Cardiovascular disease in patients with congenital heart disease

Maria Fedchenko

Department of Molecular and Clinical Medicine

Institute of Medicine

Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

Gothenburg 2020

Cover illustration: Livets gåva, by Säde Stenlund

Cardiovascular disease in patients with congenital heart disease

maria.fedchenko@gu.se

ISBN 978-91-7833-878-8 (PRINT)
ISBN 978-91-7833-879-5 (PDF)
http://hdl.handle.net/2077/63273

Printed in Gothenburg, Sweden 2020
Printed by Stema Specialtryck AB

“The more I learn, the more I realize how much I don't know.”

- Albert Einstein

To my family

ABSTRACT

Background: Today, about 95% of children with congenital heart disease (CHD) survive into adulthood and the survival in patients with CHD has increased considerably during the last decades. With increasing age, patients with CHD are at an increased risk of developing acquired cardiovascular disease, such as ischemic heart disease and myocardial infarction (MI). The overall aim of this thesis was to study ischemic heart disease and MI in patients with CHD, and to assess the prevalence of modifiable cardiovascular risk factors in patients with coarctation of the aorta (CoA).

Methods: In Paper I, III and IV we used the Swedish National Patient Register and the Cause of Death Register. In paper I, 21,982 children and young adults with CHD born in 1970-1993 were followed until December 2011. In Paper IV, 17,189 patients with CHD ≥ 40 years of age, born in 1930 to 1970, were followed during the years 1970-2017. Each patient with CHD was matched by age and sex with ~10 controls from the total population register. Kaplan Meier and Cox regression analyses were used to calculate the cumulative incidence and hazard ratios for ischemic heart disease/MI in patients with CHD compared with controls. In Paper III we validated the MI diagnoses in patients with CHD by performing a medical chart review. In Paper II, a structured assessment of the prevalence of modifiable cardiovascular risk factors in 72 patients with CoA was performed, including oral glucose tolerance test and cholesterol levels.

Results: The risk of ischemic heart disease was 16.5 times higher in children and young adults with CHD than in controls, and also the risk of MI was higher in middle aged and older patients with CHD compared with controls. However, the relative risk compared with controls was markedly higher in younger patients with CHD than in older patients with CHD (Papers I and IV). Most of the MI diagnoses in patients with CHD were correct (Paper III). Almost 9 out of 10 patients with CoA had at least one modifiable cardiovascular risk factor.

Conclusion: The risk of ischemic heart disease and MI is increased in patients with CHD compared with controls; however, the mechanisms behind the increased risk may differ between younger and older patients with CHD. Modifiable cardiovascular risk factors are common in patients with CoA and a structured assessment of these should be considered to reduce the burden of atherosclerotic disease in CHD patients.

Keywords: congenital heart disease, myocardial infarction, ischemic heart disease, cardiovascular risk factor, coarctation of the aorta

SAMMANFATTNING PÅ SVENSKA

Bakgrund: Medfödda hjärtfel drabbar ca 0,8-1% av alla nyfödda barn och är den vanligaste medfödda missbildningen. Cirka 95 % av alla barn med medfödda hjärtfel överlever idag till vuxen ålder och antalet vuxna med medfödda hjärtfel ökar. Med stigande ålder ökar dessa individers risk att drabbas av förvärvad hjärtsjukdom såsom hjärtinfarkt. Kunskapen kring förekomsten av förvärvad kardiovaskulär (hjärt-kärlrelaterad) sjukdom hos patienter med medfödda hjärtfel är begränsad. Syftet med denna avhandling var att studera ischemisk (syrebristrelated) hjärtsjukdom och hjärtinfarkt hos patienter med medfödda hjärtfel, samt att beskriva förekomsten av traditionella riskfaktorer för hjärt-kärlsjukdom hos patienter med aortakoarktation (försnävning av aortabågen).

Metodik: Delarbete ett och fyra i avhandlingen baseras på Socialstyrelsens patientregister och dödsorsaksregister. I delarbete ett har vi studerat risken för ischemisk hjärtsjukdom hos 21 982 barn och unga vuxna med medfödda hjärtfel och i delarbete fyra studerade vi risken för hjärtinfarkt hos 17 189 medelålders och äldre patienter med medfödda hjärtfel. För varje patient med medfött hjärtfel valdes det ut cirka 10 kontrollpersoner från befolkningsregistret. I delarbete tre har vi genom journalgranskning validerat diagnosen hjärtinfarkt i patientregistret hos patienter med medfödda hjärtfel. I det andra delarbetet undersökte vi förekomsten av kardiovaskulära riskfaktorer hos 72 patienter med aortakoarktation. Patienterna genomgick bl.a. ett test för att hitta förstadier till diabetes, blodprovstagning avseende blodfetter, blodtrycksmätning samt frågeformulär om hälsovanor.

Resultat: Risken för ischemisk hjärtsjukdom var 16,5 gånger högre för barn och unga vuxna med medfödda hjärtfel jämfört med kontroller. För medelålders och äldre patienter var risken för hjärtinfarkt ökad jämfört med kontroller, dock ej lika uttalat som för barn och unga vuxna. Tillförlitligheten av diagnosen hjärtinfarkt hos patienter med medfödda hjärtfel var hög. I delarbete två noterade vi att ca 9 av 10 patienter med aortakoarktation hade åtminstone en kardiovaskulär riskfaktor.

Slutsatser: Risken för ischemisk hjärtsjukdom och hjärtinfarkt är högre hos patienter med medfödda hjärtfel jämfört med kontroller, dock kan det vara så att mekanismerna för dessa tillstånd skiljer sig åt hos yngre och äldre patienter med medfödda hjärtfel. Patienter med aortakoarktation har hög förekomst av kardiovaskulära riskfaktorer vilket bör uppmärksammas i omhändertagandet av denna patientgrupp.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Fedchenko M, Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Skoglund K, Dellborg M. Ischemic heart disease in children and young adults with congenital heart disease in Sweden.
International Journal of Cardiology. 2017;248:143-8

II. Fedchenko M, Mandalenakis Z, Dellborg H, Hultsberg-Olsson G, Bjork A, Eriksson P, Dellborg M. Cardiovascular risk factors in adults with coarctation of the aorta.
Congenital Heart Disease. 2019;14(4):549-58.

III. 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.
Submitted.

IV. Fedchenko M, Mandalenakis Z, Giang WK, 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. *Submitted.*

CONTENT

ABBREVIATIONS

ASD	Atrial septal defect
BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHD	Congenital heart disease
CI	Confidence interval
CoA	Coarctation of the aorta
cTn	Cardiac troponin
ECG	Electrocardiogram
HDL	High-density lipoprotein
HR	Hazard ratio
ICD	International Classification of Disease
IQR	Interquartile range
LDL	Low-density lipoprotein
MI	Myocardial infarction
NPR	National Patient Register
NSTEMI	Non-ST elevation myocardial infarction
PCI	Percutaneous coronary intervention
PFO	Patent foramen ovale
VSD	Ventricular septal defect

INTRODUCTION

Congenital heart disease

Congenital heart disease (CHD) is commonly defined as a "structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance" (1). CHD is the most common major congenital birth defect that affects approximately 0.8%-1% of all newborn children (2-4).

CHD comprise a wide range of diagnoses with various degrees of complexity, ranging from simple defects that do not require any treatment, to complex defects that will require several surgical interventions during the first years of life for survival (5). The most common CHD defects at birth are ventricular septal defects (VSD) and atrial septal defects (ASD), which constitute approximately 36% and 15% of all CHD lesions, respectively (3). Coarctation of the aorta (CoA) constitute approximately 3.6% of all CHD while tetralogy of Fallot, the most common cyanotic congenital heart defect, constitute approximately 4.4% of all CHD (3).

Before the era when surgical treatment of CHD became widely available, the life expectancy of patients with even "simple" CHD defects was significantly lower than it is today (6, 7). There have been immense advances in the surgical, interventional (8) and medical management of children with CHD since the year 1939 when the first CHD surgery (ligation of a patent ductus arteriosus) was performed by Robert E Gross (9). In Sweden, in 1944, Clarence Craaford successfully performed surgical correction in a patient with coarctation of the aorta (10). In 1953, closure of an ASD was performed for the first time using a heart and lung machine (11), and after that, various surgical techniques have been developed; e.g. Mustard and Senning atrial corrections of transposition of the great arteries in the late 1950:s and early 1960:s (12, 13), the creation of Fontan circulation in univentricular hearts in 1971 (14) and arterial switch correction in 1976 in a patient with transposition of the great arteries (15).

Owing to the great advancements in the surgical methods, medical treatment and development of catheter based interventions, the survival of patients with CHD has improved significantly during the last 70 years (7, 16-21) and the mortality in patients with CHD has shifted away from children to adults (22). Today, 90-95% of children with CHD survive beyond the age of 18 years (21)

and the number of adults with CHD has now outgrown the number of children with CHD (23).

It can be estimated that there are approximately 40,000 adults with CHD living in Sweden today (21) and the population of patients with CHD worldwide is expected to grow continuously (23, 24). Also the number of geriatric patients with CHD is increasing (25, 26).

Cardiovascular disease in patients with congenital heart disease

Despite the improved outcomes after surgical treatment and improved survival, the patients with CHD are not "cured" and there is a great need for follow-up and management of various cardiovascular complications (27). These complications can arise either as a consequence of the CHD lesion itself, or as a consequence of the previous surgical treatment of the lesion (27). The number of patients with CHD in the United States who required hospitalization more than doubled between the years 1998 and 2005 (28), and also studies from Europe have reported an increasing trend in hospitalizations of patients with CHD (29).

One of the most commonly encountered complications in patients with surgically corrected and non-corrected CHD is heart failure. Compared with patients who do not have CHD, in whom coronary artery disease (CAD) and hypertension are the most common causes of heart failure (30), heart failure in patients with CHD is often related to the structural lesion or to the long-term complications of the surgical palliative or corrective procedures (31-35). Also atrial arrhythmias are common in patients with CHD, and are believed to be caused by e.g. volume and/or pressure overload or atrial scarring after previous surgical procedures (36-38).

With increased survival, many individuals with CHD are reaching middle age and older ages and are therefore at risk of developing also acquired cardiovascular conditions, such as ischemic heart disease/coronary artery disease and myocardial infarction (MI), in addition to complications related to the CHD lesion. While aging, patients with CHD are also exposed to modifiable cardiovascular risk factors, in the same way as patients without CHD (39). However, the structural and physiological changes that CHD is associated with may increase the risk of ischemia further. For example, patients with certain CHD diagnoses have been reported to have a high prevalence of anomalous coronary arteries (40-42); also the surgical treatment may increase

the risk of ischemia if it involves manipulation of the coronary arteries (15), among other factors. These factors will be further explored in later sections of this thesis.

The main focus of this thesis will be on ischemic heart disease/coronary artery disease and myocardial infarction in patients with CHD, with special attention to patients with coarctation of the aorta and cardiovascular risk factors.

Coronary artery disease in patients with congenital heart disease

The number of published studies that have investigated the risk of coronary artery disease and myocardial infarction in patients with CHD is still limited and most of the reports were published in the last 2-3 years, possibly reflecting the growing attention to this field.

The prevalence of CAD is highly varying in the published studies, ranging from 1% to 14% (26, 43-52), which reflects the different methodologies and definitions of CAD as well as the different age of the patients in the studies. Table 1 presents a summary of the published studies that have described CAD in patients with CHD.

The prevalence of CAD is highly variable when looking at case series from single centers. In a retrospective single center study on 250 consecutive patients with CHD who were referred for coronary angiogram for other reasons than suspected CAD (mean age 51±15 years), Giannakoulas et al reported that 14% of the patients had some degree of atherosclerosis and 9.2% had clinically significant CAD, defined as ≥50% stenosis in one or more major vessels (43). However, the prevalence of CAD was considerably lower in a single center study by Yalonetsky et al, who performed a retrospective chart review that included 12,124 patients with CHD (44). In that study, 1% of the patients had CAD, which was defined as angiographically confirmed ≥50% stenosis in one or more major vessels. The mean age at diagnosis was 56±13 years. The majority of the patients with CAD were asymptomatic and only 27% presented with an MI (44).

The prevalence of CAD, diagnosed during the preoperative work-up before CHD surgery and that required coronary artery bypass surgery, was reported to be 4.5% in a single center study that included 1,154 patients with CHD (50). The mean age of the patients was 66 years (range 41–78 years). Another single center study that included younger patients with CHD (mean age 44, range 35–

68 years), demonstrated that 2.7% had severe CAD that required concomitant coronary artery bypass surgery; however, a total of 22% of the patients had some evidence of CAD (51). The patients with CAD had a statistically significantly higher prevalence of dyslipidemia, hypertension and tobacco smoking compared with patients who did not have CAD (51).

In the recent years, several studies based on data from large nationwide administrative registers have investigated the risk of CAD and MI in patients with CHD. Furthermore, these studies also included a comparison with patients without CHD.

Using data from the Danish National Registry of Patients, Olsen et al investigated the incidence of MI in 10,501 patients with CHD who were 30 years old or older (46). In that study, the cumulative incidence of MI in patients with CHD was 10% by the age of 70 years, a risk that was twice that of controls (HR 2.0, 95% CI 1.7–2.3).

Several other large register-based studies have reported a higher prevalence of CAD, acute coronary syndrome (ACS) or MI in patients with CHD compared with controls without CHD. Saha et al conducted a study based on the UK Biobank data that included 2,006 patients with lower-complexity CHD, defined as simple CHD defects and isolated aortic valve defects, with a median age of 58 years at enrollment (49). The risk of ACS was demonstrated to be doubled in patients with CHD compared with controls after adjustment for cardiovascular risk factors (HR 2.0, 95% CI 1.5–2.8 in patients with simple CHD; HR 2.1, 95% CI 1.7–2.5 in patients with isolated aortic valve defects).

Also younger patients with CHD have been reported to have an increased risk of ACS compared with controls. At the age of 20 years, the relative risk of ACS was reported to be 12.0 times higher in women and 4.6 times higher in men with CHD than in controls (48). The relative risk of ACS in patients with CHD compared with controls declined markedly with increasing age.

The above mentioned register-based studies used the registers in Europe; however, data from Asia shows a similar trend. In a study based on administrative data from the Taiwan National Health Insurance Research Database, the authors reported a two-fold increased risk of ACS in CHD patients compared with controls (HR 2.06, 95% CI 1.37-3.10, p=0.0005) (52).

Table 1: Overview of the studies on CAD, ACS and MI in patients with CHD. The studies shown in this overview included a wide range of CHD diagnoses, and studies that investigated more specific CHD diagnoses are not included in this overview.

