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ORIGINAL ARTICLE
Adult congenital heart disease

Chronic kidney disease in patients with congenital heart disease: a nationwide, register-based cohort study

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Aims To investigate the risk of chronic kidney disease (CKD) in young patients with congenital heart disease (CHD) (age 0–47 years) compared with age- and sex-matched controls without CHD.

Methods and results Using data from the Swedish National Patient Register and the Cause of Death Register, 71,936 patients with CHD (50.2% male) born between 1970 and 2017 were identified. Each patient with CHD was matched by sex and age to 10 controls without CHD ($n = 714,457$). Follow-up data were collected for patients with CHD and controls until 2017. During a median follow-up of 13.5 (5.8; 25.5) years, 379 (0.5%) patients with CHD and 679 (0.1%) controls developed CKD. The risk of CKD was 6.4 times higher in patients with CHD than controls [95% confidence interval (CI): 5.65–7.27] and was highest in patients with severe non-conotruncal defects [hazard ratio (HR): 11.31; 95% CI: 7.37–17.36]. Compared with matched controls, the absolute and relative risks of CKD were greater for CHD patients born between 1997 and 2017 (HR: 9.98; 95% CI: 8.05–13.37) (incidence 39.5 per 100 000 person-years). The risk of CKD remained significantly higher after adjusting for hypertension, acute kidney injury, and diabetes mellitus (HR: 4.37; 95% CI: 3.83–5.00).

Conclusion Although the absolute risk of CKD in young patients with CHD is relatively low, patients with CHD are six times more likely to develop CKD than non-CHD controls up to the age of 47 years. Further data are needed to inform guidelines on the prevention and follow-up of CKD in CHD patients.

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Graphical Abstract

Key question(s)

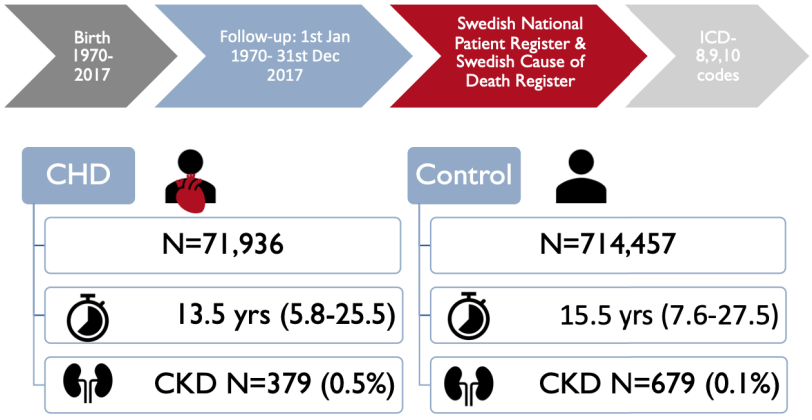
What is the risk of chronic kidney disease (CKD) in patients with congenital heart disease (CHD) (0-47 years) compared with age-and sex-matched controls without CHD?

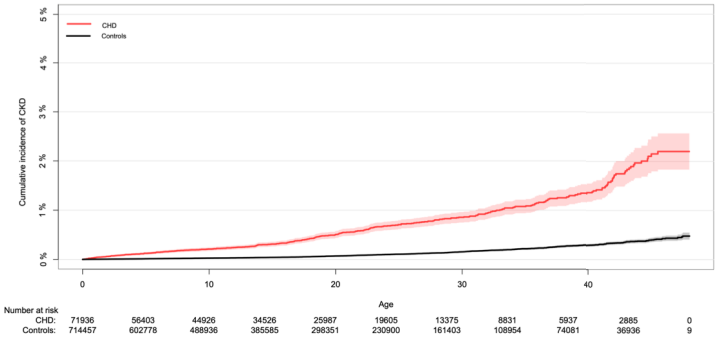
Key finding(s)

CHD patients had a 6.4 times increased risk of CKD compared with controls. The CKD incidence increased with age. The highest risk of CKD was seen in patients with complex lesions and those born between 1997-2017.

Take-home message

The absolute risk of CKD in CHD patients is relatively low, but patients with CHD are 6.4 times more likely to develop CKD compared to controls without CHD.





6.4 times increased risk of CKD compared with controls

(HR 6.41, 95% CI 5.56-7.27) AND an elevated risk remained after adjusting for AKI, HT, DM (HR 4.37, 95% CI:3.83-5.00)

CHD, congenital heart disease; CKD, chronic kidney disease; AKI, acute kidney injury; ht, hypertension; dm, diabetes mellitus; ICD, International Classification of Disease; HR, hazard ratio.

Keywords Congenital heart disease • Chronic kidney disease • Children • Adults

Introduction

Congenital heart disease (CHD) occurs in ~0.9% of live births and is one of the most common congenital abnormalites.[1,2] Although CHD used to be a condition with limited chances of survival for many patients, medical and surgical developments in recent decades have made it possible for up to 97% of children with CHD to reach adulthood.[3] Nevertheless, most patients are not considered cured and face complications related to both surgical interventions and the pathophysiology of their heart defects. As patients with CHD grow older, it has become essential to examine their risk of developing common acquired and age-related diseases, such as chronic kidney disease (CKD).

The estimated prevalence of CKD is 11–13% in adults[4] and 42–329 per million age-related population in children.[5] CKD is characterized by the slow and irreversible structural kidney damage and loss of kidney function and is defined as a glomerular filtration rate (GFR) of <60 mL/min per 1.73 m^2, or the detection of kidney damage markers (e.g. albuminuria, urine sediment abnormalities or radiographic findings) for more than 3 months.[6] The most frequent causes of CKD are hypertension and diabetes mellitus,[6] which have rapidly growing incidences.[6,7]

There is limited knowledge about the risk of CKD development in patients with CHD. Acute kidney injury (AKI) is a known complication following cardiac surgery for CHD.[8] However, studies have shown conflicting results regarding whether patients with a history of AKI after cardiac surgery for CHD have an increased risk of CKD.[9–11] Available evidence suggests there is a high occurrence of CKD in patients with CHD,[9–13] and a single centre study reported that as many as 50% of adult patients with CHD have reduced kidney function.[14] CKD has also been shown to be a significant predictor of mortality in the CHD population.[12,14]

Although there is evidence indicating a significant relationship between CHD and CKD, no nationwide population studies have outlined the risk of CKD in both children and adults with CHD compared with the general population. This study aimed to investigate the absolute and relative risks of CKD development in children and adults with CHD (age 0–47 years) compared with age- and sex-matched controls without CHD.

