ESC European Society of Cardiology

European Heart Journal (2023) **44**, 741–748
https://doi.org/10.1093/eurheartj/ehac727

CLINICAL RESEARCH
Congenital heart disease

Lifetime risk of comorbidity in patients with simple congenital heart disease: a Danish nationwide study

Mohamad El-Chouli [1]*, Alessandra Meddis [2], Daniel M. Christensen [1], Thomas A. Gerds [1,2], Thomas Sehested [1,3], Morten Malmborg [1], Matthew Phelps [1], Casper N. Bang [4], Ole Ahlehoff [5], Christian Torp-Pedersen [6], Caroline Sindet-Pedersen [7], Jakob Raunsø [7], Lars Idorn[8], and Gunnar Gislason [1,9,10]

[1]Danish Heart Foundation, Vognmagergade 7, 1120 Copenhagen, Denmark; [2]Section of Biostatistics, University of Copenhagen, Copenhagen, Denmark; [3]Department of Cardiology, Roskilde University Hospital, Zealand, Denmark; [4]Department of Cardiology, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark; [5]Department of Cardiology, The Heart Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [6]Departments of Clinical Investigation and Cardiology, North Zealand University Hospital, Hillerød, Denmark; [7]Department of Cardiology, Copenhagen University Hospital, Herlev and Gentofte, Herlev, Denmark; [8]Department of Pediatric Cardiology, Rigshospitalet, Copenhagen, Denmark; [9]Department of Cardiology, Copenhagen University Hospital, Herlev and Gentofte, Hellerup, Denmark; and [10]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Received 9 May 2022; revised 25 October 2022; accepted 23 November 2022; online publish-ahead-of-print 7 December 2022

Abstract

Aims In a continuously ageing population of patients with congenital heart disease (CHD), understanding the long-term risk of morbidity is crucial. The aim of this study was to compare the lifetime risks of developing comorbidities in patients with simple CHD and matched controls.

Methods and results Using the Danish nationwide registers spanning from 1977 to 2018, simple CHD cases were defined as isolated atrial septal defect (ASD), ventricular septal defect (VSD), pulmonary stenosis, or patent ductus arteriosus in patients surviving until at least 5 years of age. There were 10 controls identified per case. Reported were absolute lifetime risks and lifetime risk differences (between patients with simple CHD and controls) of incident comorbidities stratified by groups and specific cardiovascular comorbidities. Of the included 17 157 individuals with simple CHD, the largest subgroups were ASD (37.7%) and VSD (33.9%), and 52% were females. The median follow-up time for patients with CHD was 21.2 years (interquartile range: 9.4–39.0) and for controls, 19.8 years (9.0–37.0). The lifetime risks for the investigated comorbidities were higher and appeared overall at younger ages for simple CHD compared with controls, except for neoplasms and chronic kidney disease. The lifetime risk difference among the comorbidity groups was highest for neurological disease (male: 15.2%, female: 11.3%), pulmonary disease (male: 9.1%, female: 11.7%), and among the specific comorbidities for stroke (male: 18.9%, female: 11.4%). The overall risk of stroke in patients with simple CHD was mainly driven by ASD (male: 28.9%, female: 17.5%), while the risks of myocardial infarction and heart failure were driven by VSD. The associated lifetime risks of stroke, myocardial infarction, and heart failure in both sexes were smaller in invasively treated patients compared with untreated patients with simple CHD.

Conclusion Patients with simple CHD had increased lifetime risks of all comorbidities compared with matched controls, except for neoplasms and chronic kidney disease. These findings highlight the need for increased attention towards early management of comorbidity risk factors.

* Corresponding author. Tel: +45 70 25 00 00, Fax: +45 3393 1245, Email: moelchouli@gmail.com

Structured Graphical Abstract

Key Question

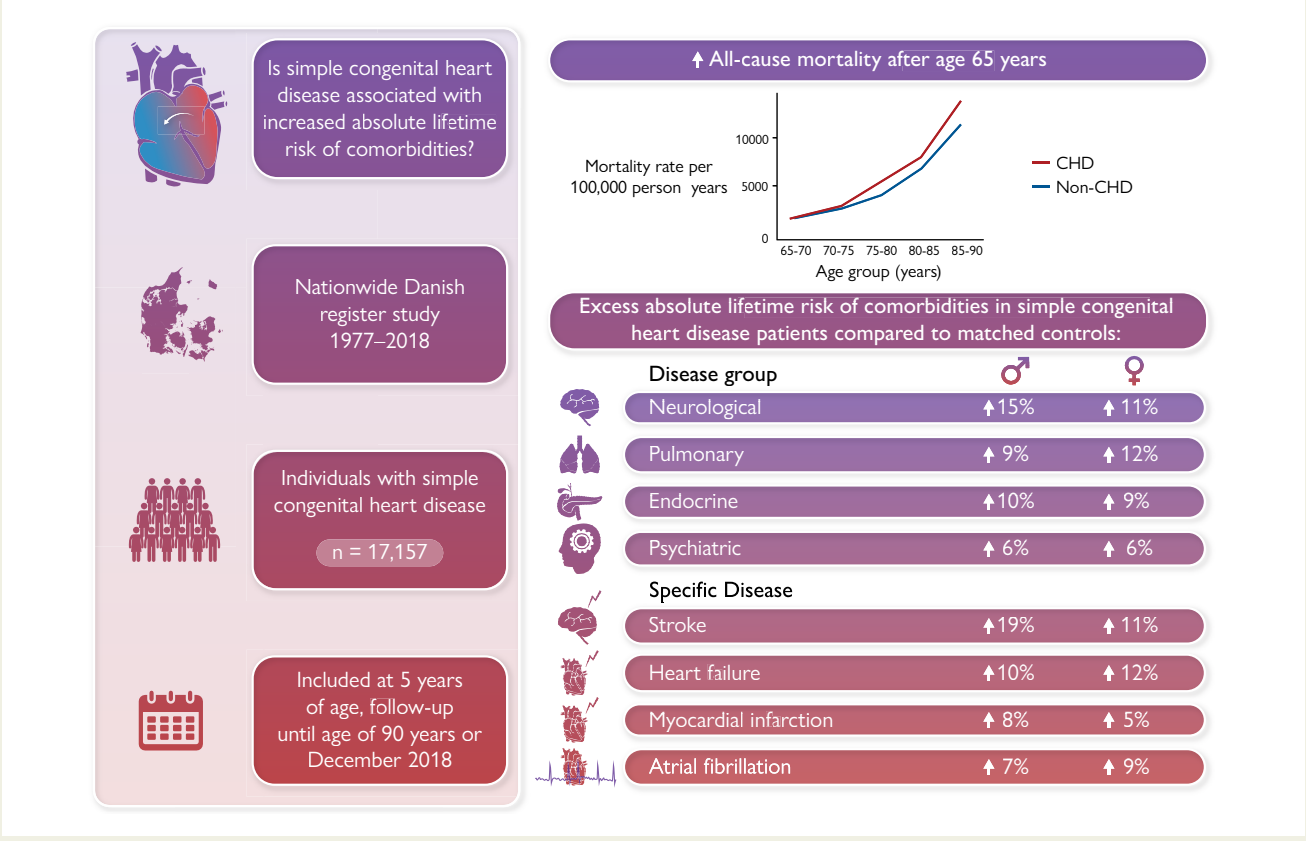
Do patients with simple congenital heart disease (CHD) face increased lifetime risk of comorbidities and increased mortality compared with matched controls without CHD?

