matched controls.

| Table 3. Risk of All-Cause Mortality in Patients With Congenital Heart Disease Compared With Matched Controls According to Birth Period and Sex |
|-----------------|-----------------|-----------------|-----------------|
| Birth Period    | Deaths in Patients With CHD, No./All Patients With CHD, n (%) | Deaths in Controls, No./All Controls, n (%) | HR (95%, CI)* |
| Born 1980–1989  | 1452/9814 (14.80) | 542/9814 (0.55) | 29.0 (26.2–32.0) |
| Born 1990–1999  | 1248/13 997 (8.92) | 647/139 970 (0.46) | 20.2 (18.4–22.2) |
| Born 2000–2009  | 688/21 459 (3.21) | 646/212 177 (0.30) | 10.7 (9.6–11.9) |
| Born 2010–2017  | 457/19 126 (2.39) | 400/188 725 (0.22) | 11.4 (10.0–13.0) |
| Sex             |                 |                 |                 |
| Male            | 2026/32 334 (6.27) | 1276/323 340 (0.39) | 16.4 (15.3–17.6) |
| Female          | 1819/32 062 (5.67) | 958/315 672 (0.30) | 19.3 (17.9–20.9) |

CHD indicates congenital heart disease; and HR, hazard ratio.
*All \(P<0.001\)

Figure 2. Kaplan–Meier survival curves of patients with congenital heart disease with or without a cardiac intervention according to birth period.
DISCUSSION

In Sweden, survival among pediatric patients with CHD has increased dramatically since the 1980s; currently, >97% can be expected to reach adulthood. However, no further improvement in survivorship was observed in children with CHD over the past decade. Although declining, mortality remains comparatively high in relative as well as absolute terms with the most complex conditions and during the first years of life: the mortality in patients with complex CHD lesions born 1980s and 2000s decreased from almost 50% to <20%, respectively, at the age of 18 years.

We observed an increase in the number of patients with CHD over time which is explained by population growth. This may in part be explained by increased diagnosis of less severe CHD cases. However, also among complex CHD we observed no further improvement in progesis in recent years (Figure S3). This is also reflected in the comparatively stable level of interventions.

Numerous studies have reported outcomes with particular diagnostic groups for post-surgical results.22,23,33–35 However, our study is the first nationwide report to cover recent trends and examine an unselected, broad, representative population of children with CHD (including matched controls), including patients where no cardiac interventions took place.

The use of antenatal screening for CHD diagnosis have increased over the past decade36,37; though feasible, it is not clear whether the use of antenatal CHD diagnosis leads to improved care or survival. There are several reports indicating that in some countries including Sweden, increasing prenatal diagnosis of highly complex malformations such as hypoplastic left heart syndrome will lead to more frequent terminations of pregnancy and fewer live born children with this condition.38,39 Prenatal screening currently detects almost 40% of fetuses with major CHD in Sweden. However, that trend does not appear to translate into increased survival—at least not on a national level. Improved detection rates, particularly with major CHD, lead to increased rates of pregnancy termination, with a subsequent decrease in the incidence of the most severe complex CHD.38,40,41

Also in Sweden, data indicate that increased antenatal CHD diagnosis leads to more pregnancy terminations, with little—if any—effect on the overall survivorship in children born with CHD.39 Live births with the most complex CHD may have become less frequent; however, other moderately complex congenital heart conditions, related to increasing maternal age and obesity, may increase.42 In the present study, we did not observe any further improvement in survivorship after the new millennium in children with CHD in general—particularly in those with complex CHD. Whether a higher rate of antenatal screening and detection can be translated into a better survival, on a national level, is still unclear. Variations in the rate of antenatal screening have not been tied to variations in outcome for children with CHD and improvements in general in outcome because of antenatal screening remains unproven.43,44