Methods

Data sources

Since 1947, all Swedish citizens have received a unique personal identification number (PIN)[15] at birth or immigration that consists of the date of birth and a combination of four digits and is managed by the Swedish National Tax Board. The Swedish National Patient Register (NPR)[16] consists of the Inpatient Register, which contains hospital discharge data since1964, and the Outpatient Register, which contains all data from all hospital-based outpatient visits since 2001. Primary and secondary diagnoses, external cause of injury/poisoning, and procedures are coded using International Classification of Diseases (ICD) codes, which are determined by treating physicians and are reported monthly by public and private caregivers. The NPR is regularly reviewed for quality and validity and holds a high standard.[16] The Swedish Cause of Death Register[17] has been available for research purposes since 1952 and includes information on the deaths of all Swedish residents, which the treating physician reports within 3 weeks of occurrence. The Cause of Death Register has high validity.[17] Both the NPR and the Cause of Death Register are administrated by the Swedish National Board of Health and Welfare and reporting to these registers is mandatory.

Study design

Data extracted from the NPR[16] and the Cause of Death Register[17] were used to identify patients with CHD born between January 1970 and December 2017. Each patient with CHD was matched for sex and birth year with approximately 10 (9.9) controls without CHD selected from the Swedish Total Population Register.[18] Follow-up data on CKD diagnosis in patients and controls were collected in the registers until death or the end of the study, which was December 2017. All patients are identified in the registers by their unique PIN[15] and diagnoses from the registers were coded according to ICD codes, Eighth Revision (ICD-8), Ninth Revision (ICD-9), and Tenth Revision (ICD-10).

Definitions of outcomes and risk factors

CKD was the primary outcome and was defined as a documented ICD code in the registers. CKD definitions according to the ICD codes are listed in Supplementary material online, *Table S1*. CKD was defined as codes N18 (ICD-10), 582 and 585 (ICD-9), and 582 and 584 (ICD-8). Risk factors for CKD were AKI, hypertension, diabetes mellitus, and CHD-related open-heart surgery, which were defined as an ICD code registered in the NPR from birth until and including the time of registration of the first CKD diagnosis in the NPR. AKI was defined as codes N17 (ICD-10), 584 (ICD-9), and 580 (ICD-8). Hypertension was defined as codes I10–112 and I15 (ICD-10) and 401–405 (ICD-9 and ICD-8). Diabetes mellitus was defined as codes E10–E14 (ICD-10) and 250 (ICD-9 and ICD-8). ICD codes for CHD-related open-heart surgery are listed in Supplementary material online, *Table S2*.

Classification of congenital heart disease

Patients with CHD were examined as a group; however, because of the heterogeneity of the CHD diagnoses, the patients were also divided into six different lesion groups classified by the severity of the diagnoses according to a well-established CHD classification that was proposed by Botto *et al.*[19] modified by Liu *et al.*[20] and has since been used for the CHD population.[21,22] The six CHD lesion groups were as follows: (i) conotruncal defects, including common truncus, aortopulmonary septum defect, and transposition of the great vessels, (ii) severe non-conotruncal defects, including endocardial cushion defect, common ventricle, and hypoplastic left heart syndrome, (iii) coarctation of the aorta, (iv) ventricular septal defects (VSDs), (v) atrial septal defects (ASDs), and (vi) all other heart and circulatory system anomalies. Lesion groups 1 through 5 are arranged by the complexity of the CHD lesion in decreasing order, and lesion group 6 comprises all lesions not included in the first five groups, of whom many are valve related. When a patient has several CHD diagnoses, the lesion group was determined based on the most severe diagnosis. The ICD codes for each lesion group are presented in Supplementary material online, *Table S3*.

Statistical methods

The following statistical analyses were pre-specified. Categorical nominal data were presented as frequencies and percentages and were compared between patients with CHD and controls using the χ^2 test. Numerical data were presented as means with standard deviations or medians with interquartile ranges and were compared between patients with CHD and controls using the Student's *t*-test. The incidence rate (IR) of CKD for patients with CHD and controls was reported as CKD cases per 100 000 person-years. Due to the extensive follow-up time and to account for the potentially increased risk of mortality in the CHD population compared with controls, death from all causes other than CKD was accounted for as a competing risk in the analysis by using the cumulative incidence function according to the Fine-Gray approach (using the R package *prodlim*). A Cox regression model was used to compare the CKD risk of patients with CHD compared with controls (reference population), to obtain hazard ratios (HRs) with 95% confidence intervals (CIs) for the risk of CKD. HRs adjusted for the risk factors of CKD development (AKI, hypertension, and diabetes mellitus) were also presented. Calculations were made for the overall group of patients with CHD, the six lesion groups, CHD groups according to two birth periods (1970–1996 when ICD-8 and ICD-9 were in use, and 1997–2017 when ICD-10 was used), and CHD groups according to sex. Because of the non-proportionality due to the long follow-up time, the risk of CKD was separately estimated at age intervals 0–17 years, 18–39 years, and ≥ 40 years for all regression models. In addition, some of the comorbidities in the age intervals did not meet the proportionality requirement and were therefore stratified in the adjusted models (see Supplementary material online, *Table S5*). In a *post hoc* analysis, HRs adjusted for AKI, hypertension, diabetes

mellitus, and CHD-related open-heart surgery were calculated (see Supplementary material online, *Table S6*). *P* values of < 0.05 were considered statistically significant. Statistical analyses were performed using the software R Studio (version 3.6.1).[23]

Ethics

The study was approved by the Gothenburg Regional Research Ethics Board and complies with the Declaration of Helsinki. All PINs were replaced by a unique code by the National Board of Health and Welfare in Sweden. As anonymous data were used, the Gothenburg Regional Research Ethics Board waived the requirement for informed consent from all participants.

