


ORIGINAL RESEARCH

Congenital Heart Disease and Risk of Suicide and Self-Harm: A Danish Nationwide Cohort Study

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BACKGROUND: In this nationwide study, we used the unique Danish registries to estimate the risk of suicide and deliberate self-harm in patients with congenital heart disease (CHD).

METHODS AND RESULTS: We identified all Danish citizens receiving a diagnosis of CHD between 1977 and 2007. As a reference cohort, we randomly selected 10 citizens for each patient, matched by sex and birth year. Using the Fine and Gray competing risk regression, we estimated the cumulative incidences of suicide and self-harm, and Cox proportional regression analysis was used to compare the risk of suicide and deliberate self-harm in patients with CHD with the reference cohort. We identified 14 433 patients with CHD. Mean follow-up was 21.3 years, with a maximum follow-up of 42 years. Since the time of diagnosis, 2659 patients had died, with a median age of death of 23 years. A total of 15 patients had died by suicide, compared with 232 suicides in the reference cohort. Patients with CHD had a low and similar risk of dying by suicide when compared with the reference cohort (cause-specific hazard ratio, 0.81; 95% CI, 0.48–1.37; and subhazard ratio, 0.68; 95% CI, 0.41–1.16). We identified 336 events of self-harm among patients with CHD, and 3484 events in the reference group. The overall risk of deliberate self-harm was not increased in patients with CHD when compared with the reference group (subhazard ratio, 0.95; 95% CI, 0.85–1.06).

CONCLUSIONS: This is the first study to estimate the risk of suicide and deliberate self-harm in patients with CHD. We found that patients with CHD do not have an increased risk of suicide or deliberate self-harm when compared with a large reference cohort.

Key Words: congenital ■ congenital cardiac defect ■ epidemiological characteristics

Early survival in patients with congenital heart disease (CHD) has increased to nearly 100%, and most patients live well into adulthood.^{1–3} The population of adults with CHD is now outnumbering the pediatric CHD population in developed countries, and, consequently, attention has advanced to other and more long-term outcomes.⁴ This includes the impact on mental health, as reports have shown an increased risk of neurodevelopmental impairment and behavioral issues in the CHD population.^{5–7} Indeed, a nationwide Danish study of all patients with CHD established that the overall risk of psychiatric

disease was substantially increased in these patients.⁸ All mental disorders are associated with increased risk of suicide and self-harm, providing a theoretical linkage between CHD and a potential increased risk of suicide.⁹ In addition, major physical health conditions are associated with increased risks of depression and suicide, including patients with chronic heart failure.^{10,11} The risks of suicide and self-harm have, nonetheless, never been investigated in the CHD population. In this study, we were able to use the unique Danish registers to estimate the risk of suicide and self-harm in a nationwide cohort of

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CLINICAL PERSPECTIVE

What Is New?

- This is the first study to estimate the risk of suicide and deliberate self-harm in patients with congenital heart disease (CHD).
- The entire Danish cohort of patients with CHD (n=14 433) was characterized using the unique Danish registries, and includes a long-term follow-up of up to 42 years.
- We found that the absolute risk of both suicide and deliberate self-harm in patients with CHD was low and comparable to the risk found in a large reference cohort.

What Are the Clinical Implications?

- Most physicians caring for pediatric and adult patients with CHD might have expected an increased risk of suicide and self-harm in these patients.
- We hope that our results will provide comfort for patients and parents, as well as assist physicians providing counseling for patients with CHD.

Non-standard Abbreviations and Acronyms

CHD	congenital heart disease
DNPR	Danish National Patient Registry
ICD-8	<i>International Classification of Diseases, Eighth Revision</i>
ICD-10	<i>International Classification of Diseases, Tenth Revision</i>

patients with CHD covering up to 42 years of follow-up.

METHODS

Anonymized data created for the study are available in a persistent repository.