First author	Type of study	Publication year	Number of patients	Age of the patients (years)	Follow-up time (years)	CHD diagnosis	Outcome	Prevalence of the outcome	Risk compared with controls
Giannakoulas et al (43)	Single-center, retrospective chart review	2009	250	51±15	1999-2006	All CHD	CAD	14% (9.2% had significant CAD)	N/A
Yalonetsky et al (44)	Single-center, retrospective chart review	2010	12,124	56±13	1999-2009	All CHD	CAD	1%	N/A
Lin et al (52)	Retrospective nationwide register-based cohort study	2014	3,267	36.5 ± 14.6	2000-2010	All CHD	ACS	2.3% (n=72/3181)	HR 2.06 for FU >4 years
Olsen et al (46)	Retrospective nationwide register-based cohort study	2017	10,501	30-70	1977-2012	All CHD	MI	Cumulative incidence at age of 70: 10%	HR 2.0
Giamberti et al (50)	Single-center, retrospective chart review	2017	1154	66 (range: 41-78)	2000-2015	All CHD	CAD requiring CABG	4.3%	N/A
Bokma et al (47)	Register based, multicenter case-control study	2018	6,904	55.1±12.4	2001-2016	All CHD	CAD	0.80%	N/A
Saha et al (49)	Retrospective register based study	2019	2,006	58 (IQR: 51-63)	2006-2010	Lower complexity CHD, isolated AoV	ACS	N/A	HR 2.0-2.1
Johnson et al (51)	Single-center, retrospective chart review	2019	73	44 (range: 35-68)	2007-2017	All CHD	CAD	CAD requiring CABG: 2.7%, Overall CAD: 22%	N/A
Kuijpers et al (48)	Restrospective nationwide register-based cohort study	2020	11,723	32.9 (IQR: 23.0-45.7)	2002-2012	All CHD	ACS	0.9% (103 / 11,723)	HR 12.0 in women and 4.6 in men aged 20 years

CHD=congenital heart disease, CAD=coronary artery disease, MI=myocardial infarction, CABG=coronary artery bypass grafting, MI=myocardial infarction, ACS=acute coronary syndrome, HR= hazard ratio, AoV=aortic valve disease, IQR=interquartile range, FU=follow up, IQR=interquartile range

Modifiable cardiovascular risk factors in patients with congenital heart disease

Atherosclerosis starts already at a young age (53) and continues throughout life; however, it is accelerated in the presence of cardiovascular risk factors. In the INTERHEART study, 9 potentially modifiable risk factors accounted for >90% of the population attributable risk of the first MI episode (39). These risk factors were regular tobacco smoking, dyslipidemia, hypertension, diabetes mellitus, abdominal obesity, psychosocial factors, irregular consumption of fruits and vegetables, no alcohol consumption, and lack of regular physical activity.

It has repeatedly been reported that patients with CHD have a high burden of cardiovascular risk factors compared with the general population. Moons et al reported that among 1,976 young patients with CHD in Belgium (median age 26, IQR 20-36 years), ~80% had at least one cardiovascular risk factor such as smoking, hypertension, diabetes mellitus, overweight/obesity and sedentary life style (54). However, data on hyperlipidemia was not available in that study.

Studies from other countries have reported similar results. In a study from the United States that enrolled 178 patients with moderate or complex CHD diagnoses (mean age 37.1±12.6 years), approximately 70% were found to have at least one modifiable cardiovascular risk factor, of which overweight/obesity and hypertension were the most prevalent (55). Also a Canadian study that used the Canadian CANHEART score to evaluate the presence of modifiable cardiovascular risk factors (smoking, hypertension, diabetes mellitus, obesity, fruit/vegetable consumption, physical exercise) reported that only 1 out of 3 adults with CHD were in ideal cardiovascular health (56).

Although patients with CHD have been shown to have a high prevalence of modifiable cardiovascular risk factors in general compared with patients without CHD, some individual risk factors are less prevalent and some are more prevalent in patients with CHD compared with controls. Below follows a brief summary of the published studies on the prevalence of the most common modifiable cardiovascular risk factors in patients with CHD.

Impaired glucose tolerance and diabetes mellitus

Several studies have shown that patients with CHD have a higher prevalence of impaired glucose tolerance and both diabetes mellitus type 1 and type 2 compared with individuals without CHD.

In a large nationwide study based on data from the Danish National Registry of Patients, patients with CHD ≥ 30 years of age were found to have a 40% increased risk of developing diabetes mellitus type 2 compared with controls (HR 1.4, 95% CI 1.1-1.6) (57). Of note, patients with cyanotic lesions were more likely to develop diabetes mellitus type 2 than CHD patients without cyanosis (HR 1.9, 95% CI 1.1–3.3). This increased risk has been suggested to be caused by acute or chronic hypoxia, a previously proposed risk factor for glucose metabolism disturbance (57).

Furthermore, a high prevalence of abnormal glucose metabolism, diagnosed by an oral glucose tolerance test, have been reported in patients with Fontan circulation (58, 59). In a recent study on 176 consecutive patients who underwent Fontan palliation procedure, 38.4% had impaired glucose tolerance and 4.7% were diagnosed with diabetes mellitus (59). This is notable, as patients with Fontan circulation have been reported to be more likely to be underweight compared with a reference population (60).

Also the risk of developing diabetes mellitus type 1 has been found to be increased in patients with CHD compared with controls (61). Furthermore, several other cohort studies have shown an increased prevalence of diabetes mellitus (unspecified type) in patients with CHD (62-66). Of note, patients with CHD and diabetes mellitus (both type 1 and type 2) have been reported to have a worse prognosis compared with patients without CHD (67, 68).

Hypertension

The prevalence of hypertension in patients with CHD varies in the literature depending on the age of the patients and the CHD diagnosis, and is reported to be between 4 and 48% (69).

Patients with CoA are especially vulnerable to develop hypertension and approximately 50% of all patients with CoA are hypertensive, despite successful surgical repair (70, 71). The risk is increased in patients operated with a graft or a stent and in those with re-coarctation (70). Hypertension in patients with CoA is discussed in more detail in section “Coarctation of the aorta” of this thesis.

Hypertension was particularly prevalent in CHD patients who have CAD: 55-63% of the CHD patients with CAD were noted to have hypertension (44, 51), and hypertension was a strong predictor of developing CAD in patients with CHD (43).

Hyperlipidemia

Several studies have described a favorable lipid profile in patients with CHD (65, 66); however, only a few reports have compared the lipid levels in patients with CHD to that of control subjects (62, 64, 72).

In a case-control study that enrolled 249 patients with CHD (mean age 50.6± 9.2) matched by age and gender with controls without CHD, the patients with CHD were found to have lower total cholesterol and LDL levels compared with controls (72). In that study, it was noted that patients with CHD were less likely to be prescribed statin treatment compared with controls with similar risk scores. Only 42.3% of the patients with CHD were appropriately prescribed a statin compared with 59.0% of controls (p=0.04) (72).

Furthermore, another case-control study on 158 patients with CHD with different levels of CHD complexity (median age 28.3 years), also reported that CHD patients had lower total cholesterol and LDL levels compared with controls after adjustment for age, sex and BMI (64). Patients with cyanotic defects had the lowest total cholesterol and HDL levels compared with non-cyanotic CHD patients and controls (64). This is supported by an another study, which described that patients with cyanosis had lower levels of total cholesterol, LDL and triglycerides compared with both controls and surgically corrected CHD patients (62). Of note, patients with CHD have been reported to also have lower HDL levels compared with controls (62, 64, 72).

Overweight and obesity

The prevalence of obesity is increasing worldwide and has been referred to as a global epidemic (73, 74). The published data on the prevalence of overweight and obesity in patients with CHD have provided variable results, and differ between the countries studied. However, several studies reported that the prevalence of overweight and obesity in CHD patients is similar to that observed in the general population (60, 63, 75, 76), and in some CHD diagnosis groups it is markedly lower (60).

Data from a Swedish cohort on 2,424 patients with CHD showed only limited differences between the rates of obesity in CHD patients with simple defects compared with controls: BMI ≥30 was reported in 12.8% of females with

simple lesions vs in 9% of controls (60). Male patients with simple CHD defects had similar rates of obesity as controls (10.1% in CHD vs 9.7% in controls) (60). However, underweight was more common in male patients with complex CHD lesions (4.9% vs 0.9% in controls) (60).

Comparable rates of overweight and obesity have been reported in a study from the UK that included 3,069 patients with CHD (77). In that study, 28.2% were reported to be overweight and 14.6% were obese with a BMI >30.

Of note, patients with CHD have a decreased isotonic muscle function compared with the general population (78) and it is possible that BMI underestimates the adiposity levels, especially in patients with complex CHD (79).

Tobacco smoking

Patients with CHD have repeatedly been reported to smoke less compared with the general population, independently of the country studied (54, 56, 63, 80-82). A large multinational study described that the prevalence of smoking in patients with CHD in Sweden was 10% in women and 11% in men, compared with approximately 23% in the general population in Sweden (80). According to a Dutch cohort study, 13% of patients with CHD vs 20% of controls smoked regularly (median age of the patients: 39 years) (63). Also a study from Belgium described the same trend with 18% of CHD patients being current smokers compared with 30% of controls (54).

Potential “congenital heart disease associated” factors

Compared with individuals without CHD, patients with CHD have additional factors that have been suggested to potentially contribute to the development of CAD and MI (83, 84).

For example, many CHD patients undergo cardiac surgeries, which might increase the risk of perioperative MI:s. It has also been suggested that surgery in itself is a stressor that can lead to intimal hyperplasia, a precursor of atherosclerotic plaques (85). Furthermore, some of the surgical methods involve manipulation of the coronary arteries, such as re-implantation of the coronary arteries during the arterial switch procedure in patients with transposition of the great arteries (15) or during the Ross procedure in patients with aortic valve disease (86). The manipulation of the coronary arteries might alter the diameter of the coronary ostia and present shear stress on the vessel

wall, potentially accelerating the atherosclerotic process (87). In addition, patients who undergo arterial switch procedure are at risk of sympathetic denervation, which might lead to silent ischemia (88).

Furthermore, patients with CHD, particularly with transposition of the great arteries and tetralogy of Fallot, have a high prevalence of coronary anomalies (40, 41, 89-93), potentially increasing the risk of ischemia and MI. Patients with venous-arterial shunts may have an increased risk of MI type 2 due to paradoxical embolization to the coronary arteries (94-96). Also, patients with CHD have been reported to have a high prevalence of atrial arrhythmias (36, 38, 97, 98) which may also increase the risk of MI type 2. Furthermore, the risk of MI type 2 increases with several chronic cardiac conditions (99), which are common in patients with CHD.

To date, it is not clear whether the increased risk of CAD/MI in patients with CHD is mainly related to the modifiable cardiovascular risk factors or to the "CHD associated" factors. In a case control study including 55 patients with CHD and CAD, Bokma et al reported that the modifiable cardiovascular risk factors were associated with CAD, and not the CHD related factors (previous palliative procedures, residual shunts and mechanical valves) (47). On the contrary, the previously mentioned study on lower complexity CHD reported a two-fold increased risk of ACS in patients with CHD compared with controls, even after adjustment for cardiovascular risk factors (49).

Coarctation of the aorta

Coarctation of the aorta (CoA) represents approximately 3.6% of all congenital anomalies at birth (3) and is characterized by a narrowing of the thoracic aorta that is most often located between the distal aortic arch and the start of the descending aorta, just after the origin of the subclavian artery (100). CoA is more common in males than in females, with a reported ratio of 1.3 to 2.0:1 (101). This lesion can occur either as an isolated defect or in conjunction with other CHD lesions, both with relatively simple defects such as a VSD or in conjunction with more complex lesions, such as transposition of the great arteries or as part of a hypoplastic left heart syndrome (101).

Life expectancy prior to the surgical era was significantly reduced in patients with CoA compared with that of today and approximately 25% did not survive to the age of 20 years and 90% did not survive to the age of 58 years (102). The first surgical repair of CoA was performed in 1944 in Sweden by Clarence Craaford (10). This surgery involved resection of the narrowed part of the

coarctation and suturing the ends of the aorta (resection and end-to-end anastomosis).

Nowadays, there are several surgical techniques and the method of choice depends on the anatomy of the lesion, age of the patient as well as presence of other congenital anomalies (103). Two common surgical treatments are the "end-to-end" anastomosis described above, and the "subclavian flap" procedure where the left subclavian artery is divided and one end is folded down over the narrowed area of the aorta (103, 104). In addition, the coarctation can also be managed by a prosthetic patch or graft, depending on the anatomy of the coarctation (101). The treatment of choice in adolescents and adults is balloon dilatation and implantation of a covered stent in the coarctation area (105). Re-coarctation (recurrent narrowing of the aorta after initial repair) has been reported in 9-31% of the patients (106, 107).

CoA occurs often in conjunction with other vascular abnormalities and is sometimes considered being a general vasculopathy rather than an isolated obstruction (45, 100, 103). More than 50% of all patients with CoA have a bicuspid aortic valve (7) which is often associated with dilation of the ascending aorta and risk of aortic dissection (100, 108). Furthermore, approximately 10% of patients with CoA have cerebral aneurysms, with aneurysms of the circle of Willis being the most common (100).

A recent study from the UK has reported that the survival of patients with CoA is still significantly reduced compared with the general population matched for age and sex and that approximately 50% of the patients required further invasive aortic intervention by the age of 50 years (71).

Of note, in some patients the arcus aortae can be either hypoplastic or show various structural anomalies which makes it difficult to achieve a complete surgical correction of the defect. The consequences of this, e.g. on the development of hypertension, are unknown.

Hypertension in patients with coarctation of the aorta

Hypertension is present in 25-68% of patients with CoA, with variations in the reported prevalence due to the differences in age of the patients and other demographical data (109). Data from the Swedish CHD register (SWEDCON) showed that of the 653 adults with repaired CoA (mean age 36.9 ± 14.4 years), 52.7% had hypertension (110).

A German study on 273 patients with CoA (age range 16-73 years) reported that 25% of the patients were taking antihypertensive drugs, and further 23% patients had an increased blood pressure diagnosed during ambulatory blood pressure measurement (70). Another 10% of the patients had hypertension during exercise testing. Most patients did not have any re-coarctation or re-stenosis. The risk factors for developing hypertension were previous surgical treatment of the coarctation with prosthetic material, male sex, older age at follow-up and increased brachial-ankle gradient (70). Also a study from Sweden reported that more than 50% of the patients with CoA who have hypertension have poorly controlled blood pressure (111). Older age and brachial-ankle blood pressure gradient even in the low ranges were risk factors for poorly controlled hypertension (111).

There are several potential causes of hypertension in patients with CoA, besides the mechanistic explanation of hypertension in the proximal part of the body that is caused by the aortic obstruction in unrepaired coarctation (100). In brief, the neuronal theory states that due to the obstruction, there is an increased stiffness in the aortic wall proximal to the coarctation which leads to hypertension at rest and during exercise, and also to an altered function of the carotid sinus baroreceptors (100). The renal theory suggests that because hypertension is present in the upper parts of the body due to the obstruction of the descending aorta, there is an abnormal neurohormonal response caused by a mismatch between the hypertension in the proximal part of the body and the lack of the hydraulic effects on the renal artery (100).

