Long-term incidence of infective endocarditis among patients with congenital heart disease

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Background Patients with congenital heart disease (CHD) are at lifelong high risk of infective endocarditis (IE). The risk of IE presumably differs among different CHD, but little knowledge exists on the area.

Methods In this observational cohort study, all CHD-patients born in 1977 to 2018 were identified using Danish nationwide registries and followed from the date of birth until first-time IE, emigration, death, or end of study (December 31, 2018). The comparative risk of IE among CHD-patients vs age- and sex-matched controls from the background population was assessed. The risk of IE was stratified according to the type of CHD and factors associated with IE including sex and relevant time-varying coefficients (ie, cyanosis, cardiac prostheses, diabetes mellitus, chronic kidney disease, and cardiac implantable electronic devices) were examined using Cox-regression analysis.

Results A total of 23,464 CHD-patients (50.0% men) were identified and matched with 93,856 controls. During a median follow-up of 17.7 years, 217(0.9%) CHD-patients and 4(0.0%) controls developed IE, corresponding to incidence rates of 5.2(95%CI 4.6-6.0) and 0.02(95%CI 0.01-0.1) per 10,000 person-years, respectively. The incidence of IE was greatest among patients with tetralogy of fallot, malformations of the heart chambers (including transposition of the great arteries, univentricular heart, and truncus arteriosus), atrioventricular septal defects, and heart valve defects. Factors associated with IE among CHD-patients included male sex, cyanosis, cardiac prostheses, chronic kidney disease, and cardiac implantable electronic devices.

Conclusions CHD-patients have a substantially higher associated incidence of IE than the background population. With the increasing longevity of these patients, relevant guidelines concerning preventive measures are important. (Am Heart J 2023;259:9–20.)

Keywords: Congenital heart disease; Epidemiology; Infective endocarditis

Patients with congenital heart disease (CHD) are considered to be at a lifelong high risk of infective endocarditis (IE)—an infection associated with high morbidity and mortality.[1-6] An increasing longevity among patients with CHD results in an expanding population of adults with CHD with an emerging number of complications including IE. CHD includes various types of structural heart defects, and the risk of IE presumably differs among different types of CHD. Yet, little knowledge exists in the area. European guidelines on the management of IE recommend antibiotic prophylaxis prior to certain dental procedures for patients in particular at high risk of IE, including CHD-patients with cardiac prostheses and untreated cyanotic CHD.[7] However, the studies on which these recommendations are based include a small number of selected patients. Most traditional risk factors for IE are strongly associated with age and are exogenous (heart valve protheses, cardiac implantable devices, etc.) and patients are exposed to these late in life.[8,9] CHD stands out by the fact that patients with CHD are at continuous lifelong risk of IE due to the nature of their disease and these patients undergo heart valve surgery earlier in life. Hence, the relative short-term risk of IE associated with CHD may be low compared with other risk factors, but along with an increased longevity, patients with CHD may carry a substantial lifetime risk of IE. Data on risk factors and differentiated long-term risk of IE among patients with CHD are limited but of great interest in the purpose of prophylactic measures. This Danish nationwide study with up to 42 years of follow-up sets out to investigate the differentiated long-term incidence

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of and prognosis associated with IE in patients with CHD relative to matched controls from the background population.

Methods

Data sources

All Danish residents are assigned a unique and permanent civil registration number allowing accurate linkage of nationwide administrative registries at an individual level. For this study, data from the following two Danish administrative registries were obtained: (1) The Danish National Patient Registry, which holds information on all hospital admissions and outpatient contacts according to the International Classification of Diseases (ICD) 8th and 10th revision and surgical procedures according to the NOMESCO Classification of Surgical Procedures (NCSP).[10] (2) The Danish Civil Registration System, which holds data on birth date, sex, and vital status (ie, whether a person is alive and resident in Denmark, disappeared [persons whose residence is unknown to Danish authorities], emigrated, or dead - along with the date of these events).[11] The Danish registries are validated and of high quality, as described in detail previously.[10-14]

Study population

All Danish citizens born in the 42-year period from January 1, 1977, to December 31, 2018, and diagnosed with CHD were included in the study. Patients with CHD were identified using the following ICD-8 and ICD-10 codes: 746-747 (except 746.7 and 747.5 to 747.9 which is non-specific for CHD) and DQ20-26 (except DQ265-266, likewise non-specific for CHD), respectively. Only patients diagnosed with in- or outpatient diagnoses at one of the four major university hospitals in Denmark were included in order to increase the validity of the diagnoses as done previously.[15] The positive predictive value of CHD diagnoses in the Danish National Patient Registry is reported to be high,[16,17] and any misclassification of overall CHD is small. Further, the diagnosis of CHD was validated by the authors by examination of 100 random CHD-patient records with a positive predictive value of 97%. Patients with CHD can be very complex, and one patient can have several coexisting types of cardiac malformations. To avoid overlap between the various diagnoses we made a hierarchy of diagnoses based on the relevance for IE: (1) tetralogy of fallot (ToF), (2) malformations of the heart chambers (ie, truncus arteriosus, transposition, and univentricular heart), (3) malformations of the heart valves, (4) atrioventricular septal defects, (5) malformations of the great arteries, (6) ventricular septal defects, (7) Atrial septal defects, and (8) other malformations. To investigate the burden of IE among patients with CHD compared with the background population, the CHD population was matched with controls from the background population in a 1:4 ratio based on sex and year of birth using risk-set matching.