Study Population

We used several medical registries in this nationwide descriptive cohort study. Registration and collection of data from all hospitals and outpatient clinics in Denmark is mandatory, with linkage of different registers made possible by the use of the unique personal identification number, the civil registration number, assigned to all Danish individuals at birth or immigration.¹² The Danish healthcare system is publicly financed, with equal accessibility for all registered

Danish residents. We used the DNPR (Danish National Patient Registry) to identify all Danish citizens receiving a diagnosis of CHD at any age between 1977 and 2007.¹³ The DNPR contains information on all hospital admissions in Denmark, dates of admission and discharge, surgical procedures, and discharge diagnoses coded according to the *International Classification of Diseases, Eighth Revision (ICD-8)*, or *International Classification of Diseases, Tenth Revision (ICD-10)*. To identify patients with CHD, we used the codes 746 to 747 from 1977 to 1994 (*ICD-8*), and codes Q20 to Q26 from 1994 to 2007 (*ICD-10*). We only included patients diagnosed at 1 of the 4 major university hospitals in Denmark to increase the validity of the diagnoses. The congenital lesions were grouped into simple, moderate, and complex lesions, according to the 2018 American Heart Association/American College of Cardiology guidelines.¹⁴

A random reference sample matched by sex and birth year with the included CHD patients was drawn using the Danish Civil Registration System, ensuring a ratio of 10 citizens per patient. To eliminate the risk of immortal time bias, diagnosis date of the congenital lesions was used as the date of matching between patients with CHD and their references.

Assessment of Suicide and Self-Harm

We linked the study population with the Danish Register of Causes of Death using the civil registration number, to obtain any information of suicide (using the codes 950–959 from the *ICD-8*, and codes X60–X84 from the *ICD-10*) and date of suicide, if any.¹⁵ This register contains information on all deaths in Denmark from 1970 through 2018. The legal regulation of death certification in Denmark states that any case of sudden and unexpected death, thereby including suicide, must be reported to the police. In these cases, the death certificate will only be completed after a medicolegal examination.

We also linked the study population with the Danish Psychiatric Central Register to obtain information about deliberate self-harm.¹⁶ This register contains data on all admissions to Danish psychiatric inpatient facilities from 1969, whereas data on outpatient visits to psychiatric departments were included from 1995. We identified deliberate self-harm using different algorithms for different periods, as procedures have changed over time. From 1987 to 1993, deliberate self-harm was identified as individuals admitted with a *reason for contact code 4* in the DNPR. After 1994, deliberate self-harm was identified as individuals fulfilling at least 1 of the following 5 criteria in the DNPR or Danish Psychiatric Central Register: (1) reason for contact code 4, (2) any psychiatric diagnosis (*ICD-10* chapter F) and a comorbid diagnosis of poisoning with medication and biological

compounds (*ICD-10* codes T36 through T50) or non-medical compounds, excluding alcohol and poisoning from food (T52 through T60), (3) any psychiatric disorder (*ICD-10* chapter F) and comorbid diagnosis reflecting lesions on the forearm, wrist, or hand (*ICD-10* codes S51, S55, S59, S61, S65, or S69), (4) any contact with a hospital because of poisoning with weak or strong analgesics, hypnotics, sedatives, psychoactive drugs, antiepileptics, and antiparkinsonian drugs or carbon monoxide (*ICD-10* codes T39, T42, T43, and T58), and (5) any somatic or psychiatric diagnosis X60 through X84. This classification of deliberate self-harm has been described in previous studies.^{9,17,18}

Statistical Analysis

Continuous variables were reported as mean and SD. Comparisons of means were performed by unpaired *t* test. Categorical variables were summarized by percentages or frequencies. Comparisons of categorical baseline characteristics between patients and the reference cohort were performed by Fisher's exact test. We followed up patients with CHD from their first hospital contact, inpatient or outpatient, with CHD until suicide, death from other causes, or December 31, 2018 (whichever came first). Comparisons between patients with CHD and their matched references were performed by Cox regression with age as time scale. In each matching cluster, individuals entered the risk set at the age of diagnosis of the CHD patient. SEs were calculated taking matching clusters into account. The cause-specific hazard ratio is supplied with the subhazard ratio, with death by other causes being the competing risk, as suggested by Latouche et al.¹⁹ Through the matching and choice of time scale, the analyses are adjusted for sex, attained age, and birth year. We estimated the cumulative incidences of suicide and self-harm in patients with CHD and compared them with the reference cohort using the Fine and Gray competing risk regression.²⁰ To illustrate the time variations of incidents rates, smoothed cause-specific hazard estimates are presented for patients and references. Finally, we used Poisson regression to calculate the incidence rate ratio for self-harm in patients with CHD and the reference cohort. All analyses were performed using Stata 15 (StataCorp LP, TX). This study was approved by The Central Denmark Region Research Committee (1-16-02-184-19). The requirement for informed consent was waived given the nature of the study.