Key Finding

Patients with simple CHD had a shorter life expectancy and excess lifetime risk of comorbidities compared with matched controls, most notably for neurological disease, pulmonary disease, heart failure and stroke.

Take Home Message

Early assessment of comorbidity risk and assessment of modifiable risk factors in simple CHD patients warrant consideration in future Guidelines for management of adult CHD.



Background, methods, and highlighted results of the current study investigating the lifetime risks of comorbidities and mortality in patients with simple congenital heart disease compared with sex- and birth-year-matched controls. 'Excess risk' means the excess risk among simple congenital heart disease patients compared with sex- and birth-year-matched controls. CHD, congenital heart disease.

Keywords Adult congenital heart disease • Lifetime risks • Comorbidity burden • Surgery • Procedures • Mortality Epidemiology • Register studies

Introduction

Since 1960s, the treatment of congenital heart disease (CHD) has improved considerably, and now >90% of children with CHD survive into adulthood.[1] This has led to a growing number of adults living with CHD, and, consequently, adults with CHD currently outnumber children.[2] Hence, focus in patients with CHD is shifting from survival in childhood to management of long-term morbidity, as well as the associated growing healthcare usage and rapidly rising costs of treatments.[3–6]

Major gaps in knowledge persist regarding the long-term morbidity of patients with simple CHD.[7] This is reflected in the international adult CHD guidelines, where the comorbidity burden is not accounted for when assessing the need for follow-up in patients with simple CHD.[7,8] This could be problematic since evidence points towards

elderly patients with CHD facing an increased mortality burden compared with the background population, mainly driven by non-cardiovascular comorbidities rather than CHD-related complications.[9–14] Across all severities, patients with CHD also face increased morbidity compared with healthy controls.[15–17] However, most studies consider CHD as one group, not specifically addressing the subgroup of patients with simple CHD. Since patients with severe CHD face much higher mortality and morbidity compared with patients with simple CHD, it is necessary to study patients with simple CHD separately. For these reasons, knowledge on the long-term excess risks of developing diseases in patients with simple CHD compared with the background population may have important clinical implications.

We used the Danish national registers to study lifetime risks of developing comorbidities in patients with simple CHD compared with non-CHD matched controls. We focused on the risks of developing neurological, endocrine, pulmonary, psychiatric, and neoplasm diseases, as well as stroke, myocardial infarction, atrial fibrillation, heart failure, infective endocarditis, and chronic kidney disease (CKD).

Methods

Data source

All Danish residents are issued a unique and permanent civil registration number at birth or immigration. The civil registration number allows linkage of all data from the national Danish registers by cross-referencing the national registers at the individual level. In this study, data regarding hospital discharge diagnoses, outpatient clinic visits, and invasive interventions were used. These data have previously been validated with high validity for cardiovascular research [positive predictive values of 89.0%–98.4% (ICD-10) and 88.2% (ICD-8)].[18] Between 1977 and 1993, diagnoses were coded according to the International Classification of Diseases (ICD), 8th revision. Since 1994, the more comprehensive ICD-10 has been used.

Study population

The CHD population consists of all individuals diagnosed with simple CHD between 1977 and 2018. Simple CHD is defined as an isolated ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), or pulmonary stenosis (PS), consistent with international guidelines.[7,8] A defect was not considered simple and thus excluded from the study, if the individual died during the first 5 years of life or if they were diagnosed at any time with Eisenmenger syndrome, pulmonary hypertension, had invasive treatment for more than one type of simple CHD, or had missing data, as inspired by a previous study and described previously.[9,10] To reduce classification error attributable to unregistered moderate or severe CHD at the time of diagnosis, we conditioned simple CHD diagnosis on future diagnoses. We identified 10 controls per patient with CHD, matched by sex and birth year. Birth year was chosen as a matching variable to account for temporal trends.

The diagnosis codes and invasive procedure codes used in this study are listed in Supplementary material online, *Table S1*.

Outcomes

The primary outcome was lifetime risk of first-time occurrence of the comorbidities of interest (incident comorbidities). Comorbidities of interest were neurological disease, endocrine disease, pulmonary disease, psychiatric disease, or neoplasm. The secondary outcome was the lifetime risk of specific diagnoses, including incident myocardial infarction, ischaemic stroke, heart failure, atrial fibrillation, or flutter (which will be referred to as 'atrial fibrillation' in the rest of the manuscript), infective endocarditis, and CKD. The ICD codes are listed in Supplementary material online, *Table S1*.

Supplementary outcomes

All-cause mortality rates per 100 000 person-years were reported, stratified by CHD and controls. The age-specific rates used to calculate the lifetime risks of comorbidities were reported per 100 000 person-years. To explore the potential effect of surgery or invasive interventions for CHD, the lifetime risks of comorbidities were stratified by treated and untreated CHD. To investigate whether specific simple CHD diagnoses had an increased risk for selected comorbidities, the lifetime risks of comorbidities were stratified by CHD diagnosis (ASD, VSD, PDA, and PS).

Statistical analysis

All individuals were followed from either 5 years of age or 1977, whichever came last, until emigration, death, or 31 December 2018 (end-of-study period), whichever came first. All analyses were performed separately for females and males, and separately for simple CHD and their matched controls. We categorized ages into 5-year long intervals between age 5 and age 90 and calculated age-specific rates of the comorbidity of interest as well as age-specific mortality rates. We report the age-standardized all-cause mortality rates and the age-standardized all-cause mortality rate ratio for simple CHD vs. matched controls.

We calculated the comorbidity lifetime risk between age 5 and age 90 using multiple decrement life-table methods using a radix of 100 000.[19] Note that the calculation of the lifetime risk is based on the observed age-specific comorbidity and mortality rates and that its interpretation is based on a hypothetical population of 100 000 5-year-old individuals. The lifetime risk is the probability of comorbidity occurrence between 5 and 90 years in the population. The standard errors of the estimated lifetime risks were obtained with the non-parametric bootstrap using 10 000 bootstrap samples. Based on the standard errors, we computed 95% Wald confidence intervals (CIs) for the lifetime risks and Wald tests for the differences in the lifetime risks between simple CHD and matched controls. Reported were the lifetime risks of incident comorbidities with 95% CI, the risk difference as the excess risk in patients with simple CHD compared with matched controls, and two-sided *P*-values for testing risk differences. In a supplementary analysis, we calculated age-specific comorbidity and mortality rates based on age-specific pre-intervention rates and compared them to lifetime comorbidity risks based on age-specific post-intervention rates. Using the same methods as for the main analysis, we reported the lifetime comorbidity risks in a pre-intervention population and compared them to the lifetime comorbidity risks in a post-intervention population.

All statistical analyses were performed using the statistical software R, version 4.0.3.[20]

Ethics

Retrospective register-based studies using Danish nationwide register data do not require ethical approval in Denmark. The data-responsible institution (the capital region of Denmark) approved the study (approval number P-2019-348).