Covariates

Comorbidities and congenital malformations were obtained by inpatient and outpatient diagnoses (Supplementary Table 1 for ICD-8 codes and ICD-10 codes). The presence of a cardiac implantable electronic device was defined as implantation of a pacemaker or implantable cardioverter defibrillator (Supplementary Table 1 for NCSP codes). Cyanotic yet surgically untreated CHD was defined as a diagnosis of ToF, transposition of the great arteries, truncus arteriosus, or cyanosis before surgery (Supplementary Table 1 for ICD-8 codes, ICD-10 codes, and NCSP codes), thus, conditions we assume to be associated with presence of cyanosis. Cardiac prostheses were defined as either presence of heart valve prostheses or septal patches (Supplementary Table 1 for NCSP codes). Among those who developed IE, presence of prostheses was defined before admission for IE, thus, patients who underwent first-time heart valve replacement during admission for IE were defined by not having prostheses at time of IE. Associated anomalies among patients with CHD and controls from the background were compared. Likewise, concomitant congenital malformations were compared among patients with CHD vs those without IE.

Outcomes

The primary outcome was incident IE. IE was defined from the following ICD-8 and ICD-10 codes: acute endocarditis (42,100), subacute endocarditis (42,101), acute and sub-acute endocarditis (42,108, 42,109, 42,199, DI33), endocarditis with valve unspecified (DI38), and endocarditis unspecified (DI398). We were not able to differentiate between the location of IE (ie, prosthetic valve, native valve, or cardiac implantable electronic devices). The diagnosis of IE in the Danish National Patient Registry has previously been validated with a positive predictive value of 90% and we applied the same definition of IE for this study.[18] An additional analysis was performed examining the differentiated incidence of IE according to specific types of CHD. Mortality was the secondary outcome. In a secondary analysis, we compared the incidence of death among CHD-patients with and without IE. Patients were followed from the day of birth until the outcome of interest, death, emigration, or end of the study (December 31, 2018), whichever came first.

Among those who developed IE, we compared the subsequent incidence of mortality between patients with CHD and controls. In this analysis, patients were followed from the day of IE until death, emigration, or end of study (December 31, 2018).

In a supplementary analysis, the incidence of IE was examined among patients and controls of 18 years or more.

Those who developed IE, died, or emigrated before the age of 18 years were excluded. Further, we performed a second supplementary analysis investigating the impact of surgery on the incidence of IE by: (1) investigating the cumulative incidence of IE from day of birth until surgery, the outcome of interest, death, emigration, or end of the study (December 31, 2018), whichever came first, and (2) investigating the cumulative incidence of IE from day of surgery until the outcome of interest, death, emigration, or end of the study (December 31, 2018), whichever came first.

Statistical analysis

Characteristics of patients with CHD and controls from the background population were reported as frequencies with percentages for categorical variables and medians with 25th to 75th percentiles for continuous variables.

Cumulative incidences of IE among patients with CHD and controls were estimated using the Aalen-Johansen estimator incorporating the competing risk of death. Differences between groups were assessed using Gray's test. Cumulative incidences of all-cause mortality according to groups were estimated using the Kaplan-Meier estimator. Differences between groups were assessed using the Log-rank test. Crude incidence rates of all outcomes were calculated as a number of events per 10,000 person-years (PY). Further, in cause-specific Cox regression models conditional on the matching (ie, comparing cases with their matched control), the rates of IE and all-cause mortality were calculated as hazard ratios (HR) with 95% confidence intervals (CI). These models were adjusted for time-varying coefficients including presence of cardiac prostheses and relevant comorbidities (ie, chronic renal failure, diabetes mellitus, and presence of cardiac implantable electronic devices). The coefficients were included in the model as time-varying variables as the variables (eg, presence of cardiac prostheses during the life course of an individual patient) may change over time in the follow-up period.[19] Further, factors associated with IE among patients with CHD were examined using Cox regression analysis including sex and relevant time-varying coefficients (ie, cyanotic yet surgically untreated CHD [ie, tetralogy of fallot, transposition, truncus arteriosus, or cyanotic diagnosis], CHD repaired with prostheses, diabetes mellitus, chronic kidney disease, and presence of cardiac implantable devices).

In the secondary analysis, assessing the IE-associated rate of death among patients with CHD, IE was included as a time-varying variable, and reported HRs for all-cause mortality were further adjusted for the abovementioned covariates.

Due to rules on anonymity by Statistics Denmark, exact numbers on data from the registries are known but cannot be reported if the number of patients is less than 4. Relevant interactions including sex and year of birth were tested and found insignificant, unless otherwise stated. All statistical analyses were performed with SAS statistical software (SAS 9.4, SAS Institute, Cary, NC). A two-sided *P*-value $<.05$ was considered statistically significant.

Sensitivity analysis

To test the robustness of our findings, 3 sensitivity analyses were performed: First, a sensitivity analysis starting follow-up on the day of CHD diagnosis was conducted to investigate if the results remained similar even if follow-up was started when the CHD diagnosis was established. Presumably, different attention may have been given to preventive measures and symptoms after the diagnosis of CHD, and one could expect that this potentially could have altered the development of the infective disease. Thus, index was defined as the day of CHD diagnosis among patients. Patients with a history of IE prior to CHD diagnosis were excluded ($n = 1$) from this analysis. Among controls, index was defined as the day of diagnosis for their matched CHD patient making sure that the control was born and alive on that day.

Further, a second sensitivity analysis was performed including patients with a CHD diagnosis at any Danish hospital, thus, including those who had a diagnosis code from other hospitals than one of the 4 university hospitals. Moreover, a third sensitivity analysis was performed including all CHD diagnoses (ie, performing no hierarchy) so that patients could belong to more than 1 CHD group. Supplementary Table 3 depicts coexisting CHD diagnoses.