Results

Baseline characteristics of the study population

We identified 71 936 patients with CHD and 714 457 matched controls without CHD born between 1 January 1970 and 31 December 2017. Among the patients with CHD, 50.2% ($n = 36\,099$) were male, and the mean birth year was 1999 ($\pm$ 12.9 years). The two most common lesion groups were patients with VSD (31.9%, $n = 22\,950$) and patients with heart and circulatory system anomalies not included in the first five lesion groups (30.2%, $n = 21\,718$). Among the patients with CHD, 15 865 (22.1%) underwent open-heart surgery for their CHD. The baseline characteristics of the study population are displayed in *Table 1*.

Incidence of chronic kidney disease

During a median follow-up of 13.5 (5.8; 25.5) years for patients with CHD and 15.5 (7.6; 27.5) years for controls, almost 0.5% ($n = 379$) and 0.1% ($n = 679$) developed CKD, respectively. The IR of CKD between 1970–2017 was 32.06 per 100 000 person-years for patients with CHD compared with 5.16 per 100 000 person-years for controls (*Table 2*). The lesion group with the highest IR of CKD was patients with severe non-conotruncal defects (*Table 2*). Male patients with CHD had a slightly higher IR of CKD than female patients with CHD (*Table 3*). The IR of CKD was higher in the late birth cohort (1997–2017) than the early birth cohort (1970–1996), but increased with age in both patients with CHD and controls (*Table 3*).

The cumulative incidence of CKD between the age of 0 to 47 years from 1970 to 2017 was notably elevated in patients with CHD compared with the control group (*Figure 1*). The cumulative incidence of CKD at 47 years of age was 2.2% (95% CI: 1.83–2.57) in patients with CHD and 0.4% (95% CI: 0.38–0.49) in controls. Among the lesion groups, the cumulative incidence of CKD at age 47 was highest in patients with conotruncal defects (2.7%, 95% CI: 1.44–3.87), and lowest in patients with ASD (1.7%, 95% CI: 1.00–2.37) (*Figure 2*). *Figure 3* illustrates the cumulative incidence of CKD according to the birth cohorts. At 20 years of age, the cumulative incidence of CKD in patients with CHD was higher in those born in the second birth period (1.0%, 95% CI: 0.78–1.23) than in those born in the first birth period (0.3%, 95% CI: 0.19–0.31). The cumulative incidence of CKD at age 47 was also higher among males with CHD (2.5%, 95% CI: 1.93–3.05) compared with females with CHD (1.9%, 95% CI: 1.43–2.39) (*Figure 4*).

Risk of chronic kidney disease

The risk of developing CKD was 6.4 times higher in patients with CHD compared with controls without CHD (HR 6.41, 95% CI: 5.65–7.27) (*Table 2*). The lesion group with the highest risk compared with controls was the group with severe non-conotruncal defects, which displayed a CKD risk of more than 11-fold (HR: 11.31, 95% CI: 7.37–17.36) compared with controls. The lesion group with the lowest risk of CKD compared with controls was the group with VSD (HR: 5.39, 95% CI: 4.13–7.05). Both male and female patients with CHD displayed an increased risk of CKD compared with controls (*Table 3*). Patients with CHD born in the second birth period (1997–2017) had

Table 1 Baseline characteristics of the study population of patients with congenital heart disease and controls

	Patients with congenital heart disease	Controls	*P*-value
	($n = 71\,936$)	($n = 714\,457$)	
Sex			0.08
Male	36 099 (50.2%)	361 016 (50.5%)	
Female	35 837 (49.8%)	353 441 (49.5%)	
Year of birth (years), mean $\pm$ SD	1 999.2 $\pm$ 12.9	1 999.1 $\pm$ 12.9	0.15
Birth period			0.16
1970–1996	27 587 (38.3%)	275 890 (38.6%)	
1997–2017	44 349 (61.7%)	438 567 (61.4%)	
Place of birth			<0.00
Sweden	67 809 (94.3%)	583 704 (81.7%)	
Other	4 127 (5.7%)	130 753 (18.3%)	
Lesion group[19]			0.10
1. Conotruncal defects	5 421 (7.5%)	53 990 (7.6%)	
2. Severe non-conotruncal defects	3 855 (5.4%)	38 440 (5.4%)	
3. Coarctation of the aorta	3 358 (4.7%)	33 459 (4.7%)	
4. Ventricular septal defects	22 950 (31.9%)	227 305 (31.8%)	
5. Atrial septal defects	14 634 (20.3%)	145 149 (20.3%)	
6. Other heart and circulatory system anomalies	21 718 (30.2%)	216 114 (30.2%)	
CHD-related open-heart surgery	15 865 (22.1%)	130 (0.0%)	

P < 0.05 was considered statistically significant.

Table 2 Risk of chronic kidney disease in the study population according to lesion group

	No. (%) of patients with congenital heart disease with chronic kidney disease	No. (%) of controls with chronic kidney disease	Incidence rate of concomitant chronic kidney disease and congenital heart disease[a]	Incidence rate of chronic kidney disease in controls[a]	Hazard ratio for chronic kidney disease (95% CI)	Adjusted hazard ratio for chronic kidney disease (95% CI)[b]
Lesion group[19]						
CHD total	379 (0.5%)	679 (0.1%)	32.06	5.16	6.41 (5.65–7.27)	4.37 (3.83–5.00)
1. Conotruncal defects	39 (0.7%)	74 (0.1%)	41.97	6.05	7.62 (5.17–11.24)	6.62 (4.43–9.89)
2. Severe non-conotruncal defects	34 (0.8%)	55 (0.1%)	60.56	5.79	11.31 (7.37–17.36)	6.79 (4.24–10.82)
3. Coarctation of the aorta	25 (0.7%)	30 (0.0%)	37.44	3.96	9.66 (5.68–16.42)	6.74 (3.62–12.55)
4. Ventricular septal defects	81 (0.4%)	158 (0.0%)	24.86	4.68	5.39 (4.13–7.05)	4.31 (3.25–5.72)
5. Atrial septal defects	64 (0.4%)	88 (0.0%)	28.86	3.91	7.40 (5.36–10.21)	6.57 (4.67–9.26)
6. Other heart and circulatory system anomalies	136 (0.6%)	274 (0.1%)	32.47	5.96	5.58 (4.55–6.86)	3.59 (2.88–4.49)

[a]Per 100 000 person-years.
[b]Adjusted for the following risk factors: AKI, hypertension, diabetes mellitus.

almost a 10-fold increased risk of CKD compared with controls (HR 9.98, 95% CI: 8.05–13.37), while patients with CHD born in the first period (1970–1996) were five times more likely to develop CKD compared with controls (HR: 5.02, 95% CI: 4.28–5.89).