RESULTS

We identified 14 433 patients with CHD (mean age, 33 years; 50% women) diagnosed between 1977 and

2007 in Denmark. Baseline characteristics and types of congenital lesions are presented in Table 1. A total of 2659 patients had died, with a median age of death of 23 years. Mean follow-up was 21.3 years, with a maximum follow-up of 42 years. The reference cohort was composed of 143 606 individuals from the general population (mean age, 36 years; 50% women).

Risk of Suicide

A total of 15 patients (0.56% of all deaths; median age at suicide, 39 years) had died by suicide, compared with 232 suicides (2.7% of all deaths; median age at suicide, 39 years) in the reference cohort (Table 2). Patients with CHD had a low and similar risk of dying by suicide when compared with the reference cohort (hazard ratio, 0.81; 95% CI, 0.48–1.37; and subhazard ratio, 0.68; 95% CI, 0.41–1.16) (Table 3). The difference between hazard ratio and subhazard ratio is explained by the increased mortality among CHD patients. The cumulative incidence of suicide by time since the CHD diagnosis is shown in Figure 1, demonstrating no difference between the 2 groups. Interestingly, the smoothed cause-specific hazard estimates illustrate that the occurrence of suicide in patients with CHD starts later in life when compared with the reference cohort (Figure 2). Finally, the rates of suicide did not differ between patients with simple, moderate, or complex lesions.

Risk of Self-Harm

We identified 336 events of self-harm among patients with CHD, and 3484 events in the reference group. For patients with CHD, the overall risk of deliberate self-harm was not increased when compared with the reference group (hazard ratio, 1.06; 95% CI, 0.95–1.18; and subhazard ratio, 0.95; 95% CI, 0.85–1.06) (Table 3). The results did not differ when only including the incident event per individual. The cumulative incidence of self-harm was comparable between patients with CHD and the reference cohort, as displayed in Figure 3. The smoothed cause-specific hazard estimates of self-harm were also almost identical, and, interestingly, the incidence of self-harm peaked in the late teens and in middle-aged individuals (Figure 4). The prevalence of self-harm was higher in the patients with simple lesions (2.7%) when compared with patients with complex lesions (1.2%; *P*=0.002). Last, the incidence rate ratio showed that there was no difference between patients and references.

DISCUSSION

This is the first study to estimate the risk of suicide and deliberate self-harm in patients with CHD. The

Table 1. Characteristics of Patients

Characteristic	Congenital Heart Defects (n=14 433)
Age, mean (SD), y	33 (20)
Sex, women, %	50.1
Age at diagnosis, mean (SD), y	11.4 (18.2)
Follow-up, mean (minimum-maximum), y	21.3 (0–42)
Simple defect, n (%)	7734 (53.6)
VSD	3559 (24.6)
ASD	2749 (19)
PDA	991 (6.8)
PS	435 (3)
Moderate complexity, n (%)	5571 (38.6)
CoA	862 (6.0)
AS	364 (2.5)
TAPVD	51 (0.4)
PAPVD	27 (0.2)
Valve malformation or disease	1430 (9.9)
ToF	892 (6.2)
AVSD	824 (5.7)
Ebstein anomaly	54 (0.4)
Aortopulmonary septum defect	10 (0.07)
Malformation of the pulmonary veins	18 (0.1)
Other malformations of the great veins	79 (0.6)
Subaorta stenosis	75 (0.5)
Abnormalities of the coronary arteries	31 (0.2)
Heart block	39 (0.3)
Myocardial malformation	45 (0.3)
Aorta atresia/aorta stenosis	80 (0.6)
Other aorta malformation	215 (1.5)
Pulmonary artery stenosis	392 (2.7)
Malformation of the great arteries	15 (0.1)
Other	68 (0.5)
Great complexity, n (%)	1128 (7.8)
TGA	636 (4.4)
TAC	119 (0.8)
Eisenmenger	25 (0.2)
Pulmonary valve atresia	61 (0.4)
HLHS	138 (1.0)
HRHS	24 (0.2)
Ventriculus cordis communis or inversio ventriculorum cordis	125 (0.9)

AS indicates aorta stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; other, other cardiac malformation, levocardia, cor triatriatum, or isomerismus auricularum atriorum with asplenia or polysplenia; PAPVD, partial anomalous pulmonary venous drainage; PDA, persistent ductus arteriosus; PS, pulmonary stenosis; TAC, truncus arteriosus communis; TAPVD, total anomalous pulmonary venous drainage; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; and VSD, ventricular septal defect.