Ethics

In Denmark, registry-based studies that are conducted for the sole purpose of statistics and scientific research do not require ethical approval or informed consent by law. However, the study is approved by the data responsible institute (the Capital Region of Denmark [approval number: P-2019-523]) in accordance with the general data protection regulation.

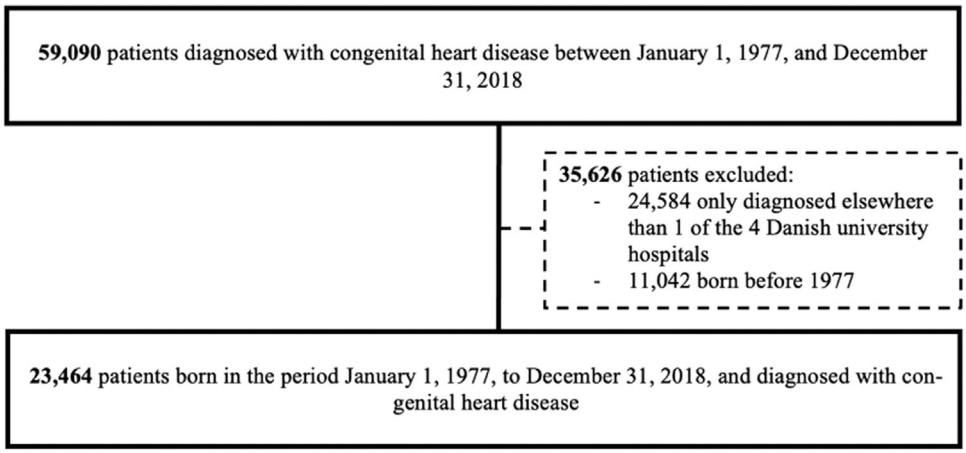
No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

Baseline characteristics

In the period from January 1, 1977, to December 31, 2018, 23,464 patients (50% men) were born and diagnosed with CHD in Denmark at one of the 4 university hospitals (Figure 1). These patients were matched with 93,856 controls from the background population. In total, 1,144 (4.9%) CHD-patients were born in the 70s, 4,159 (17.7%) in the 80s, 6,318 (26.9%) in the 90s, 7,063 (30.1%) in the 00s, and 4,780 (20.4%) in the 10s. The median age at time of CHD diagnosis was 1.0 years

Figure 1



Flow chart of the selection of the study population. The figure shows a flow chart of the patient selection.

(25th-75th percentile 0.1-8.2). Table I depicts the median age at time of CHD diagnosis according to type of CHD and summarizes anomalies and congenital malformations among patients with CHD and controls. Among patients with CHD, the most common diagnosis was atrial septal defect (32.1%), followed by ventricular septal defect (30.7%) and malformations of the great arteries (29.5%). Overall, patients with CHD had a higher prevalence of congenital syndromes and concomitant congenital malformations including malformations of extremities and digestive system compared with controls. In total, 8,125 (24.6%) patients and 45 (0.1%) controls underwent cardiac surgery during follow-up. Among these 2,278 (9.7%) patients and <4 (<0.004%) controls underwent implantation of heart valve prostheses ($n = 578$ for patients) or septal prostheses ($n = 1,700$ for patients).

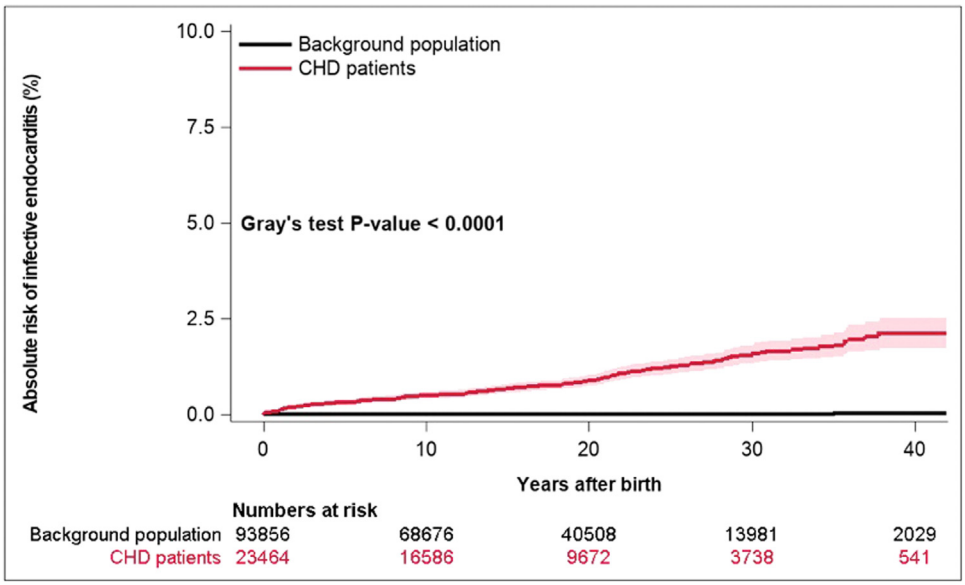
Incident IE

Median time of follow-up from day of birth until diagnosis of IE, death, emigration, or end of the study period (December 31, 2018) was 17.7 years (17.0 [25th-75th percentile 8.6-25.8] and 17.8 [25th-75th percentile 9.5-25.5] among patients and controls, respectively). In total, 217 (0.9%) patients with CHD and 4 (0.004%) controls developed IE during follow-up. Among patients with cardiac prostheses ($n = 2,278$), 56 (2.5%) of these developed IE before undergoing surgery, while 48 (2.1%) developed IE after undergoing surgery. Median time from surgery to incident IE was 4.6 years (25th-75th percentile 0.7-8.6 years). The median age at time of diagnosis of IE was 11.6 years (25th-75th percentile 2.8-21.5) among patients with CHD while it was 19.5 years (25th-75th percentile 9.7-28.2) among controls. The cumulative incidence of IE according to groups is displayed in Figure 2. During follow-up, the incidence rates of IE per 10,000 PY were 5.2 (95% CI: 4.6-6.0) and 0.02 (95% CI: 0.01-0.1) among patients with CHD and controls, respectively, yielding a HR of 168.2 (95% CI: 62.1-455.3).