After adjusting for risk factors (hypertension, AKI, and diabetes mellitus), the increased risk of CKD in patients with CHD compared with controls remained (HR: 4.37, 95% CI: 3.83–5.00) (*Table 2*). The same pattern was observed among patients with CHD of both sexes, both birth periods, and all lesion groups (*Tables 2 and 3*). The adjusted estimated risks of CKD at age 0–17 years, 18–39 years, and ≥ 40 years are presented in Supplementary material online, *Table S4*. Patients with CHD had an increased risk of CKD compared with controls at all age intervals except for patients with ASD ≥ 40 years. Among patients with CHD, there was a higher relative risk of CKD at 0–17 years (HR: 5.73, 95% CI: 4.72–6.96) compared with 18–39 years (HR: 2.34, 95% CI: 1.90–2.88). The same age-correlated risk difference was seen in patients with CHD divided by sex, in patients with ASD, and in patients with other heart and circulatory anomalies. Supplementary material online, *Table S5* presents the adjusted HRs when CHD-related open-heart surgery was added as an adjusting factor along with AKI, hypertension, and diabetes mellitus. The addition of open-heart surgery lowered the HRs further, and the most prominent reduction was among those with conotruncal defects and severe non-conotruncal defects.

Characteristics of patients with both congenital heart disease and chronic kidney disease

In the CHD population with CKD, the most prevalent risk factor before a CKD diagnosis was hypertension (21.1%, $n = 80$), followed by AKI (15.0%, $n = 57$), and diabetes mellitus (4.2%, $n = 16$) (*Table 4*). The only significant difference in the occurrence of risk factors between patients with CHD vs. controls, apart from CHD-related open-heart surgery which for obvious reasons was more common among CHD patients, regarded diabetes mellitus, which was more common among controls (8.4% vs. 4.2%, $P = 0.015$).

Discussion

This retrospective cohort study examined the absolute and relative risks of CKD in patients with CHD and controls without CHD (aged 0–47 years). The most clinically relevant finding was that patients with CHD had a 6.4-fold increased relative risk of developing CKD compared with controls. Furthermore, both the IRs and the cumulative incidence of CKD were considerably higher for patients with CHD than controls.

The occurrence of CKD in patients with CHD (0.5%, $n = 379$) in the present study is lower than that reported in previous cohorts where kidney function was clinically measured.[9,11,14] Dimopoulos *et al.*[14] showed that of 1102 adults with CHD, 41% had a mildly decreased GFR of < 90 mL/min per 1.73 m^2 and 9% had a GFR of < 60 mL/min per 1.73 m^2 (from mildly to moderately decreased to kidney failure). In the TRIBE-AKI study, 18% of 131 paediatric patients with CHD were diagnosed with CKD within 5 years after cardiac surgery.[11] The CKD detection rates in the abovementioned studies where each subject was screened for a diagnosis are naturally higher than the rates in observational register-based studies, especially when the subjects are often asymptomatic. The prevalence of CKD in the present study is comparable with the prevalence reported in previous register-based studies. Afilalo *et al.*[12] showed that 2% of 3 239 geriatric (65 + years) patients with CHD had a registered CKD diagnosis. A similar study by Billett *et al.*[13] that also included controls without CHD reported that the prevalence of CKD was 0.8% in patients with CHD (mean age 28 years) and 0.2% in controls.

Patients with CHD had higher absolute and relative risks of CKD compared with controls without CHD. The highest risk of CKD was observed in the two most complex lesion groups: severe non-conotruncal defects and conotruncal defects. This is consistent with previous studies suggesting that anatomical complexity and cyanosis are highly associated with kidney dysfunction.[10,14] Patients with complex lesions often require multiple cardiac surgeries, which causes AKI and is thus associated with an increased risk of CKD.[8–10] The pathophysiology behind the transition from AKI to CKD is not completely clarified but is proposed to be due to mechanisms of

Table 3 Risk of chronic kidney disease in the study population according to sex and birth period

	No. (%) of patients with congenital heart disease with chronic kidney disease	No. (%) of controls with chronic kidney disease	Incidence rate of concomitant chronic kidney disease and congenital heart disease[a]	Incidence rate of chronic kidney disease in controls[a]	Hazard ratio for chronic kidney disease (95% confidence interval)	Adjusted hazard ratio for chronic kidney disease (95% confidence interval)[b]
Sex						
Male	208 (0.6%)	388 (0.1%)	35.06	5.82	6.22 (5.26–7.37)	3.88 (3.23–4.66)
Female	171 (0.5%)	291 (0.1%)	29.04	4.48	6.68 (5.53–8.07)	5.87 (4.84–7.11)
Birth period						
1970–1996	215 (0.8%)	510 (0.2%)	28.05	5.73	5.2 (4.28–5.89)	3.01 (2.53–3.56)
1997–2017	164 (0.4%)	169 (0.0%)	39.45	3.97	9.98 (8.05–12.37)	7.51 (5.99–9.43)
Age group						
0–17 years	NA	NA	24.49	2.87	NA	6.16 (5.11–7.43)
18–39 years	NA	NA	44.96	9.61	NA	2.98 (2.44–3.64)
40 + years	NA	NA	154.06	22.67	NA	5.03 (3.19–7.94)

[a]Per 100 000 person-years.
[b]Adjusted for the following risk factors: AKI, hypertension, diabetes mellitus. NA, not applicable.

maladaptive repair and fibrogenesis.[24] Periods of longstanding cyanosis also have a destructive effect on the kidneys, causing glomerular and tubular dysfunction.[25,26] The reduced cardiac output caused by chronic heart failure also results in decreased kidney perfusion over time.

The adjusted risk of CKD in patients with CHD compared with controls remained statistically and clinically significantly increased, even though it was slightly lower than the unadjusted relative risk. This suggests that there are additional CHD-specific risk factors for CKD development apart from diabetes mellitus, hypertension, and AKI. Additionally, as the adjusted HRs were lower than the unadjusted HRs throughout our CHD subgroups, this indirectly suggests that these known risk factors for CKD make up a meaningful proportion of the risk of CKD in patients with CHD.