Coronary artery disease in patients with coarctation of the aorta

Several studies published 20-40 years ago reported that CAD was the most common cause of death in patients with CoA (107, 112, 113) and traditionally, patients with CoA have been considered to have a particularly increased risk of CAD and MI (45, 112, 113).

Two contemporary studies have compared the risk of CAD in patients with CoA with the risk in patients with other CHD lesions. Both these studies have concluded that patients with CoA do not have an increased risk of developing CAD after adjustment for cardiovascular risk factors and that CoA alone does not predict CAD (45, 114).

Definition of myocardial infarction

Current definition

MI is, apart from sudden cardiac death, the most severe and acute manifestation of CAD. Currently, MI is defined according to the "Fourth universal definition of myocardial infarction" (115). This definition requires the presence of myocardial injury, which is present when there is "evidence of elevated cardiac troponin values (cTn) with at least 1 value above the 99th percentile upper reference limit (URL)" (115). For the myocardial injury to be defined as acute, there should be a rise and/or fall of cTn levels.

Acute myocardial infarction is defined as "acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and at least 1 of the following: symptoms of myocardial ischemia; new ischemic ECG changes; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology" (115). This refers to MI type 1, 2 and 3. Further, there are specific criteria for coronary procedure related MI (type 4 and 5) and for silent MI (115).

Historical definitions

The definition of MI has changed considerably during the last decades. For a long time, different definitions have been used, making epidemiological research and comparisons between countries difficult. It was not until 1971 that the first general definition of MI was introduced by the World Health Organization (WHO) work group (116). This definition was based on typical symptoms and ECG changes.

Over the years, the MI definition has developed and the International Society and Federation of Cardiology and WHO criteria for MI from 1979 added cardiac enzymes as a marker of myocardial cell necrosis to the definition (117). Later, the MI criteria were further modified by introducing Minnesota coding to the ECG evaluation, as a contrast to the prior less nuanced ECG criteria (118).

The first biomarkers that were used in the MI diagnosis criteria were Glutamic oxaloacetic transaminase (GOT) and lactate dehydrogenase (LD) which were later replaced by creatine kinase (CK) and the MB-fraction of CK (CK-MB) (119, 120). After introduction of the more cardiac specific troponins in the

1990s (121), the European Society of Cardiology (ESC) and American College of Cardiology published a consensus document on the definition of the myocardial infarction in 2000 (122). This definition emphasized the mandatory rise and fall in cardiac biomarkers (troponin or CK-MB) together with either symptoms, ECG changes, coronary artery intervention or pathology findings (122). In 2007, the first universal definition of myocardial infarction was published, in which also the different MI types were introduced (123).

Myocardial infarction diagnosis in patients with congenital heart disease

The diagnosis of MI in patients with CHD may be challenging. For example, many patients with CHD have abnormal electrocardiogram (ECG) patterns, due to anatomical malformations and displacement, as well as due to previous surgeries or volume/pressure overload (124). Further, patients with CHD more often present with chest pain, even in the absence of an MI (125, 126). In addition, as heart failure is common in patients with CHD, these patients may show chronically increased levels of troponins without any presence of ischemia (127).

THE RATIONALE OF THIS THESIS

With increased life expectancy (21, 23), patients with congenital heart disease are at risk of developing acquired cardiovascular disease, such as ischemic heart disease and myocardial infarction. Besides the atherosclerotic burden that aging is associated with, patients with congenital heart disease may possess additional factors that can contribute to the development of ischemic heart disease and MI. These are, among other factors, history of surgical procedures and the sequelae that follows, coronary artery anomalies, and endothelial dysfunction (40-42, 83, 128, 129).

At the time when this thesis work started, there were only a few published studies investigating the risk of ischemic heart disease and myocardial infarction in patients with congenital heart disease. Furthermore, large nationwide data on the risks of ischemic heart disease in children and young adults with CHD was lacking. Therefore, we aimed to study the risk of ischemic heart disease and MI in patients with CHD of different ages but also to compare this risk to control subjects without CHD, in order to explore the potential differences between the groups.

To date, the long-term outcomes after MI in patients with CHD are unknown. However, it has been suggested that CAD is a significant predictor of mortality in older patients with CHD (25). Therefore, our aim was to describe the long-term outcomes after myocardial infarction in older patients with CHD. As patients with CHD are aging, this knowledge is important in clinical practice for both predicting the outcomes after MI and for primary and secondary prevention, as an increased risk may motivate more extensive prevention measures.

The diagnosis of MI in patients with CHD is potentially challenging in clinical practice, due to a high prevalence of abnormal ECG:s, structural abnormalities and heart failure in patients with CHD (124, 130). The accuracy of MI diagnosis in patients with CHD is unknown. Therefore, we aimed to validate the MI diagnoses in patients with CHD.

Patients with CoA have historically been considered having an increased risk of CAD and MI (45, 112, 113). More than 50% of patients with CoA have hypertension (109), and it is well established that the presence of additional risk factors increases the risk of atherosclerosis. Therefore, we aimed to conduct a structured assessment of other modifiable cardiovascular risk factors in patients with CoA.

AIM

The overall aim of this thesis was to study the risk of cardiovascular disease with emphasis on ischemic heart disease and myocardial infarction, as well as to study cardiovascular risk factors in patients with congenital heart disease. We also aimed to describe the long-term adverse outcomes after myocardial infarction in patients with congenital heart disease.

The specific aims of the four papers included in this thesis were:

Paper I: To study the risk of ischemic heart disease in children and young adults with congenital heart disease and to compare this risk to control subjects without congenital heart disease.

Paper II: To describe the prevalence of modifiable cardiovascular risk factors (impaired glucose tolerance, diabetes mellitus, hypertension, hyperlipidemia, smoking, obesity, sedentary lifestyle) in adult patients with coarctation of the aorta.

Paper III: To validate the myocardial infarction diagnosis in patients with congenital heart disease in the Swedish National Patient Register.

Paper IV: To study the risk of myocardial infarction in patients with congenital heart disease who are ≥40 years of age, and to compare this risk to control subjects without congenital heart disease. Also to describe the long-term outcomes after myocardial infarction in patients with congenital heart disease compared with control subjects without congenital heart disease.

PATIENTS AND METHODS

Data sources

In paper I, III and IV we used the Swedish National Patient Register (NPR) and Cause of Death Register. Below follows a brief description of the registers:

Swedish National Patient Register

The NPR (initiated in 1964) is administered by the Swedish National Board of Health and Welfare and covers all regions in Sweden since 1987. This register contains both the primary and all the secondary diagnoses listed in the discharge summaries of the patients who have received hospital care in Sweden (Inpatient Register). Besides the primary and secondary diagnoses, the NPR also contains data on the name of the hospital where the care took place, type of department, length of stay at the hospital as well as the admission and discharge dates, among other data (131).

Since 2001 the NPR also includes diagnoses registered during visits in the hospital-based outpatient clinics and other specialized outpatient clinics (Outpatient Register) (131). However, primary care is not included.

The patients are identified in the NPR by a unique personal identity number (PIN). Since the introduction of PIN in 1947, each individual who is permanently living in Sweden is assigned a unique PIN either at birth or immigration (132). This enables linkage between the different registers, e.g. between the NPR and the Cause of Death Register.

It is mandatory for all hospitals in Sweden to report to the NPR and this is done on a monthly basis. The incoming data is checked for quality and completeness, and if a care episode contains a considerable amount of missing or invalid data, the National Board of Health and Welfare requests new data from the hospital (131). The amount of missing data on PIN:s and the primary diagnoses is reported to be less than 1% (131).

The diagnoses in the NPR are reported according to the ICD (International Classification of Diseases) coding system. The ICD-8 version was used in the years 1969─1986, the ICD-9 version in the years 1987─1996 and the ICD-10 version (the current version) has been used since 1997.

Several validation studies of the diagnoses in the NPR have been published. Ludvigsson et al conducted a comprehensive review of 132 validation studies of the diagnoses in the NPR and concluded that the validity of the diagnoses is generally high, with a positive predictive value at 85-95% for most diagnoses (133). For MI diagnoses, the positive predictive value was reported to be as high as 98-100% (133).

Cause of Death Register

The Cause of Death Register is also administered by the Swedish National Board of Health and Welfare and was initiated in 1961. When an individual dies, it is mandatory for the treating physician to report the primary and the underlying causes of death to the National Board of Health and Welfare within three weeks. The register also contains the causes of deaths that occurred abroad for individuals permanently living in Sweden (134).

Methods

A brief overview of the four papers that are included in this thesis is shown in Table 2.

Table 2: Overview of the four papers included in this thesis.

	Paper I	Paper II	Paper III	Paper IV
Type of study	Retrospective register-based cohort study	Descriptive cross sectional study	Descriptive retrospective study (diagnosis validation study)	Retrospective register-based cohort study
Data sources	NPR, Cause of Death Register	Clinical and laboratory data, medical records	NPR, Cause of Death Register, medical records	NPR, Cause of Death Register
Study population	Children and young adults with CHD and control subjects	Adults with CoA	Children and adults with CHD who also had received an MI diagnosis	Middle aged and older patients with CHD and control subjects
Years of birth of the patients	1970-1993	1941-1993	1930-2012	1930-1970
Follow-up time (years)	1970-2011	N/A	1970-2015	1970-2017
Statistical analyses	Kaplan Meier survival analysis and Cox regression analyses	Descriptive only	Descriptive only	Kaplan Meier survival analysis and Cox regression analyses
Main outcomes	Ischemic heart disease	Prevalence of cardiovascular risk factors[1]	Number of correct MI diagnoses in patients with true CHD	Index MI at ≥40 years. In patients with index MI: the composite of a recurrent MI, new onset of heart failure or death
Definitions of cardiovascular risk factors	Defined as present if diagnosed before and during the care episode for ischemic heart disease	See table 5	Defined as present if diagnosed before the MI episode	Defined as present if diagnosed before and within a year after the index MI

[1] impaired glucose tolerance, diabetes mellitus, hyperlipidemia, hypertension, overweight/obesity, smoking, sedentary lifestyle

CHD=Congenital heart disease, MI=myocardial infarction, CoA=Coarctation of the aorta, NPR=National Patient Register, N/A=not applicable

Paper I and Paper IV

In Paper I we used the NPR and Cause of Death register to identify all individuals with a CHD diagnosis who were born in the years 1970─1993. In Paper IV we used the same registers and identified all patients with a CHD diagnosis who were born in the years 1930─1970 and alive at the age of 40 years.

In both studies, approximately ten control subjects without a CHD diagnosis were randomly selected from the Total Population Register and matched with each CHD patient by age and sex (in Paper I also for the county of residence). The selection of the control subjects was undertaken by Statistics Sweden.

In Paper I the follow-up period was between January 1970 and December 2011. In the NPR and Cause of Death Register we identified all patients with CHD and all control subjects who received a diagnosis of ischemic heart disease (defined as acute myocardial infarction, stable/unstable angina, previous myocardial infarction and chronic ischemic heart disease) during follow- up.

In Paper IV the follow-up period was between January 1970 and December 2017. In the NPR and Cause of Death registers we identified all patients with CHD and all control subjects who have had an index MI at the age of 40 years or older. For the patients who have had an index MI, we evaluated the long-term outcomes by calculating the risk of a composite event that included the first event of the following (whichever happened first): recurrent MI (re-MI), new onset of heart failure or death.

The ICD diagnostic codes for the CHD diagnoses that were used to identify the study population in Paper I and Paper IV are presented in the supplementary material of the manuscript of Paper I and Paper IV. The ICD diagnostic codes for outcomes and comorbidities in Paper I and Paper IV are shown in Table 3.

Table 3: ICD diagnostic codes for the outcomes and comorbidities in Paper I and Paper IV

Diagnosis	ICD-8	ICD-9	ICD-10
Ischemic heart disease	410, 411, 412, 413, 414	410, 411, 412, 413, 414	I20, I21, I22, I23, I24, I25
Myocardial infarction	410	410	I21
Heart failure	427.00	428	I50
Diabetes mellitus	250	250	E10, E11, E12, E13, E14
Hypertension[1]	400, 401, 402, 403, 404	401, 402, 403, 404, 405	I10, I11, I12, I13, I14, I15
Hypercholesterolemia	272	272A, 272E	E78.0, E78.2, E78.4, E78.5
Atrial fibrillation	427.92	427D	I48

[1] In Paper I the diagnostic codes 401-405 were used in both ICD-8 and -9 versions

ICD=International Classification of Diseases

In Paper I and IV the CHD diagnoses were divided into six different CHD diagnosis groups based on the complexity of the diagnoses according to a previously published hierarchical classification system (135-137) (Table 4). If a patient had several CHD diagnoses, the most complex CHD diagnosis determined the diagnosis group.

Table 4: Congenital heart disease diagnosis groups, and corresponding diagnoses in ICD versions 10, 9 and 8 used in Paper I and Paper IV.

CHD group	CHD diagnosis	ICD-10	ICD-9	ICD-8
Group I	Truncus arteriosus	Q200	745A	746.09
	Aortopulmonary septum defect	Q214	745A	746.09
	Double outlet right ventricle	Q201	745B	746.19
	Double outlet left ventricle	Q202	745B	746.19
	Transposition of great vessels	Q203	745B	746.19
	Discordant atrioventricular connection	Q205[1]	745B	746.19
	Tetralogy of Fallot	Q213	745C	746.29
Group II	Endocardial cushion defects	Q212	745G	746.43[2] 746.46[2] 746.47
	Common ventricle	Q204	745D	746.37
	Hypoplastic left heart syndrome	Q234	746H	746.74
Group III	Coarctation of the aorta	Q251	747B	747.19
Group IV	Ventricular septal defect[3]	Q210	745E	746.39
Group V	Atrial septal defect	Q211	745F	746.42
Group VI	All other congenital heart disease diagnoses that are not included in the five lesion groups above			

[1] Included in Group VI in Paper I

[2] Included in Group V in Paper I

[3] In Paper I, group IV also contains the diagnoses Q218, 745W, 746.89 ("other congenital malformations of cardiac septa")

CHD=Congenital heart disease, ICD=International Classification of Diseases

Paper II

Patients ≥18 years of age with a diagnosis of CoA who were registered at the adult congenital heart disease outpatient clinic at Östra Hospital in Gothenburg were invited to participate in the study (n=192). Altogether, 72 patients (37.5%) agreed to participate.

The patients underwent a clinical examination including the following: measurement of height, weight, waist/hip ratio, BMI and blood pressure. Blood was sampled for analyses of the lipid profile (total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) levels). The patients also underwent measurements of fasting blood glucose levels, hemoglobin A1c (HbA1c) levels and an 2h oral glucose tolerance test. Also 24-h ambulatory blood pressure measurements were undertaken.