Characteristics of patients with CHD who developed IE ($n = 217$) compared with those who did not ($n = 23,247$) are summarized in Table II (CHD-diagnoses are after the hierarchy has been applied). Patients who developed IE were more often men (Supplementary Figure 1), more often had more than one CHD-diagnosis and had a higher burden of concomitant malformations (Table II). Moreover, patients with IE have a higher age at diagnosis of CHD, which could reflect that IE unmasks previously unknown CHD. The incidence of IE has remained stable during the last decades (Supplementary figure 2). Figure 3 shows the cumulative incidence of IE among specific types of CHD. Cyanotic yet surgically untreated CHD (HR 5.21 [95% CI 3.52-7.71]), cardiac prostheses (HR 5.19 [95% CI 3.58-7.53]), chronic kidney disease (HR 3.08 [95% CI 1.25-7.56]), and presence of cardiac implantable devices (HR 3.05 [95% CI 1.51-6.17]) were all factors associated with a significantly increased risk of IE among patients with CHD (Figure 4). In sensitivity analyses including heart valve prostheses only or patches only in the category "cardiac prostheses" similar results were found, yet a stronger association was found among those with valve prostheses than those with patches.

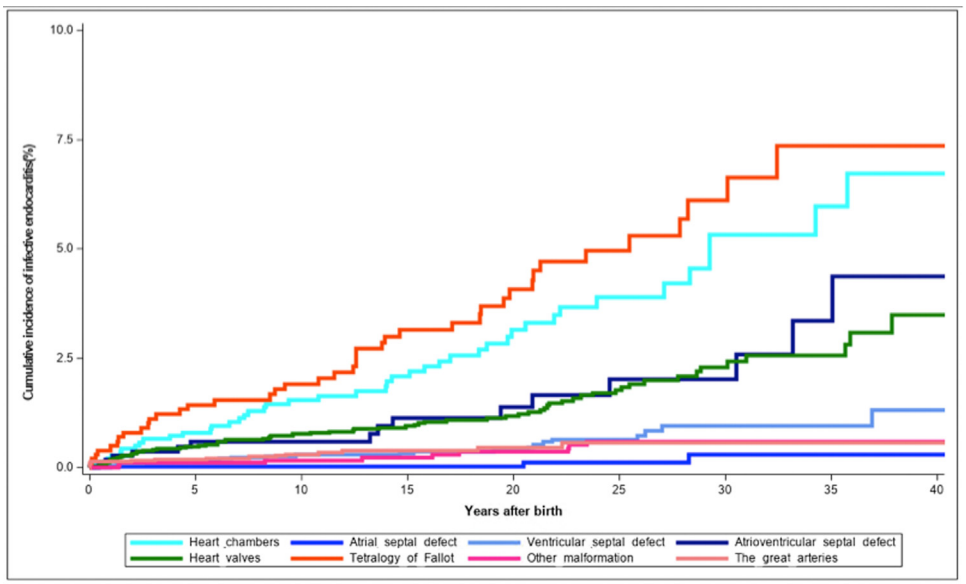
The risk of IE was greatest among patients with ToF, malformations of the heart chambers (including transposition of the great arteries, univentricular heart, and truncus arteriosus), atrioventricular septal defects, and heart valve defects. Table III depicts the number of events, incidence rates, as well as unadjusted and adjusted hazard ratios of IE stratified on type of CHD (after the hierarchy has been applied). The results remained relatively similar

Figure 2



Cumulative incidences of IE among patients with CHD and controls. The figure shows the cumulative incidences of IE among patients with CHD and controls from the background population. *CHD,* congenital heart disease; *IE,* infective endocarditis.

Figure 3



Cumulative incidences of IE according to different types of CHD. The figure shows the cumulative incidences of IE stratified according to type of CHD. *CHD,* congenital heart disease; *IE,* infective endocarditis.

Table I. Characteristics of patients with CHD and controls.