From a clinical perspective, the risk factors impacting the CKD risk may have been present to varying degrees among the subgroups. Because adjusting for the risk factors lowered the prominently high relative risks of CKD among patients with conotruncal and severe non-conotruncal defects compared with controls, the risk factors seem to play an essential role in CKD development among the complex lesion groups. A similar considerable reduction in relative risk was also seen in males with CHD but not among females with CHD. This suggests that male patients with CHD may have more risk factors for CKD development compared with controls than female patients with CHD.

CHD-related surgery has previously been suggested as a risk factor for CKD.[9,10] This is supported by our results that showed a lower HR of CKD in CHD patients compared with controls when CHD-related open-heart surgery was added to the adjusted risk model. It is neither surprising nor inconsistent that the groups with complex CHD lesions are seemingly more affected by the risk of CKD posed by open-heart surgery related to long cardiopulmonary bypass time and young age at first surgery.[27] However, the low absolute risk of CKD in the study population and the design of the present study prevented the evaluation of the exact effects of AKI, hypertension, diabetes mellitus, and CHD-related open-heart surgery on the CKD risk in patients with CHD; this issue requires further investigation.

Our findings add to the current evidence showing that the cumulative incidence of CKD is elevated in patients with CHD compared with controls without CHD.[10] The cumulative incidence of CKD reported in the present study was lower than that reported by Madsen *et al.*, who found that CKD occurred at 5 years after cardiac surgery for CHD in 12.2% of children who developed post-operative AKI, and in 2.6% of those without an AKI event.[9] This is somewhat expected because the prevalence of AKI in the patients with CHD in the present study was far less than that observed in other studies,[9,11] probably due to the nationwide nature of our study that included all patients with CHD born between 1970 and 2017. This might suggest that the lower incidence of CKD was correlated with the lower frequency of AKI (15.0%) and, perhaps more significantly, CHD-related open-heart surgery (22.1%), indicating an overall healthier CHD population. Among the patients with CHD who developed CKD, the rate of CHD-related surgery was higher but was still only 36.1%. The incidence of CKD was higher in males than females with CHD, and a similar sex discrepancy was observed among the controls. In general, CKD is slightly more prevalent in females than males, which may be partly due to the slower progression of the disease in females or a different age demographic for males and females in the studies.[4,28] Finally, the IRs of CKD increased with age in all subgroups, which is also seen in the general population.[4]

Another surprising finding is that the risk of CKD was higher in patients born in the second birth period (1997–2017) compared with those born in the first birth period (1970–1996). The higher incidence of CKD among the more recent birth period may be partly explained by a survival bias where the increased survival for all patients with CHD[3] meant that more patients with CHD from the second birth period had survived long enough to develop CKD. The increased survival of patients with CHD has also resulted in an increased prevalence of complex lesions in the CHD population, and the complexity of the CHD lesion correlates with an increased risk of CKD.[10,14,29] However, complex lesions only accounted for less than 13% of the current CHD study population.

The high HR of CKD for patients with CHD born in the recent birth period and for those in the youngest age interval (0–17 years) is probably due to the scarce number of CKD cases among the young individuals of the control group. A compiled higher burden of disease in patients with CHD compared with controls may be more evident in a younger study population than in an older population where the controls have acquired comorbidities that also put them at risk.

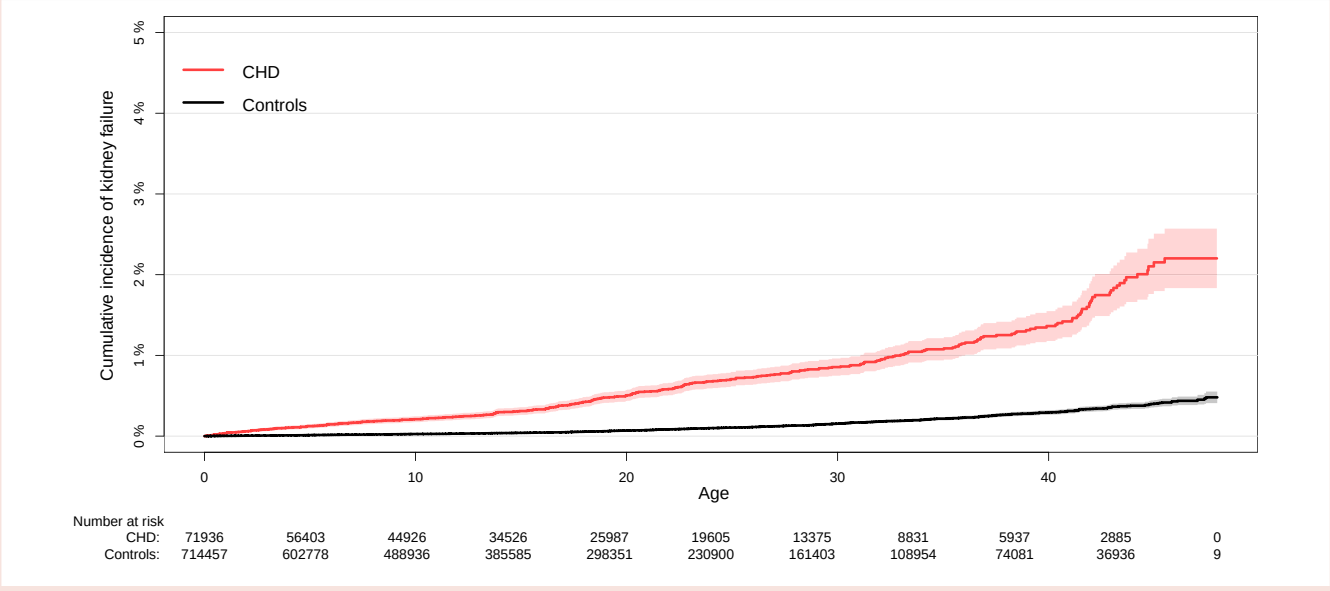


Figure 1 Cumulative incidence of chronic kidney disease in the study population. The competing risk is death in all other causes than chronic kidney disease.