The patients filled in a questionnaire that included questions about their education level, physical activity levels, and dietary intake among other questions. Further, we reviewed the patients' medical records to identify previously known comorbidities such as e.g. diagnosis of hypertension and myocardial infarction.

Table 5 shows the definitions of the cardiovascular risk factors that were used in Paper II.

Table 5: Definitions of the cardiovascular risk factors that were used in Paper II

Variable	Definition
Hypertension	Any of the following (138, 139): • previously known diagnosis of hypertension (treated or non-treated with medication) • office blood pressure ≥140/90 mmHg • any of the following on 24-hour ambulatory blood pressure measurements: 24-hour blood pressure of ≥ 130/80 mmHg, or mean daytime blood pressure of ≥ 135/85 mm Hg, or mean night time blood pressure of ≥ 120/70 mmHg
Diabetes mellitus	Any of the following (140): • fasting plasma glucose levels ≥7.0 mmol/l • 2-hour OGTT plasma glucose levels ≥11.1 mmol/l
Impaired glucose tolerance	Fasting glucose levels <7.0 mmol/l and 2-hour OGTT glucose levels ≥7.8 and <11.1 mmol/l (140)
Hyperlipidemia	Any of the following (139) • Total cholesterol levels ≥5 mmol/l • LDL levels ≥3 mmol/l
Overweight	BMI ≥25.0-29.9 kg/m2
Obesity	BMI ≥30.0 kg/m2
Sedentary lifestyle	Less than 150 minutes/week of moderate physical activity or less than 75 minutes/week of intense physical activity, or a combination of these (139)

OGTT=oral glucose tolerance test

Paper III

In Paper III we performed a review of medical records to validate the MI diagnosis in patients with CHD. From a register excerpt compiled by the National Board of Health and Welfare we identified patients who had received both a CHD and an MI diagnosis in the NPR and/or Cause of Death Register. The patients were born in the years 1930─2012 and the follow-up was between the years 1970─2015.

In the registers we identified 249 patients with at least one CHD diagnosis and an MI diagnosis. Letters were sent out to the individual hospitals and regional archive facilities requesting the medical records required for the validation process. Clinical, imaging and laboratory data were requested.

For the MI diagnoses that were identified in the Inpatient Register, validation of only the primary diagnoses was performed, while for the MI diagnoses in the Outpatient Register we validated both primary and secondary MI diagnoses. We also assessed the CHD diagnoses for accuracy and validated the MI diagnoses only in patients who had true CHD diagnoses.

In the validation process of the MI diagnoses we used the "Fourth universal definition of myocardial infarction" that requires "detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and at least 1 of the following: symptoms of myocardial ischemia; new ischemic ECG changes; development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; identification of a coronary thrombus by angiography or autopsy" (acute MI type 1-3) (115).

Because our study included patients with MI:s in the 1970s, 1980s and 1990s, i.e. before the introduction of cardiac troponins, we also accepted an MI diagnosis as correct even if there was missing data on biomarkers, as long as the diagnosis was stated by the physician in charge and was supported by clinical symptoms and/or ECG changes and/or coronary artery intervention. The medical charts were reviewed by one study coordinator as well as either the first author and/or a senior consultant in cardiology, or reviewed by the first author who consulted the senior consultant in cardiology in unclear cases (Manuscript Paper III).

Statistical analysis

For descriptive purposes in Paper I, II, III and IV, continuous variables are presented as means with standard deviations or as medians with interquartile ranges or total ranges. Categorical variables are presented as frequencies and percentages.

In Paper I and IV, Kaplan-Meier survival analysis was performed to calculate the cumulative incidence of ischemic heart disease in CHD patients compared with controls (Paper I), and the cumulative incidence of MI in patients with CHD compared with controls (Paper IV). Competing risk was accounted for in the analyses. The competing event was death due to all causes except ischemic heart disease (Paper I) and death in all causes except MI (Paper IV).

In Paper I and Paper IV we used Cox regression methods to calculate the hazard ratios and 95% confidence intervals for developing ischemic heart disease (Paper I) or MI (Paper IV) in patients with CHD compared with controls. In Paper IV, Cox regression models were also used to calculate the hazard ratios of developing an adverse outcome (composite of re-MI, new onset of heart failure or death) after the index MI in patients with CHD compared with controls.

In Paper I, the model was adjusted for sex and age and the patients were censored at emigration, end of study (31/12/2011) or death in other causes than ischemic heart disease. In Paper IV, we present an unadjusted model as well as a second model that was adjusted for cardiovascular risk factors (hypertension, diabetes mellitus, and hypercholesterolemia). Censoring was done at emigration, last date of the follow-up (31/12/2017) or death in all causes except MI. A p-value of less than 0.05 was considered as statistically significant.

Software used

In Paper I, SAS software (version 9.4; SAS Institute, Cary, NC, USA) and R software (version 3.1; R Foundation for Statistical Computing, Vienna, Austria) were used for the statistical analyses. In Paper III and Paper IV, R software (version 3.5.2) was used. The statistical analyses in Paper II were performed in Microsoft Excel and the figures in Paper III were created using Microsoft Excel.

The statistical analyses in Paper I and IV were performed by a statistician, and by the first author in Paper II. The analyses in Paper III were performed by the first author with assistance of a statistician.

Ethical approval

All the four studies were approved by the Gothenburg Regional Research Ethics Board. In the study presented in Paper II, all the participants gave their written and oral informed consent. In the studies presented in Paper I and Paper IV, the consent was waived because only anonymized register data was used and all the personal identifiable data was removed in the final dataset that we received from the National Board of Health and Welfare. In the study presented in Paper III, the informed consent was waived due to the nature of the study. All four studies complied with the Declaration of Helsinki.

RESULTS

Ischemic heart disease in children and young adults with congenital heart disease in Sweden (Paper I)

In Paper I we investigated the risk of ischemic heart disease in children and young adults with CHD and compared this risk to control subjects without CHD.

In the registers (NPR and Cause of Death Register) we identified 21,982 patients with CHD and 219,816 control subjects (48.4% female). Mean age at registration of the CHD diagnosis in the registers was 9.6 years (standard deviation (SD) ±11.3 years). The mean age at the end of the study was 26.6 (SD ±9.1) years in patients with CHD and 28.2 (SD±7.4) years in control subjects.

Patients with CHD had a 16.5 fold increased risk of developing ischemic heart disease compared with controls (HR 16.5, 95% CI: 13.7–19.9, $p<0.0001$). During follow-up, altogether 1.3% (n=278) of patients with CHD and 0.08% (n=183) of controls received a diagnosis of ischemic heart disease. Myocardial infarction was diagnosed in 33.5% (n=93) of patients with CHD and ischemic heart disease compared with 30.1% (n=55) control subjects with ischemic heart disease (hazard ratio for MI in CHD patients vs controls: 18.4, 95% CI 13.2–25.7). Female patients with CHD had a lower risk of developing ischemic heart disease compared with male patients with CHD (HR 0.74, 95% CI 0.59–0.94).

Patients with the most severe CHD diagnoses (conotruncal defects and severe non-conotruncal defects) had the highest risk of developing ischemic heart disease compared with controls (Table 6). Patients with CoA did not have an increased risk of developing ischemic heart disease relative to patients in the other CHD diagnosis groups.

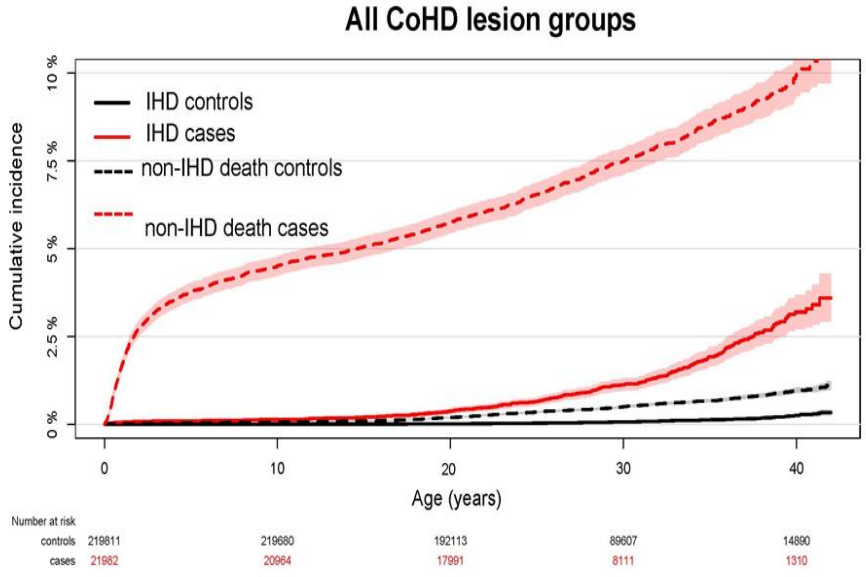
Table 6: Risk of ischemic heart disease in patients with CHD and in control subjects. Reprinted with permission from the publisher. Fedchenko et al, Int J Cardiol. 2017 Dec 1;248:143-148. doi: 10.1016/j.ijcard.2017.06.120.

Lesion group	Cases IHD (n)/total no. of patients in lesion group	Controls IHD (n)/ total no. of controls in lesion group	IHD per 100,000 person-years, cases (n)	IHD per 100,000 person-years, controls (n)	HR for IHD (CI, 95%)
All CoHD	278/21,982	183/219,816	46.8	2.9	16.5 (13.7–19.9)
1. Conotruncal defects[a]	33/2,022	17/20,230	71.1	2.9	25.8 (14.4–46.4)
2. Severe nonconotruncal defects[b]	14/1,087	7/10,870	56.3	2.3	26.3 (10.6–65.3)
3. Coarctation of the aorta[c]	16/1,306	8/13,060	44.6	2.1	21.5 (9.2–50.3)
4. Ventricular septal defect[d]	36/4,369	31/43,689	31.2	2.6	12.5 (7.7–20.2)
5. Atrial septal defect[e]	26/2,405	26/24,049	39.1	3.4	10.4 (6.0–17.9)
6. Other heart and circulatory system anomalies[f]	153/10,793	94/107,918	50.2	3.0	17.0 (13.2–22.0)

CI= confidence interval; CoHD = congenital heart disease; HR = hazard ratio; IHD= ischemic heart disease

[a] Defined as common truncus, aortopulmonary septum defect, transposition of great vessels, tetralogy of Fallot.
[b] Defined as endocardial cushion defects, common ventricle, hypoplastic left heart syndrome.
[c] Defined as coarctation of the aorta.
[d] Defined as ventricular septal defect.
[e] Defined as atrial septal defect.
[f] Defined as diagnoses not classified into the other five lesion groups.

The cumulative incidence of ischemic heart disease increased markedly more in patients with CHD compared with control subjects after the age of 20 years (Figure 1).



CoHD=Congenital heart disease, IHD=Ischemic heart disease.

Figure 1: Cumulative incidence of ischemic heart disease in patients with congenital heart disease and in controls. Competing event (death in non-IHD related causes) is shown as dotted lines. Reprinted with permission from the publisher. Fedchenko et al, Int J Cardiol. 2017 Dec 1;248:143-148. doi: 10.1016/j.ijcard.2017.06.120.

Cardiovascular risk factors

Patients with CHD who had received a diagnosis of ischemic heart disease had a lower prevalence of diabetes and hypertension compared with control subjects with ischemic heart disease. Overall, 1.8% (n=5) of the patients with CHD and ischemic heart disease had diabetes mellitus compared with 7.7 (n=14) of control subjects; and 9.7% (n=27) of the patients CHD and ischemic heart disease had hypertension, compared with 19.7% (n=36) of control subjects. However, the prevalence of heart failure was higher in CHD patients compared with control subjects; almost 20% of patients with CHD and ischemic heart disease had a heart failure diagnosis (19.4%, n=54) compared with 7.1% (n=13) control subjects.

Cardiovascular risk factors in adults with coarctation of the aorta (Paper II)

Altogether 72 patients with CoA were included in the study (median age 43.5 years, range 20-71 years). Of the patients who participated, 41.7% were women.

Overall, more than 90% of the patients (91.7%, n=66) patients had one or more modifiable cardiovascular risk factors that were either previously known or newly diagnosed during the study: impaired glucose tolerance, diabetes mellitus, hypertension, hyperlipidemia, regular tobacco smoking, overweight or obesity, and a sedentary lifestyle. Figure 2 shows the number of cardiovascular risk factors in the study population.

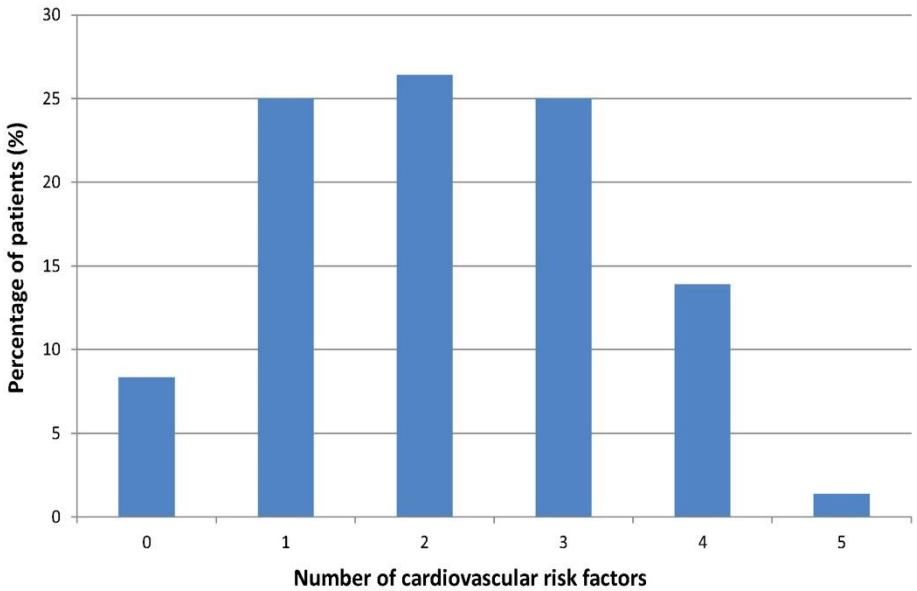


Figure 2: Number of modifiable cardiovascular risk factors and percentage of the patients with 1-5 risk factors. Reprinted with permission from the publisher. Fedchenko et al. Congenital Heart Disease. 2019;14(4):549-58.

During the study, a total of 4.2% (n=3) patients were newly diagnosed with diabetes mellitus or impaired glucose tolerance; of these, two patients (2.8%) were found to have a previously undiagnosed diabetes mellitus and 1.4% (n=1) patient was found to have impaired glucose tolerance.