Results

Out of 34 512 patients with ASD, VSD, PDA, or PS between 1977 and 2018, 17 157 individuals with simple CHD were eligible for inclusion in our study (*Figure 1*). In the simple CHD population, 52% were females (*Table 1*). The median follow-up time was 21.2 years [interquartile range (IQR): 9.4–39.0] for patients with simple CHD and 19.8 years (IQR: 9.0–37.0) for matched controls. Patients with simple CHD contributed a total of 348 137 patient-years, while matched controls contributed a total of 3 328 002 patient-years. The largest CHD subgroup consisted of ASD (37.7%), followed by VSD (33.9%), PDA (23.9%), and PS (4.5%; *Table 1*). Between 1977–86 and 2007–18, the median age at the time of diagnosis decreased (7 years to 1 year), but the span of diagnosis age increased (0–21 years to 0–40 years; *Table 1*). A total of 2994 (17.5%) patients with

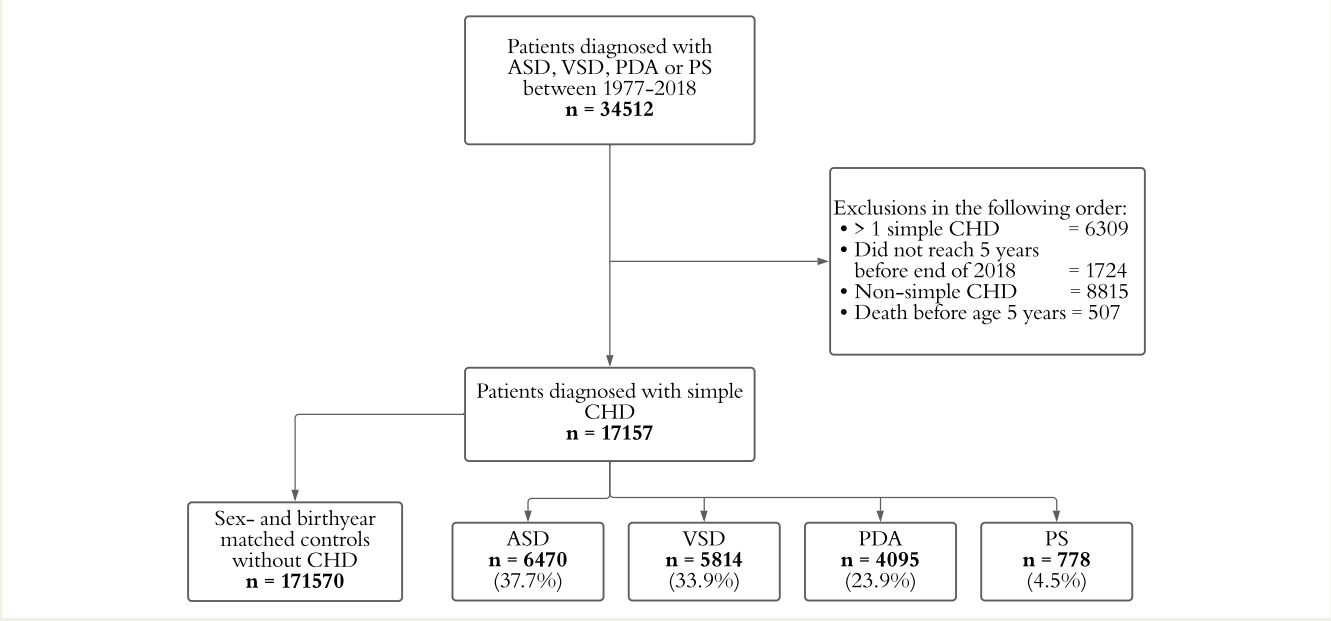


Figure 1 Flow chart depicting study inclusion, exclusion, and sampling of cases and controls from the Danish nationwide registers. Of 34 512 patients with the relevant simple congenital heart disease diagnoses (atrial septal defect, ventricular septal defect, patent ductus arteriosus, pulmonary stenosis), 6470 (37.7%) were diagnosed with simple atrial septal defect, 5814 (33.9%) with simple ventricular septal defect, 4095 (23.9%) with simple patent ductus arteriosus, and 778 (4.5%) with simple pulmonary stenosis. The 10 controls per simple congenital heart disease ($n = 171\,570$) case, matched on sex and birth year, were identified using the nationwide Danish registers. Non-simple congenital heart disease = any additional congenital heart disease diagnosis other than atrial septal defect, ventricular septal defect, patent ductus arteriosus, or pulmonary stenosis.

Table 1 Baseline characteristics of the study population, stratified by calendar-year groups at time of diagnosis

		1977–1986	1987–1996	1997–2006	2007–2018	Total
Patients, *n*		2687	3462	4218	6790	17 157
Median age of diagnosis, years (IQR)		7 (0–21)	0 (0–7)	0 (0–10)	1 (0–40)	1 (0–23)
Sex, male, *n* (%)		1318 (49.0)	1640 (47.4)	1938 (45.9)	3348 (49.3)	8242 (48.0)
Simple CHD diagnosis, *n* (%)	Ventricular septal defect	1180 (43.9)	1383 (39.9)	1560 (37.0)	1691 (24.9)	5814 (33.9)
	Atrial septal defect	676 (25.2)	793 (22.9)	1388 (32.9)	3613 (53.2)	6470 (37.7)
	Patent ductus arteriosus	703 (26.2)	1142 (33.0)	1058 (25.1)	1192 (17.6)	4095 (23.9)
	Pulmonary stenosis	128 (4.8)	144 (4.2)	212 (5.0)	294 (4.3)	778 (4.5)
Invasive intervention during 1977–2018, *n* (%)		491 (18.3)	490 (14.2)	558 (13.2)	1455 (21.4)	2994 (17.5)
Genetic syndrome, *n* (%)		37 (1.4)	71 (2.1)	160 (3.8)	155 (2.2)	423 (2.5)

IQR, interquartile range, using the 25th and 75th quartiles.

simple CHD had undergone an interventional surgery or procedure, of which the majority were ASD [ASD: 1834 (61.3%) and median age at intervention time: 42 years; VSD: 323 (10.8%) and median age at intervention time: 1 year; PDA: 785 (26.2%) and median age at intervention time: 2 years; PS: 52 (1.7%) and median age at intervention time: 3 years; *Table 1*]. All-cause mortality rates were comparable between patients with simple CHD and the matched controls in the overall analysis [rates per 1000 person-years for males: CHD 82.2 (75.5–89.2) vs. controls 80.0 (77.7–82.1)]. Rate ratio: 1.0 (0.9–1.1). For females: CHD 75.6 (69.5–82.1) vs. controls 71.8 (69.8–73.8). Rate ratio: 1.1 (1.0–1.1)] and younger age groups, but were higher in patients with simple CHD after ages 70–75 years (mortality rate per 100 000 person-years in the age group 75–80 years: CHD: 5536, non-CHD: 4303; see Supplementary material online, *Figure S1*).

Around 423 (2.5%) of the patients with simple CHD had a genetic syndrome. Due to the small sample size in this group (total person-years = 6266), calculating the lifetime risk of comorbidities in this group was not possible. Calculating the lifetime risk in patients with simple CHD without genetic syndrome ($n = 16\,734$) yielded no significant different results compared with the main analysis (data not shown).