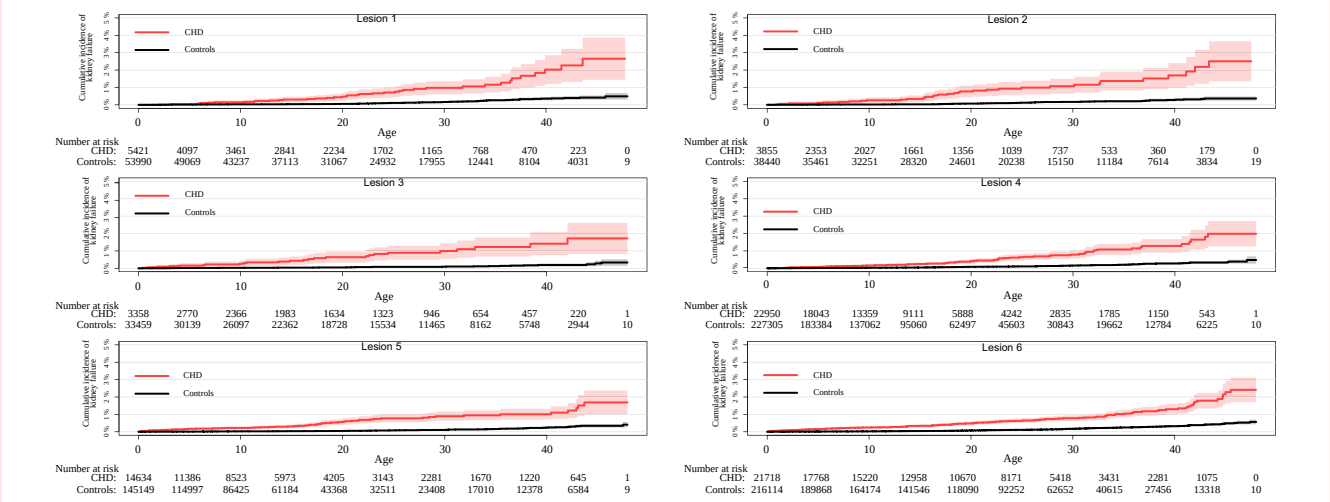


Figure 2 Cumulative incidence of chronic kidney disease in the study population according to lesion group. The competing risk is death in all other causes than chronic kidney disease. Lesion Group 1 includes conotruncal defects. Lesion Group 2 includes severe non-conotruncal defects. Lesion Group 3 includes coarctation of the aorta. Lesion Group 4 includes ventricular septal defects. Lesion Group 5 includes atrial septal defects. Lesion Group 6 includes all other heart and circulatory system anomalies not included in the other five lesion groups.

Strengths and limitations

The primary strength of this retrospective register-based cohort is the large size of the study population that included all patients with hospital-diagnosed CHD in Sweden with little risk of loss to follow-up. Another strength of our study is that it included and separately examined the CKD risk in groups with several types of CHD lesions, in adult and paediatric patients and in patients with and without a history of CHD-related open-heart surgery. The study design also permitted an extensive follow-up with minimal loss.

While the Swedish NPR is an extensive register that provides an excellent opportunity for the creation of epidemiological retrospective cohorts, the National Inpatient Register did not have complete national coverage until 1987 (1970 for CHD care) and the National Outpatient Register was not developed until 2001. Moreover, primary care diagnoses are still not included in the NPR. However, the likelihood of missing patients with CHD, because they are only registered in primary care, is very low. Therefore, the potential bias is that controls with early and mild stages of CKD might have been missed because they were only followed in primary care.

Another uncertainty related to registry-based studies is the validation of the ICD codes. The Swedish NPR maintains high quality with an average positive predictive value of diagnoses of 85–95%.[16] The errors lie in the physician's diagnostic ability but also in translation and

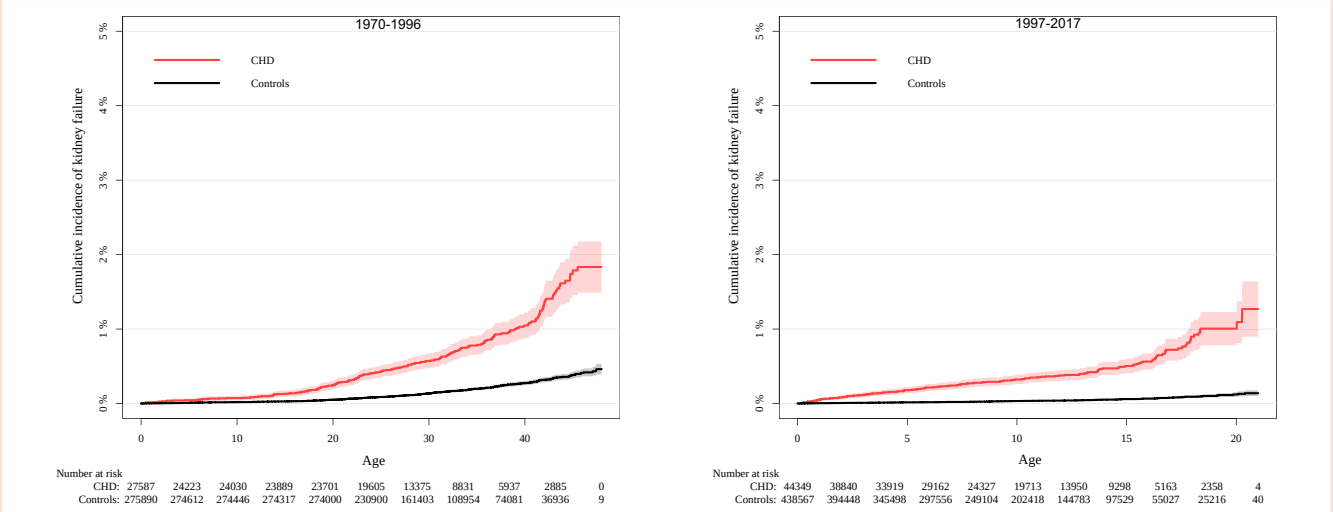


Figure 3 Cumulative incidence of chronic kidney disease in the study population according to birth period. The competing risk is death in all other causes than chronic kidney disease.