Table 2. Overview of Suicide and Self-Harm (per Subtype of Congenital Lesion)

Congenital Heart Defect	Suicide (n=15)	Self-Harm (n=336)
Simple defect, total, n (%)	9 (60)	209 (62.2)
VSD	3 (20)	87 (25.9)
ASD	4 (26.7)	89 (26.5)
PDA	1 (6.7)	18 (5.4)
PS	1 (6.7)	15 (4.5)
Moderate complexity, total, n (%)	6 (40)	113 (33.6)
CoA	2 (13.3)	16 (4.8)
AVSD	1 (6.7)	18 (5.4)
ToF	...	15 (4.5)
Ebstein anomaly	...	1 (0.3)
Valve malformation or disease	3 (20)	50 (14.8)
Heart block	...	1 (0.3)
Aorta atresia/aorta stenosis	...	4 (1.2)
Pulmonary artery stenosis	...	6 (1.8)
Malformation of the great arteries or veins	...	2 (0.6)
Great complexity, total, n (%)	0 (0)	14 (4.2)
TGA	...	8 (2.4)
TAC	...	2 (0.6)
Ventriculus cordis communis	...	4 (1.2)

ASD indicates atrial septal defect; AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; PDA, persistent ductus arteriosus; PS, pulmonary stenosis; TAC, truncus arteriosus communis; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; and VSD, ventricular septal defect.

entire Danish cohort of CHD patients was characterized using the unique Danish registries, and includes a long-term follow-up of up to 42 years. We found that the absolute risk of both suicide and self-harm in patients with CHD was low and comparable to the risk found in a large reference cohort.

Major physical health conditions, including chronic and acute heart disease, are associated with an increased risk of suicide.^{11,21} A similar association has never been investigated for patients with CHD, despite the impact of a CHD diagnosis has been suggested to have effects beyond physical functioning. A study by Olsen et al⁸ concluded that patients with CHD had an increased risk of psychiatric disorders, including developmental disorders. As mentioned previously, the risk of suicide is increased in all the psychiatric disorders,⁹ which created our hypothesis; patients with CHD have a higher risk of suicide and deliberate self-harm. This theoretical linkage could, despite sufficient power to detect even small differences, not be established, making our findings counterintuitive. Although the present study does not provide an explanation, it might be speculated that patients with CHD are better cared for and have stronger family

Table 3. Risk of Suicide and Self-Harm in Patients With CHD Compared With Matched References

Variable	No. of Cases	HR (95% CI)	SHR (95% CI)	Poisson
Suicide				
Patients with CHD	15	0.81 (0.48–1.37)	0.68 (0.41–1.16)	...
Self-harm				
Patients with CHD	336	1.06 (0.95–1.18)	0.95 (0.85–1.06)	0.99 (0.92–1.07)

CHD indicates congenital heart disease; HR, hazard ratio; and SHR, subhazard ratio.

bonds, counteracting the negative impact of psychiatric disorders. Indeed, children and adolescence operated on for CHD had comparable functional health status when compared with healthy normal children.²² Patients with simple lesions even scored higher in terms of mental health and family activities, and patients across the spectrum of CHD reported higher scores in freedom from bodily pain/discomfort. Similar hardiness has been reported in children with cancer and juvenile rheumatoid arthritis.^{23,24} No matter what the cause, we could, reassuringly, dismiss the hypothesis that patients with CHD have an increased risk of suicide and self-harm.

Although the risk of suicide in patients with CHD has never been investigated before, the proportionate mortality of suicide (including overdose) was reported in a novel overview of causes of death in a contemporary adult CHD cohort.²⁵ In this single-center review, Yu et al²⁵ found that 1.8% (6 suicides of a total of 341 deaths) of deaths were caused by suicide or overdose.

This is well above the proportionate mortality of 0.56% reported in the present study. Whether this difference is related to Yu et al²⁵ only including patients from an adult CHD database, the difference in follow-up (6.2 versus 21.3 years), or the fact that they also included cases with overdose is not known.