Mortality has declined for patients with CHD who underwent cardiac intervention (surgical or catheter intervention) from the early (1980–1989) to the latest era (2010–2017); despite the introduction and expansion of complicated and high-risk procedures, such as Fontan palliation for univentricular heart defects and Norwood surgery for hypoplastic left heart syndrome during this period. This strongly implies that improved therapy was an important explanation for the improved survival seen in the entire population. However, we have also observed that mortality among children who did not undergo a cardiac intervention decreased over time. This may reflect improved selection of patients with CHD for cardiovascular surgery or catheter interventions; but it may also reflect improved diagnostic techniques, especially on echocardiography, for example an increased rate of diagnosis of less complex congenital heart malformations such as mild shunts.1

During the last study period cohort (2010–2017), we observed a worse outcome among children with CHD who underwent a cardiac intervention, different from results from earlier birth periods. This most likely reflects an increase in detection of mild conditions of CHD where no intervention is needed, and the condition has little if any impact on the health of the child. It may also reflect a further improvement in interventional techniques with CHD children with extremely high risk undergoing reparative or palliative procedures. This is further supported by results from patients with the most complex CHD groups, such as the lesion group 1 and lesion group 2, doing better until the turn of the millennium, after which no further improvement is observed. Sweden’s 6 cardiothoracic surgery clinics have registered all hospitalizations and interventions since 1970. Swedish hospital records have been mandatory since 1987, based on each individual in the country having a unique 10-digit personal identity number, which includes their sex and date of birth. Administrative health databases have become a powerful resource for studying several medical conditions; they are valuable owing to the large sample sizes and possibility of long observation periods. The strength of the present report is that it is a nationwide study based on the Swedish healthcare system, which is mainly government funded, universal, and offers free access to all citizens. The current data are representative for Sweden but may be less applicable to other countries with different access to and organization and financing of the healthcare system. Our data may be considered
as support for regionalization and centralization of the care of the complex congenital heart conditions. By using national registers, we were able to achieve almost complete follow-up, with limited risk because of emigration as a possible cause of the loss to follow-up.

One of the study’s limitations is that administrative data from Swedish outpatient clinics before 2001 and data for primary care were unavailable. Thus, they were not included in this study: that could have led to an underestimation of the mortality of patients with less severe lesions that were not detected at birth or detected during follow-up at outpatient clinics or by primary care physicians. Another limitation is that there have been no published formal validations of CHD diagnostic codes in the Swedish registry system; however, several cardiovascular and other medical conditions or interventions have been shown to have high validity. The limited number of variables available for analysis may also limit the assertion of both cases and causes of death. One should also acknowledge that our results may be less valid in a different healthcare setting with less centralization and different access to care, different rate of antenatal diagnosis as well as differences in public opinion and regulations on termination of pregnancy. The classification and grouping of CHD into larger groups such as the 6 lesion groups used in the present study will by definition group together conditions that may have had different evolution over the last decades. Our data may be an example of Simpson paradox i.e., that while prognosis improves for some of the CHD conditions included in e.g., lesion group 1, other conditions in the same group may have changed in a different direction. Dividing, congenital cardiac malformations into smaller or more distinct groups may provide further insights but at the cost of statistical power.

The significant improvements made in cardiovascular care since the 1970s and 1980s have resulted in a dramatic improvement in survival for children with CHD. Further advances in the past 2 decades have not yet resulted in increased survival for patients with CHD in general nor for specific lesion groups of patients. Clearly, there is still room for improvement in survival and development of care in patients with the most complex lesion groups, where mortality is still high and where 10% to 20% of those born die before becoming adults. Our data may be interpreted as a sign of optimized surgical procedures, interventional techniques, and diagnostic improvements but where no further improvement, given today’s technology and knowledge, may be difficult to obtain. Our data may reflect the, as yet, unfulfilled hope for improvement in a case with antenatal diagnostics. Our finding may also indicate a place for improved surgical supporting techniques, such as better ventricular assist devices, improvements in myocardial and cerebral protection to push the dramatic improvement in congenital heart care over the last decades of the 19th century, even further.