Hyperlipidemia was common in patients with CoA included in our study and altogether 58.3% (n=42) had hyperlipidemia. More than every second patient in our study had LDL cholesterol levels ≥3 mmol/l (56.9%, n=41/72). More than every third patient (36.1%, n=26/72) had total cholesterol levels ≥5 mmol/l and more than 10% (11.1%, n=8) had total cholesterol levels ≥6 mmol/l. Only ~30% of the patients (31.9%, n=23) had "ideal" LDL levels below <2.6 mmol/l.

Also hypertension was common in our study cohort. Approximately half of the participants (51.4%, n=37/72) had a previously known diagnosis of hypertension. A total of 60 patients underwent 24-hour ambulatory blood pressure measurements and approximately half (55.0%, n=33) had high systolic and/or diastolic blood pressure. Of these, one third of the patients (36.4%, n=12) were newly found to have hypertension during the 24-hour ambulatory blood pressure measurement and 70% of the patients (n=21) with elevated blood pressure on 24-hour ambulatory blood pressure measurement had a previously known diagnosis of hypertension.

Almost every second patient was overweight or obese (n=35, 48.6%). More than half of the patients (61.1%. n=44) met the European Society of Cardiology recommendations on physical exercise (at least 150 minutes/week of moderate physical activity or 75 minutes/week of intense physical activity, or a combination of these) (139). Smoking was uncommon in our cohort with only three (n=4.2%) patients being regular smokers.

Validation of myocardial infarction diagnosis in patients with congenital heart disease in Sweden (Paper III)

Validation of the CHD diagnoses could be performed in ≥95% of the patients whose medical records were requested (n=249). The most common diagnosis was secundum atrial septal defect/patent foramen ovale. Approximately one third of the patients were women and nearly 3 out of 4 patients had a true CHD diagnosis (numbers and percentages are presented in the manuscript of Paper III).

Most patients with true CHD diagnoses had correct MI diagnoses (manuscript Paper III). The causes for the incorrect MI diagnoses and the corresponding numbers and percentages are presented in the manuscript of Paper III. The patients with correct MI diagnoses were older than the patients who received incorrect MI diagnoses in the registers.

The median age of the patients with true CHD diagnoses and correct MI diagnoses was around 60 years when they had MI. The most common MI type was NSTEMI and most MI:s were judged as being type 1 MI:s. Approximately one fourth of the MI:s were judged as being type 2 MI:s. Smoking and hypertension were the most common cardiovascular risk factors in patients with true CHD and correct MI diagnoses.

The most frequent causes for incorrect CHD diagnoses were the following: falsely assignment of a congenital CHD diagnosis to an acquired VSD after an MI, typographical inaccuracies, and assignment of CHD diagnostic codes to acquired valvular conditions (manuscript Paper III).

Long-term outcomes after myocardial infarction in middle aged and older patients with congenital heart disease – a nationwide study (Paper IV)

In this study we investigated the risk of developing an MI and long-term adverse outcomes after MI in patients with CHD older than 40 years compared with control subjects without CHD.

In total, 17,189 patients with a CHD diagnosis (approximately half of whom were female) and 180,131 control subjects were identified in the registers and hence included in the study. Patients with CHD and the control subjects were born between the years 1930 and 1970 and alive at the age of 40 years. Demographic data is presented in the manuscript of Paper IV. The mean follow-up of the patients with CHD and control subjects was over 20 years.

Patients with CHD had a 40% higher risk of being diagnosed with an MI compared with control subjects (risk adjusted for cardiovascular risk factors). The unadjusted and adjusted hazard ratios and 95% confidence intervals for the risk of MI in patients with CHD and control subjects are presented in the manuscript of Paper IV. Patients with the most severe CHD diagnoses had the highest risk of being diagnosed with an MI (manuscript Paper IV).

The most common cardiovascular risk factor in patients with CHD and MI was hypertension. Also diabetes mellitus and hypercholesterolemia were common. There were no significant differences in the prevalence of hypertension, diabetes mellitus and hypercholesterolemia in patients with CHD and MI compared with control subjects who have had an MI. The numbers and corresponding percentages of the cardiovascular risk factors are shown in the manuscript of Paper IV.

Compared with control subjects, patients with CHD had an increased risk of developing an adverse composite event (re-MI or being diagnosed with heart failure or death) after the index MI. Manuscript Paper IV shows the unadjusted and adjusted hazard ratios and 95% confidence intervals for the risk of developing a composite event after the index MI in patients with CHD and control subjects.

The increased risk of the adverse composite event after the index MI in patients with CHD was mainly caused by a high incidence of newly diagnosed heart failure (manuscript Paper IV).

The risk of developing a re-MI after the index MI was slightly lower in patients with CHD compared with control subjects as shown in Figure 3.

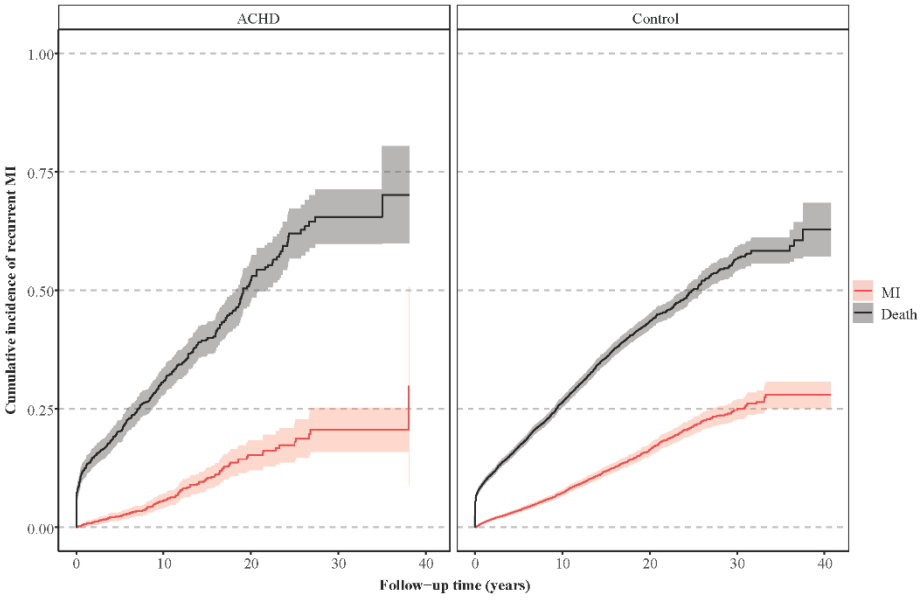


Figure 3: The cumulative incidence of developing a re-MI after the index MI in patients with CHD and controls aged 40 years or older. The red line represents the cumulative probability of developing a re-MI, while the black line represents the competing event (death in other causes than MI).

DISCUSSION

Risk of ischemic heart disease and myocardial infarction in patients with congenital heart disease

In paper I we studied the risk of ischemic heart disease in children and young adults with CHD. We found that the relative risk of developing ischemic heart disease was more than 16 times increased in patients with CHD compared with controls matched for age, sex and county of residence. However, the absolute risk was low both in patients with CHD and in controls.

The majority of the published studies on ischemic heart disease/CAD in patients with CHD included adult patients ≥18 years of age (43-47, 49, 52) and to the best of our knowledge, the present paper was the first nationwide paper that investigated the risk of ischemic heart disease in children and young adults with CHD. Recently, Kuijpers et al published a study on the risk of CAD (defined as MI or unstable angina or death due to CAD) in 11,723 patients with CHD ≥ 18 years of age, based on the national registers in the Netherlands (48). The results in that study were comparable to our study: by the age of 20 years, the relative risk of CAD was 12 times higher in women with CHD (HR 12.0, 95% CI 2.5–56.3) and 4.6 higher in men with CHD compared with control subjects (HR 4.6, 95% CI 1.7–12.1) (48). Also other studies reported an increased risk of ischemic heart disease/CAD in patients with CHD compared with controls (46, 49, 52); however, direct comparisons with these studies are difficult to carry out because of the younger age of the patients included in our paper.

In Paper I, we found that patients with CHD who were diagnosed with ischemic heart disease had a lower prevalence of hypertension and diabetes mellitus compared with controls diagnosed with ischemic heart disease: diabetes was present in 1.8% of patients with CHD compared with 7.7% of controls and hypertension was diagnosed in 9.7% of patients with CHD compared with 19.7% of controls. This suggests that atherosclerosis may not be the main cause of ischemic heart disease in younger patients with CHD and that factors associated with CHD might be of more importance in children and young adults with CHD.

As discussed earlier, patients with CHD are exposed to several additional factors that have been suggested to contribute to the development of ischemic heart disease (83, 84). The patients with CHD who undergo surgery might be at an increased risk of perioperative MI:s, and also at an increased risk of

ischemia due to physiological responses to the surgical procedures (85). Also, some surgical procedures require manipulation and re-implantation of the coronary arteries, such as in the arterial switch and Ross procedures (15, 86), which may alter the size of the coronary ostia and leading to shear stress on the vessel wall (87). Furthermore, patients with transposition of the great arteries and tetralogy of Fallot have a high prevalence of coronary anomalies (40, 41, 89-91) which can further increase their risk of ischemia and MI.

In addition, many patients with CHD experience a mismatch between the increased oxygen demand (due to volume/pressure overload) and reduced maximum oxygen supply. This may lead to ischemia, even without abnormalities in the coronary artery anatomy (141). Also endothelial dysfunction has been described in patients with CHD, with a potential to contribute to the increased risk of ischemia (128, 129). Patients with a wide range of CHD diagnoses may also have an increased risk of paradoxical embolization to the coronary arteries due to venous-arterial shunts (94-96). There might even be unknown physiological or genetic factors that contribute to the increased risk of CAD and MI in patients with CHD.

In paper IV we investigated the risk of MI in middle aged and older patients with CHD compared with control subjects. In this paper, we focused on middle aged and older patients with CHD, as atherosclerotic disease becomes clinically evident at these ages. We studied only the MI diagnoses and not all ischemic heart disease diagnoses because MI is, apart from sudden death, the most serious complication of ischemic heart disease that causes significant morbidity and mortality. Furthermore, it has been reported that the validity of MI diagnoses in the NPR is one of the highest compared with other cardiovascular disease diagnoses (133).

In Paper IV, we found that patients with CHD had a 40% increased risk of developing MI compared with control subjects. Our results are consistent with the findings of several other studies that included patients of comparable age. In a study based on the Danish National Registry of Patients, Olsen et al reported that the risk of MI in patients with CHD was two times higher compared with controls (46). Also Saha et al reported that the risk of ACS in patients with lower complexity CHD is approximately twice as high in CHD patients compared with controls after adjustment for cardiovascular risk factors (49). A register based study from Taiwan reported similar findings (52).

In both Paper I and Paper IV we found that patients with the most complex CHD diagnoses have the highest risk of developing ischemic heart disease and MI. The high presumed prevalence of surgical procedures in patients with

complex CHD diagnoses, as well as the high prevalence of coronary anomalies in patients with e.g. tetralogy of Fallot and transposition of the great arteries are possible explanations for the observed increased risk. This finding is in line with two other studies that have reported an increased risk of CAD/ACS in patients with complex CHD (46, 48).

There were several similarities but also differences between the results in Paper I and Paper IV. Firstly, in both papers we found an increased risk of developing ischemic heart disease/MI in patients with CHD compared with controls. However, compared with controls, the risk was markedly more increased in children and young patients with CHD than in middle aged and older patients with CHD. In Paper I the risk of ischemic heart disease was 16.5 times higher and the risk of MI was 18.4 times higher in patients with CHD than in controls. However, in Paper IV the risk of MI was 40% higher in patients with CHD than in controls. The difference in the age of the patients in Paper I and Paper IV is likely to explain why younger patients had a much higher relative risk of developing ischemic heart disease and MI compared with controls: while ischemic heart disease is uncommon in children and young adults without CHD, it becomes more prevalent with increasing age of the patients, and the relative difference between patients with CHD and controls is reduced. This finding is similar to that reported by Kuijpers et al who found that younger patients with CHD have a higher risk of developing ACS compared with older patients with CHD in comparison with controls (48).

Our findings imply that the mechanisms behind ischemic heart disease may be somewhat different between young and middle aged and older patients with CHD. It appears from our results that in children and younger patients with CHD, the "CHD associated" factors are more important for developing ischemic heart disease than the modifiable cardiovascular risk factors. However, in older patients with CHD it seems that the modifiable cardiovascular risk factors are of most importance for developing MI, and that the "CHD associated" factors contribute at a lesser extent. In Paper I we found that the prevalence of hypertension and diabetes mellitus was markedly lower in CHD patients with ischemic heart disease than in controls with ischemic heart disease. However, in Paper IV the prevalence of cardiovascular risk factors was similar in the two groups and also higher in both cases and controls compared with Paper I.

In Paper IV we found that the risk of MI was increased in patients with CHD compared with controls even after adjustment for cardiovascular risk factors. This is similar to the findings of Saha et al who reported that the risk of ACS is almost doubled in CHD patients with lower complexity diagnoses than in

controls, even after accounting for cardiovascular risk factors (49). Bokma et al reported that the modifiable cardiovascular risk factors are of most importance (rather than the CHD related factors) for development of CAD in middle aged patients with CHD (47). Our findings add to the body of evidence that cardiovascular risk factors are the greatest contributors to myocardial infarction in middle aged and older patients with CHD; however, the CHD associated factors contribute too, increasing the relative risk compared with individuals who do not have CHD. In children and young adults, however, the CHD associated risk factors are of a greater importance for developing ischemic heart disease than the modifiable cardiovascular risk factors.

Long-term outcomes after myocardial infarction

In paper IV we also studied the long-term outcomes after the index MI in patients with CHD. We found that the risk of a re-MI is similar in patients with CHD and in control subjects. Therefore, it is likely that modifiable cardiovascular risk factors are of more importance for developing a re-MI than the CHD associated factors.

After the index MI, the risk of the composite outcome of either a re-MI, new onset of heart failure or mortality was higher in patients with CHD than in control subjects. This was mainly caused by a high incidence of new onset heart failure in patients with CHD. Heart failure is common in patients with CHD (31, 33-35, 142-144) and is conventionally described as a consequence of the structural cardiac abnormalities, previous surgeries and related complications (130). This is in contrast with patients who do not have CHD, in whom coronary artery disease and hypertension are the most common etiologic causes. However, from our results it seems that heart failure in CHD patients can also be driven by ischemia.

There are several potential explanations for the increased incidence of new onset heart failure in patients with CHD compared with control subjects. Firstly, it is possible that patients with CHD are more vulnerable to develop heart failure after MI because of a high prevalence of various shunts, valvular disease, flow obstruction or arrhythmia – factors that are common in CHD patients and that increase the risk of developing heart failure (130). Secondly, an MI can potentially uncover previously undiagnosed heart failure in patients with CHD, especially in patients with less severe conditions that are not regularly followed at adult CHD clinics. Thirdly, diagnosing heart failure in CHD is challenging as patients with e.g. systemic right ventricles and univentricular circulation might have a decreased ventricular function

habitually. It is therefore plausible that some over diagnosis occurs when the CHD patients are admitted for an MI.