Characteristics	Patients with CHD	Controls
Number	23,464	93,856
Male sex, *N* (%)	11,730 (50.0%)	46,920 (50.0%)
Ethnicity, *N* (%)		
Native Danish	20,902 (89.1%)	71,486 (76.2%)
Immigrant	686 (2.9%)	15,683 (16.7%)
Descendant from immigrant	1,875 (8.0%)	6,667 (7.1%)
Age at diagnosis, years (median, 25th-75th percentile)	1.0 (0.1-8.2)	-
Malformation of the heart chambers	3.8 (0.2-14.9)	
Atrial septal defect	0.6 (0.1-5.4)	
Ventricular septal defect	0.6 (0.1-4.6)	
Atrioventricular septal defect	0.7 (0.1-8.2)	
Malformation of the heart valves	7.1 (1.0-15.9)	
Malformation of the great arteries	0.2 (0.02-2.2)	
Tetralogy of fallot	5.5 (0.6-16.4)	
Other cardiac malformation	1.4 (0.03-7.6)	
Cardiac malformations, *N* (%), before hierachy		
Malformation of the heart chambers	1,599 (6.8%)	-
Atrial septal defect	7,531 (32.1%)	-
Ventricular septal defect	7,195 (30.7%)	-
Atrioventricular septal defect	1,493 (6.4%)	-
Malformation of the pulmonary or tricuspid valve	2,510 (10.7%)	-
Ebsteins anomaly	120 (0.5%)	
Malformation of the aortic or mitral valve	3,029 (12.9%)	-
Bicuspid aortic valve	787 (3.4%)	-
Malformation of the great arteries	6,925 (29.5%)	-
Patent ductus arteriosus	5,316 (22.7%)	-
Aortic coarctation	1,406 (6.0%)	-
Tetralogy of fallot	1,008 (4.3%)	-
Other cardiac malformation	6,318 (5.4%)	
Cardiac malformations, *N* (%), after hierarchy applied		
Malformations of the heart chambers	1,432 (6.1%)	
Atrial septal defect	3,391 (14.5%)	
Ventricular septal defect	4,598 (19.6%)	
Atrioventricular septal defect	1,086 (4.6%)	
Malformations of the heart valves	4,461 (19.0%)	
Malformations of the great arteries	4,827 (20.6%)	
Tetralogy of fallot	1,008 (4.3%)	
Other cardiac malformations	1,848 (7.9%)	
Other congenital malformations, *N* (%)		
Malformation of the peripheral circulation	193 (0.8%)	96 (0.1%)
Malformation of eyes, eyelid, the lacrimal apparatus, or the orbit	499 (2.1%)	280 (0.3%)
Malformation of ears	490 (2.1%)	908 (1.0%)
Malformation of nose, pharynx, larynx, trachea, or the lungs	514 (2.2%)	183 (0.2%)
Malformation of the palate, tongue, or lips	538 (2.3%)	462 (0.5%)
Malformation of the digestive system	777 (3.3%)	296 (0.3%)
Malformation of the reproductive system	289 (1.2%)	337 (0.4%)
Malformation of the urinary system	421 (1.8%)	387 (0.4%)
Malformation of the extremities	1,581 (6.7%)	2,446 (2.6%)
Congenital syndromes	2,354 (10.0%)	260 (0.3%)
DiGeorge syndrome	120 (0.5%)	6 (0.01%)

after adjustment as malformations of the heart chambers, ToF, and heart valve defects remained associated with a particular high risk of IE, whereas the risk of IE among those with atrioventricular septal defects became less in the adjusted analysis.

Sensitivity analyses

In the sensitivity analysis following patients from date of CHD diagnosis, similar results were found: 212 (0.9%) patients with CHD and 4 (0.00%) controls developed IE during follow-up corresponding to incidence rates of 7.8 (95% CI: 7.5-8.1) and 0.5 (0.5-0.6) per 10,000 PY, respectively.

In the second sensitivity analysis including patients with a CHD-diagnosis at any Danish hospital, 38,347 CHD-patients were included. Supplementary Table 2 compares the study population (ie, patients with a diagnosis from a university hospital) and patients with

Table II. Congenital malformations among patients with CHD with vs without IE.

Characteristics	CHD-patients with IE	CHD-patients without IE
Number, *N* (%)	217	23,247
Male sex, *N* (%)	134 (61.8%)	11,596 (49.9%)
Age at CHD diagnosis in years, median (25th-75th percentile)	14.0 (4.7-20.6)	0.9 (0.1-8.0)
Ethnicity, *N* (%)		
Native Danish	191 (88.0%)	20,711 (89.1%)
Immigrant	7 (3.2%)	679 (2.9%)
Descendant from immigrant	19 (8.8%)	1,856 (8.0%)
Cardiac malformations, *N* (%), after hierarchy applied		
Malformation of the heart chambers	43 (19.8%)	1,389 (6.0%)
Atrial septal defect	222 (31.7%)	7,309 (32.1%)
Ventricular septal defect	23 (10.6%)	4,575 (19.7%)
Atrioventricular septal defect	3 (1.4%)	3,388 (14.6%)
Malformation of the heart valves	66 (30.4%)	4,395 (18.9%)
Malformation of the great arteries	17 (7.8%)	4,810 (20.7%)
Tetralogy of fallot	41 (18.9%)	967 (4.2%)
Other cardiac malformation	9 (4.2)	1,839 (7.9%)
Other congenital malformations, *N* (%)		
Malformation of the peripheral circulation	4 (1.8%)	189 (0.8%)
Malformation of eyes, eyelid, the lacrimal apparatus, or the orbit	11 (5.1%)	488 (2.1%)
Malformation of ears	5 (2.23%)	485 (2.1%)
Malformation of nose, pharynx, larynx, trachea, or the lungs	10 (4.6)	504 (2.2%)
Malformation of the palate, tongue, or lips	7 (3.2%)	531 (2.3%)
Malformation of the digestive system	8 (3.7%)	769 (3.3%)
Malformation of the reproductive system	5 (2.3%)	284 (1.2%)
Malformation of the urinary system	5 (2.3%)	416 (1.8%)
Malformation of the extremities	16 (7.4%)	1,565 (6.7%)
Congenital syndromes	38 (17.5%)	2,316 (10.0%)
DiGeorge syndrome	5 (2.3%)	115 (0.5%)