Furthermore, our results point to the obvious need for more cardiologists, nurses, physiotherapist to develop skills and knowledge of how to care for adults with CHD, since they are increasing in number and will continue to do so in the future.

In summary, our study shows that survival among patients with CHD has improved dramatically in the past 40 years. Over the past decade, no further improvement has been observed, and survivalship in children with CHD has been at about 97% since the beginning of this century. Despite these trends, the most complex conditions are still characterized by a high early mortality. For patients with less complex conditions, focusing on lifetime management and preventing acquired diseases may be the key to future improvement.

ARTICLE INFORMATION
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Disclosures
None.

Table 1: Supplementary Material

Table S1–S4

Figures S1–S3

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SUPPLEMENTAL MATERIAL
| Diagnosis                                      | ICD 8  | ICD 9  | ICD 10 |
|-----------------------------------------------|--------|--------|--------|
| Common arterial trunk                         | 746.09 | 745A   | Q200   |
| Transposition of the great vessels            | 746.19 | 745B   | Q203   |
| Tetralogy of Fallot                           | 746.29 | 745C   | Q213   |
| Ventricular septal defect                     | 746.39 | 745E   | Q210   |
| Atrial septal defect or patent foramen ovale  | 746.42 | 745F   | Q211   |
| Congenital tricuspid stenosis or atresia      | 746.54 | 746B   | Q224   |
| Ebstein’s anomaly                             | 746.54 | 746C   | Q225   |
| Congenital stenosis of the aortic valve       | 746.73 | 746D   | Q230   |
| Congenital insufficiency of the aortic valve  | 746.79 | 746E   | Q231   |
| Congenital mitral stenosis                    | 746.59 | 746F   | Q232   |
| Congenital mitral insufficiency               | 746.59 | 746G   | Q233   |
| Hypoplastic left heart syndrome                | 746.74 | 746H   | Q234   |
| Congenital subaortic stenosis                 | 746.79 | 746W   | Q244   |
| Cor triatriatum                               | 746.89 | 746W   | Q242   |
| Infundibular pulmonic stenosis                | 746.63 | 746W   | Q243   |
| Congenital coronary vessel anomalies          | 747.69 | 746W   | Q245   |
| Congenital heart block                        | 746.89 | 746W   | Q246   |
| Coarctation of the aorta                     | 747.19 | 747B   | Q251   |
| Interruption of the aortic arch               | 747.19 | 747B   | Q252   |
| Other unspecified congenital malformations of the aorta | 747.29 | 747C   | Q254   |
| Congenital malformations of the pulmonary artery | 747.34 | 747D   | Q255   |
| Congenital malformations of the great veins   | 747.49 | 747E   | Q260   |
|                                               | 747.59 |        | Q261   |
| Cor biloculare                                | 746.89 | 745H   | Q208   |
| Double outlet right ventricle                 | 746.19 | 745B   | Q201   |
| Double outlet left ventricle                  | 746.19 | 745B   | Q202   |
| Double inlet ventricle                        | 746.37 | 745D   | Q204   |
| Discordant atrioventricular connection        | 746.19 | 745B   | Q205   |
| Isomerism of atrial appendages                | 746.89 | 745W   | Q206   |
| Condition                                              | Code  | Code  | Code  |
|--------------------------------------------------------|-------|-------|-------|
| Unspecified congenital malformations of the cardiac chambers | 746.89 | 746X | Q208  
|                                                        |       |      | Q209  |
| Atrioventricular septal defect                         | 746.47 | 745G | Q212  |
|                                                        | 746.46 |      |       |
|                                                        | 746.43 |      |       |
| Aortopulmonary septum defect                           | 746.09 | 745A | Q214  |
| Other congenital malformations of the cardiac septum   | 746.89 | 745W | Q218  |
| Unspecified congenital malformations of the cardiac septum | 746.99 | 745X | Q219  |
| Pulmonary valve atresia                                | 746.64 | 746A | Q220  |
| Congenital stenosis of the pulmonary valve             | 746.63 | 746A | Q221  |
| Congenital pulmonary valve insufficiency               | 746.69 | 746A | Q222  |
| Other congenital malformations of the pulmonary valve  | 746.69 | 746A | Q223  |
| Hypoplastic right heart syndrome                        | 746.69 | 746B | Q226  |
| Other congenital malformations of the tricuspid valve  | 746.54 | 746B | Q228  
|                                                        |       |      | Q229  |
| Other congenital malformations of aortic and mitral valves | 746.89 | 746W | Q238  
|                                                        |       |      | Q239  |
| Other specified congenital malformations of the heart   | 746.89 | 746W | Q248  |
| Unspecified congenital malformations of the heart       | 746.99 | 746X | Q249  |
| Patent ductus arteriosus                               | 747.09 | 747A | Q250  |
Table S2. Hierarchic classification of congenital heart disease according to the International Statistical Classification of Diseases and Related Health Problems.