The same can be said for the differences in suicide and self-harm that we found across the spectrum of CHD. We were anticipating that patients with the most complex lesions would have the highest burden because of the adversity and distress that can follow these severe conditions. Nonetheless, patients with simple defects were found with the highest prevalence of both suicide and self-harm. This lends further support to the notion that simple defects may not be as benign as originally anticipated. Indeed, patients with simple defects have increased long-term mortality and cardiac morbidity when compared with the general population, but also an increased risk of psychiatric disorders that cannot be explained on the basis

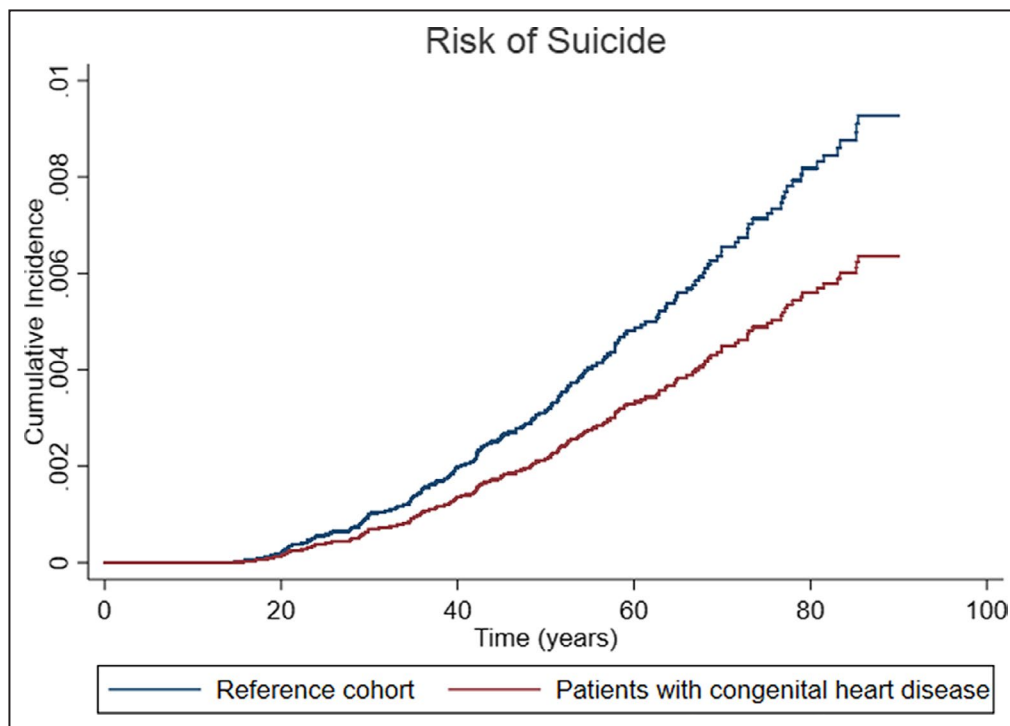


Figure 1. Cumulative incidence of suicide by time of diagnosis among patients with congenital heart disease.