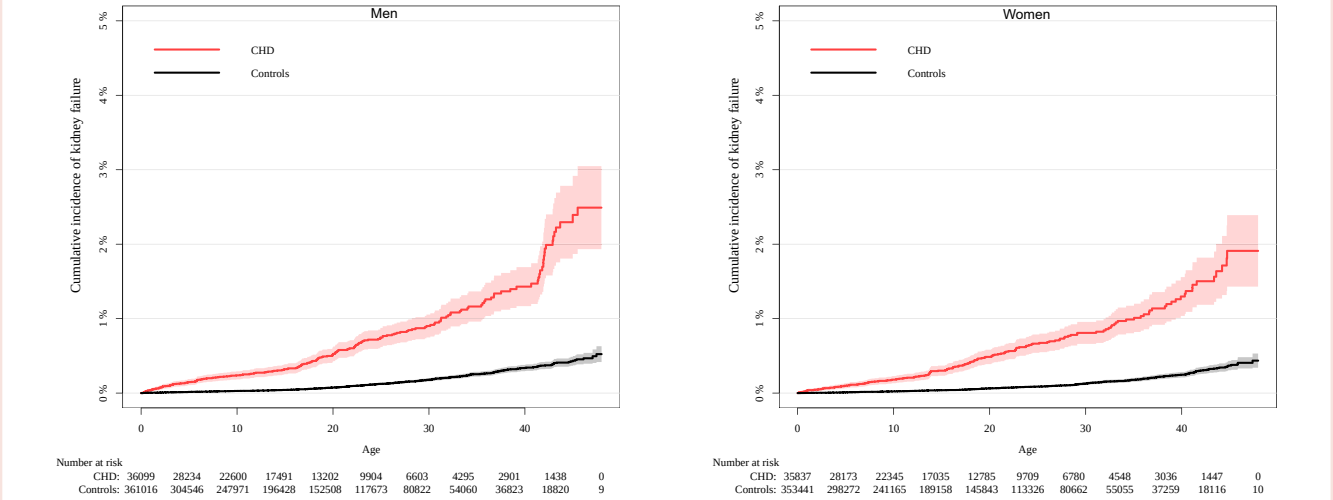


Figure 4 Cumulative incidence of chronic kidney disease in the study population according to sex. The competing risk is death in all other causes than chronic kidney disease.

coding.[16] A previous study validating CHD diagnosis in patients with CHD with myocardial infarction found that the ICD codes for CHD are 70.2% correct, with the most misdiagnoses occurring in patients with complex lesions.[22] Hence, caution is needed when interpreting lesion groups. A Swedish register study that compared the CKD diagnosis based on the ICD-10 codes in the patient charts vs. measured kidney function found that younger patients were correctly diagnosed with higher sensitivity compared with older adult patients.[30] Their results suggest that our patient cohort (age 0–47 years) were likely to have received a correct CKD diagnosis.

The treating physician's diagnostic ability regarding diseases such as CKD greatly depends on the diagnostic criteria and the methods used to assess the disease. For example, the choice of filtration marker or equation used to determine the estimated GFR impacts the accuracy compared with the measured GFR. As the methods of kidney function assessment have evolved since the start of our data collection, it is reasonable to suggest that the diagnostic ability has increased, causing bias.

Although the Health and Social Services Act declares that all Swedish citizens have equal rights and access to health services, patients with CHD are generally under closer follow-up than controls in our study population (age 0–47 years). As the early stages of CKD are asymptomatic in many cases, there is a risk of underdiagnosing asymptomatic controls and thereby overestimating the risk of CKD in patients with CHD compared with controls without CHD. Another consideration regards the hierarchic CHD lesion classification used in the present study. Although this classification is widely recognised, any grouping of lesions always has variation within the group, causing over- and underestimation of the actual risk associated with each lesion.

Table 4 Baseline characteristics of the study population with chronic kidney disease

	Patients with congenital heart disease ($n = 379$)	Controls ($n = 679$)	*P*-value
Sex			0.52
Male	208 (54.9%)	388 (57.1%)	
Female	171 (45.1%)	291 (42.9%)	
Diabetes mellitus	16 (4.2%)	57 (8.4%)	0.02
Hypertension	80 (21.1%)	174 (25.6%)	0.12
Acute kidney injury	57 (15.0%)	85 (12.5%)	0.29
CHD-related open-heart surgery	137 (36.1%)	6 (0.9%)	

$P < 0.05$ was considered statistically significant.

Clinical implications

The explanation for the increased risk of CKD among patients with CHD is not clear and is probably multifactorial and more complex than in the general population. Some of the proposed mechanisms, including longstanding cyanosis and conventional CKD risk factors, have been briefly described, but there are doubtless many others that are yet to be explored.

The current study found a relatively low absolute risk of CKD in patients with CHD. However, patients with CHD had a significantly increased relative risk of CKD compared with their age- and sex-matched individuals in the population without CHD. The high relative risk of CKD is likely partly derived from having a relatively young study population (age 0–47 years) in which the CKD incidence among the controls was still low. Observing the study population until the age of 47 years naturally also affects the absolute risk of CKD for patients with CHD and controls, which according to the trend of the current results could be expected to be higher if older individuals were included.

To further determine the absolute risk of CKD in patients with CHD, future research should clinically investigate the risk of CKD in the Swedish CHD population. A physical examination of patients would generate more detailed personalized data on possible risk factors for CKD such as comorbidities, lifestyle, or state of their CHD, and an exact GFR measurement which we do not have access to through our registers. Neither did we in the present study have access to data from The National Prescribed Drug Register and hence were not able to study the relationship between prescribed drugs and CKD development. However, it would be of great interest in future research to study the nephrotoxicity of medical treatment in patients with and without CHD. More details on the patient's state of, and the circumstances around, their CKD would increase our understanding of how and why patients with CHD develop CKD and would also help to identify patients with CHD who are at particularly high risk of CKD. The results of such future studies will help to establish guidelines for screening and follow-up of kidney function in patients with CHD. Thus, in the future, we will be able to detect signs of reduced kidney function early, slow down disease progression, and perhaps recognise patterns of risk factors for which intervention can prevent CKD development altogether.

Conclusion

In the present nationwide cohort study, although the absolute risk of CKD for patients with CHD was relatively low, children and adults with CHD had more than a six-fold increased risk of developing CKD from age 0–47 years compared with matched controls without CHD. The IR of CKD increased with age; however, the younger CHD birth cohort was at high risk. Therefore, there is a need to further clinically investigate the risk of CKD in patients with CHD to establish guidelines for regular follow-up of kidney function. Additionally, the clinical risk factors for CKD in patients with CHD need to be clearly outlined to prevent CKD development in adults with CHD.