Patients with coarctation of the aorta

Traditionally, patients with CoA have been considered to have a high risk of MI as a consequence of the generalized vascular disease related to the CoA (45, 100). In Paper I and Paper IV we did not find any evidence of a particularly increased risk of ischemic heart disease or MI in patients with CoA compared with patients with other CHD diagnoses.

This is in line with two other studies where patients with CoA have been reported to have a similar risk of CAD compared with other CHD patients after adjustment for cardiovascular risk factors (45, 114). Of note, the patients in both these studies were younger than in Paper IV. Hence, from our results it can be concluded that also middle aged and older patients with CoA do not have a particularly increased risk of MI compared with patients with other CHD diagnoses after adjustment for cardiovascular risk factors.

Cardiovascular risk factors in patients with coarctation of the aorta

In paper II we studied the prevalence of modifiable cardiovascular risk factors (impaired glucose tolerance, diabetes mellitus, hypertension, hyperlipidemia, regular tobacco smoking, overweight or obesity, and a sedentary lifestyle) in adult patients with CoA. We found that the prevalence of cardiovascular risk factors was high, with approximately 9 out of 10 patients with CoA having at least one modifiable cardiovascular risk factor. Of note, 4.3% of the patients were newly diagnosed with impaired glucose tolerance or diabetes mellitus.

Compared with other studies on cardiovascular risk factors in patients with CoA, we noticed a lower prevalence of diabetes mellitus; however, a higher prevalence of hyperlipidemia in our cohort (45, 114). The differences noted are likely to be explained by the different methodologies in the studies: the patients in our study underwent a structured risk factor assessment including blood sampling, however, in the two above-mentioned studies the risk factors were identified via either a chart review or via an administrative database. In our study, we found a low prevalence of tobacco smoking in patients with CoA, which is consistent with other studies on patients with CHD (54, 62, 63, 65).

The high prevalence of cardiovascular risk factors in patients with CoA that were found in the present study is noteworthy considering that the risk of atherosclerotic disease increases with increasing number of cardiovascular risk

factors (145, 146). Several studies have reported poor risk factor control in patients with CHD. Patients with CHD have been shown to be less likely to be prescribed a statin than patients without CHD with similar cardiovascular risk scores (72) and a study from Sweden reported that approximately 50% of patients with CoA had poorly controlled hypertension (111), which was also noted in Paper II. Considering that approximately 50% of all patients with CoA have hypertension (70, 71, 114), and that several studies reported poor risk factor control in this patient group (72, 111), there is a need for a systematic approach to both screening for and treatment of cardiovascular risk factors in patients with CoA. This is likely to be important for improving the long-term survival and reducing the burden of atherosclerotic disease in patients with CoA.

Validation of myocardial infarction diagnoses

In Paper III we performed a chart review to validate the MI diagnoses in patients with CHD. We found that the validity of the MI diagnoses in NPR was high. From our results, it seems that having a CHD does not considerably affect the validity of the MI diagnosis, despite that patients with CHD often show abnormal ECG changes (124), and might have increased cardiac troponin levels due to a high prevalence of heart failure (31, 32, 35, 144, 147).

Comparisons to other validation studies of MI in patients with CHD are difficult to make as we are not aware of any other studies that have validated the MI diagnosis in patients with CHD. However, our results are in line with previously published validation studies of MI in the Swedish NPR (148, 149) and also in the Danish Patient Register (150, 151).

In our study, we found that nearly 3 out of 4 CHD diagnoses were correct. The validity of CHD diagnoses is variable in the published studies (152-155); however, although our study did not primarily aim to validate the CHD diagnoses, it seems from our results that the NPR is dependable for studying the CHD diagnoses.

Strengths and limitations

Paper I and IV

The strength of Paper I and Paper IV are the large number of individuals that were included in both studies. Paper I included 21,982 children and young adults with CHD aged 0 to 42 years and 219,816 control subjects matched for age, sex and county of residence. In Paper IV, 17,189 patients with a CHD diagnosis aged 40 years or older and 180,131 control subjects matched for sex

and age were included. Because the national registers were used, we believe that almost all events were identified as it is mandatory to report to the registers. By the design of our study, the loss to follow-up is minimal. A further strength is the long follow-up time that was more than 20 years on average in both studies.

However, there are several limitations in both studies. Firstly, as in all register based studies that use administrative data, there is an inherent risk of misdiagnosis and miscoding in the registered data. Being aware of this, and especially considering the diagnostic challenges of MI in patients with CHD, in Paper III we validated the MI diagnoses. We found that the validity of MI diagnoses was high in patients with CHD. However, we did not validate the ischemic heart disease diagnoses in Paper I. Nevertheless, based on the results of Paper III and on other validation studies of the diagnoses in the NPR (133), we believe that although there is likely to be some degree of misclassified and incorrect diagnoses, the NPR is dependable when studying the ischemic heart disease diagnoses. As we used register data, we did not have information on the exact mechanisms for the MI:s and ischemic heart disease in the patients. Also, we did not have data on tobacco smoking, BMI and physical activity level of the patients.

In Paper III we also assessed the correctness of the CHD diagnoses and found that the number of correct CHD diagnoses was lower than the number of correct MI diagnoses. One of the reasons for misclassification of the CHD diagnoses was a wrongly assignment of the congenital heart disease diagnosis code to an acquired condition. Therefore, we believe that the potential for misclassification of the CHD diagnoses was higher in Paper IV than in Paper I, because Paper I only included children and young adults. In the patient selection in Paper IV, we excluded patients with certain criteria to reduce the risk of including incorrect CHD diagnoses (described in detail in Paper IV).

In Paper I, the patients were born in 1970 and later and the follow-up of the diagnoses in the NPR started at birth for the whole cohort. However, in Paper IV the patients were born before the year 1970 when follow-up started. This introduces an immortal time bias in Paper IV as we do not have reliable data on the number of patients with CHD who developed an MI or who died before the year 1970 when follow-up started. Also, for the same reasons, we could not reliably study how surgical procedures affected the risk of developing MI in paper IV.

Furthermore, it is possible that patients with simple CHD diagnoses, who have never been hospitalized since the year 1970 and only followed in the primary

care, were not identified in the registers. Furthermore, it is possible that not all of the cardiovascular risk factors are captured in the registers since hypertension and diabetes mellitus, for example, are most often followed in primary care. In paper IV we included cardiovascular risk factors diagnosed up to and within a year after the index MI episode. This was done because many patients with e.g. diabetes mellitus are diagnosed in conjunction with the MI episode. Also, this is likely to reduce the detection bias between cases and controls because patients with CHD might have more contact with health care facilities than patients who not have CHD.

Paper II

We performed a comprehensive assessment of the modifiable cardiovascular risk factors that included venipuncture and oral glucose tolerance test. The structured assessment also included a life style questionnaire where patients reported their physical activity levels and smoking habits, among other factors.

The limitations included that the participation rate was moderate with approximately one third of the patients who were contacted participated. One reason for this was that not all patients who were invited to participate lived in the Gothenburg region and some lived in the distant parts of Sweden.

Also, not all patients underwent the 24h ambulatory blood pressure measurements leading to missing data in our analyses.

Further, because of the different prevalence of cardiovascular risk factors in different countries, the results of our study may not be generalizable to patients in other countries. We did not include a control group for our patients; however, our aim was to describe the prevalence of the modifiable risk factors in patients with CoA only.

Paper III

The strength of this paper is that we included individuals with CHD from the different hospitals in various parts of Sweden in the MI validation process. Furthermore, the number of missing medical records was low. However, one limitation is that some of the medical records we received had some missing data on e.g. symptoms, biomarkers and ECG:s. The definition of MI have changed considerably over time, and it is possible that some of the diagnoses that we assessed as correct MI:s would be classified as unstable angina if all biomarkers and ECG:s would be available. Also, when assessing the validity of the CHD diagnoses, we only accepted the CHD diagnoses as being correct

if there was a clear mentioning of the diagnosis in the notes or if it was supported by imaging data or evidence of a surgical procedure. Hence, suspected diagnoses were assessed as incorrect. It is possible that we could have misclassified a few CHD diagnoses as incorrect due to the lack of supportive data, or when diagnostic procedures were not performed. However, in the “true CHD” group we included also PFO:s, e.g. in cases where an atrial shunt was seen, however, we did not include cases with “suspected” shunts of unknown origin.

CONCLUSIONS

- Patients with congenital heart disease of all ages have an increased risk of developing ischemic heart disease and/or myocardial infarction compared with individuals who do not have congenital heart disease. The relative risk compared with control subjects is greater in children and young adults but is still significant in middle aged and older patients with congenital heart disease.

- Factors that are related to congenital heart disease, rather than the modifiable cardiovascular risk factors, seem to be of most importance for developing ischemic heart disease in children and young adults with congenital heart disease. However, modifiable cardiovascular risk factors contribute most to the development of myocardial infarction in middle aged and older patients, and the congenital heart disease associated factors contribute to a lesser extent.

- The accuracy of the myocardial infarction diagnosis in patients with congenital heart disease is high.

- Patients with congenital heart disease who develop myocardial infarction are at an increased risk of developing adverse outcomes after the index myocardial infarction compared with control subjects. The increased risk is mainly driven by a high prevalence of new onset of heart failure in patients with congenital heart disease.

- The risk of developing ischemic heart disease and myocardial infarction is not particularly increased in patients with coarctation of the aorta compared with other congenital heart disease diagnosis groups.

- Patients with coarctation of the aorta have a high prevalence of cardiovascular risk factors detected by a systematic risk factor assessment. Systematic screening in patients with coarctation of the aorta and in patients with congenital heart disease in general needs to be considered in order to identify and treat the individuals with the highest risk factor burden in order to prevent development of acquired cardiovascular disease.

FUTURE PERSPECTIVES

The results of this thesis work show that the risk of ischemic heart disease and myocardial infarction is increased in patients with congenital heart disease compared with controls. Future studies are needed to investigate the exact mechanisms behind this increased risk and to quantify the contribution of both the modifiable cardiovascular risk factors and the factors associated with congenital heart disease. Further, the various factors that are associated with congenital heart disease that are believed to increase the risk of ischemic heart disease need to be explored. The mechanisms on how these factors contribute to ischemia need to be studied in more detail. Furthermore, the presence of potentially unknown factors, either genetic or physiological, that can be associated with the increased risk of ischemic heart disease in patients with CHD should be considered in research projects in the future. This knowledge on both the risk of ischemic heart disease and the factors contributing to the development of it in patients with congenital heart disease is important for increasing the quality of care and for reducing morbidity and mortality in this growing patient group.

More research is needed on the prevalence of modifiable cardiovascular risk factors in patients with CHD and their contribution to development of coronary artery disease in patients with CHD, as well as interaction with CHD associated factors. Further, studies that explore the evidence for establishing specific guidelines for screening for modifiable cardiovascular risk factors in patients with congenital heart disease could be undertaken. Also, studies on the specific optimal levels for various cardiovascular risk factors that are tailored to this patient group might also be undertaken.

The validity of various diagnoses in the Swedish registers is reported to be generally high (133) and also this thesis report a high validity of myocardial infarction diagnoses in patients with congenital heart disease. However, it would be valuable to carry out further validation studies on other diagnoses in patients with congenital heart disease, as well as to validate the congenital heart disease diagnoses.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to everyone who have contributed to making this work possible. In particular, I would like to thank:

Mikael Dellborg, my main supervisor, for providing the best possible environment for my PhD education. Thank you for always being available for questions and discussions, for your enthusiasm and for continuously encouraging me. I am forever grateful for everything you have done and taught me during these years.

Zacharias Mandalenakis, my co-supervisor, for always being helpful and approachable, and for all your support, advice and guidance, both in research and in clinical work. Thank you for inspiring and encouraging me.

Peter Eriksson, my co-supervisor, for your enthusiasm about our research work and for teaching me about congenital heart disease and the physiology of it. Thank you for your valuable input on our papers and in my thesis and for all your encouragement during these years.

Annika Rosengren, my co-supervisor, for sharing your immense knowledge about cardiovascular epidemiology with me and for all your valuable input on my papers, as well as for your manuscripts writing tips.

Helena Dellborg and **Görel Hultsberg-Olsson,** my co-authors and research coordinators, for all your great help with papers II and III, and for your ideas and input. Thank you also for teaching me many practicalities of research work, and equally important for your encouragement and support.

Wai Giang Kok and **Georg Lappas,** my co-authors, for teaching me statistics and explaining complex matters in a way that I could understand.

My co-author **Kristofer Skoglund,** for all your tips and advice since the first day I started working in this research group, and for your encouragement during the last months before my dissertation.

My co-author and fellow PhD student **Anna Björk**, for efficient team-work when we started working as research assistants together and for your help and input on Paper II.

Ulrika Forslund-Grenheden and **Eva Thydén**, for your excellent administrative help during this thesis work.

Helen Sjöland, head of the Cardiology Department at Östra Hospital, for employing me and for providing me time to do research alongside with my specialty training.

Maria Taranger, the head of the Internal Medicine, Emergency and Geriatric Department at Östra Hospital, for providing a stimulating and friendly environment that allows combining both clinical work and research.

Per-Olof Hansson, the current head of the research unit, for ensuring optimal research environment.

Erik Thunström, director of studies at the Cardiology department, for all the advice and enthusiasm about research work and cardiology training that you have shared with me.

Current and former PhD colleagues at Östra Hospital, for your advice and support during this time.

Anna-Clara Collén, Jacob Odenstedt and Paulin Andréll for your valuable input on my work and all your tips during my half-time seminar.

The nurses, doctors and **administrative personnel** at the ACHD-center at Östra Hospital, for welcoming me and teaching me about congenital heart disease just at the start of my research journey.

The **participants of Paper II**, for taking time to participate in this study and contribute to this work.

The **secretaries** and **administrative personnel** at the different hospitals and medical archive services around the country, for the help with retrieving the medical notes.

All my **fellow colleagues** and **co-workers** at the Cardiology and Internal Medicine Department at Östra hospital, for your friendliness and support.

All my dear friends, for your support and encouragement. **Säde,** for taking the cover picture. **Birgitta** and **Ida**, for all your great tips and for thoroughly proofreading this thesis.

My brother-in-law, **Jesper**, for your tips on layout and for thoroughly proofreading this thesis. My sister-in-law, **Lovisa**, for your encouragement.

My parents-in-law, **Susanne** and **Johnny**, for all your support, kindness and encouragement.

My parents, **Elena** and **Nikolai**. Thank you for all your endless love, and for everything you have done for me. My brother, **Anton**, for being the best brother I could ever have.

My dear husband **Mikael**, for your love and for always supporting and encouraging me. I am forever grateful for your patience and all support during the time I was writing this thesis.