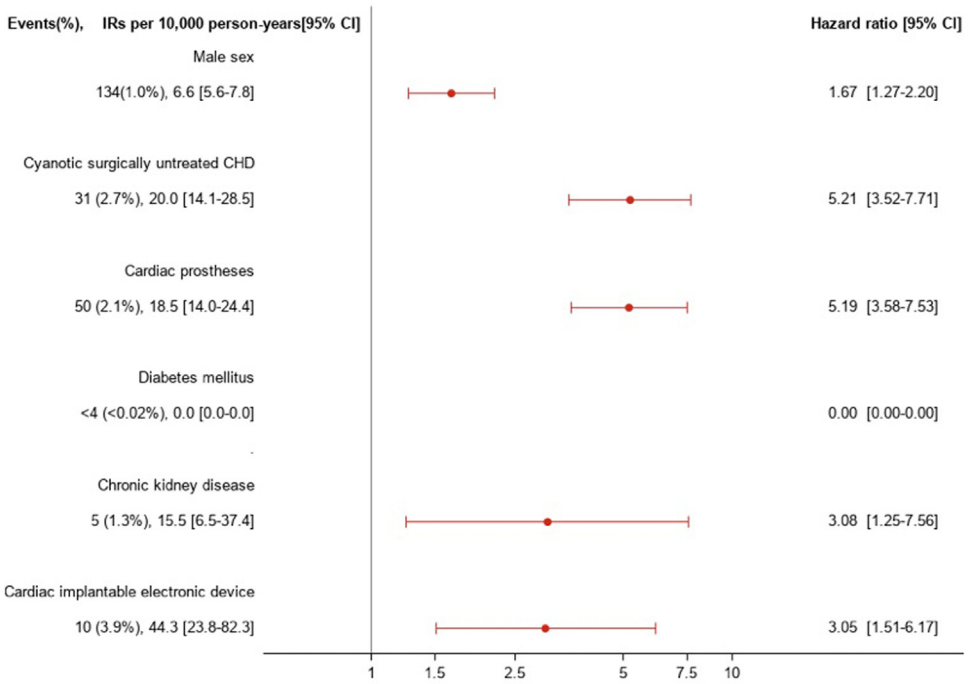
Table III. Number of events, incidence rates, unadjusted, and adjusted hazard ratios of infective endocarditis stratified on the type of congenital heart disease (after hierarchy applied).

	Number of events	Incidence rates per 10.000 PY	Unadjusted HR	Adjusted HR
Malformations of the heart chambers	43 (3.0%)	18.1 (13.5-24.5)	21.4 (15.5-29.8)	9.1 (6.2-13.4)
- Truncus arteriosus	- 13 (7.7%)			
- Transposition	- 27 (2.7%)			
- Univentricular heart	- 11 (3.8%)			
ToF	41 (4.1%)	23.6 (17.3-32)	27.3 (19.4-38.3)	9.7 (6.4-14.7)
ASD	<4 (<0.1%)	0.5 (0.2-1.7)	0.5 (0.2-1.6)	0.5 (0.2-1.6)
VSD	23 (0.5%)	2.8 (1.9-4.2)	2.9 (1.9-4.5)	1.3 (0.8-2.1)
AVSD	15 (1.4%)	9.3 (5.6-15.4)	9.2 (5.5-15.6)	2.3 (1.2-4.1)
Heart valves	66 (1.5%)	7.7 (6.0-9.8)	10.1 (7.5-13.4)	6.3 (4.6-8.6)
Great arteries	17 (0.4%)	2.6 (1.6-4.1)	2.6 (1.6-4.3)	2.1 (1.3-3.4)
- Patent Ductus arteriosus	- 12 (0.3%)			
- Aortic coarctation	- 6 (0.9%)			
Other	9 (0.5%)	1.9 (1.0-3.6)	1.8 (0.9-3.5)	1.5 (0.7-3)

ASD, atrial septal defect; AVSD, atrioventricular septal defect; ToF: tetralogy of fallot; VSD, ventricular septal defect.

a CHD-diagnosis at any Danish hospital. The number of patients with "other cardiac malformation" is substantially higher when including patients diagnosed at the smaller hospitals, the incidence of IE is lower ($n = 233$, 0.6%) but the relative incidences of IE among specific types of CHD-patients is simi lar (Supplementary Figure 3). In the third sensitivity analysis including all CHD-diagnoses and performing no hierarchy, similar findings were found; patients with the highest incidence of IE included those with ToF, malformations of

Figure 4



Factors associated with the risk of IE among patients with CHD. The Figure shows the absolute numbers, incidence rates, and hazard rates for factors associated with IE among patients with CHD. *CHD,* congenital heart disease; *IE,* infective endocarditis; *IRs,* incidence rates.

the heart chambers, malformations of the heart valves, and atrioventricular septal defects (Supplementary Figure 4).

All-cause mortality

The cumulative incidence of death according to groups is depicted in Figure 5. In total, 1,046 (4.5%) patients and 316 (0.3%) controls died during follow-up, corresponding to incidence rates of 2.5 (95% CI 2.4-2.7) and 0.2 (95% CI 0.2-0.2) per 10.000 PY, respectively, and a HR of 14.0 (95% CI 12.3-16.0).

In total, 26 (12.0%) CHD-patients with IE and 1,020 (4.4%) CHD-patients without IE died during follow-up. Less than 4 of the controls who developed IE died during follow-up. Among patients with CHD, the median time from diagnosis of IE until death was 4.8 years (25^{th} to 75^{th} percentile: 0.9-12.1 years). During follow-up, the unadjusted incidence rates of all-cause mortality per 10,000 PY with versus without IE were 9.9 (95% CI: 6.7-14.6) and 2.4 (95% CI: 2.3-2.6), respectively. In a time-varying multivariable Cox regression analysis, IE was associated with a significantly higher rate of death with an adjusted HR of 3.1 (95% CI 2.1-4.6). Notably, the specific CHDs with vs without IE associated with the highest relative rate of death includes ToF, malformations of the heart chambers (including transposition of the great arteries, univentricular heart, and truncus arteriosus), and malformations of the great arteries (including patent ductus arteriosus and coarctation of the aorta).