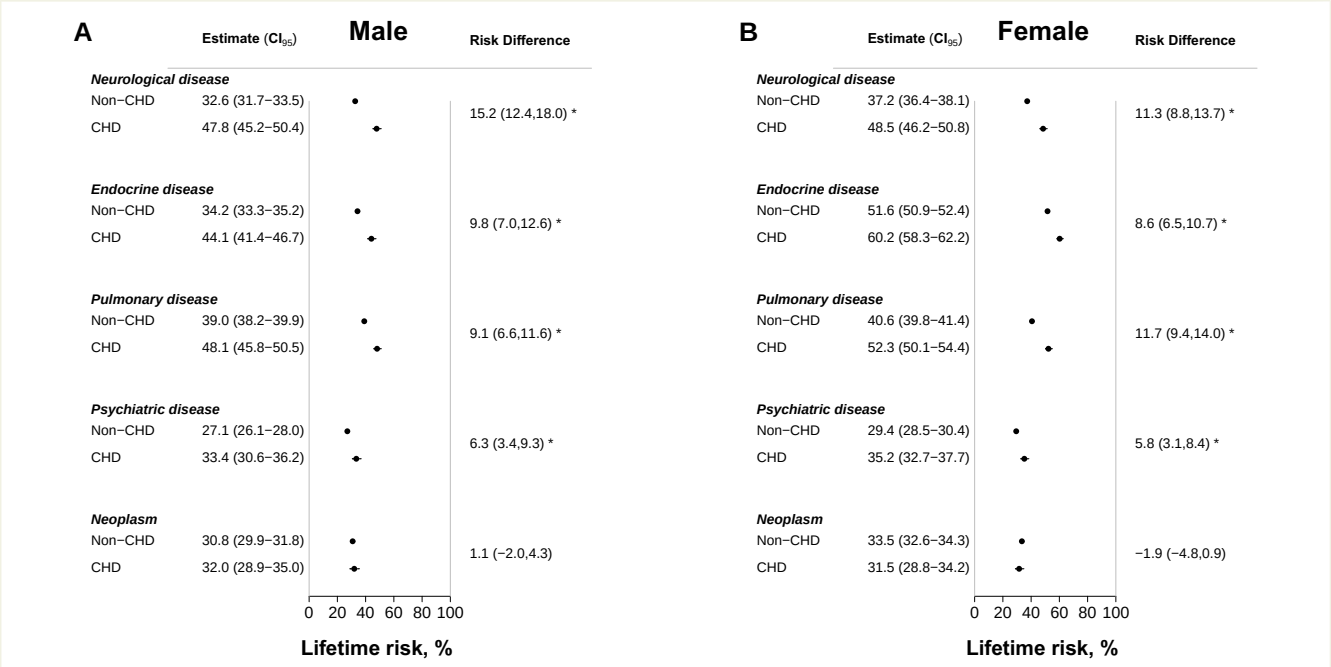


Figure 2 Forest plot showing the lifetime risk of developing first-time comorbidities for patients with simple congenital heart disease and matched controls. The *x*-axis depicts the lifetime risk estimates (bullet) with 95% confidence interval (parentheses) and the *y*-axis depicts the comorbidity groups stratified by patients with congenital heart disease and matched controls (non-congenital heart disease). Risk difference depicts excess risk among patients with congenital heart disease compared with non-congenital heart disease controls, an asterisk (*) after the 95% confidence interval signals that the risk difference is statistically significant. (*A*) Analyses for male patients. (*B*) Analyses for female patients. The specific lifetime risk estimates and the 95% confidence intervals are provided to the left of the graph, while the risk difference between simple congenital heart disease and matched controls with corresponding 95% confidence intervals is provided to the right.

Lifetime risk for comorbidity groups

For both males and females, the lifetime risks of all comorbidities groups of interest were higher for patients with CHD than for controls, the exception being neoplasms (*Figure 2*). The largest lifetime risks were observed for pulmonary disease (male: CHD 48.1%, non-CHD 39.0%; female: CHD 52.3%, non-CHD 40.6%), endocrine disease (male: CHD 44.1%, non-CHD 34.2%; female: CHD 60.2%, non-CHD 51.6%), and neurological disease (male: CHD 47.8%, non-CHD 32.6%; female: CHD 48.5%, non-CHD 37.2%). The largest risk difference between CHD and non-CHD was seen for neurological disease, where patients with CHD had an excess risk [male: 15.2% (CI: 12.4%–18.0%); female: 11.3% (CI: 8.8%–13.7); *Figure 2*].

For most comorbidity groups, the excess in age-specific rates in patients with simple CHD compared with controls was seen in the eldest age groups but began at earlier ages (age 50–60 years for endocrine and pulmonary disease, 35–40 years for neurological disease; see Supplementary material online, *Figs S2–S4*). For psychiatric diseases, the excess in age-specific rates in patients with simple CHD was largest at the younger age groups, while the rates were comparable through all age groups for neoplasms (see Supplementary material online, *Figs S5* and *S6*).

The lifetime risks stratified by simple CHD diagnosis showed that while the number of patients with CHD in each group was low, yielding insufficient power to detect small differences, the risk difference in neurological disease was mainly driven by patients with ASD (male: 21.7%, female: 16.2%; see Supplementary material online, *Figs S13, S15, S17,* and *S19*). The associated lifetime risks for comorbidity groups stratified by treated and untreated CHD showed a significantly increased associated risk of psychiatric diseases in treated CHD patients. The analysis for treated ASD showed a significantly increased risk among treated CHD patients of psychiatric disease for both sexes and neoplasms for males only (see Supplementary material online, *Figs S21* and *S23*). However, these risk differences had wide CIs. Stratification by treatment for VSD, PDA, or PS was not possible due to small sample size.

Lifetime risk for specific comorbidities

For both males and females, the risk of developing the specific comorbidities of interest was higher for CHD than controls (*Figure 3*). Among males, the risk was highest for stroke, heart failure, and myocardial infarction, while among females, it was highest for stroke, heart failure, and atrial fibrillation. For both sexes, the largest risk difference was for stroke (male: 18.9%, female: 11.4%), while there was no significant risk difference for CKD [male: 0.3% (CI: −1.4 to 1.9), female: 2.2% (CI: 0.0–4.4)].

The age-specific rates of stroke increased for patients with simple CHD compared with controls at around age 25–30 years and accelerated around age 40–45 years for both sexes (see Supplementary material online, *Figure S7*). The age-specific rates of myocardial infarction, atrial fibrillation, heart failure, and infective endocarditis in simple CHD increased considerably more than controls later in life, around age 50–60 years for males and 5–15 years later for females (see Supplementary material online, *Figs S8–S11*). There were no discernible differences in age-specific rates between simple CHD and controls of CKD (see Supplementary material online, *Figure S12*).