Lead author biography

Mikaela Gillesén received her MD in January 2022 when she graduated from Sahlgrenska Academy, University of Gothenburg, Sweden. She is now undertaking the Foundation Programme while also working with a research group led by Zacharias Mandalenakis MD, PhD, focusing on Congenital Heart Disease within the Department of Molecular & Clinical Medicine/Cardiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Author contributions

- M.G. contributed equally to methodology and writing—review and editing; a lead role in visualization and writing—original draft; a supporting role in formal analysis. M.F. contributed equally to conceptualization, methodology, project administration, supervision, and writing—review and editing and a supporting role in validation and writing—original draft. K.W.G. contributed equally to conceptualization and methodology; lead role in data curation, software, and formal analysis; and a supporting role in writing—original draft and writing—review and editing. K.D. contributed equally to writing—review and editing and a supporting role in conceptualization, methodology, supervision, and writing—original draft. P.E. contributed equally to writing—review and editing and a supporting role in conceptualization, methodology, supervision, and writing—original draft. M.D. contributed equally to conceptualization, funding acquisition, investigation, methodology, project administration, resources, writing—review and editing and a supporting role in supervision and writing—original draft. Z.M. contributed equally to formal analysis and writing—original draft and a lead role in conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, and writing—review and editing.

Data availability

All relevant aggregated data underlying this article are available in the article and in its online supplementary material.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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References

1. Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol* 2019;**48**:455–463.
2. *EUROCAT Access Prevalence Tables*. https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en (21 September 2021).
3. Mandalenakis Z, Giang KW, Eriksson P, Liden H, Synnergren M, Wåhlander H, Fedchenko M, Rosengren A, Dellborg M. Survival in children with congenital heart disease: have we reached a peak at 97%? *J Am Heart Assoc* 2020;**9**:e017704.
4. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FDR. Global prevalence of chronic kidney disease - A systematic review and meta-analysis. *PLoS One* 2016;**11**:e0158765.
5. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. *Pediatr Nephrol* 2012;**27**:363–373.
6. Group KDIGOCW. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1–150.
7. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;**365**:217–223.
8. Li D, Niu Z, Huang Q, Sheng W, Wang T. A meta-analysis of the incidence rate of postoperative acute kidney injury in patients with congenital heart disease. *BMC Nephrol* 2020;**21**:350.
9. Madsen NL, Goldstein SL, Frøslev T, Christiansen CF, Olsen M. Cardiac surgery in patients with congenital heart disease is associated with acute kidney injury and the risk of chronic kidney disease. *Kidney Int* 2017;**92**:751–756.
10. Parikh CR, Greenberg JH, McArthur E, Thiessen-Philbrook H, Everett AD, Wald R, Zappitelli M, Chanchlani R, Garg AX. Incidence of ESKD and mortality among children with congenital heart disease after cardiac surgery. *Clin J Am Soc Nephrol* 2019;**14**:1450–1457.
11. Greenberg JH, Zappitelli M, Devarajan P, Thiessen-Philbrook HR, Krawczeski C, Li S, Garg AX, Coca S, Parikh CR. Kidney outcomes 5 years after pediatric cardiac surgery: the TRIBE-AKI study. *JAMA Pediatr* 2016;**170**:1071–1078.
12. Afilalo J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Marelli AJ. Geriatric congenital heart disease: burden of disease and predictors of mortality. *J Am Coll Cardiol* 2011;**58**:1509–1515.
13. 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.
14. Dimopoulos K, Diller GP, Koltsida E, Pijuan-Domenech A, Papadopoulou SA, Babu-Narayan SV, Salukhe TV, Piepoli MF, Poole-Wilson PA, Best N, Francis DP, Gatzoulis MA. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. *Circulation* 2008;**117**:2320–2328.
15. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;**24**:659–667.
16. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450.
17. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, Feychting M, Ljung R. The Swedish cause of death register. *Eur J Epidemiol* 2017;**32**:765–773.
18. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaëlsson K, Neovius M, Stephansson O, Ye W. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol* 2016;**31**:125–136.
19. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A. Seeking causes: classifying and evaluating congenital heart defects in etiologic studies. *Birth Defects Res A Clin Mol Teratol* 2007;**79**:714–727.
20. Liu S, Joseph KS, Luo W, León JA, Lisonkova S, Van den Hof M, Evans J, Lim K, Little J, Sauve R, Kramer MS. Effect of folic acid food fortification in Canada on congenital heart disease subtypes. *Circulation* 2016;**134**:647–655.
21. Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Gilljam T, Hansson PO, Skoglund K, Fedchenko M, Dellborg M. Atrial fibrillation burden in young patients with congenital heart disease. *Circulation* 2018;**137**:928–937.
22. Fedchenko M, Mandalenakis Z, Hultsberg-Olsson G, Dellborg H, Eriksson P, Dellborg M. Validation of myocardial infarction diagnosis in patients with congenital heart disease in Sweden. *BMC Cardiovasc Disord* 2020;**20**:460.
23. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria; 2019. https://www.R-project.org/
24. Liu J, Kumar S, Dolzhenko E, Alvarado GF, Guo J, Lu C, Chen Y, Li M, Dessing MC, Parvez RK, Cippà PE, Krautzberger AM, Saribekyan G, Smith AD, McMahon AP. Molecular characterization of the transition from acute to chronic kidney injury following ischemia/reperfusion. *JCI Insight* 2017;**2**:e94716.
25. Hongsawong N, Khamdee P, Silvilairat S, Chartapisak W. Prevalence and associated factors of renal dysfunction and proteinuria in cyanotic congenital heart disease. *Pediatr Nephrol* 2018;**33**:493–501.
26. Zheng J, Yao Y, Han L, Xiao Y. Renal function and injury in infants and young children with congenital heart disease. *Pediatr Nephrol* 2013;**28**:99–104.
27. Larsen SH, Emmertsen K, Johnsen SP, Pedersen J, Hjortholm K, Hjortdal VE. Survival and morbidity following congenital heart surgery in a population-based cohort of children—up to 12 years of follow-up. *Congenit Heart Dis* 2011;**6**:322–329.
28. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006;**69**:375–382.
29. 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.
30. Friberg L, Gasparini A, Carrero JJ. A scheme based on ICD-10 diagnoses and drug prescriptions to stage chronic kidney disease severity in healthcare administrative records. *Clin Kidney J* 2018;**11**:254–258.