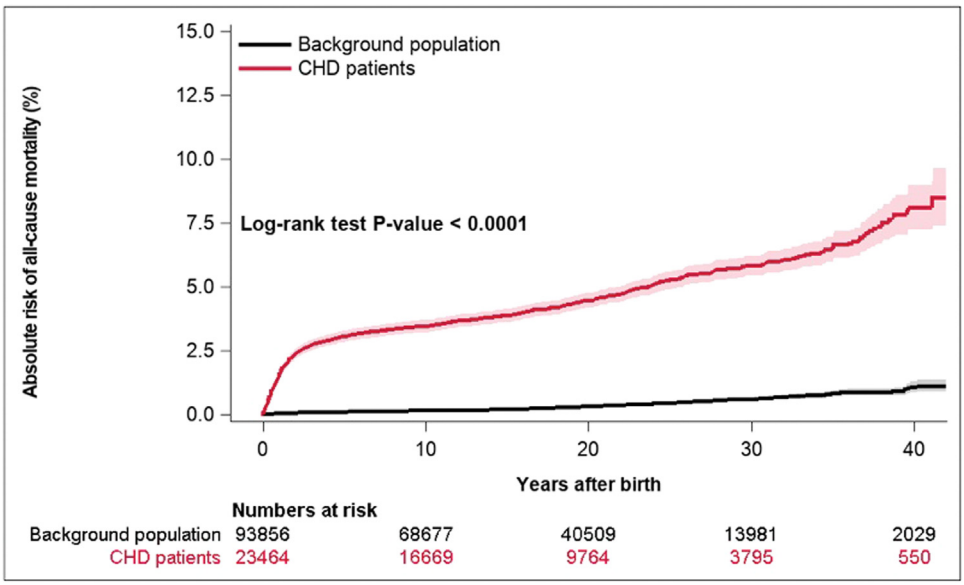
Supplementary analysis

In the supplementary analysis, the risk of IE was examined among grown-ups (ie, ≥ 18 years of age) and similar results were found. Supplementary Figure 5 shows the cumulative incidences of IE among patients with CHD and controls ≥18 years of age. Patients had a significantly higher rate of IE compared with controls (incidence rates of 17.1 [8.5-3.4] and 0.0 [0.0-0.0], respectively. In the second supplementary analysis investigating the impact of surgery on the cumulative incidence of IE, Supplementary Figures 6 and 7 show similar risks of IE among CHD groups irrespective of cardiac surgery. Thus, patients with ToF and malformations of the heart chambers remain in particular high risk of IE regardless of surgery.

Discussion

In this nationwide study, we examined the long-term incidence of IE in a birth cohort of Danish residents diagnosed with CHD during a 42-year observation period

Figure 5



Cumulative incidence of all-cause mortality among patients with CHD and controls. The figure shows the cumulative incidences of all-cause mortality among patients with CHD and controls from the background population. *CHD,* congenital heart disease.

from 1977 to 2018. The study yielded the following major four findings: First, the burden of IE among patients with CHD was substantial with an incidence rate of 5.2 per 10,000 PY corresponding to a more than 50 times higher rate of IE than that of age- and sex-matched controls from the background population. Second, the CHDs with the heaviest burden of IE included ToF and malformations of the heart chambers, but also atrioventricular septal defects and heart valve defects. Third, factors associated with an increased risk of IE among patients with CHD included male sex, cyanotic yet surgically untreated CHD, cardiac prostheses, chronic kidney disease, and presence of cardiac implantable devices. Fourth, among patients developing IE, patients with CHD (particularly those with ToF, malformations of the heart chambers, and malformations of the great arteries) had a substantially higher mortality risk than those without CHD.

Incidence of IE

An increasing longevity among patients with CHD results in an expanding population of adults with CHD with an emerging number of complications including IE. Some previous studies have investigated the risk of IE among patients with CHD; however, the studies are limited by immortal time bias, lack of long-term follow up, or small number of patients. A Swedish nationwide study from 2019 by Snygg-Martin et al. examined the cumulative incidence of IE in 89,541 patients with CHD from 1930 to 2017 and found an IR of 6.56 per 10,000 PY(20), however, the study was limited by immortal time bias from 1930 to 1987. Additionally, a Canadian study from 2013 by Rushani et al. on 47,517 CHD children (0-18 years) from 1988 to 2010 found an IR of 4.1/10,000 PY.[21] Lastly, an Australian single-center study from 2017 by Moore et al. examined the incidence of IE among 2,935 CHD adults (≥ 16 years) and found an IR of 9.9 per 10.000 PY with a 15% IE related mortality during follow-up, thus a similar IE related mortality compared to our study.[22] Hence, the incidence rate of IE in previous studies ranges from 4.1 to 9.9 per 10,000 PY which is similar to our findings (ie, 5.2 per 10,000 PY). However, our study stands out due to complete nationwide data following patients with CHD from the day of birth up to 42-years of age, therefore this study adds valuable information, but the risk of IE may have been even higher if the follow-up period had been longer. This substantially increased risk of IE among patients with CHD compared with the background population could be due to altered hemodynamics and fragile endocardium, prosthetic material due to multiple surgical and invasive procedures, or a distorted immune system due to associated syndromes and neonatal thymectomy. However, the exact pathophysiological mechanism underlying this considerably increased risk remains to be explored.