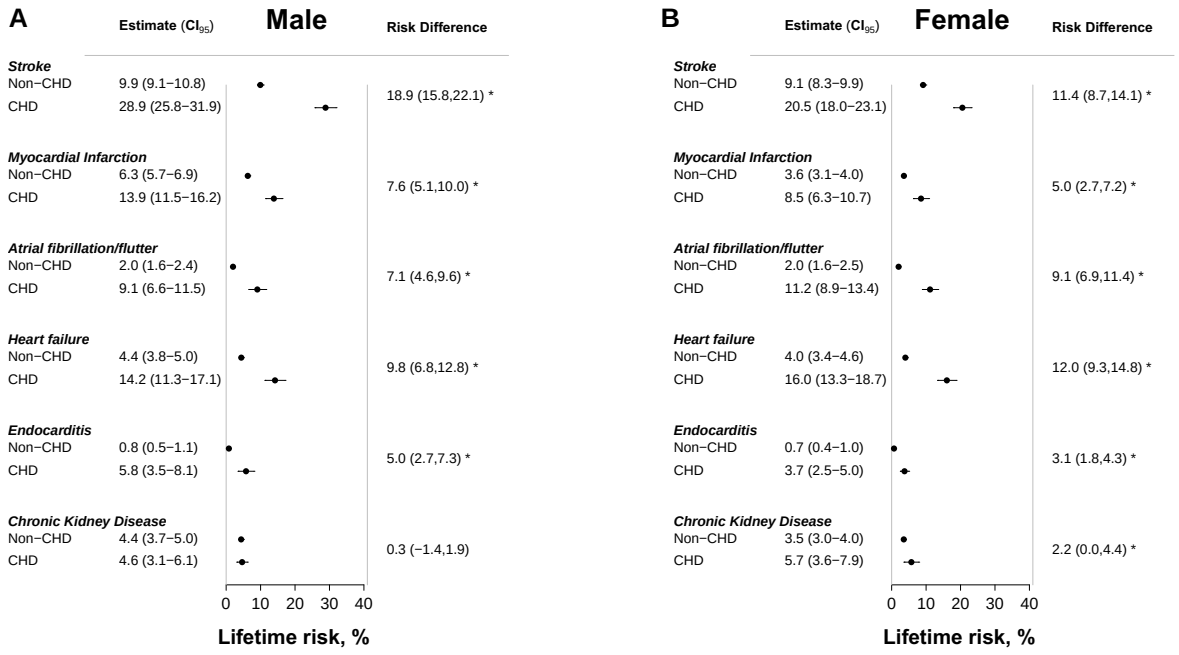


Figure 3 Forest plot showing the lifetime risk of developing first-time specific comorbidities for patients with simple congenital heart disease and matched controls. The *x*-axis depicts the lifetime risk estimates (bullet) with 95% confidence interval (parentheses) and the *y*-axis depicts the specific comorbidities stratified by patients with congenital heart disease and matched controls (non-congenital heart disease). Risk difference depicts excess risk among patients with congenital heart disease compared with non-congenital heart disease controls, an asterisk (*) after the 95% confidence interval signals that the risk difference is statistically significant. (*A*) Analyses for male patients. (*B*) Analyses for female patients. The specific lifetime risk estimates and the 95% confidence intervals are provided to the left of the graph, while the risk difference between simple congenital heart disease and matched controls with corresponding 95% confidence intervals is provided to the right.

The results stratified by CHD diagnosis show that the observed risk differences for stroke and, to a lesser degree, atrial fibrillation were mainly driven by ASD (stroke: male 28.9%, female 17.5%; atrial fibrillation: male 9.3%, female 11.2%). The risk differences for myocardial infarction (male: 16.1%, female: 11.1%) and heart failure (male: 14.7%, female: 13.9%) were mainly driven by VSD (see Supplementary material online, *Figs S14*, *S16*, *S18*, and *S20*), whereas the risk difference for stroke in VSD patients was not significant. The analysis of specific comorbidities stratified by treatment showed a significantly reduced associated risk in treated simple CHD patients for stroke [risk difference male: −17.7% (CI: −24.2 to −11.2), female: −6.3% (CI: −12.3 to −0.2)], myocardial infarction [risk difference male: −15.0% (CI: −19.2 to −10.8), female: −8.3% (CI: −12.0 to −4.7)], and heart failure [risk difference male: −12.1% (CI: −17.6 to −6.6), female: −10.8% (CI: −16.2 to −5.4)] for both sexes compared with untreated patients (see Supplementary material online, *Figure S22*). The analysis of treated ASD patients showed a significantly reduced associated risk in treated ASD patients for stroke [risk difference male: −24.8%, (CI: −32.3 to −17.2), female: -12.4% (CI: −21.2 to -3.5)] and heart failure [male: −8.7% (CI: −13.9 to −3.6), female: −11.9% (-19.8 to −4.0)] in both sexes (see Supplementary material online, *Figure S24*).

Discussion

The main finding in this study was that patients with simple CHD had a significantly higher lifetime risk for most of the investigated comorbidities compared with sex- and birth-year-matched controls without CHD. Among comorbidity groups, the risk difference was largest for neurological disease, pulmonary disease, and, among specific diagnoses, stroke and heart failure (*Structured Graphical Abstract*). While the difference in comorbidity rates was largest in the eldest age groups, we observed that the differences between simple CHD and the control group began at much earlier ages for many comorbidities. Furthermore, we found that treated simple CHD, compared with untreated simple CHD, had a lower associated risk of stroke, myocardial infarction, and heart failure for both sexes, but did not have a significantly different associated risk for infective endocarditis or non-cardiovascular comorbidities. While genetic syndromes may generally influence the rate of comorbidities, they did not affect our results, probably due to the low prevalence of these patients in our population with isolated CHD.[21–23] This study reports novel data on the lifetime risks of comorbidities in a population of simple CHD individuals and helps to bridge a major knowledge gap in for the largest subgroup of patients with CHD.[7] In the older age group (70 years and older), we also found an increased risk of mortality in patients with CHD compared with the matched controls without simple CHD. In this age group, mortality is mainly driven by non-cardiovascular comorbidities rather than complications from the cardiac defect itself, which emphasizes the importance of our findings.[14] These findings highlight the need for attention among clinicians towards the early identification and management of risk factors for said comorbidities in patients with simple CHD.

Previous studies comparing patients with CHD of all severities, including simple CHD, to controls found similar tendencies of patients with CHD having a higher prevalence of comorbidities compared

with non-CHD controls.[15,24,25] In contrast to our findings, one study found that patients with CHD had a higher prevalence of neoplasms compared with controls in a 18- to 64-year-old cohort.[15] The difference may be due to their inclusion of severe CHD, as repeated radiation from chest X-rays, computed tomography scans, and procedures with catheterizations, often required in patients with severe CHD, is associated with a higher risk of neoplasms.[26] A recent study found that CHD, both simple and severe, was associated with an increased risk of childhood cancer.[27] Reassuringly, our study suggests that such findings do not pertain to patients with simple CHD.

Several mechanisms may explain the association between CHD and other non-cardiovascular comorbidities. Neurological disease risk may be related to the structural changes in CHD, such as the possibility of venous to arterial shunt lesions leading to paradoxical embolisms, increased prevalence of intracranial aneurysms, and increased rates of atrial arrhythmias.[28] Furthermore, some patients received surgical closure using cardiopulmonary bypass, which would also increase the risk of cerebral micro thrombi or periprocedural cerebral hypoxia leading to cerebral damage.[29] Intrinsic abnormalities and iatrogenic changes in the thoracic area and spine may explain the risk of increased pulmonary disease,[26] both sternotomy and thoracotomy can cause scoliosis and restrictive lungs.[30–32] Increased pulmonary blood flow, as seen in ASD, VSD, and PDA, can lead to tunica media proliferation, leading to increased pulmonary vessel resistance.[32,33] Furthermore, acquired conditions that elevate left atrial pressure (e.g. hypertension or valvular heart disease) may increase the left-to-right shunt in simple ASD. This can lead to increased flow through the right side of the heart and in the pulmonary circulation, right ventricle volume overload, and the risk of atrial arrhythmias and increased pulmonary pressure later in life.[8] The Risk of endocrine disease is increased in individuals with genetic syndromes, or advanced heart failure, which are more common in patients with CHD compared with the background population.[28] Increased risk of psychiatric diseases may be attributed to many factors, including the higher rates of genetic syndromes in these patients as well as the physical, social, and mental impact of living with a chronic disease, including frequent healthcare contacts that lead to depression, anxiety, and social isolation.[25,26,34] In this study, it was mainly patients with PDA who drove the risk of psychiatric diseases. This study did not exclude premature children. Prematurity has previously been associated with psychiatric disease and may also explain the low rate of interventions seen in patients with PDA (19%).[35] Furthermore, patients with PDA underwent interventions at younger ages compared with patients with ASD. The young age of the patient at time of intervention has been associated with psychiatric disease.[36,37] This was particularly underlined in the treatment analysis, where a higher associated risk was seen in treated patients compared with untreated.