The present study was supported by grants from the Swedish state (under the agreement between the Swedish government and the county councils concerning economic support of research and education of doctors, ALF-agreement); grants from the Swedish Heart and Lung Foundation and the Swedish Research Council.

REFERENCES

1. Mitchell SC, Korones SB, Berendes HW. Congenital heart disease in 56,109 births. Incidence and natural history. Circulation. 1971;43(3):323-32.

2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890-900.

3. Liu Y, Chen S, Zuhlke L, Black GC, Choy MK, Li N, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol. 2019;48(2):455-63.

4. Khoshnood B, Lelong N, Houyel L, Thieulin AC, Jouannic JM, Magnier S, et al. Prevalence, timing of diagnosis and mortality of newborns with congenital heart defects: a population-based study. Heart (British Cardiac Society). 2012;98(22):1667-73.

5. Roberts NK, Cretin S. The changing face of congenital heart disease. A method for predicting the influence of cardiac surgery upon the prevalence and spectrum of congenital heart disease. Med Care. 1980;18(9):930-9.

6. Campbell M. Natural history of persistent ductus arteriosus. British heart journal. 1968;30(1):4-13.

7. Hoffman JIE, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. American Heart Journal. 2004;147(3):425-39.

8. Waldhausen JA, Boruchow I, Miller WW, Rashkind WJ. Transposition of the great arteries with ventricular septal defect. Palliation by atrial septostomy and pulmonary artery banding. Circulation. 1969;39(5 Suppl 1):I215-21.

9. Gross RE, Hubbard JP. Landmark article Feb 25, 1939: Surgical ligation of a patent ductus arteriosus. Report of first successful case. By Robert E. Gross and John P. Hubbard. JAMA : the journal of the American Medical Association. 1984;251(9):1201-2.

10. Crafoord N. Congenital coarctation of the aorta and it´s surgical management J Thorac Surg 1945;14:347-62.

11. Castaneda A. Congenital heart disease: a surgical-historical perspective. Ann Thorac Surg. 2005;79(6):S2217-20.

12. Senning A. Surgical correction of transposition of the great vessels. Surgery. 1959;45(6):966-80.

13. Mustard WT. SUCCESSFUL TWO-STAGE CORRECTION OF TRANSPOSITION OF THE GREAT VESSELS. Surgery. 1964;55:469-72.

14. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax. 1971;26(3):240-8.

15. Jatene AD, Fontes VF, Paulista PP, Souza LC, Neger F, Galantier M, et al. Anatomic correction of transposition of the great vessels. J Thorac Cardiovasc Surg. 1976;72(3):364-70.

16. Erikssen G, Liestol K, Seem E, Birkeland S, Saatvedt KJ, Hoel TN, et al. Achievements in congenital heart defect surgery: a prospective, 40-year study of 7038 patients. Circulation. 2015;131(4):337-46; discussion 46.

17. Raissadati A, Nieminen H, Jokinen E, Sairanen H. Progress in late results among pediatric cardiac surgery patients: a population-based 6-decade study with 98% follow-up. Circulation. 2015;131(4):347-53; discussion 53.

18. Boneva RS, Botto LD, Moore CA, Yang Q, Correa A, Erickson JD. Mortality associated with congenital heart defects in the United States: trends and racial disparities, 1979-1997. Circulation. 2001;103(19):2376-81.

19. Pillutla P, Shetty KD, Foster E. Mortality associated with adult congenital heart disease: Trends in the US population from 1979 to 2005. Am Heart J. 2009;158(5):874-9.

20. 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(5):474-83.

21. Mandalenakis Z, Rosengren A, Skoglund K, Lappas G, Eriksson P, Dellborg M. Survivorship in Children and Young Adults With Congenital Heart Disease in Sweden. JAMA Intern Med. 2017;177(2):224-30.

22. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. J Am Coll Cardiol. 2010;56(14):1149-57.

23. 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(2):163-72.

24. Marelli AJ, Therrien J, Mackie AS, Ionescu-Ittu R, Pilote L. Planning the specialized care of adult congenital heart disease patients: from numbers to guidelines; an epidemiologic approach. Am Heart J. 2009;157(1):1-8.

25. Tutarel O, Kempny A, Alonso-Gonzalez R, Jabbour R, Li W, Uebing A, et al. Congenital heart disease beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality. European heart journal. 2014;35(11):725-32.

26. 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(14):1509-15.

27. Warnes CA. The adult with congenital heart disease: born to be bad? J Am Coll Cardiol. 2005;46(1):1-8.

28.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(5):460-7.

29. 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 (British Cardiac Society). 2008;94(3):342-8.

30. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol. 1993;22(4 Suppl A):6a-13a.

31. Piran S, Veldtman G, Siu S, Webb GD, Liu PP. Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. Circulation. 2002;105(10):1189-94.

32. Bolger AP, Coats AJ, Gatzoulis MA. Congenital heart disease: the original heart failure syndrome. European heart journal. 2003;24(10):970-6.

33. Dinardo JA. Heart failure associated with adult congenital heart disease. Seminars in cardiothoracic and vascular anesthesia. 2013;17(1):44-54.

34. Zomer AC, Vaartjes I, van der Velde ET, de Jong HM, Konings TC, Wagenaar LJ, et al. Heart failure admissions in adults with congenital heart disease; risk factors and prognosis. International journal of cardiology. 2013;168(3):2487-93.

35. Stefanescu A, DeFaria Yeh D, Dudzinski DM. Heart failure in adult congenital heart disease. Current treatment options in cardiovascular medicine. 2014;16(9):337.

36. Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Gilljam T, Hansson PO, et al. Atrial Fibrillation Burden in Young Patients with Congenital Heart Disease. Circulation. 2017.

37. Bouchardy J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Bottega N, et al. Atrial arrhythmias in adults with congenital heart disease. Circulation. 2009;120(17):1679-86.

38. Bernier M, Marelli AJ, Pilote L, Bouchardy J, Bottega N, Martucci G, et al. Atrial arrhythmias in adult patients with right- versus left-sided congenital heart disease anomalies. The American journal of cardiology. 2010;106(4):547-51.

39. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.

40. Tanel RE, Wernovsky G, Landzberg MJ, Perry SB, Burke RP. Coronary artery abnormalities detected at cardiac catheterization following the arterial switch operation for transposition of the great arteries. The American journal of cardiology. 1995;76(3):153-7.

41. Koifman B, Egdell R, Somerville J. Prevalence of asymptomatic coronary arterial abnormalities detected by angiography in grown-up patients with congenital heart disease. Cardiol Young. 2001;11(6):614-8.

42. Angelini P, Velasco JA, Flamm S. Coronary anomalies: incidence, pathophysiology, and clinical relevance. Circulation. 2002;105(20):2449-54.

43. Giannakoulas G, Dimopoulos K, Engel R, Goktekin O, Kucukdurmaz Z, Vatankulu MA, et al. Burden of coronary artery disease in adults with congenital heart disease and its relation to congenital and traditional heart risk factors. The American journal of cardiology. 2009;103(10):1445-50.

44. Yalonetsky S, Horlick EM, Osten MD, Benson LN, Oechslin EN, Silversides CK. Clinical characteristics of coronary artery disease in adults with congenital heart defects. International journal of cardiology. 2013;164(2):217-20.

45. Roifman I, Therrien J, Ionescu-Ittu R, Pilote L, Guo L, Kotowycz MA, et al. Coarctation of the aorta and coronary artery disease: fact or fiction? Circulation. 2012;126(1):16-21.

46. Olsen M, Marino B, Kaltman J, Laursen H, Jakobsen L, Mahle W, et al. Myocardial Infarction in Adults With Congenital Heart Disease. The American journal of cardiology. 2017;120(12):2272-7.

47. 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 (British Cardiac Society). 2018;104(7):574-80.

48. Kuijpers JM, Vaartjes I, Bokma JP, van Melle JP, Sieswerda GT, Konings TC, et al. Risk of coronary artery disease in adults with congenital heart disease: A comparison with the general population. International journal of cardiology. 2020;304:39-42.

49. 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(16):1889-99.

50. Giamberti A, Lo Rito M, Conforti E, Varrica A, Carminati M, Frigiola A, et al. Acquired coronary artery disease in adult patients with congenital heart disease: a true or a false problem? Journal of cardiovascular medicine (Hagerstown, Md). 2017;18(8):605-9.

51. Johnson B, Buelow M, Earing M, Cohen S, Bartz P, Ginde S. Coronary artery disease screening in adults with congenital heart disease prior to cardiac surgery. Congenital heart disease. 2019;14(6):895-900.

52. Lin YS, Liu PH, Wu LS, Chen YM, Chang CJ, Chu PH. Major adverse cardiovascular events in adult congenital heart disease: a population-based follow-up study from Taiwan. BMC Cardiovasc Disord. 2014;14:38.

53. Tuzcu EM, Kapadia SR, Tutar E, Ziada KM, Hobbs RE, McCarthy PM, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. Circulation. 2001;103(22):2705-10.

54. Moons P, Van Deyk K, Dedroog D, Troost E, Budts W. Prevalence of cardiovascular risk factors in adults with congenital heart disease. Eur J Cardiovasc Prev Rehabil. 2006;13(4):612-6.

55. Lui GK, Rogers IS, Ding VY, Hedlin HK, MacMillen K, Maron DJ, et al. Risk Estimates for Atherosclerotic Cardiovascular Disease in Adults With Congenital Heart Disease. The American journal of cardiology. 2017;119(1):112-8.

56. Harris KC, Voss C, Rankin K, Aminzadah B, Gardner R, Mackie AS. Modifiable cardiovascular risk factors in adolescents and adults with congenital heart disease. Congenital heart disease. 2018;13(4):563-70.

57. Madsen NL, Marino BS, Woo JG, Thomsen RW, Videboek J, Laursen HB, et al. Congenital Heart Disease With and Without Cyanotic Potential and the Long-term Risk of Diabetes Mellitus: A Population-Based Follow-up Study. J Am Heart Assoc. 2016;5(7).

58. Ohuchi H, Miyamoto Y, Yamamoto M, Ishihara H, Takata H, Miyazaki A, et al. High prevalence of abnormal glucose metabolism in young adult patients with complex congenital heart disease. Am Heart J. 2009;158(1):30-9.

59. Ohuchi H, Negishi J, Hayama Y, Miike H, Suzuki D, Nakajima K, et al. Abnormal glucose metabolism in patients with Fontan circulation: Unique characteristics and associations with Fontan pathophysiology. Am Heart J. 2019;216:125-35.

60. Sandberg C, Rinnstrom D, Dellborg M, Thilen U, Sorensson P, Nielsen NE, et al. Height, weight and body mass index in adults with congenital heart disease. International journal of cardiology. 2015;187:219-26.

61. Bjork A, Mandalenakis Z, Giang KW, Rosengren A, Eriksson P, Dellborg M. Incidence of Type 1 diabetes mellitus and effect on mortality in young patients with congenital heart defect - A nationwide cohort study. International journal of cardiology. 2020.

62. Moon JR, Song J, Huh J, Kang IS, Park SW, Chang SA, et al. Analysis of Cardiovascular Risk Factors in Adults with Congenital Heart Disease. Korean Circ J. 2015;45(5):416-23.

63. Zomer AC, Vaartjes I, Uiterwaal CS, van der Velde ET, Sieswerda GJ, Wajon EM, et al. Social burden and lifestyle in adults with congenital heart disease. The American journal of cardiology. 2012;109(11):1657-63.

64. Martinez-Quintana E, Rodriguez-Gonzalez F, Nieto-Lago V, Novoa FJ, Lopez-Rios L, Riano-Ruiz M. Serum glucose and lipid levels in adult congenital heart disease patients. Metabolism: clinical and experimental. 2010;59(11):1642-8.

65. Lui GK, Rogers IS, Ding VY, Hedlin HK, MacMillen K, Maron DJ, et al. Risk Estimates for Atherosclerotic Cardiovascular Disease in Adults With Congenital Heart Disease. The American journal of cardiology. 2017;119(1):112-8.

66. Hacker AL, Oberhoffer R, Hager A, Ewert P, Muller J. Age-related cardiovascular risk in adult patients with congenital heart disease. International journal of cardiology. 2019;277:90-6.

67. Dellborg M, Bjork A, Pirouzi Fard MN, Ambring A, Eriksson P, Svensson AM, et al. High mortality and morbidity among adults with congenital heart disease and type 2 diabetes. Scand Cardiovasc J. 2015;49(6):344-50.

68. Bjork A, Svensson AM, Fard MNP, Eriksson P, Dellborg M. Type 1 diabetes mellitus and associated risk factors in patients with or without CHD: a case-control study. Cardiol Young. 2017:1-8.

69. Engelfriet P, Boersma E, Oechslin E, Tijssen J, Gatzoulis MA, Thilen U, et al. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. The Euro Heart Survey on adult congenital heart disease. European heart journal. 2005;26(21):2325-33.

70. Hager A, Kanz S, Kaemmerer H, Schreiber C, Hess J. Coarctation Long-term Assessment (COALA): significance of arterial hypertension in a cohort of 404 patients up to 27 years after surgical repair of isolated coarctation of the aorta, even in the absence of restenosis and prosthetic material. J Thorac Cardiovasc Surg. 2007;134(3):738-45.

71. Lee MGY, Babu-Narayan SV, Kempny A, Uebing A, Montanaro C, Shore DF, et al. Long-term mortality and cardiovascular burden for adult survivors of coarctation of the aorta. Heart (British Cardiac Society). 2019;105(15):1190-6.

72. Flannery LD, Fahed AC, DeFaria Yeh D, Youniss MA, Barinsky GL, Stefanescu Schmidt AC, et al. Frequency of Guideline-Based Statin Therapy in Adults With Congenital Heart Disease. The American journal of cardiology. 2018;121(4):485-90.

73. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, et al. The global obesity pandemic: shaped by global drivers and local environments. The Lancet. 2011;378(9793):804-14.

74. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. The Lancet. 2011;377(9765):557-67.

75. Deen JF, Krieger EV, Slee AE, Arslan A, Arterburn D, Stout KK, et al. Metabolic Syndrome in Adults With Congenital Heart Disease. J Am Heart Assoc. 2016;5(2).

76. Lerman JB, Parness IA, Shenoy RU. Body Weights in Adults With Congenital Heart Disease and the Obesity Frequency. The American journal of cardiology. 2017;119(4):638-42.

77. Brida M, Dimopoulos K, Kempny A, Liodakis E, Alonso-Gonzalez R, Swan L, et al. Body mass index in adult congenital heart disease. Heart (British Cardiac Society). 2017;103(16):1250-7.

78. Kroonstrom LA, Johansson L, Zetterstrom AK, Dellborg M, Eriksson P, Cider A. Muscle function in adults with congenital heart disease. International journal of cardiology. 2014;170(3):358-63.