| Categorical hierarchy group | CHD diagnosis | ICD-8 | ICD-9 | ICD-10 |
|-----------------------------|---------------|-------|-------|--------|
| **Lesion group 1. Conotruncal defects** | Common arterial trunk | 746.09 | 745A | Q200 |
| | Aortopulmonary septum defect | 746.09 | 745A | Q214 |
| | Double outlet right ventricle | 746.19 | 745B | Q201 |
| | Double outlet left ventricle | 746.19 | 745B | Q202 |
| | Transposition of great vessels | 746.19 | 745B | Q203 |
| | Discordant atrioventricular connection (ccTGA) | 746.19 | 745B | Q205 |
| | Tetralogy of Fallot | 746.29 | 745C | Q213 |
| **Lesion group 2. Severe non-conotruncal defects** | Endocardial cushion defects | 746.43, 746.46, 746.47 | 745G | Q212 |
| | Common ventricle | 746.37 | 745D | Q204 |
| | Hypoplastic left heart syndrome | 746.74 | 746H | Q234 |
| **Lesion group 3. Coartation of the aorta** | Coarctation of the aorta | 747.19 | 747B | Q251 |
| **Lesion group 4. Ventricular septal defect** | Ventricular septal defect | 746.39 | 745E | Q210 |
| **Lesion group 5. Atrial septal defect** | Atrial septal defect | 746.42 | 745F | Q211 |
| **Lesion group 6. Other heart and circulatory system anomalies** | All other congenital heart disease diagnoses that are not included in the above five lesion groups | | | |

ccTGA, congenitally corrected transposition of the great arteries
Table S3. Characteristics of the study population according to sex.

| Characteristics                  | Patients with congenital heart disease | Controls |
|----------------------------------|---------------------------------------|----------|
|                                  | Men                                   | Women    | Men               | Women                   |
| no. (%)                          | 32,334 (50.2)                         | 32,062 (49.8) | 323,340 (50.6) | 315,672 (49.4)          |
| Mean follow-up, years (SD)       | 11.4 (6.4)                            | 11.3 (6.3) | 12.2 (6.0)       | 12.1 (5.9)              |
| Median follow-up, years (IQR)    | 12.5 (5.6–18.0)                       | 12.5 (5.7–18.0) | 13.8 (6.8–18.0) | 13.6 (6.8–18.0)         |
| Born in Sweden, no. (%)          | 30,734 (95.1)                         | 30,320 (94.6) | 268,221 (83.0) | 263,645 (83.5)          |

| Birth Period                     |                                        |          |                  |                        |
|----------------------------------|---------------------------------------|----------|------------------|------------------------|
| Born 1980–1989, no. (%)          | 5,001 (15.5)                          | 4,813 (15.0) | 50,010 (15.5) | 48,130 (15.2)          |
| Born 1990–1999, no. (%)          | 7,266 (22.5)                          | 6,731 (21.0) | 72,660 (22.5) | 67,310 (21.3)          |
| Born 2000–2009, no. (%)          | 10,610 (32.8)                         | 10,855 (33.9) | 106,040 (32.8) | 106,137 (33.6)         |
| Born 2010–2017, no. (%)          | 9,463 (29.3)                          | 9,663 (30.1) | 94,630 (29.3) | 94,095 (29.8)          |