Lifetime risk of specific diseases

In our study, the lifetime risks of all the included cardiovascular comorbidities were higher in individuals with simple CHD compared with controls. The risks were highest for stroke and, to a lesser degree, myocardial infarction, heart failure, and atrial fibrillation. However, the lifetime risk for CKD was comparable between simple CHD and controls.

In line with our findings, previous cohort-based studies found that patients with CHD had a higher prevalence of atrial fibrillation, heart failure, and stroke compared with matched controls.[15,24] The population of both studies consisted mainly of simple or 'non-severe' CHD, but both included severe CHD in their analyses. Unlike our findings, both studies found a lower prevalence of stroke compared with other cardiovascular diseases. This difference may be attributed to the young average age in both studies, their results not being stratified by CHD severity, and their use of short-term estimates compared with our lifetime risks.[7,13,38]

The two cohort-based studies found an association between patients with stroke and CHD regardless of CHD severity compared with matched controls, most notably in men.[39,40] However, the risk differed according to the type of CHD. In fact, previous studies suggested that the CHD type was a better predictor of stroke than atherosclerotic risk factors in patients with CHD.[41] In accordance with this, we found that the association between stroke and simple CHD was mainly driven by ASD. The risk of stroke in ASD is increased by paradoxical embolism and atrial fibrillation.

Chronic kidney disease is a significant predictor of mortality in patients with CHD.[14,42] While we found a comparable risk between simple CHD and controls for CKD, others did not.[15,24] Those studies included people with severe CHD and a younger population. Severe CHD is associated with a higher risk of developing CKD compared with simple CHD, which may explain the difference in our results.[43]

Among invasively treated simple CHD patients, we found a reduced associated risk for stroke, myocardial infarction, and heart failure compared with untreated simple CHD. Some of these findings were not surprising, as persisting shunts dispose to, among others, heart failure, and stroke.[44,45] Previous studies have found an increased myocardial infarction risk in both ASD and VSD, but those who compared treated and untreated CHD had limited sample size.[13,46] We found no difference in the risk of infective endocarditis between treated and untreated simple CHD patients. The majority of our treated patients had isolated ASD, which has a negligible infective endocarditis risk, which also applies to isolated PS or VSD without valvular heart disease.[47] Thus, the potential difference would likely be small, requiring a much larger sample size of treated patients.

While the association between CHD and some diseases is well understood, including stroke risk in ASD or infective endocarditis in shunts, further research in the mechanisms behind the association with other comorbidities is warranted.[8] Previous studies have shown that untreated shunts are a risk factor for infective endocarditis, heart failure, and stroke and untreated PS for atrial arrhythmia.[44,45,48,49] Yet, cardiac invasive treatment can be a risk factor for atrial arrhythmia.[50] Several mechanisms behind the increased risk of comorbidities in patients with CHD have been suggested. Increased risk of myocardial infarction in patients with CHD has come to focus in recent years due to increased life expectancy, and the risk seems to be CHD-related lesion dependent rather than based on atherosclerotic basis.[51] Due to the observational nature of our study, we can only speculate on the mechanisms behind this risk, being mainly driven by VSD patients and not, e.g. ASD. In this study, 10.8% of the patients with VSD had undergone interventional treatment. While interventricular shunts are more commonly left-to-right shunts, certain conditions can, over time, reverse the untreated shunt, which may facilitate intra-cardiac shunt-paradoxical coronary embolism.[52] Obesity, partly related to a reduced physical fitness and sedentary lifestyle, and endocrine diseases can cause hyperlipidaemia and can cause hormonal disruption, leading to an increased risk of arrhythmias.[28,43] Lastly, structural changes stemming from CHD can alter the structural and molecular properties of the heart and lung vasculature.[53]

Strengths and limitations

The main strengths of this nationwide study include the unique large sample size, long-term inclusion period, low risk of selection bias, and minimal loss to follow-up due to the tax-supported healthcare system

with universal access for all Danish citizens. The low incidence and increasing prevalence of CHD make large-scale observational studies optimal to investigate long-term outcomes.

The main limitation in this study relates to the absence of some clinical data from the nationwide registers. This includes detailed descriptions of the lesions or lifestyle information (such as smoking or body mass index). These data may be important to determine the exact severity of the CHD or can affect the long-term risk of developing comorbidities. Furthermore, ICD-8 and ICD-10 do not discern between CHD severity, raising the possibility of misclassification. We have therefore chosen a proxy for simple severity where the included patients have an isolated CHD lesion and have survived the first 5 years. This was partly inspired by the American Heart Association guidelines and partly by a previous registry-based study.[7,10] To reduce the registration problem related to individuals with multiple CHDs with different diagnosis dates, we excluded patients if they received a second CHD diagnosis later in life. We have described this in more detail in a previous paper.[9]

Another limitation to our study is the possibility of surveillance bias, which may lead to an overestimation of the lifetime risks of comorbidities. Patients diagnosed with simple CHD compared with individuals without CHD could be more likely to have frequent contacts to their physicians. This may lead to more frequent tests. Some outcomes lead to diagnostic workup resulting in simple CHD diagnosis. As the authors have previously shown, an increasing percentage of the annually diagnosed patients with ASD had a stroke preceding their ASD diagnosis within 1 year.[9] This may lead to an overestimation of the lifetime risk of stroke in patients with ASD, as there is an unknown, undiagnosed part of the ASD population that did not have a stroke diagnosis but was never diagnosed with ASD and, thus, does not contribute to the lifetime risk analysis. While this form of bias cannot be ruled out, we reassuringly did not find an increased neoplasm risk in patients with simple CHD, as some forms of neoplasms are sensitive to overdiagnosis.[54]

An additional limitation concerns the comparison of lifetime risks between patients who received invasive treatment and untreated patients. Treated and untreated patients have different distributions of birth year, making comparison difficult. Since patients who were treated before age *x* contributed to comorbidity events and risk time to the analysis of lifetime risks in the treated group after age *x*, it is difficult to adjust the comparison of the lifetime risks for predictors (confounders) that change during life. Secondly, some of the observed significant differences in risks favouring treated patients may be due to the relatively small number of treated patients compared with untreated for VSD, PDA, and PS, thus limiting the number of events and underestimating the risk in the treated group.

Lastly, we calculated the lifetime risk of comorbidities based on the current registry data. Extrapolation of the results to children born with simple CHD in the future must therefore be done cautiously with this in mind.

Conclusion

The current study found that both men and women with simple CHD face a considerably increased lifetime risk of both cardiovascular and non-cardiovascular morbidity compared with individuals without CHD. These findings highlight the need for increased attention among clinicians for long-term morbidity in patients with simple CHD and early identification and management of risk factors. Future studies should determine the optimal course and degree of follow-up.