79. Shiina Y, Murakami T, Matsumoto N, Okamura D, Takahashi Y, Nishihata Y, et al. Body composition, appetite-related hormones, adipocytokines, and heart failure in adult patients with congenital heart disease: A preliminary study. Congenital heart disease. 2018;13(1):79-84.

80. Moons P, Luyckx K, Kovacs AH, Holbein CE, Thomet C, Budts W, et al. Prevalence and Effects of Cigarette Smoking, Cannabis Consumption, and Co-use in Adults From 15 Countries With Congenital Heart Disease. The Canadian journal of cardiology. 2019;35(12):1842-50.

81. Reid GJ, Webb GD, McCrindle BW, Irvine MJ, Siu SC. Health behaviors among adolescents and young adults with congenital heart disease. Congenital heart disease. 2008;3(1):16-25.

82. Engelfriet PM, Drenthen W, Pieper PG, Tijssen JG, Yap SC, Boersma E, et al. Smoking and its effects on mortality in adults with congenital heart disease. International journal of cardiology. 2008;127(1):93-7.

83. Lui GK, Fernandes S, McElhinney DB. Management of cardiovascular risk factors in adults with congenital heart disease. J Am Heart Assoc. 2014;3(6):e001076.

84. Roche SL, Silversides CK. Hypertension, obesity, and coronary artery disease in the survivors of congenital heart disease. The Canadian journal of cardiology. 2013;29(7):841-8.

85. Guerri-Guttenberg RA, Castilla R, Francos GC, Müller A, Ambrosio G, Milei J. Transforming growth factor β1 and coronary intimal hyperplasia in pediatric patients with congenital heart disease. The Canadian journal of cardiology. 2013;29(7):849-57.

86. Herrmann JL, Stram AR, Brown JW. Ross Procedure: How to Do It and How to Teach It. 2019;10(5):624-7.

87. Raisky O, Bergoend E, Agnoletti G, Ou P, Bonnet D, Sidi D, et al. Late coronary artery lesions after neonatal arterial switch operation: results of surgical coronary revascularization. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2007;31(5):894-8.

88. Kondo C, Nakazawa M, Momma K, Kusakabe K. Sympathetic denervation and reinnervation after arterial switch operation for complete transposition. Circulation. 1998;97(24):2414-9.

89. Fellows KE, Freed MD, Keane JF, Praagh R, Bernhard WF, Castaneda AC. Results of routine preoperative coronary angiography in tetralogy of Fallot. Circulation. 1975;51(3):561-6.

90. Massoudy P, Baltalarli A, de Leval MR, Cook A, Neudorf U, Derrick G, et al. Anatomic variability in coronary arterial distribution with regard to the arterial switch procedure. Circulation. 2002;106(15):1980-4.

91. Yu FF, Lu B, Gao Y, Hou ZH, Schoepf UJ, Spearman JV, et al. Congenital anomalies of coronary arteries in complex congenital heart disease: diagnosis and analysis with dual-source CT. J Cardiovasc Comput Tomogr. 2013;7(6):383-90.

92. Dabizzi RP, Teodori G, Barletta GA, Caprioli G, Baldrighi G, Baldrighi V. Associated coronary and cardiac anomalies in the tetralogy of Fallot. An angiographic study. European heart journal. 1990;11(8):692-704.

93. Moll M, Michalak KW, Sobczak-Budlewska K, Moll JA, Kopala M, Szymczyk K, et al. Coronary Artery Anomalies in Patients With Transposition of the Great Arteries and Their Impact on Postoperative Outcomes. Ann Thorac Surg. 2017;104(5):1620-8.

94. Hastings RS, McElhinney DB, Saric M, Ngai C, Skolnick AH. Embolic myocardial infarction in a patient with a Fontan circulation. World J Pediatr Congenit Heart Surg. 2014;5(4):631-4.

95. Wasek WC, Samul W, Ryczek R, Skrobowski A. Unique case of ST-segment-elevation myocardial infarction related to paradoxical embolization and simultaneous pulmonary embolization: clinical considerations on indications for patent foramen ovale closure in no-guidelines land. Circulation. 2015;131(13):1214-23.

96. Shamoon R, Habib H, Rampal U, Hamdan A, Bikkina M, Shamoon F. A Rare Case of Embolic ST-Elevation Myocardial Infarction in an Adult Patient With Repaired Hypoplastic Left Heart Syndrome. World J Pediatr Congenit Heart Surg. 2017;8(4):543-9.

97. Harrison DA, Siu SC, Hussain F, MacLoghlin CJ, Webb GD, Harris L. Sustained atrial arrhythmias in adults late after repair of tetralogy of fallot. The American journal of cardiology. 2001;87(5):584-8.

98. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation. 2010;122(9):868-75.

99. Alfredsson J, Alexander KP. Multiple Chronic Conditions in Older Adults with Acute Coronary Syndromes. Clinics in geriatric medicine. 2016;32(2):291-303.

100. Perloff JK. The variant associations of aortic isthmic coarctation. The American journal of cardiology. 2010;106(7):1038-41.

101. Kaemmerer H, Szatmári A, Ewert P. Aortic Coarctation and Interrupted Aortic Arch. In: Gatzoulis MAMDPFF, Webb GDMDCMF, Daubeney PEFDMFF, editors. Diagnosis and Management of Adult Congenital Heart Disease2018. p. 409-20.

102. Campbell M. Natural history of coarctation of the aorta. British heart journal. 1970;32(5):633-40.

103. Kenny D, Hijazi ZM. Coarctation of the aorta: from fetal life to adulthood. Cardiol J. 2011;18(5):487-95.

104. Barreiro CJ, Ellison TA, Williams JA, Durr ML, Cameron DE, Vricella LA. Subclavian flap aortoplasty: still a safe, reproducible, and effective treatment for infant coarctation. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2007;31(4):649-53.

105. Hamdan MA, Maheshwari S, Fahey JT, Hellenbrand WE. Endovascular stents for coarctation of the aorta: initial results and intermediate-term follow-up. J Am Coll Cardiol. 2001;38(5):1518-23.

106. Choudhary P, Canniffe C, Jackson DJ, Tanous D, Walsh K, Celermajer DS. Late outcomes in adults with coarctation of the aorta. Heart (British Cardiac Society). 2015;101(15):1190-5.

107. Toro-Salazar OH, Steinberger J, Thomas W, Rocchini AP, Carpenter B, Moller JH. Long-term follow-up of patients after coarctation of the aorta repair. The American journal of cardiology. 2002;89(5):541-7.

108. Evangelista A, Gallego P, Calvo-Iglesias F, Bermejo J, Robledo-Carmona J, Sanchez V, et al. Anatomical and clinical predictors of valve dysfunction and aortic dilation in bicuspid aortic valve disease. Heart (British Cardiac Society). 2018;104(7):566-73.

109. Canniffe C, Ou P, Walsh K, Bonnet D, Celermajer D. Hypertension after repair of aortic coarctation--a systematic review. International journal of cardiology. 2013;167(6):2456-61.

110. Rinnstrom D, Dellborg M, Thilen U, Sorensson P, Nielsen NE, Christersson C, et al. Hypertension in adults with repaired coarctation of the aorta. Am Heart J. 2016;181:10-5.

111. Rinnstrom D, Dellborg M, Thilen U, Sorensson P, Nielsen NE, Christersson C, et al. Poor blood pressure control in adults with repaired coarctation of the aorta and hypertension: a register-based study of associated factors. Cardiol Young. 2017;27(9):1708-15.

112. Cohen M, Fuster V, Steele PM, Driscoll D, McGoon DC. Coarctation of the aorta. Long-term follow-up and prediction of outcome after surgical correction. Circulation. 1989;80(4):840-5.

113. Cokkinos DV, Leachman RD, Cooley DA. Increased mortality rate from coronary artery disease following operation for coarctation of the aorta at a late age. J Thorac Cardiovasc Surg. 1979;77(2):315-8.

114. Egbe AC, Rihal CS, Thomas A, Boler A, Mehra N, Andersen K, et al. Coronary Artery Disease in Adults With Coarctation of Aorta: Incidence, Risk Factors, and Outcomes. J Am Heart Assoc. 2019;8(12):e012056.

115. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138(20):e618-e51.

116. WHO. Working Group on the Establishment of Ischemic Heart Disease Registers: Report of the Fifth Working Group, Copenhagen. In Report No. Geneva: World Health Organization. 1971.

117. Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. Circulation. 1979;59(3):607-9.

118. Mendis S, Thygesen K, Kuulasmaa K, Giampaoli S, Mähönen M, Ngu Blackett K, et al. World Health Organization definition of myocardial infarction: 2008–09 revision. International Journal of Epidemiology. 2010;40(1):139-46.

119. Wroblewski F. Clinical significance of serum enzyme alterations associated with myocardial infarction. Am Heart J. 1957;54(2):219-24.

120. Wagner GS, Roe CR, Limbird LE, Rosati RA, Wallace AG. The importance of identification of the myocardial-specific isoenzyme of creatine phosphokinase (MB form) in the diagnosis of acute myocardial infarction. Circulation. 1973;47(2):263-9.

121. Katus HA, Remppis A, Neumann FJ, Scheffold T, Diederich KW, Vinar G, et al. Diagnostic efficiency of troponin T measurements in acute myocardial infarction. Circulation. 1991;83(3):902-12.

122. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. European heart journal. 2000;21(18):1502-13.

123. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol. 2007;50(22):2173-95.

124. Khairy P, Marelli AJ. Clinical use of electrocardiography in adults with congenital heart disease. Circulation. 2007;116(23):2734-46.

125. Berghammer M, Karlsson J, Ekman I, Eriksson P, Dellborg M. Self-reported health status (EQ-5D) in adults with congenital heart disease. International journal of cardiology. 2013;165(3):537-43.

126. Gales J, Krasuski RA, Awerbach JD. Emergency department evaluation of chest pain among adult congenital heart disease patients. Am Heart J. 2020;222:191-8.

127. Eindhoven JA, Roos-Hesselink JW, van den Bosch AE, Kardys I, Cheng JM, Veenis JF, et al. High-sensitive troponin-T in adult congenital heart disease. International journal of cardiology. 2015;184:405-11.

128. Gardiner HM, Celermajer DS, Sorensen KE, Georgakopoulos D, Robinson J, Thomas O, et al. Arterial reactivity is significantly impaired in normotensive young adults after successful repair of aortic coarctation in childhood. Circulation. 1994;89(4):1745-50.

129. Binotto MA, Maeda NY, Lopes AA. Evidence of endothelial dysfunction in patients with functionally univentricular physiology before completion of the Fontan operation. Cardiol Young. 2005;15(1):26-30.

130. Stout KK, Broberg CS, Book WM, Cecchin F, Chen JM, Dimopoulos K, et al. Chronic Heart Failure in Congenital Heart Disease: A Scientific Statement From the American Heart Association. Circulation. 2016;133(8):770-801.

131. Socialstyrelsen. National Patient Register [Webpage]. Socialstyrelsen; 2019 [updated 20/5/2019. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-national-patient-register/.

132. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. European journal of epidemiology. 2009;24(11):659-67.

133. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

134.Socialstyrelsen. Dödsorsaksregistret (Cause of Death Register) Internet2019 [Available from: https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/dodsorsaksregistret/.

135. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A, National Birth Defects Prevention S. Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies. Birth Defects Res A Clin Mol Teratol. 2007;79(10):714-27.

136. Liu S, Joseph KS, Lisonkova S, Rouleau J, Van den Hof M, Sauve R, et al. Association between maternal chronic conditions and congenital heart defects: a population-based cohort study. Circulation. 2013;128(6):583-9.

137. Liu S, Joseph KS, Luo W, Leon JA, Lisonkova S, Van den Hof M, et al. Effect of Folic Acid Food Fortification in Canada on Congenital Heart Disease Subtypes. Circulation. 2016;134(9):647-55.

138. O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. Journal of hypertension. 2013;31(9):1731-68.

139. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice

(constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European heart journal. 2016;37(29):2315-81.

140. WHO. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Report of a WHO/IDF consultation. . 2006.

141. Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, et al. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life--single centre experience and review of published data. European heart journal. 2012;33(11):1386-96.

142. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoege M, et al. Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. The American journal of cardiology. 2006;97(8):1238-43.

143. Wang F, Harel-Sterling L, Cohen S, Liu A, Brophy JM, Paradis G, et al. Heart failure risk predictions in adult patients with congenital heart disease: a systematic review. Heart (British Cardiac Society). 2019;105(21):1661-9.

144. Gilljam T, Mandalenakis Z, Dellborg M, Lappas G, Eriksson P, Skoglund K, et al. Development of heart failure in young patients with congenital heart disease: a nation-wide cohort study. Open heart. 2019;6(1):e000858.

145. Berenson GS, Srinivasan SR, Bao W, Newman WP, 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med. 1998;338(23):1650-6.

146. Lowe LP, Greenland P, Ruth KJ, Dyer AR, Stamler R, Stamler J. Impact of major cardiovascular disease risk factors, particularly in combination, on 22-year mortality in women and men. Archives of internal medicine. 1998;158(18):2007-14.

147. 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(15):e008775.

148. Lindblad U, Rastam L, Ranstam J, Peterson M. Validity of register data on acute myocardial infarction and acute stroke: the Skaraborg Hypertension Project. Scand J Soc Med. 1993;21(1):3-9.

149. Hammar N, Alfredsson L, Rosen M, Spetz CL, Kahan T, Ysberg AS. A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. Int J Epidemiol. 2001;30 Suppl 1:S30-4.

150. Sundboll J, Adelborg K, Munch T, Froslev T, Sorensen HT, Botker HE, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. BMJ Open. 2016. https://doi.org/10.1136/bmjopen-2016-012832.

151. Joensen AM, Jensen MK, Overvad K, Dethlefsen C, Schmidt E, Rasmussen L, et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. Journal of clinical epidemiology. 2009;62(2):188-94.

152. Cohen S, Jannot A-S, Iserin L, Bonnet D, Burgun A, Escudié J-B. Accuracy of claim data in the identification and classification of adults with congenital heart diseases in electronic medical records. Archives of Cardiovascular Diseases. 2019;112(1):31-43.

153. Khan A, Ramsey K, Ballard C, Armstrong E, Burchill LJ, Menashe V, et al. Limited Accuracy of Administrative Data for the Identification and Classification of Adult Congenital Heart Disease. J Am Heart Assoc. 2018;7(2).

154. Jepsen B, Jepsen P, Johnsen SP, Espersen GT, Sørensen HT. Validity of diagnoses of cardiac malformations in a Danish population-based hospital-discharge registry. International Journal of Risk and Safety in Medicine. 2006;18(2):77-81.

155. Agergaard P, Hebert A, Bjerre J, Sørensen KM, Olesen C, Østergaard JR. Children diagnosed with congenital cardiac malformations at the national university departments of pediatric cardiology: Positive predictive values of data in the Danish National Patient Registry. Clinical Epidemiology. 2011;3(1):61-6.