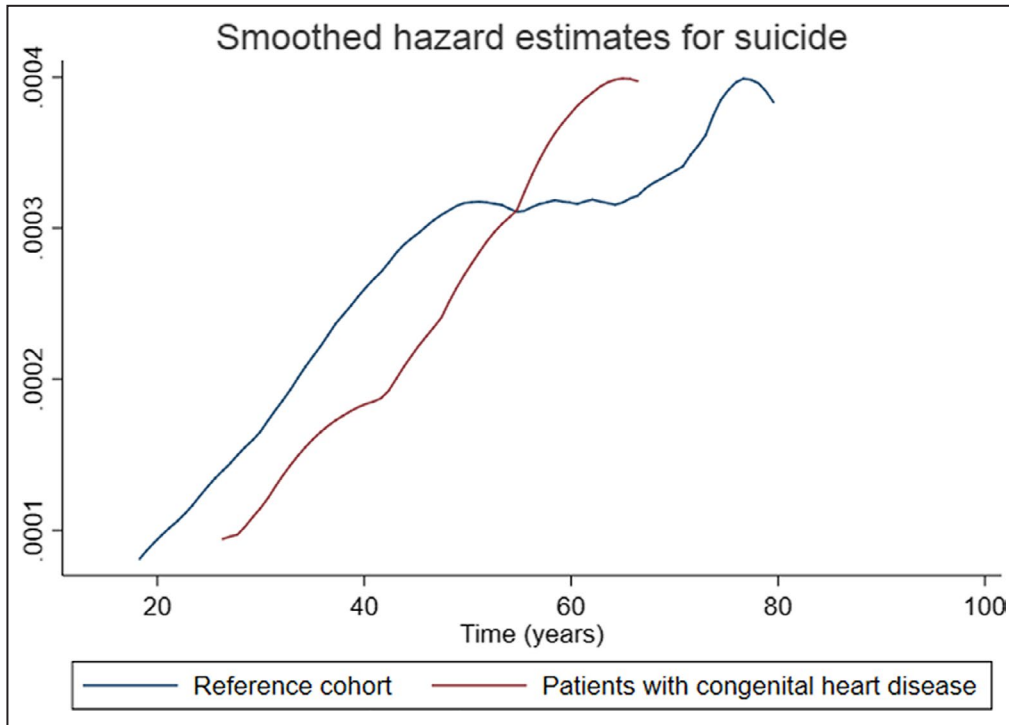


Figure 2. Smoothed cause-specific hazard estimate of suicide by time of diagnosis among patients with congenital heart disease.

of contemporary hemodynamic effects.^{8,26} In regard to the demographic profile of patients with CHD who self-harm, it is noticeably similar to what is described

in the literature, with the most common age for first onset at ~16 years, and the greatest risk from age 15 to 30 years.²⁷

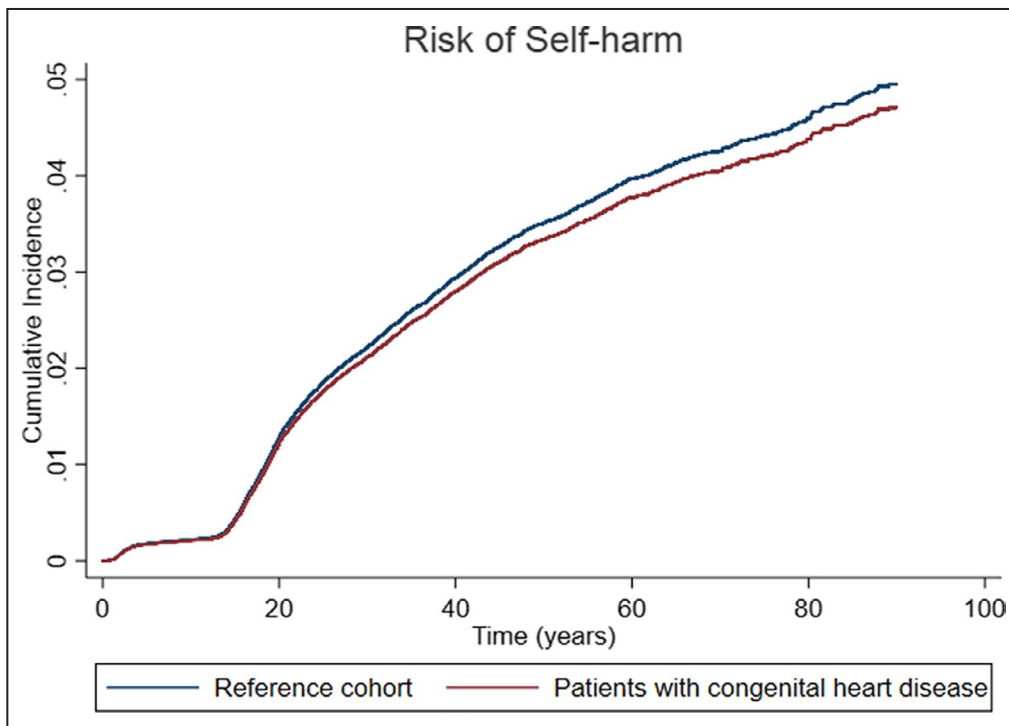


Figure 3. Cumulative incidence of self-harm by time of diagnosis among patients with congenital heart disease.