Supplementary data

Supplementary data is available at *European Heart Journal* online.

Funding

This project was financed fully by the Danish Heart Foundation [grant number: A8874-18-20207].

Conflict of Interest: Christian-Torp Pedersen has received grants for studies from Bayer and Novo Nordisk unrelated to the current study. Matthew Phelps has, after the initial submission of this paper, been employed by Novo Nordisk unrelated to this study. The other authors have no potential conflicts of interest to declare in relation to the publication this article.

Data Availability

The data for this study were obtained through the nationwide registers in Denmark. This data cannot be made publicly available as access must be granted to institutions by the Danish Data Protection Agency and The Danish Health Data Authority.

References

1. Warnes CA. The adult with congenital heart disease. *J Am Coll Cardiol* 2005;**46**:1–8. https://doi.org/10.1016/j.jacc.2005.02.083.
2. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation* 2007;**115**:163–172. https://doi.org/10.1161/CIRCULATIONAHA.106.627224.
3. Opotowsky AR, Siddiqi OK, Webb GD. Trends in hospitalizations for adults with congenital heart disease in the U.S. *J Am Coll Cardiol* 2009;**54**:460–467. https://doi.org/10.1016/j.jacc.2009.04.037.
4. Mylotte D, Pilote L, Ionescu-Ittu R, Abrahamowicz M, Khairy P, Therrien J, *et al.* Specialized adult congenital heart disease care: the impact of policy on mortality. *Circulation* 2014;**129**:1804–1812. https://doi.org/10.1161/CIRCULATIONAHA.113.005817.
5. Burchill LJ, Gao L, Kovacs AH, Opotowsky AR, Maxwell BG, Minnier J, *et al.* Hospitalization trends and health resource use for adult congenital heart disease–related heart failure. *J Am Heart Assoc* 2018;**7**:e008775. https://doi.org/10.1161/JAHA.118.008775.
6. Wren C. Survival with congenital heart disease and need for follow up in adult life. *Heart* 2001;**85**:438–443. https://doi.org/10.1136/heart.85.4.438.
7. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, *et al.* 2018 AHA/ACC Guideline for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;**139**:e637–e697. https://doi.org/10.1161/CIR.0000000000000602.
8. Baumgartner H, De Backer J. The ESC clinical practice guidelines for the management of adult congenital heart disease 2020. *Eur Heart J* 2020;**41**:4153–4154. https://doi.org/10.1093/eurheartj/ehaa701.
9. El-Chouli M, Mohr GH, Bang CN, Malmborg M, Ahlehoff O, Torp-Pedersen C, *et al.* Time trends in simple congenital heart disease over 39 years: a Danish nationwide study. *J Am Heart Assoc* 2021;**10**:e020375. https://doi.org/10.1161/JAHA.120.020375.
10. Videbæk J, Laursen HB, Olsen M, Høfsten DE, Johnsen SP. Long-term nationwide follow-up study of simple congenital heart disease diagnosed in otherwise healthy children. *Circulation* 2016;**133**:474–483. https://doi.org/10.1161/CIRCULATIONAHA.115.017226.
11. Kuijpers JM, van der Bom T, van Riel ACMJ, Meijboom FJ, van Dijk APJ, Pieper PG, *et al.* Secundum atrial septal defect is associated with reduced survival in adult men. *Eur Heart J* 2015;**36**:2079–2086. https://doi.org/10.1093/eurheartj/ehv097.
12. Nyboe C, Karunanithi Z, Nielsen-Kudsk JE, Hjortdal VE. Long-term mortality in patients with atrial septal defect: a nationwide cohort-study. *Eur Heart J* 2018;**39**:993–998. https://doi.org/10.1093/eurheartj/ehx687.
13. Fedchenko M, Mandalenakis Z, Giang KW, Rosengren A, Eriksson P, Dellborg M. Long-term outcomes after myocardial infarction in middle-aged and older patients with congenital heart disease—a nationwide study. *Eur Heart J* 2021;**42**:2577–2586. https://doi.org/10.1093/eurheartj/ehaa874.