Differentiated risk

Patients with CHD are considered at high risk of IE(7, 8, 23), however, CHD includes various types of structural

heart defects, and the risk of IE presumably differs among different types of CHD, yet there has been little emphasis on the area. Guidelines recommend antibiotic prophylaxis prior to certain dental procedures to patients in particular high risk of IE including patients with untreated cyanotic CHD and CHD-patients with cardiac prostheses,[7] however these guidelines are based on small and selected studies. Snygg-Martin et al.[20] found similar incidences among different CHD categories in adult life but higher incidence among children with complex lesions including ToF and malformations of the heart chambers, which is in accordance with our findings. Also, Moore et al.[22] found that patients with complex lesions, ventricular septal defects, and aortic valve replacement were at higher risk of IE, with the first- and latter-mentioned in line with our findings. Lastly, a UK study from 2019 by Cahill et al.,[24] investigated 736 CHD-patients with IE and the most common CHD diagnoses were ToF, ventricular septal defect, and bicuspid aortic valve, again with the first- and latter-mentioned similar to the findings in our study. Thus, some consensus exists on the question "which patients with CHD are in particular high risk of IE?": cyanotic heart defects (such as ToF, transposition of the great arteries, and truncus arteriosus) are considered at high risk of IE confer guidelines. This consideration is supported by the present study and previous studies. However, atrioventricular septal defects and heart valves defects are also found to be in high risk of IE, which should be kept in mind in the daily clinical work and patients should be advised of the importance of dental and cutaneous hygiene. Thus, our study suggests that the risk of IE differs among different types of CHD from high-risk CHD-patients to relatively low-risk CHD-patients; this calls for more studies on the stratified risk of IE in order to update guidelines.

Further, among CHD-patients developing IE, those with ToF, malformations of the heart chambers, and malformations of the great arteries had the highest IE-associated mortality. However, numbers on IE-associated mortality are limited but suggest that we pay extra attention to patients with these specific CHDs developing IE.

Factors associated with IE

In the general population, risk factors of IE are well investigated,[7-9] but among subgroups such as patients with CHD little is known. Snygg-Martin et al.[20] and Moore et al.[22] found a significantly higher risk of IE among men compared with women, whereas Rushani et al.[21] found similar incidences among men and women. Likewise, we found an almost twice as high risk of IE among men compared with women even though the sex distribution among patients with CHD were equal. The majority of previous studies on IE shows a higher incidence of IE among men,[6-8,23] however, the reason for this matter remains to be explained fully. Further, Moore et al.[22] and Rushani et al.[21] found that patients with cardiac prostheses were associated with an increased risk of IE, which is in line with our findings and also in line with treatment guidelines.[7] Notably, besides male sex and cardiac prostheses, we also found that chronic kidney disease and the presence of cardiac implantable electronic devices were associated with a significantly increased risk of IE among patients with CHD. In the general population, patients with cardiac implantable electronic devices are considered at moderate risk of IE,[9] but to our knowledge, no prior study has shown that CHD-patients with cardiac implantable electronic devices are in a further increased risk of IE. Severe kidney disease and diabetes mellitus are known risk factors for IE in the general population,[25] but to our knowledge no prior study has investigated the associated risk among patients with CHD. We found an increased risk of IE among CHD-patients with chronic kidney disease but not diabetes mellitus. Thus, not only male sex and cardiac prostheses but also cardiac implantable electronic devices and chronic kidney disease are associated with a significantly increased risk of IE among patients with CHD. Thus, our findings confirm that these known risk factors also should be considered as risk factors among this high-risk group of patients with CHD. Correction of cyanotic CHD by surgery was associated with a decreased risk of IE, yet presence of a cardiac prostheses was associated with an increased IE-risk as shown in Figure 4. We suggest that guidelines include these risk factors in the recommendations on antibiotic prophylaxis among patients with CHD.

Strengths and limitations

The main strength of this study is the completeness of data in a large nationwide cohort of all patients diagnosed with CHD in a 42-year observation period. The Danish health care system, funded by taxes, provides equal access to health care services for all residents regardless of socioeconomic or insurance status. However, the findings in this study should be viewed in the context of its limitations. The accuracy of the data relies upon the coding in nationwide administrative registries which have been validated previously.[26,18] When diagnosed at a smaller hospital, patients are usually followed at one of the university hospitals, therefore they should have a diagnosis registered at one of these if they have a congenital heart defect. When including patients with a CHD-diagnosis from any Danish hospital as done in the second sensitivity analysis, unfortunately, too many patients were classified as "other congenital heart disease". Therefore, we only included patients diagnosed at one of the four major university hospitals in Denmark to increase the validity of the diagnoses as done previously.[15] However, there is a possible misclassification bias due to the hierarchy of diagnosis, but in the third sensitivity analysis including all CHD-diagnoses, the overall findings of this large epidemiological study remained similar, thus we did not find evidence that the results were ex-

plained by bias. Moreover, the diagnosis of IE have previously been validated with high positive predictive values.[18] We were not able to differentiate between the location of IE (ie, prosthetic valve, native valve, or cardiac implantable electronic devices) and data on microbiology, use of antibiotic therapy, echocardiographic findings, and other imaging modalities (eg, CT) were not available. Further, we were not able to compare surgical versus transcatheter interventions due to few patients in the transcatheter group. Patients were followed up to 42 years with a median follow-up of 17.7 years. Thus, most of the patients in our study are children and adolescents, we expect the incidence of IE to increase to increasing age, but this remains speculative. The observational nature of this study precludes the assessment of cause-effect relationships, and the influence of potential confounders including potentially applied preventive measures and thus residual confounding cannot be omitted despite adjustment for potential confounders in the Cox regression models; therefore, our results are conservative.

Conclusion

The long-term incidence of IE among patients with CHD is substantial and significantly higher compared with the background population. Patients with CHD in high risk of IE is a heterogenous group including patients with cyanotic heart defects, but also atrioventricular septal defects, and heart valve defects, meanwhile factors associated with an increased risk of IE among patients with CHD include male sex, cardiac prosthesis, chronic kidney disease, and presence of cardiac implantable electronic devices. With an increasing longevity of these patients, preventive measures are important to improve morbidity, mortality, and the quality of life among this growing group of patients.

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Conflict of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.01.012.

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