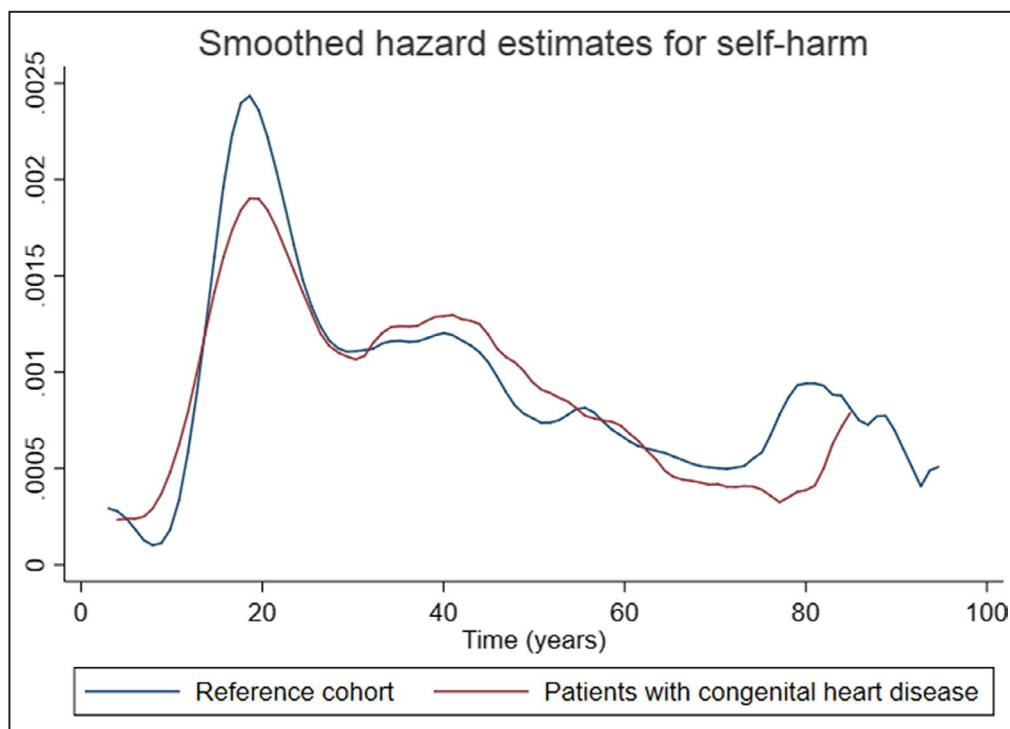


Figure 4. Smoothed cause-specific hazard estimate of self-harm by time of diagnosis among patients with congenital heart disease.

Limitations

The validity of our estimates depends on the accuracy of coding CHD in the registers, which consecutively depends on the physicians generating the data. Reports do, however, state that the positive predictive value of CHD diagnoses in the DNPR is high.²⁸ To strengthen the validity of our data further, we only chose to include patients diagnosed at 1 of the 4 university hospitals in Denmark. Also, any misclassification of overall CHD status is small and independent of future events with suicide or deliberate self-harm.

Unfortunately, only 37% of deliberate self-harm is reported correctly with contact code 4.²⁹ We consequently chose to also include codes covering methods often used for deliberate self-harm. This procedure includes a risk of including some incidents with accidental harm. However, the chosen procedure has been validated as the best estimate for self-harm, and would not influence the overall interpretation of our data, as we used same procedure for both cases and references.

On the basis of our data, it did not seem imperative to estimate the risk of suicide and self-harm for the detailed subgroups of CHD. Furthermore, the low incidence of suicide in the patient group made it impossible to adjust for this aspect, perhaps suggesting that the model might lack power.

Finally, although large prospective study with a long follow-up is suited to provide good estimates of suicide risk, it inherently has some limitations. One limitation is

that the risk for new patients with CHD might be different after improvements in treatment, caretaking, and other factors. Generally, suicide rates in Denmark have changed over time, as rates have been evidently lower since year 2000 when compared with rates in the previous decades.^{30,31}

CONCLUSIONS

The data presented in this national cohort are the first analysis of risk of suicide and self-harm in patients with CHD followed up from time of diagnosis. Our estimates clearly demonstrate that patients with CHD do not have an increased risk of suicide or deliberate self-harm when compared with a large reference cohort. We hope that our results will provide comfort for patients and parents, as well as assist physicians providing counseling for patients with CHD.

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Disclosures

None.

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