14. Afilalo J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Marelli AJ. Geriatric congenital heart disease. *J Am Coll Cardiol* 2011;**58**:1509–1515. https://doi.org/10.1016/j.jacc.2011.06.041.
15. Agarwal A, Thombley R, Broberg CS, Harris IS, Foster E, Mahadevan VS, *et al.* Age- and lesion-related comorbidity burden among US adults with congenital heart disease: a population-based study. *J Am Heart Assoc* 2019;**8**:e013450. https://doi.org/10.1161/JAHA.119.013450.
16. Billett J, Majeed A, Gatzoulis M, Cowie M. Trends in hospital admissions, in-hospital case fatality and population mortality from congenital heart disease in England, 1994 to 2004. *Heart* 2008;**94**:342–348. https://doi.org/10.1136/hrt.2006.113787.
17. Schlichting LE, Insaf TZ, Zaidi AN, Lui GK, Van Zutphen AR. Maternal comorbidities and complications of delivery in pregnant women with congenital heart disease. *J Am Coll Cardiol* 2019;**73**:2181–2191. https://doi.org/10.1016/j.jacc.2019.01.069.
18. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–490. https://doi.org/10.2147/CLEP.S91125.
19. Preston SH, Patrick H, Michel G. *Demography: Measuring and Modeling Population Processes.* Oxford: Blackwell; 2001.
20. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2021. https://www.R-project.org/
21. Oyen N, Poulsen G, Boyd HA, Wohlfahrt J, Jensen PKA, Melbye M. National time trends in congenital heart defects, Denmark, 1977–2005. *Am Heart J* 2009;**157**:467–473.e1. https://doi.org/10.1016/j.ahj.2008.10.017.
22. Sobey CG, Judkins CP, Sundararajan V, Phan TG, Drummond GR, Srikanth VK. Risk of major cardiovascular events in people with down syndrome. *PLoS ONE* 2015;**10**:e0137093. https://doi.org/10.1371/journal.pone.0137093.
23. Aaberg KM, Bakken IJ, Lossius MI, Lund Søraas C, Håberg SE, Stoltenberg C, *et al.* Comorbidity and childhood epilepsy: a nationwide registry study. *Pediatrics* 2016;**138**:e20160921. https://doi.org/10.1542/peds.2016-0921.
24. Billett J, Cowie MR, Gatzoulis MA, Vonder Muhll IF, Majeed A. Comorbidity, healthcare utilisation and process of care measures in patients with congenital heart disease in the UK: cross-sectional, population-based study with case-control analysis. *Heart* 2008;**94**:1194–1199. https://doi.org/10.1136/hrt.2007.122671.
25. Yang HL, Chang NT, Wang JK, Lu CW, Huang YC, Moons P. Comorbidity as a mediator of depression in adults with congenital heart disease: a population-based cohort study. *Eur J Cardiovasc Nurs* 2020;**19**:732–739. https://doi.org/10.1177/1474515120923785.
26. Cohen SB, Ginde S, Bartz PJ, Earing MG. Extracardiac complications in adults with congenital heart disease: extracardiac complications. *Congenit Heart Dis* 2013;**8**:370–380. https://doi.org/10.1111/chd.12080.
27. Daltveit DS, Klungsøyr K, Engeland A, Ekbom A, Gissler M, Glimelius I, *et al.* Cancer risk in individuals with major birth defects: large Nordic population based case-control study among children, adolescents, and adults. *BMJ* 2020;**371**:m4060. https://doi.org/10.1136/bmj.m4060.
28. Lui GK, Saidi A, Bhatt AB, Burchill LJ, Deen JF, Earing MG, *et al.* Diagnosis and management of noncardiac complications in adults with congenital heart disease: a scientific statement from the American Heart Association. *Circulation* 2017;**136**:348–e392. https://doi.org/10.1161/CIR.0000000000000535.
29. Caldas JR, Haunton VJ, Panerai RB, Hajjar LA, Robinson TG. Cerebral autoregulation in cardiopulmonary bypass surgery: a systematic review. *Interact Cardiovasc Thorac Surg* 2018;**26**:494–503. https://doi.org/10.1093/icvts/ivx357.
30. Hawkins SMM, Taylor AL, Sillau SH, Mitchell MB, Rausch CM. Restrictive lung function in pediatric patients with structural congenital heart disease. *J Thorac Cardiovasc Surg* 2014;**148**:207–211. https://doi.org/10.1016/j.jtcvs.2013.07.080.
31. Feiz HH, Afrasiabi A, Parvizi R, Safarpour A, Fouladi RF. Scoliosis after thoracotomy/sternotomy in children with congenital heart disease. *Indian J Orthop* 2012;**46**:77–80. https://doi.org/10.4103/0019-5413.91639.
32. Healy F, Hanna BD, Zinman R. Pulmonary complications of congenital heart disease. *Paediatr Respir Rev* 2012;**13**:10–15. https://doi.org/10.1016/j.prrv.2011.01.007.
33. Muneuchi J, Ochiai Y, Masaki N, Okada S, Iida C, Sugitani Y, *et al.* Pulmonary arterial compliance is a useful predictor of pulmonary vascular disease in congenital heart disease. *Heart Vessels* 2019;**34**:470–476. https://doi.org/10.1007/s00380-018-1263-9.
34. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, *et al.* Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation* 2012;**126**:1143–1172. https://doi.org/10.1161/CIR.0b013e318265ee8a.
35. Rogvi RÁ, Forman JL, Greisen G. Prematurity, smallness-for-gestational age and later hospital admissions: a nation-wide registry study. *Early Hum Dev* 2015;**91**:299–306. https://doi.org/10.1016/j.earlhumdev.2015.02.010.
36. Miatton M, De Wolf D, François K, Thiery E, Vingerhoets G. Neuropsychological performance in school-aged children with surgically corrected congenital heart disease. *J Pediatr* 2007;**151**:73–78.e1. https://doi.org/10.1016/j.jpeds.2007.02.020.
37. Olsen M, Sørensen HT, Hjortdal VE, Christensen TD, Pedersen L. Congenital heart defects and developmental and other psychiatric disorders. *Circulation* 2011;**124**:1706–1712. https://doi.org/10.1161/CIRCULATIONAHA.110.002832.
38. Triedman JK. Arrhythmias in adults with congenital heart disease. *Heart* 2002;**87**:383–389. https://doi.org/10.1136/heart.87.4.383.
39. Pedersen MGB, Olsen MS, Schmidt M, Johnsen SP, Learn C, Laursen HB, *et al.* Ischemic stroke in adults with congenital heart disease: a population-based cohort study. *J Am Heart Assoc* 2019;**8**:e011870. https://doi.org/10.1161/JAHA.118.011870.
40. Lanz J, Brophy JM, Therrien J, Kaouache M, Guo L, Marelli AJ. Stroke in adults with congenital heart disease: incidence, cumulative risk, and predictors. *Circulation* 2015;**132**:2385–2394. https://doi.org/10.1161/CIRCULATIONAHA.115.011241.
41. Bokma JP, Zegstroo I, Kuijpers JM, Konings TC, van Kimmenade RRJ, van Melle JP, *et al.* Factors associated with coronary artery disease and stroke in adults with congenital heart disease. *Heart* 2018;**104**:574–580. https://doi.org/10.1136/heartjnl-2017-311620.
42. Engelings CC, Helm PC, Abdul-Khaliq H, Asfour B, Bauer UMM, Baumgartner H, *et al.* Cause of death in adults with congenital heart disease—an analysis of the German national register for congenital heart defects. *Int J Cardiol* 2016;**211**:31–36. https://doi.org/10.1016/j.ijcard.2016.02.133.
43. Singh S, Desai R, Fong HK, Sadolikar A, Samani S, Goyal H. Extra-cardiac comorbidities or complications in adults with congenital heart disease: a nationwide inpatient experience in the United States. *Cardiovasc Diagn Ther* 2018;**8**:814–819. https://doi.org/10.21037/cdt.2018.09.12.
44. Geva T, Martins JD, Wald RM. Atrial septal defects. *Lancet* 2014;**383**:1921–1932. https://doi.org/10.1016/S0140-6736(13)62145-5.
45. Penny DJ, Vick GW. Ventricular septal defect. *Lancet* 2011;**377**:1103–1112. https://doi.org/10.1016/S0140-6736(10)61339-6.
46. Kidd L, Driscoll DJ, Gersony WM, Hayes CJ, Keane JF, O'Fallon WM, *et al.* Report from the second joint study on the natural history of congenital heart defects (NHS-2): second natural history study of congenital heart defects: results of treatment of patients with ventricular septal defects. *Circulation* 1993;**87**:I38–I51.
47. Baumgartner H. Infective endocarditis in adults with congenital heart disease: is it time to change our approach to prophylaxis based on new insights into risk prediction? *Eur Heart J* 2011;**32**:1835–1837. https://doi.org/10.1093/eurheartj/ehr037.
48. Giroud JM, Jacobs JP. Evolution of strategies for management of the patent arterial duct. *Cardiol Young* 2007;**17**:68–74. https://doi.org/10.1017/S1047951107001175.
49. Roos-Hesselink JW, Meijboom FJ, Spitaels SEC, van Domburg RT, van Rijen EHM, Utens EMWJ, *et al.* Long-term outcome after surgery for pulmonary stenosis (a longitudinal study of 22–33 years). *Eur Heart J* 2006;**27**:482–488. https://doi.org/10.1093/eurheartj/ehi685.
50. Li W, Somerville J. Atrial flutter in grown-up congenital heart (GUCH) patients. Clinical characteristics of affected population. *Int J Cardiol* 2000;**75**:129–137. https://doi.org/10.1016/S0167-5273(00)00308-9.
51. Saha P, Potiny P, Rigdon J, Morello M, Tcheandjieu C, Romfh A, *et al.* Substantial cardiovascular morbidity in adults with lower-complexity congenital heart disease. *Circulation* 2019;**139**:1889–1899. https://doi.org/10.1161/CIRCULATIONAHA.118.037064.
52. Hakman EN, Cowling KM. *Paradoxical Embolism.* Treasure Island, FL: StatPearls Publishing; 2022.
53. Romans RA, Rockefeller TA, Hancock HS. The physiologic implications of congenital heart defects. *Semin Pediatr Surg* 2021;**30**:151042. https://doi.org/10.1016/j.sempedsurg.2021.151042.
54. Chiolero A. Cancer surveillance, obesity, and potential bias. *Lancet Public Health* 2019;**4**:e219. https://doi.org/10.1016/S2468-2667(19)30062-3.