SD, standard deviation; IQR, interquartile range
Table S4. Risk of all-cause mortality in patients with congenital heart disease compared to matched controls according to birth period and age.

| Birth period and age | No. of deaths in CHD patients / Controls | Incidence rate of death in CHD patients / Controls * | HR (95%, CI) † |
|----------------------|------------------------------------------|-----------------------------------------------------|----------------|
| Born 1980–1989       |                                          |                                                     |                |
| 0 – 4 year           | 1,314 / 409                              | 303.36 / 8.38                                       | 34.3 (30.7–38.3) |
| 5 – 9 year           | 66 / 40                                  | 15.59 / 0.82                                        | 19.04 (12.9–28.2) |
| 10 – 14 year         | 42 / 35                                  | 9.99 / 0.71                                         | 13.9 (8.9–21.8) |
| 15 – 18 year         | 30 / 58                                  | 11.94 / 1.95                                        | 6.1 (3.9–9.5) |
| Born 1990–1999       |                                          |                                                     |                |
| 0 – 4 year           | 1,118 / 489                              | 172.20 / 7.02                                       | 23.7 (21.4–26.4) |
| 5 – 9 year           | 48 / 54                                  | 7.62 / 0.76                                         | 10.0 (6.8–14.8) |
| 10 – 14 year         | 47 / 43                                  | 7.34 / 0.63                                         | 11.6 (7.7–17.5) |
| 15 – 18 year         | 35 / 61                                  | 9.14 / 1.46                                         | 6.3 (4.1–9.5) |
| Born 2000–2009       |                                          |                                                     |                |
| 0 – 4 year           | 627 / 541                                | 60.05 / 5.12                                        | 11.6 (10.3–13.0) |
| 5 – 9 year           | 33 / 56                                  | 3.29 / 0.55                                         | 6.0 (3.9–9.2) |
| 10 – 14 year         | 26 / 35                                  | 4.79 / 0.63                                         | 7.6 (4.6–12.7) |
| 15 – 18 year         | 2 / 14                                   | 2.61 / 1.74                                         | NA             |
| Born 2010–2017       |                                          |                                                     |                |
| 0 – 4 year           | 450 / 389                                | 66.18 / 5.69                                        | 11.5 (10.1–13.2) |
| 5 – 9 year           | 7 / 11                                   | 5.77 / 0.90                                         | 6.4 (2.5–16.5) |
| 10 – 14 year         | - / -                                    | - / -                                               | NA             |
| 15 – 18 year         | - / -                                    | - / -                                               | NA             |

CHD, congenital heart disease; HR, hazard ratio; CI, confidence interval
*Incidence rate per 10,000 person-years
†All P <0.001
Figure S1. Kaplan-Meier survival curves of the study population.

![Kaplan-Meier survival curves](image-url)
Figure S2. Kaplan-Meier survival curves of the patients with congenital heart disease and matched controls according birth period and sex.
Figure S3. Kaplan-Meier survival curves of the patients with congenital heart disease and matched controls according to lesion group and birth period.

Lesion group 1 was defined as patients with conotruncal defects (such as common arterial trunk, transposition of the great vessels, double-outlet right ventricle, double-outlet left ventricle, discordant atrioventricular connection, tetralogy of Fallot, and aortopulmonary septal defect). Lesion group 2 was defined as patients with non-conotruncal defects (such as endocardial cushion defects, common ventricle, and hypoplastic left heart syndrome). Lesion group 3 was defined as patients with coarctation of the aorta. Lesion group 4 was defined as patients with ventricular septal defect. Lesion group 5 was defined as patients with atrial septal defect. Lesion group 6 included all other heart and circulatory system anomalies and all other CHD diagnoses not included in lesion groups 1–5.